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Biomedicine & Pharmacotherapy

Volume 161, May 2023, 114457

Review

Strategy and application of manipulating DCs chemotaxis in disease treatment and vaccine design

Yichao Lu [a 1], Jian You [a b c]

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https://doi.org/10.1016/j.biopha.2023.114457

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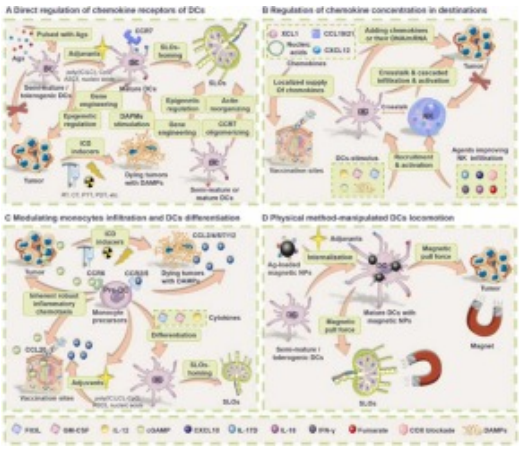
Highlights

- Diversified migratory modes and exquisite chemotaxis behavior of DCs modulate their multifunctional biological activities.
- Spatiotemporal positioning of DCs in either SLOs or inflammatory foci endows DCs with appropriate immunological competence.
- Regulating chemokines and their receptors expression, altering pre-DCs trafficking, and physical measure are main strategies.
- Modulating DCs trafficking in clinic may be conductive to augment anti-tumor therapy effect and optimize vaccine design.

Abstract

As the most versatile antigen-presenting cells (APCs), dendritic cells (DCs) function as the cardinal commanders in orchestrating innate and adaptive immunity for either eliciting protective immune responses against canceration and microbial invasion or maintaining immune homeostasis/tolerance. In fact, in physiological or pathological conditions, the diversified migratory patterns and exquisite chemotaxis of DCs, prominently manipulate their biological activities in both secondary lymphoid organs (SLOs) as well as homeostatic/inflammatory peripheral tissues in vivo. Thus, the inherent mechanisms or regulation strategies to modulate the directional migration of DCs even could be regarded as the crucial cartographers of the immune system. Herein, we systemically reviewed the existing mechanistic understandings and regulation measures of trafficking both endogenous DC subtypes and reinfused DCs vaccines towards either SLOs or inflammatory foci (including neoplastic lesions, infections, acute/chronic tissue inflammations, autoimmune diseases and graft sites). Furthermore, we briefly introduced the DCs-participated prophylactic and therapeutic clinical application against disparate diseases, and also provided insights into the future clinical immunotherapies development as well as the vaccines design associated with modulating DCs mobilization modes.

Graphical Abstract



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In brief: Manipulating DCs chemotaxis in vivo could be efficacious in either immune responses amplification or tolerance induction, which may contribute to either prevention and cure against malignancies/infections or amelioration of autoimmune disorders in clinical. The existing regulation strategies to modulate DCs migratory ma0.nners mainly include direct regulation of chemokine receptors, regulation of chemokine concentration in destinations, modulating monocyte precursors infiltration and DCs differentiation, and physical method-manipulated DCs locomotion.

Keywords

Dendritic cells; Chemotaxis; Regulation strategy; Anti-tumor and anti-virus clinical application; Autoimmune disease

1. Introduction

Dendritic cells (DCs), the most professional antigen-presenting cells (APCs), are the critical components of orchestrating innate immunity and adaptive immunity for either immune homeostasis maintenance [1], [2] or facilitating rapid and robust immune responses against tumorigenesis [3] and viral infections [4] according to diversified microenvironment cues. Notably, the diversiform DC subpopulations deployed over the body, the overall amounts and distribution frequency, the positioning and locomotion together with the biological capacity/maturity of DCs, prominently impact the immunological landscape construction in local and systematic immune environment as well as subsequent DCs-mediated appropriate elicitation of immune amplification and tolerance.

Under normal circumstances, to coordinate optimal antigen (Ag)-specific immune responses, peripheral circulating/patrolling APCs (particularly DCs) usually randomly sample, process and cross present disparate innocuous or pathogenic Ags in non-inflamed and inflammatory tissues. Subsequently, the Ag-carrying DCs would be endowed with the competence to enter secondary lymphoid organs (SLOs, i.e. lymph nodes (LNs), spleens, adenoids, tonsils and Peyer's patches) via afferent lymphatics/high endothelial venules mainly in a chemokine receptor 7 (CCR7)-dependent manner [5], [6]. The SLOs-homing DCs function as the "transit pivots" of Ag-specific adaptive immunity to boost antigenic information intercommunication with resident DCs, T cells and B cells in differential spatiotemporal localization within SLOs [7], [8]. Therefore, accurate in vivo chemotaxis and migratory behavior towards SLOs and peripheral tissues serve as the fundamental prerequisites for DCs to accommodate versatile immunoregulatory efficacy in both protective immune initiation and tolerance induction [9].

However, multiple diseases featuring hypo-immunoresponsiveness could diminish the local infiltration of immunoreactive cells, including direct inhibiting immunoresponsive DCs' *de novo* development and aggregate abundance, impairing the immunological capability, and disturbing chemotactic recruitments (e.g. SLOs-homing instincts and inflamed foci-infiltrating ability) [10], [11]. For instance, the frequency of blood circulating conventional DCs (cDCs) and plasmacytoid DCs (pDCs) is strikingly depressed in patients with chronic hepatitis C virus (HCV) infection, and their migratory responses towards SLOs are crippled either[12]. Besides, to escape from immune surveillance, in very early phase of canceration, tumor microenvironment (TME) with immunosuppressive contexture could induce tumor-infiltrating DCs (TIDCs) dysfunction, and/or almost drastically eliminate competent type 1 DCs (cDC1) with tumor rejection Ags

cross-presentation and natural killer (NK) cells with powerful cytotoxicity [11], [13]. Thus, mobilizing diseases-reactive DCs to deploy within the lesion regions may be an effective approach to defense from malignant carcinomas and infections.

On the other hand, inappropriately massive accumulations of inflammatory DCs are the "criminal chieftains" in persistent and morbigenous inflammation diseases (e.g. local or even general autoimmune disorders, organic inflammations and graft rejections) [14]. For example, CXCL10 + DCs and their attracted CXCR3 + effector T cells are gradually deemed as the crucial contributors to immunopathology in several inflammatory destructions encompassing type 1 diabetes[14], steatohepatitis[15] and lethal neuropathological syndrome[16].

Consequently, adopting appropriate regulation measures to manipulate chemotaxis in vivo of immune orchestrator DCs may contribute a lot to acquire optimized immune responses for either provoking immune activation or inducing regulatory immunity. Nevertheless, insufficient attention has been payed into the modulating mechanisms and the (clinical) applications of diversified DCs trafficking modes, although the charming migratory dynamics of DCs indeed potentiate their immunological multifunction. In these regards, we systemically elaborated current mechanism understandings and manipulating strategies about regulating directional mobilization towards either SLOs or inflamed focus (including neoplastic lesions, pathogenic infections, acute/chronic tissue inflammations, autoimmune disorders and graft sites) of endogenous DC subsets and exogenous DCs-based vaccines. Besides, we briefly reviewed the DCs-participated prophylactic and therapeutic clinical explorations, and proposed the existing bottlenecks and potential countermeasures for the future design or development of clinical immunotherapies associated with regulating DCs chemotaxis manners.

2. Manipulating mechanisms of DCs in vivo migration

As the most professional APCs and the versatile orchestrators of innate and adaptive immunity, DCs are characterized with multiform inherent peculiarities, including: **1)** ingenious endocytic receptor repertoires, and functional compartments adept at internalized Ag processing and (cross) presenting; **2)** disparate phenotypes and transcriptionally controlled DC subgroups (e.g. cDCs (cDC1 and cDC2), pDCs, monocyte-derived DCs (mo-DCs), and Langerhans' cells (LCs))[17], whose patrolling over peripheral tissues constructs intricate DCs-based sentinel network; **3)** dramatic metabolic reprogramming and transition in motility patterns in response to microenvironmental stimulations[18]; **4)** active membrane processes and abundant cell-cell interactions[7], [19].

Furthermore, spatiotemporal location heavily dictates DCs' biological function[9]. In fact, whether disparate immune cell populations are positioning in correct localizations and spatiotemporal organizations (including homeostatic or inflamed peripheral tissues, focus of infection, tumor lesions and SLOs) indeed possess profound implications for the amplification and persistence of the optimal immune responses[20]. Generally, tissue-resident and/or circulating DCs would continuously sample environmental suspicious

stimulators or harmless Ags via several methods (including directly capturing as well as Ag transfer)[8], and the Ag-(cross)presenting DCs could rapidly migrate to SLOs, where they share antigenic information with SLOs-resident APCs and initiate Ag-reactive T/B cells within specific compartments within SLOs[21]. And the complicated actin cytoskeleton systems[22], [23] along with diversiform chemotactic signal-chemokine receptor systems accurately power DCs chemotaxis fashions[24] (Fig. 1, Fig. 2, Fig. 3).

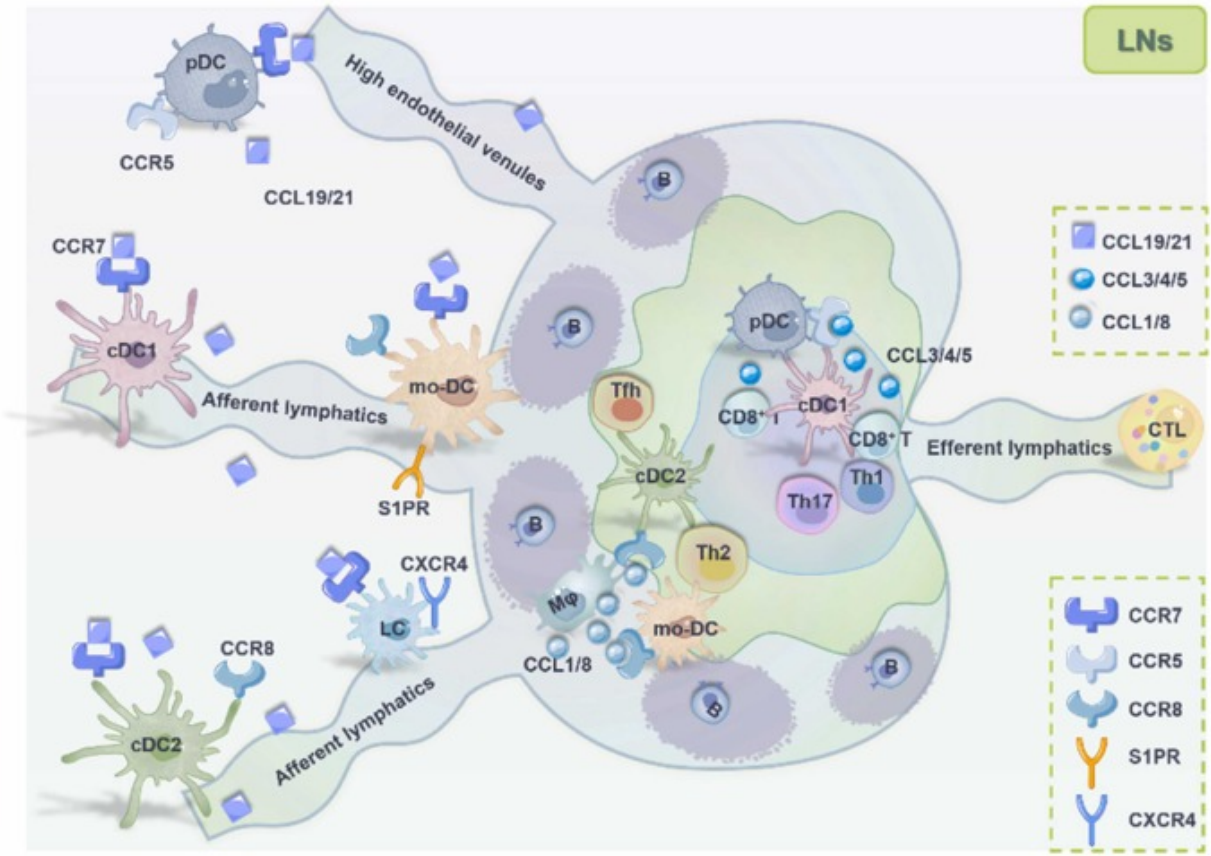

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Fig. 1. Migratory manners of diversified DC subtypes towards LNs and compartments within LNs. All mature or semi-mature DC subsets could be endowed with the ability to LNs under the guidance of CCL19/CCL21 (mainly produced by stromal cells of LNs)-CCR7 axis via afferent lymphatics or high endothelial venules, for an amplified immune response or tolerance induction. Ag-carrying cDC1 could enter T cell-localized medullary zone to initiate Ag-specific CD4 + Th1/Th17 and CD8 + CTLs immunity, and the cDC1-T could secrete CCL3/4/5 during their intercommunions to attract CCR5 + (CCR9 +) pDCs for a promoted immune response. The subcapsular sinus (SCS) macrophages could generate CCL1/8 to recruit CCR8 + cDC2 and/or CCR8 + mo-DCs to activate Th2 and Tfh in T-B boundary. In addition, CXCL12-CXCR4 system and S1P-S1PR axis also participate in regulate the locomotion modes of LCs and mo-DCs respectively. Mφ: macrophages; cDC1: conventional type 1 DCs ; cDC2: conventional type 2 DCs; pDCs: plasmacytoid DCs; LCs: Langerhans cells; CTLs: cytotoxicity T lymphocytes; Th: T helper; Tfh: follicular T helper.

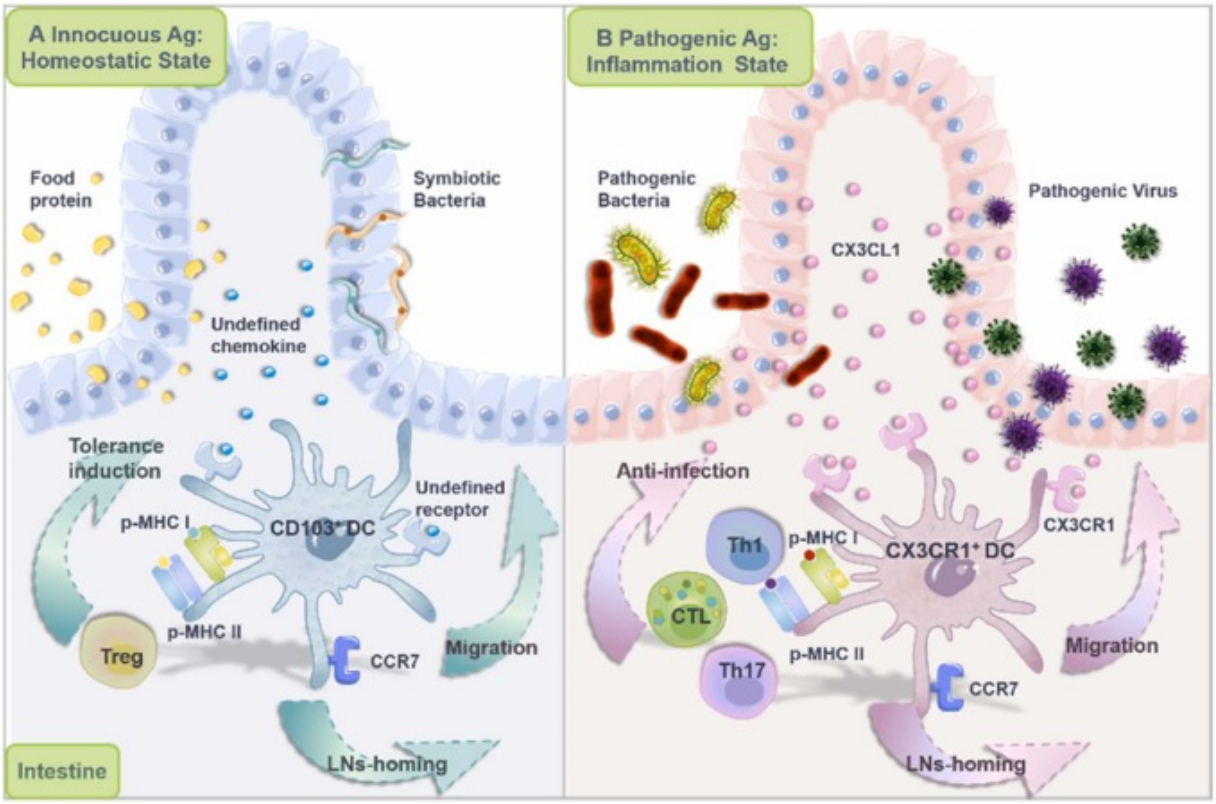

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Fig. 2. Migratory manners of DCs towards intestine during homeostatic or inflammatory state. **(A)** In homeostatic state. Intestine resident/migratory CD103 + DCs could engulf innocuous Ag from symbiodinium and food protein/peptide Ags, and then migrate to LNs for Ag-specific Treg initiation and further food allergy prevention as well as intestinal flora homeostasis. **(B)** In inflammatory state. When facing pathogenic virus and bacteria entry, CX3CL1 produced by inflamed or inflected small intestinal epithelial cells could attract CX3CR1 + DCs to internalize harmful Ags for Th1/Th17/CTLs-based anti-infection effect. MHC I: major histocompatibility complex class I molecule; MHC II: MHC class II molecule; CTLs: cytotoxicity T lymphocytes; Th: T helper.

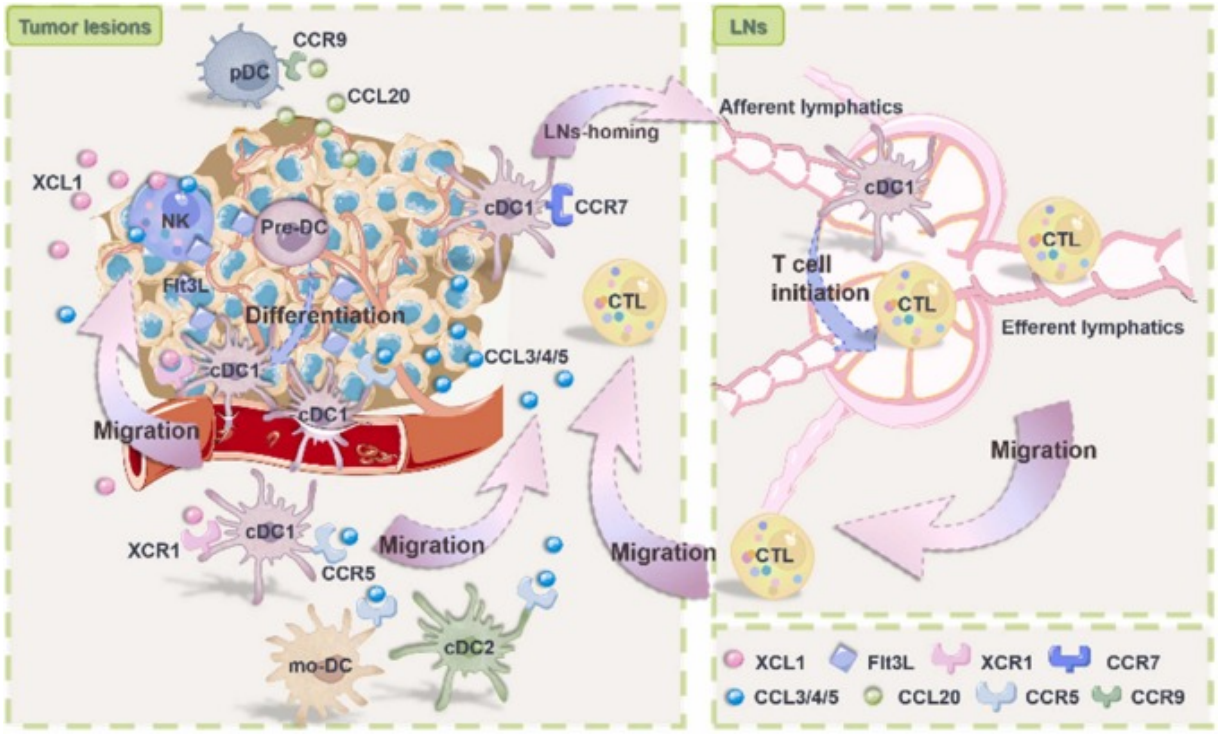

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Fig. 3. Migratory patterns of various DC subgroups towards tumor regions. Almost all DC subpopulations could be recruited into tumor lesions via CCL3/4/5-CCR5 systems, and the chemokines CCL3/4/5 could be produced by NK cells, cancer cells themselves and stromal cells within TME. In addition, XCR1 + cDC1 are granted the ability infiltration into cancer regions through the guidance of XCL1/2 secreted by activated NK cells and/or CTLs, and activated cDC1 further migrate to SLOs to expand CTL populations. Furthermore, NK cells within TME could manufacture FlT3L to in situ differentiate pre-DCs (especially mononuclear progenitors) into DCs (particularly cDC1). On the other hand, CCR9 +pDCs are attracted into TME through chemotactic agent CCL20 secreted by tumor cells, whereas they are tolerogenic and promote immunologic escape of tumor. cDC1: conventional type 1 DCs ; cDC2: conventional type 2 DCs; pDCs: plasmacytoid DCs; LCs: Langerhans cells; CTLs: cytotoxicity T lymphocytes; NK: natural killer; FlT3L: FMS-like tyrosine kinase 3 ligand.

Modulators to manipulate DCs locomotion under physiological and pathological conditions are presented in Table 1.

Table 1. Modulators to manipulate DCs chemotaxis.

Immune cell type	Chemokine receptor	Chemotactic stimulus	Chemokine producers	Destinations or directions	Results	R

All DC subsets	CCR7	CCL19 and CCL21	mainly LNs stromal cells	LNs	sharing antigenic information in diversified LNs compartments and inducing immune response or tolerance	[5 [6
	CXCR5	CXCL13	stromal cells approaching to B cell follicles	B cell follicles within LNs	potentiating Th2 differentiation	[2]
	CCR5	CCL5 and CCL4	maybe infected endothelia	mycobacterial infection site	generating immune responses against mycobacterium and tuberculosis	[2]
			NK and tumor cells	tumor region	promoting the abundance of TIDCs	[1 , [2]
	FPR1	ANXA1	dying tumor cells	dying tumor cells	cross-presenting Ag of dying tumor cells and activating nearby tumor-killing T cells	[2]
cDC1	undefined	undefined	undefined	SI	inducing Foxp3 + Treg differentiation and oral tolerance	[2], [3]
	CCR4	CCL17/CCL21	intracephalic cDCs	CNS	inducing Th17-based experimental autoimmune encephalomyelitis	[3]
	XCR1	XCL1	maybe inflamed liver	liver during NASH	accumulation of cDC1 in liver and inducing NASH	[1
			iNKT cells	allergic locus	inducing harmless Ag-specific hypersensitivity	[3]
			NK and activated	tumor region	recruitment of intratumoral cDC1	[1

			CD8 + T cells			
	CX3CR1	CX3CL1	pancreatic islets maybe	pancreatic islets	reactive autoreactive T cells	[1
			SIECs during infection	inflammatory SI	supporting Th1/Th17 differentiation and anti-infection	[2], [3]
	CXCR2	CXCL2	dermal M2	allergic locus	inducing DC clusters-mediated skin sensibility	[3]
cDC2	CCR8	CCL1 and CCL8	macrophages within the IFRs	LNs parenchyma	Initiating Th2- and Tfh-based allergic immune response	[3]
	CCR2	CCL2	mTECs	thymus	central tolerance	[3]
	CCR6	CCL20	skin, mucosal epithelium	SI mucosa during viral/bacterial attack	triggering humoral response and maintaining immune homeostasis in SI	[3]
mo-DCs	CCR8	CCL1 and CCL8	maybe LNs stromal cells	LNs	initiating Ag-specific immunity	[3]
	S1PR	S1P	maybe LNs stromal cells	LNs	Th2-based asthma	[3], [4]
	CCR6	CCL20	skin, mucosal epithelium,	immunization sites and inflamed lung	cross-priming of CD8 + T cells	[4], [4]
	CCR5	CCL5 and CCL4	neurons	CNS	infiltration to CNS under cerebral malaria	[1
	CCR2	CCL2	endothelial cells	perivascular region	airway inflammatory responses	[4], [4]
	CXCR2	CXCL2	dermal M2	allergic locus	inducing DC clusters-	[3

					mediated skin sensibility	]
	Fpr2	CRAMP	bronchiolar endothelial cells	bronchiolar area	airway inflammatory responses	[4], [4]
pDCs	CXCR3	CXCL9/CXCL10	infected macrophages	SCS region of LNs	interaction with infected macrophages	[4]
	CCR2	CCL2	mTECs	thymus	central tolerance	[3]
	CCR5	CCL3/CCL4/CCL5	CD8 + T cells, XCR1 +cDCs	cDCs—CD8 + T interaction sites in LNs	active co-localization of XCR1 + DCs and pDCs to optimize priming	[4]
	CCR6	CCL20	skin, mucosal epithelium	infection regions or inflammatory /autoimmune disorders	anti-pathogenic bacteria/virus effect or autoimmune/allergic diseases development	[4], [4]
			tumor cells	tumor sites	immunologic escape of tumor	[4]
	CCR9	CCL25	SIECs	SI	suppressing intestinal inflammation	[4]
			mTECs	thymus	central tolerance	[4]
			SIECs	SI	oral tolerance	[5]
	ChemR23	Chemerin	fibroblasts, inflamed vascular, endothelial	autoimmune disease sites	driving the activation of pathogenetic T cells in autoimmune diseases	[5 , [5]
	CXCR3	CXCL12/CXCL9/CXCL10	inflamed epithelium or infected cells	virus-invaded sites	IFN-α production for anti-infection or inflammatory	[4], [5]
	CCR10	CCL27 and CCL28	inflamed skin and	infection foci, inflammatory/autoimmune	IFN-α production in infection sites or	[4]

			SIECs	disorders	inflammatory/autoimmune sites	
LCs	CXCR4	CXCL12	stromal cells in LNs	LNs	promoting anti-virus immunity	[5], [5], [5]
	CXCR2	CXCL2	dermal M2	allergic locus	inducing DC clusters-mediated skin sensibility	[3]
tolDCs	XCR1	XCL1	maybe mTECs	thymus	central tolerance and prevent autoimmunity	[1 [2
CD16 + DCs	CCR5	CCL3/4/5	maybe the immune cells in graft	graft	detection of increased CCR5 + CD16 + DCs can predict GvHD	[5]

Tfh: follicular T helper; IFRs: interfollicular regions; ChemR23: Chemerin receptor 23; FPR1: protein formyl peptide receptor 1; ANXA1: annexin A1; NASH: non-alcoholic steatohepatitis; Treg: regulatory T cells; tolDCs: tolerogenic DCs; GvHD: graft versus host disease; S1P: sphingosine-1-phosphate; S1PR: S1P receptor; mTECs: medullary thymic epithelial cells; SI: small intestine; SIECs: small intestinal epithelial cells; iNKT: invariant natural killer T cells

2.1. Homing to SLOs

When DCs patrolling in peripheral tissues sense danger signals (including pathogen-associated molecular patterns (PAMPs, microbial components) and danger-associated molecular patterns (DAMPs)), they are rapidly activated and traffic to the draining LNs (dLNs). And within these SLOs, they transfer engulfed Ags to LNs-resident DCs[7] and (corss)present Ags to T cells in paracortex[19] for amplifying protective as well as detrimental adaptive immune response. Crucially, for a rapid initiation of Ag-responsive immunity, DCs trafficking to dLNs undergoes a prominent migratory mode shift from a slow and random patrol behavior of peripheral immature DCs to a faster and directional migration pattern[58].

As a matter of fact, compared to the mechanisms involving mobilizing to intricate inflamed lesions, the underlying mechanism understandings related to SLOs-homing ability of DCs are relatively clear (Fig. 1), which mainly encompass various conventional and/or atypical chemokine-chemokine receptor system-mediated migration, as well as other molecules serving as chemoattractants to directly regulate actin skeleton and/or promote chemokine receptor oligomerization of DCs. Notably, typical chemokines are classified with the relative position of a conserved cysteine motif, namely, CC, CXC, XC, and CX3C[24].

Remarkably, trafficking patterns of DCs are vary distinctly among diverse DC subpopulations (Table 1)[6], [59]. For instance, **1)** CCL19/CCL21-CCR7 pathway regulates all mature DC subsets LNs homing in varying degrees[5], [6]; **2)** CCL1/CCL8-CCR8 axis affects lymphatic-trafficking cDC2[35] and mo-DCs[38]; **3)** CD31, CD99, C5a receptor (CD88)[60] and CXCL12-CXCR4 engagement devote to LCs' fascinating journey from epidermis to lymph system[54], [55]; **4)** sphingosine-1-phosphate (S1P)-S1P receptor subtypes ($S1PR_{1-5}$) mediates chemotactic migration of DCs boosting Th2 immune responses[39], [40] and priming long-lived memory CD8 + T cell precursors in spleen[56]; **5)** CXCL13- CXCR5 axis devotes to Ags-bearing DCs' emigration to the LNs region where is adjacent to B cell follicles[25]; **6)** CXCL9/CXCL10-CXCR3 systems manipulate pDCs mobilization to infected macrophages residing in the subcapsular sinus (SCS) area in LNs, upon viral infection[45]; **7)** CCL3/CCL4/CCL5-CCR5 axis endows pDCs with the competence to navigate into XCR1 + cDCs—CD8 + T-cell interaction sites[45]; **8)** loss of programmed death-ligand 1 (PD-L1) seems to impair dermal DCs chemotactic responses to CCL19/CCL21 signals[61].

Thereinto, the most important cues to modulate an influx of DCs into LNs are CCL19 and CCL21, secreted mainly by LNs stromal cells[5]. The concentration gradients of CCL19 and CCL21, essentially contribute to orchestrate initial accurate cross-talk between DCs and naïve T cells in LN T-cell zones as well as for stimulating chemokinesis of T-cell within LNs[62]. Interestingly, CCRL1[63], atypical chemokine receptor 4 (ACKR4), could locally scavenges circumambient CCL19 and CCL21 to generate/reshape chemokine gradients, which engenders CCR7-sufficient DCs to directionally migrate away from the cellular sources of CCRL1 expression *ex vivo* and leads to the transition of migrated DCs from the subcapsular sinus (SCS) into the parenchyma of the LNs in vivo[64]. In addition, CCL21 and CCL19 may respectively polymerize with CXCL13 to synergistically trigger CCR7 at a relatively lower ligand (or agonist) concentration[65].

2.2. Migration to inflammatory sites

The chemotactic cues that guide DCs entry peripheral homeostatic/inflammatory regions (e.g. virus-induced pathologic lesions, neoplastic lesions, (vaccine) immunization sites, destructive inflamed tissues, allografts and autoimmune regions) are quite sophisticated (Table 1), whereas are still inadequate in systematic researches and summarizations or reviews. In brief, DCs residing in peripheral tissues could not only participate in capturing and analyzing innocuous and pernicious Ags for further orchestrating Ag-reactive T-cell responses or inducing Ag-specific tolerance in T-B border and T-cell paracortex within SLOs[7], but also directly regulate T-cell-based immunological activities in situ/in inflammatory foci for maintaining local immune balance or providing persistent protections[66]. For example, TIDCs are the central force in initiating and sustaining defensive immunity against malignancies, which could expand and re-stimulate cytotoxicity T lymphocytes (CTLs) (including reinfused CAR-T vaccines) in tumor regions (mainly in tertiary lymphoid structures (TLS) [67]within TME) [68], [69]. Actually, CD103 + cDC1 are the main producers of potent chemoattractant CXCL9, which are necessary for augmenting the efficacy of programmed cell death-1 (PD-1) inhibitors and boosting chemotactic recruitment of CXCR3 + T cells into TME[70].

Briefly, it's indispensable for migration of DCs to a certain target destination in DC-mediated responses,

whether in maintenance of tissue tolerance and homeostasis or manipulation of protective immunity to pathogens and canceration. In consequence, summarizing the unambiguous regulation mechanisms that control DCs' directional motility to peripheral tissues, may devote a lot to develop symptomatic treatments against diseases with hypo-immunoresponsiveness or overwhelming immunoresponsiveness.

Generally, chemotactic and nonchemotactic signals to manipulate inflammatory recruitment of DCs, include but are not limited to PAMPs (bacterial and viral products, e.g. lipopolysaccharide (LPS)), necrotic cell-derived or lesional tissue-released DAMPs (e.g. adenosine triphosphate (ATP)[71], high mobility group protein B1 (HMGB1)[72]), ectogenous adjuvants (polyinosinic:polycytidylic acid (poly (I:C))[73], chemokines (e.g. chemerin[51], [52], [74], XCL1[15], CCL20[41]), proinflammatory cytokines (e.g. IL-25), bioactive lipid molecules, formyl peptides (or their analogs) [43], antimicrobial proteins (e.g. eosinophil-derived neurotoxin (EDN)[75]) and complement fragments (e.g. complement protein C1q[76]), which function both individually and in concert by forming an intricate chemotaxis regulatory meshwork[24].

2.2.1. Gastrointestinal tract

During pathogenic bacteria attack gastrointestinal tract (Fig. 2), inflammatory CX3CR1 + DCs emigrate to infected sites under the guidance of CX3CL1 secreted by intestinal epithelial and endothelial cells. Then, CX3CR1 + DCs preferentially support Th1/Th17 CD4 + T cell and CD8 + effector T cell differentiation to boosts protective immunity against potentially pathogens[29], [33].

On the other hand, establishing immune tolerance to harmless dietary protein-Ags and commensal bacteria is indispensable for maintenance of organism homeostasis. Therefore, to prevent food allergies and inflammatory bowel disease (even colorectal cancer), migratory CD103 + DCs and CCR9 + pDCs induce lymphatic tolerance to harmless non-self commensal bacteria and food-Ag with the Ag-transfer behavior with gut-resident CX3CR1 + macrophages by IL-10-medited regulatory T cells (Treg) differentiation, although how to recruit such migratory CD103 + DCs still remains largely unexplored [29], [30], [48], [50], [77].

2.2.2. Infection sites

An efficacious immune response against viral or bacterial infection must control pathogen dissemination in vivo without inducing immunopathology. Considering that DCs play a critical role in coordinating both innate and adaptive immune responses to pathogen infection, appeal for a highly deployed and manoeuvred microbial-engendered DCs responses to balance an appropriate anti-infection response and slight immunopathology inducement. During causative agent-provoked infections, CCR6 is generally thought to be the important receptor responsible for trafficking of peripheral patrol DC subsets to the infected tissues in response to pro-inflammatory stimuli during viral/bacterial entry. In detail, peripheral circulating or certain tissue-resident DC subpopulations (including cDCs, pDCs and mo-DCs) could directionally migrate to infected sites in a CCL20-CCR6-based mechanism, and subsequently elicit a synergistic humoral and/or cellular immunity in infected tissues (e.g. lung and SI) [37], [41], [42], [46]. Besides, CCL20/CCL27/CCL28-

CCR10 and CXCL12/CXCL9/CXCL10-CXCR3 pathways endow pDCs with the capacity to migrate peripheral sites of inflammation/infection as well[45], [46], [53]. In addition, CCR5 + DCs could rapidly race to invading mycobacterial region and generate effector immune responses in response to constitutively overexpressed heat shock protein (myHsp70) from mycobacterium[26].

2.2.3. Tumor sites

Tumors are unique in comparison to other tissues for their suppression to immunoresponsive immunity. Furthermore, both of DCs accumulating into immunosuppressive tumor regions as well as detecting tumor cells (that could act as library with abundant antigenic information) in a complex maze-like TME, are heavily dependent on the pinpoint navigation mediated by the intensity of chemical gradients and the degree of spatial confinement (Fig. 3), during tumorigenesis and cancer progression[78]. However, the underlying mechanistic details of immature DCs' migratory behavior in and/or towards TME still remains much unexplored and needs to be further defined.

XCL1 (and XCL2, a paralog of XCL1 found in humans), also known as lymphotactin, which is mainly produced by NK cells[11] as well as activated CD8 + T cells[79], is one of the most significant chemotactic factors for attracting Ag-cross-presenting XCR1 + cDC1. It seems that the lymphotactin even could induce more robust DCs-dependent CD8 + effector and memory T-cell stimulation in comparison to poly(I:C) commonly utilized in clinical research[80]. Besides, the expression of CCR5 in DCs is also regards as a significant biomarker in their potential chemotaxis to intratumoral area[11], [27]. And pathological diagnosis results from several patients with melanoma suggested that CCL20 could guide circulating CCR6 + pDCs entry into melanoma primary lesions[47]. In addition, after tumor cells undergo immunogenic cell death (ICD), annexin A1 (ANXA1), a ubiquitously expressed cytosolic protein, is massively released into TME. Then, ANXA1 could facilitate DCs expressing protein formyl peptide receptor 1 (FPR1) positioning to the most proximal Casp3a+ (dying) cancer cells, capturing Ag fragments of dying tumor cells and in situ (re)activating neighboring tumor-killing T cells[28].

On the other hand, to excluded TIDCs in the early tumor stages, "tricky" tumor always down-regulates several chemotactic cues significant for DCs' chemotaxis towards tumor region. For examples, for immune evasion, invasive carcinoma types (e.g. mammary cancer[81], melanoma[82] and hepatocellular carcinoma[83]) always decease production and section of chemerin[74] to escape from immune tracking of chemokine-like receptor 1 + (CMKLR1) DCs and NK cells, which can serve as an independent risk factor for survival[84]. Further, to diminish the abundance of tumor-residing DCs, not only tumor itself can whittle down the emission of DCs-recruiting chemoattractants (such as CCL4 and CCL5[85]), but also can prevent immunoreactive or chemokines-producing cells from providing guidance cues (such as CCL5, FMS-like tyrosine kinase 3 ligand (Flt3L) and XCL1) for peripheral DCs [11].

2.2.4. Autoimmune disease sites and tissue inflammation

Inflamed endothelial cells and fibroblasts in autoimmune diseases (i.e. lupus erythematosus, psoriasis, and

rheumatoid arthritis) and in other inflammatory sites could express chemoattractant chemerin, to attract ChemR23-expressing DCs (especially pDCs) and NK, which locally promotes activation and expansion of pathogenetic T cells[51], [52], [86]. What's more, Fcγ receptors (FcγRs) engagement by IgG immune complexes further induces autoantigen-bearing DCs homing to the T-cell paracortex of dLNs, which may worsen or increase the burden of autoimmune diseases. during autoimmune disease sites[87]. Moreover, CX3CR1 directs CD103 + /CD11b+ DCs positioning to pancreatic islets, where DCs reactivate and interact with islet-infiltrating autoreactive T cells, which is deemed as a contributor to immunopathology in type 1 diabetes[33]. Beside, in the sensitization phase in cutaneous immunity, dermal macrophages initiate the formation of DC clusters through producing CXCL2[34]. Further, after generated from splenic inflammatory monocytes, CCR5 +CXCL9 +CXCL10 + mo-DCs enter central nervous system (CNS) during cerebral malaria and boost the influx of CXCR3 +CD8 + CTLs, provoking a lethal neuropathological syndrome[16]. XCR1 +cDC1 are a pivotal regulator of pathogenesis in non-alcoholic steatohepatitis (NASH), whose large-scale entry into liver may greatly foster liver inflammation and injury in NASH[15]. CCR4 + cDCs could respond to the chemotactic recruitment of CCL17/CCL22 secreted by intracephalic cDCs themselves, and subsequently migrate into CNS, leading to Th17-based development/deterioration of experimental autoimmune encephalomyelitis[31]. Interestingly, thymic tolerogenic DCs also feature XCR1 and respond to the chemoattraction to XCL1 as well, whose predominant accumulation in the medulla devotes to establish central tolerance[1]. Besides, the lack of XCR1 + tolerogenic DCs may cause the development and progression of autoreactive diseases, such as spondyloarthritis[2].

Hence, to relieve the burden of autoimmune disorders and local harmful inflammation, there are two main strategies, including **1)** increasing tolerogenic DCs SLOs- or thymus-homing to expand immunosuppressive Treg subpopulation, and **2)** directly restricting biological function of autoreactive or inflammatory DCs via immunologic or migratory suppression drugs. For example, Regmi et al. prepared a FK506-loaded ROS-responsive microsphere, whose oral administration could inhibit colonic DCs' LNs-homing and corresponding accumulation of colon-reactive Th1/Th17 in inflamed foci to ultimately alleviate inflammatory bowel diseases (IBD)[88].

2.2.5. Allergic locus

Similar to autoimmune diseases, allergy, is featured with persistent chronic/acute local/systemic inflammation responses and hypersensitivity to exposed typically harmless Ags. For instance, when exposed to innocuous house dust mite (HDM), airway epithelial cells could generate massive DAMPs, chemokines and cytokines to promote the inflammatory infiltration of monocytes and invariant natural killer T (iNKT) cells, and the latter could further produce chemotactic cue XCL1 to grant XCR1 + CD103 + DCs entry into the lung. Then, the accumulation of activated XCR1 + DCs favors the development of pulmonary-based allergic asthma ultimately[32]. In addition, CCL2-CCR2, CRAMP-Fpr2, and CCL20-CCR6 participate in sequential trafficking of mo-DCs and pDCs from the circulation to the inflammatory lung, leading to allergic airway inflammation and acute asthma exacerbations[42], [43], [44].

What' more, CCR9 + pDCs seems to devote a lot to damp allergic reactions by inducing Treg initiation[49], [89], [90]. Besides, given that the expression of ectonucleotidases CD39 is evidently impaired in the anaphylactic foci, administration of apyrase, whose enzymatic activity essentially identical to CD39, could decrease the chemotactic migration of hypersensitive DCs and accordingly relieve allergic airway inflammation[91].

2.2.6. Allografts

Since introducing organ transplantation into medical practice, improvement and expectation have been accumulated, though establishment of hosts' long-term immune tolerance (>5-year) to alloantigen is still a main unsolved target in clinical transplantation. In fact, the rapid acquisition of graft organ's antigenic information by host APCs often provokes severe (even destructive) immune rejection and allograft necrosis through host's DCs-mediated autoreactive T-cell proliferation[7] and diversiform T-cell differentiation (especially CD8 + effector T-lymphocyte and memory T-lymphocyte subpopulations[92]). In clinical practice, the upregulation of CCR5 on CD16 + myeloid blood DCs in allogeneic hemopoietic cell graft patients could be intertwined with the development of moderate to severe graft versus host disease (GvHD), and the detection of amplified CCR5 + CD11c+ CD16 + DCs subtype in patients' peripheral blood may enable pre-emptive therapeutic intervention prior to the clinical diagnosis of GvHD[57]. Interestingly, to avoid graft rejection during allograft postoperation, Fiorina and colleagues pre-cultured langerhans' islets with CCL21 (the ligand for CCR7) before transplantation, to enhance the efflux of donor's DCs from islet preparations and accordingly restrain donor's DCs rapid migration to recipient's LNs after transplant surgery, which prominently prolongs islet allotransplantation survival[93].

Some evidence demonstrates that alloantigen-specific unresponsiveness and a long-term graft survival happen when CCR2 + pDCs migrate to graft site in response to the guidance of CCL2 produced by the graft and then alloantigen-carrying CCR2 +CCR7 + pDCs home to LNs where the "tolerance-executors" (Treg) differentiate[94]. Analogously, CCR2 + pDCs and cDCs contribute to the establishment of central tolerance for avoiding autoimmune responses, with the chemotactic recruitment of CCL2 secreted by mTECs in thymus[36]. Therefore, adoptive transfer of alloantigen-carrying CCR2 +CCR7 + pDCs may become an efficacious strategy to prevent lethal local inflammation or transplantation necrosis[94]. Moreover, it seems that volunteer donors' pDCs are the significant pathogenesis of GvHD after allogeneic hematopoietic stem cell transplantation, but the donors' pDCs with secretory function of vasoactive intestinal peptide (VIP) could migrate to multiple organs (including spleen, lung, colon and small intestine) of recipients, and engender immune tolerance[95].

3. Regulation strategies to manipulate DCs migration

In general, the principle and the foremost quest of applying diversified regulation strategies to modulate DCs in vivo chemotaxis, is preserving the immune homeostasis and rebuilding immune balance in host, no matter the host is challenged with immune-deficiency disorders (e.g. pathogenic infections and malignant

carcinomas) or immune- hypersensitivity diseases (e.g. allergy, autoimmunity and tissue inflammation). **1)** Therefore, when facing malignancy invasion and pathogenic viral/bacterial attack, it's of necessity to boost Ag-reactive immune responses for rapidly eliminating mutational or infected cells as well as pernicious pathogens. Potentiating competent DCs' capacity to accumulate in the lesions (neoplasm and/or infection) for amplified cross presentation of microbial/tumor Ag epitopes, and/or boosting mature DCs' SLOs-homing talent for improved antigenic information-based cell-cell crosstalk and coordinated activation, may contribute to enlarge activated Ag-specific T-cell subpopulations-mediated systemic immune responses. **2)** Moreover, after vaccine-mediated local immunization, mobilizing DCs' and mononuclear progenitors' entry into injection sites could facilitate maturation and SLOs-homing of vaccinal Ag-carrying DCs, which may significantly magnify the strength and duration of vaccine-induced immune response. **3)** On the other hand, when the hosts are faced with immune-overreaction-mediated destructive conditions, either inhibiting the assemblage of inflammatory DC subgroups (pDCs, cDCs, mo-DCs and monocyte precursor cells) or heightening the infiltration of heterogeneous tolDCs in the region suffering from pathologic inflammation, may ease the burden of pathological progress to a certain degree.

Furthermore, cancer, which features the increased incidence and high lethality, can structure an intricate and immunosuppressive meshwork composed of heterogeneous immunoregulatory components for constant immune privilege. Additionally, the captivating immune contexture within TME profound impacts clinical outcomes of diversified immunization therapies. Besides, given that DCs act as the cardinal orchestrators or commanders both in innate and adaptive immune responses, the increased intratumoral/peritumoral amount of DCs benefit to both mobilize tumor associated Ags/tumor-specific Ags (TAAs/TSAs)-specific CTLs-mediated tumor suppression and augment the immunoresponsiveness of various immunotherapies in clinical. Moreover, considering the restrained length of this review and the universal or analogous property of regulation measures in diverse types of diseases as mentioned above, we herein mainly took cancers for instance to elaborate the modulation strategies in manipulating migration of endogenous DCs and exogenous DCs vaccines for amplified anti-tumor immunity.

Generally, regulation strategies of controlling DCs chemotaxis are composed of **1)** direct regulation of chemokine receptors, **2)** regulation of chemokine concentration in destinations, **3)** modulating monocyte precursors infiltration and DCs differentiation, and **4)** physical method-manipulated DCs locomotion. And the specific approaches have been described in Table 2, Table 3 and Fig. 4 respectively.

Table 2. Direct regulation of chemokine receptors of DCs.

Strategies	Specific measures	Target cell subtypes	Regulated receptors	Chemotaxis directions	Results	Ref.
Adjuvant administration	co-delivery of OVA and (poly (I:C))	All DCs	CCR7 mainly	LNs	boosting DCs-based anti-tumor cellular immunity	[73]

	co-deliver Ag and TLR4 agonist MPL	All DCs	CCR7 mainly	LNs	irritate DCs maturation and cytokines secretion	[98]
	programmable delivery of CpG-ODNs towards TME	TIDCs	CCR7 mainly	LNs	facilitating the maturation and activation of TIDCs	[99]
	co-deliver OVA, CpG-ODNs and GM-CSF by MSRs-based nanosytems	All DCs	CCR7 mainly	LNs	recruit immature DCs in situ and promote mature DCs LNs-homing	[100]
	self-adjuvant effect of DNA vaccine expressing OVA + GM-CSF loaded MSRs	dermal DCs and mo-DCs mainly	CCR7 mainly	LNs	increased DCs recruitment in situ and improved DCs maturity and vaccine-Ag cross presentation	[101]
	self-adjuvant effect of protamine mRNA vaccine (i.d.)	dermal DCs and mo-DCs mainly	CCR7 mainly	LNs	massively activated migratory DCs and triggered an effective migration of DCs	[102]
	injected (i.t.) mRNA-based adjuvant (CD70 + CD40L + active TLR4) and TAA	TIDCs	CCR7 mainly	LNs	malfunctioned TIDCs into functionally Ag-presenting and T-cell priming types	[103]
DAMPs inducer administration	deliver PLGA microspheres loading Ags and photosensitizer + PCI	dermal DCs and mo-DCs mainly	CCR7 mainly	LNs	enhanced vaccine-Ag cross presentation in attracted DCs and their LNs-homing ability	[104]
	DCs-targeting epicutaneous immunization via laser microporation	dermal DCs and mo-DCs mainly	CCR7 mainly	LNs	improved humoral and cellular immune responses compared to simply i.d. vaccination without PCI	[105]
	co-culture mo-DCs with tumor cells or their intracellular substances	mo-DCs generated in vitro	CCR5 mainly	tumor regions	identifying complicated TME and locomotion towards tumors	[27]
	oxaliplatin	all DCs	CCR7 mainly	LNs	activated DCs via NOD-stimulated	[106]
	combining oxaliplatin and cyclophosphamide + ICBs	all DCs	CCR7 mainly	LNs	activated DCs via TLR4-stimulated and improved efficacy of ICBs	[107]
Gene	reinfusion of mo-DCs co-	mo-DCs	CCR7	LNs	unleashed an effective Ag-	[10

engineering	transduced with CCR7 and TAA/TSA (gp100/OVA) gene through an Ad vector	generated *ex vivo*			specific immune response against melanoma in a low dosage	[8], [109]
	reinfusion of mo-DCs co-transfected with chimeric E/L-selectin	mo-DCs generated *ex vivo*	PNAd	LNs	extravasation of DCs from the blood into the LNs after reinfusion	[110]
	reinfusion of immature DCs co-expressed CCR7 and BTLA	immature DCs	CCR7	LNs	elevated motility potential and immune tolerance of DCs	[111]
	intradermal injection of a OVA- and CCR7 pDNA-co-loaded micelles	skin DCs and mo-DCs	CCR7	LNs	supporting DC migration to LNs and boost MHC I-restricted Ag presentation	[112]
	co-expressing CCR7 and immunomodulatory IL-10 in immature DCs	immature DCs	CCR7	LNs	prolonging cardiac allograft survival	[113]
epigenetic reprogramming	IFN-α2b + romidepsin + 5-azacytidine	all DCs	CXCR4	tumor regions	reactivating malfunctioned DCs in colorectal cancer-bearing mice	[114]
	chidamide- and BMS-202-co-delivered liposomes	all DCs	CCR7 mainly	LNs	boosted the anti-tumor immunity against TNBC	[115]
	NY-ESO-1 vaccine (CDX-1401 + poly-(IC:LC)) + decitabine	CD141 + cDC1	maybe XCR1 and CCR7	tumor regions and LNs respectively	reduced promoter methylation, increased Ag cross-presentation and humoral/ cellular immunity	[116]
Promoting CCR7 oligomerization	cholesterol-lowering drugs	all DCs	forming CCR7 oligomers	LNs	positively modulated DCs migration to LNs	[117], [118]
	PGE2	all DCs	forming CCR7 oligomers	LNs	promoting DCs migration to LNs	[117]
	2-DG	all DCs	CCR7 oligomers ↓	LNs-homing ability ↓	allergic asthma models	[18]

Activating motion-related proteins/axis	activating lysosome-associated TFEB-TRPML1 pathway	all DCs	maybe forming CCR7 oligomers	LNs	F-actin cytoskeleton reorganization-based migration manner change	[22]
	low dose PGE2	all DCs	CCR7	LNs	F-actin cytoskeleton reorganization-based LNs-towards motility increasing	[119]
	downregulating Arc/Arg3.1 pathway	migratory skin DCs	CCR7 or its oligomers ↓	LNs-homing ability ↓	remission of allergic contact dermatitis reaction	[23]
	downregulating Eps8	all DCs	CCR7 or its oligomers ↓	LNs-homing ability ↓	remission of hypersensitivity	[120]
	downregulating fascin1	all DCs	CCR7 or its oligomers ↓	LNs-homing ability ↓	defective LNs migration	[121]

poly (I:C): polyinosinic:polycytidylic acid; TLR: toll-like receptor; MPL: monophosphoryl lipid A; ODNs: oligodeoxynucleotides; GM-CSF: granulocyte-macrophage colony stimulating factor; MSRs: mesoporous silica microrods; PCI: photochemical internalization; i.d.: intradermal injection; MSRs: mesoporous silica microrods; PNAd: peripheral node addressin; TFEB: transcription factor EB; TRPML1: transient receptor potential cation channel, mucolipin subfamily, member 1; F-actin: filamentous actin; Arc/Arg3.1: activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1; PGE2: Prostaglandin E2; 2-DG: 2-Deoxy-D-glucose; BTLA: B and T lymphocyte attenuator; BMS: Bristol-Myers Squibb; TNBC: triple-negative breast cancer; UCNPs: upconversion nanoparticles; COX: cyclooxygenase; PC7A: cyclic seven-membered ring; FPR1: protein formyl peptide receptor 1; ANXA1: annexin A1; ICB: immune checkpoint blockade

Table 3. Regulation of chemokine concentration in destinations.

Strategies	Specific measures	Target cell subtypes	Regulated chemokines	Chemotaxis directions	Results	Ref.
Chemokines or their	XCL1-OVA + adjuvant LPS	XCR1 + cDC1	XCL1	immunization sites	leading to XCR1 + cDC1-mediated	[156]

DNA/mRNA administration					E.G7-OVA prevention or suppression	
	delivery of mXCL1-V21C/A59C + OVA	XCR1 + cDC1	mXCL1-V21C/A59C	immunization sites	protected mice from E.G7-OVA tumor development in both prophylactic and therapeutic protocols	[157]
	XCL1/Glypican-3 fusion pDNA immunization	XCR1 + cDC1	XCL1 mainly and CCL5	tumor regions and immunization sites	elevated production of IFN-γ, granzyme B, CCL5, CXCL19, and XCL1 in hepatocellular carcinoma	[158]
	Ad-mediated CCL19 or XCL1 cDNA transfection	all mature DCs or XCR1 + cDC1	CCL19 or XCL1, respectively	tumor regions	delayed murine lung cancer A549 and melanoma B16 progression	[159]
	Ad-mediated CCL19 or XCL1 cDNA transfection	all mature DCs or XCR1 + cDC1	CCL19 or XCL1, respectively	tumor regions	CCL19 transfection induced ovarian carcinoma suppression but XCL1 did not	[160]
	folate-modified CCL21-loaded UCNPs	mature DCs	CCL21	tumor regions	restored the impaired host immune response in ovarian cancer	[161]
	hydrogels constituted by CCL21-loaded polymer–nanoparticles	mature DCs	CCL21	injection site	invasive subcutaneous administration recruited DCs to injection site	[162]
	intratumoral injection of CCL21/IL-15-loaed Ad carrier	mature DCs	CCL21	tumor regions	recruitment and stimulation of DCs,	[163]

					T cells and NK in CT-26-bearing mice	
	folate-modified CCL19 pDNA-loaded cationic nanoparticles	mature DCs	CCL19	tumor regions	activated anti-tumor potency against colon carcinoma	[164]
	co-transfected CCL21 and costimulatory molecule LIGHT via an Ad vector	mature DCs	CCL21	tumor regions	engendered co-localization of mature DCs and T cells within tumor nodules	[165]
	transfection of Ad-loaded CXCL12	CXCR4 + DCs	CXCL12	tumor regions	promoting an influx of immature CXCR4 + DCs into tumor sites	[166]
	CXCL12-loaded gold nanoparticles	CXCR4 + DCs	CXCL12	tumor regions	initiated acquired immune response.	[167]
	systematically administrated small amounts of CXCL12	CXCR4 + DCs	CXCL12	spleen	promoting immune control against *Plasmodium berghei* malaria	[168]
Augmentation of NK-DCs cascaded tumor-infiltration	COX-2 blockade-based tumor-infiltrating NK increase	XCR1 + and/or CCR5 + DCs	XCL1 and CCL5	tumor regions	decreased PGE_2-based NK and DCs accumulation in TME and enhanced anti-tumor immunity	[11]
	ICBs and aspirin combination therapy-based tumor-infiltrating NK increase	XCR1 + and/or CCR5 + DCs	XCL1 and CCL5	tumor regions	reinforced interaction between NK and DCs, and aroused efficacious anti-tumor immunity	[169]
	monomethyl fumarate and dimethyl fumarate-based CCR10 upregulation in NK and increased	maybe XCR1 + CCR5 +	maybe XCL1 and CCL5	tumor regions	activated NK cells migrated to TME and unleashed	[170]

	NK accumulation in TME	DCs			tumor-killing ability	
	adding chemerin and its synthetic derivatives	ChemR23 + DCs	Chemerin	tumor regions	augmented anti-tumor defense in tumors	[81], [82], [83], [84]
	applied CXCL10 or delivered CXCL10 cDNA-loaded retroviral vector	maybe XCR1 + /CCR5 + DCs	maybe XCL1 and CCL5	tumor regions	expanded intratumoral CXCR3 + NK population and prolonged NK cell–dependent survival	[171].
	anti-tumor agent ONC201-based CXCL10-mediated NK accumulation in TME	XCR1 + /CCR5 + DCs	XCL1 and CCL5	tumor regions	arousing robust NK-, DCs- and CTLs-based immunity against tumor progression	[172]
	reinfusion of IL-18-primed “helper” NK cells	CCR5 + DCs	CCL5	tumor regions	sculptured CTLs (recruited by DCs)-based immunity	[173]
	adding IL-17D or cancer- treated by doxycycline	maybe XCR1 + /CCR5 + DCs	maybe XCL1 and CCL5	tumor regions	recruit NK cells into TME	[174]
Administration of DCs-stimulus	co-deliver IL-12 and GM-CSF via Ad + immature DCs	all DCs types	undefined	tumor regions	prolonged release of both therapeutics within tumor lesions	[175]
	cGAMP or cGAMP–like agonists (PC7A)	maybe XCR1 + / CCR5 + DCs	maybe XCL1 and CCL5	tumor regions	promoting synergistic infiltration and activation of DCs-NK cells	[176], [177], [17

					8]
autologous tumor transfected with GM-CSF and bi-shRNA-furin + atezolizumab	mo-DCs mainly	undefined	tumor regions	prolonged overall survival rate in advanced oophoroma patients	[179]
co-delivery mRNA (IFN-γ, IL-12, CD86, CD70, OX40L and CD80)	maybe XCR1 + / CCR5 + DCs	maybe XCL1 and CCL5	tumor regions	elicited a systemic immune response and repress tumor invasion in distal (untreated) tumors	[180]
reinfusion Flt3L-releasing T cells + poly (I:C) + anti-4–1BB	cDC1	undefined	tumor regions	augmented DC-T cell synergistic infiltration and activation	[181]
intratumoral Flt3L + poly (I:C) + low-dose RT	cDC1 and FPR1 + DCs	ANXA1, etc.	tumor regions	convert B cell lymphomas into DCs vaccine manufacturing factories	[182]
anthracyclines triggered ICD	FPR1 + DCs	ANXA1	tumor regions	engulfed and cross presented Ags released from dying cancer cells	[28]

FPR1: protein formyl peptide receptor 1; Flt3L: FMS-like tyrosine kinase 3 ligand; poly (I:C): polyinosinic:polycytidylic acid; RT: radiotherapy; NK: natural killer; COX: cyclooxygenase; ANXA1: annexin A1; pDNA: plasmid DNA; UCNPs: upconversion nanoparticles; ICB: immune checkpoint blockade

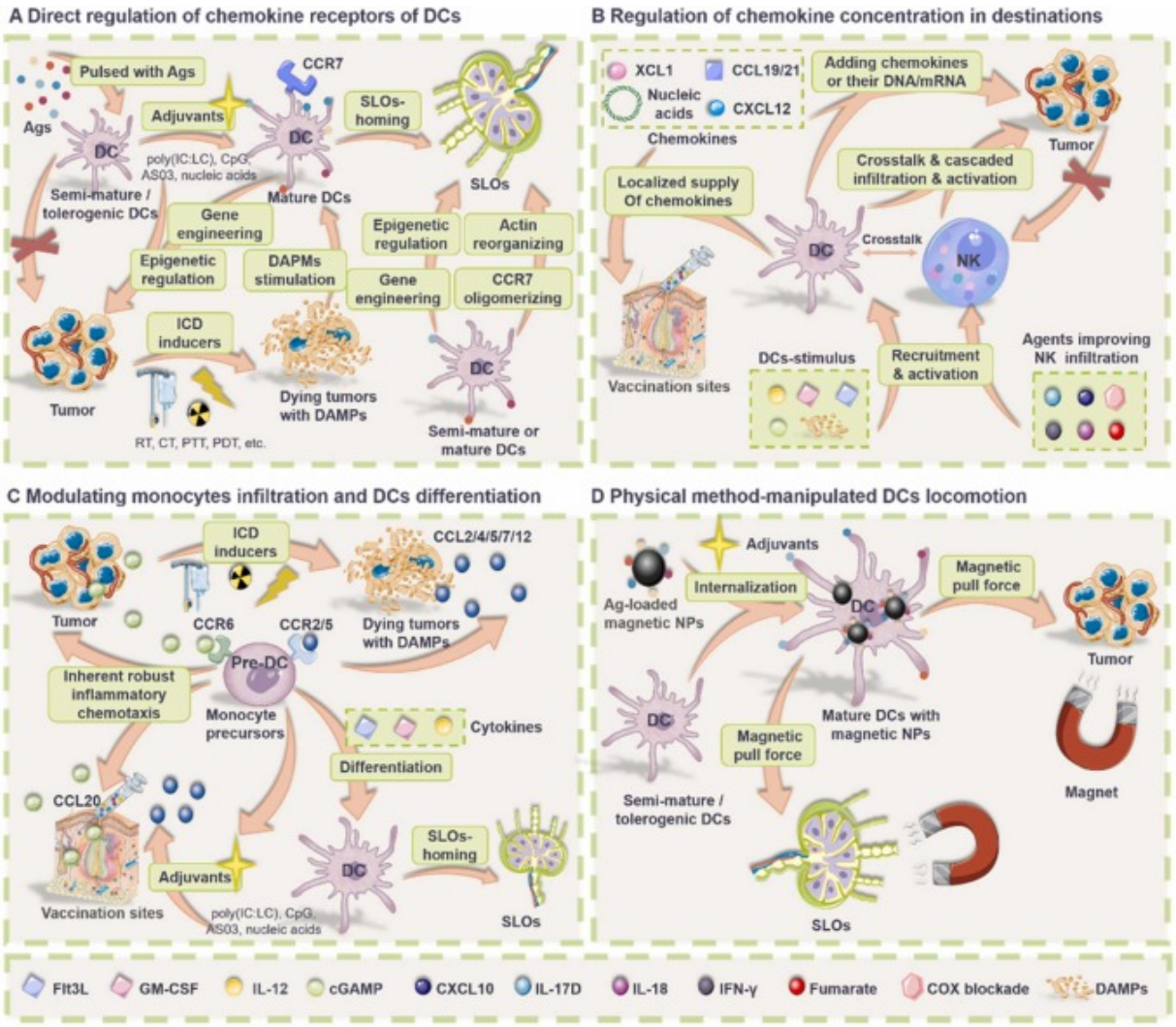

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Fig. 4. Current regulation strategies of manipulating DCs chemotaxis. **(A)** Direct regulation of chemokine receptors of DCs, including administration of "danger signals" (adjuvants and ICD inducers), applying gene engineering and epigenetic reprogramming methods, and modulation of action skeleton and chemokine receptor oligomerization. **(B)** Regulation of chemokine concentration in destinations, composed of supplying chemokines or their DNA/mRNA modes, augmenting NK-DCs interaction-based synergetic/cascaded infiltration and activation, and adding multifarious DCs-stimulus. **(C)** Modulating monocyte precursors infiltration and DCs differentiation, consisting of ICD inducers administration, adjuvants administration and adding DCs-differentiation cytokines or molecules. **(D)** Physical method-manipulated DCs locomotion, which currently mainly refers to magnetic pull force-mediated DCs direction migration via Ag-loaded magnetic NPs. NPs: nanoparticles; ICD: immunogenic cell death; SLOs: secondary lymphoid organs; FlT3L: FMS-like tyrosine kinase 3 ligand; GM-CSF: granulocyte-macrophage colony stimulating factor; COX: cyclooxygenase. PTT: photo-thermotherapy; PDT: photodynamic therapy; CT:

chemotherapy; RT: radiotherapy.

3.1. Direct regulation of chemokine receptors of DCs

On the one hand, canceration regions could restrict the entry of DCs by both direct downregulation of the expression of chemokine receptors associated with tumor-infiltration competence in DCs and hampering the interaction-modulated synergetic recruitment of DCs with other immunoreactive and immunoresponsive cells (especially NK). For example, tumor-derived liver X-α receptor (LXRα) agonists could restrict CCR7 expression on activated DCs and correspondingly dampen the expansion of anti-tumor effector T cell populations in SLOs[96]. On the other hand, the immunosuppressive TME can convert tumor-infiltrating DCs into dysfunctional or immature phenotypes, leading to hindered migration capability of endogenous DCs or DC vaccines to LNs where they share antigenic information and cross prime T cells[97].

Accordingly, **1)** directly upregulating chemokine receptors that endow DCs with the potentiality to migrate into neoplastic lesions, and/or **2)** boosting the maturation along with maintaining the immunological competence of intratumoral TAAs/TSAs-crosspresenting DCs to foster DCs locomotion to tumor dLNs (TdLNs) or TLS (the intratumoral/peritumoral tertiary lymphoid structures similar to secondary follicles in LNs)[67], may both be considerable attempts to ameliorate DCs-based anti-tumor immunity (Table 2, Fig. 4**A**).

3.1.1. Administration of "danger signals"

Subunit vaccines, recombinant protein and/or polysaccharide subunit vaccines particularly, always suffer from its low immunogenicity and insufficient cross presentation by DCs after administration in a high dose. Such immunological hypo-responsiveness usually leads to Treg-mediated tolerance induction and restricts CTLs-mediated cellular immunity and antibodies-based humoral immunity in vivo[122]. As a matter of fact, using Ags alone without combining any other immunogenic molecules to pulse in vitro-derived autologous DCs could yield regulatory DCs, whose adoptive transfer could sculpture Ag-specific immunomodulation through amplification of tolerogenic Treg population in vivo and accordingly may enable robust and prolonged protection against autoimmune destruction in clinical researches and pre-clinical studies for autoimmune disorders[123].

In this connection, to amplify immune responses in vaccine immunization or anti-tumor treatment, adjuvants, the analogues of "danger signals" (or pathogen-associated molecular patterns (PAMPs) / damaged cell-associated molecular patterns (DAMPs)) with prominent immunomodulatory effect, are significant vaccine components to amplify the breadth, magnitude and durability of vaccines-mediated immunological capacity[19].

Although currently we are into a new age for human vaccine adjuvants[124], underlying mechanisms about how FDA-approved adjuvants contained in vaccines on the market actually function still keeps incomprehension. In fact, PAMPs, the conserved motifs in microorganisms' components or danger signals,

along with DAMPs released by damaged cells or tissues[125] are endogenous adjuvants, which could be recognized by all DC subtypes through multifarious pattern recognition receptors (PRRs) on or within DCs. In detail, PRRs could be divided into several main types, including toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG)-like helicases (RLHs) and recently identified stimulator of interferon genes (STING) proteins[126], [127], [128], [129]. Additionally, once PRRs are stimulated by different environmental "danger signals", these activated distinct PRRs could prominently modulate activation modes of DCs and subsequent DCs-based differentiation modes of T cells to varying degrees, inducing amplification and/or tolerance in cellular immunity and humoral immunity[130].

3.1.1.1. Adjuvant administration

In brief, appropriately administrating adjuvant components may ameliorate the maturity of DCs, hallmarked with a prominent upregulation of LN-homing chemotactic factor receptors as well as co-stimulatory molecules, and polish up the intensity and persistence of Ag-reactive immunity. For example, Carson and colleagues endowed DCs with fostered capacity to enter T cell paracortex of LNs and stimulate tumor-killing CTLs by coupling the model Ag OVA with double-stranded RNA (dsRNA) analogue poly (I:C), which potently augmented mature DCs-based anti-tumor cellular immunity[73]. Zhuang et al. co-delivered MHC I- and MHC II-restricted antigenic peptides and TLR4 agonist monophosphoryl lipid A by lipid-enveloped zinc phosphate hybrid nanoparticles to irritate DCs maturation and multiple T-cell-priming cytokines secretion, boosting robust effectiveness on tumor prevention and therapy[98]. Liu et al. designed a dual-sensitive dendrimer cluster-based nanoadjuvant to delivering CpG oligodeoxynucleotides (CpG-ODNs) into TIDCs, facilitating the maturation and activation of TIDCs[99]. Beside, Nguyen et al. yielded a multipurpose nano-system coupling nanovaccines (pre-loading both OVA and TLR9 agonist CpG-ODNs) and the DC-recruiting macroporous scaffold containing granulocyte-macrophage colony stimulating factor (GM-CSF), which inspired recruitment of immature DCs in injection sites and LNs-homing of mature DCs[100].

Importantly, nucleic acid-based vaccines, which provide a promising platform for prophylactic and therapeutic vaccines development in anti-cancer and anti-viral immunotherapies, possess a powerful self-adjuvant effect that could directly serve as PAMPs and interact with PRRs (such as TLR3/7/8/9) of DCs. That's to say, under normal circumstances nucleic acid-based vaccines are adequate in immunogenicity compared with simple protein or polysaccharide subunit vaccines mentioned above[102], [131]. For example, Thanh et al. created a DNA vaccine mixed with chemoattractant GM-CSF-loaded injectable mesoporous silica microrods (MSRs), which provoked a robust immunological activity of DCs and initiated effective Ag-specific Th1 immune response[101]. Moreover, Kowalczyk et al. intradermally delivered a protamine mRNA vaccine, which massively activated migratory DCs and induced Ag-specific immune response[102]. Van Lint and colleagues intratumorally injected TAA and an mRNA-based adjuvant, which comprised of three mRNA molecules encoding costimulatory molecule CD70, constitutively active TLR4 and activation stimulator CD40 ligand (CD40L), which reprogrammed malfunctioned TIDCs into functional types in various murine cancer models[103].

3.1.1.2. DAMPs inducer administration

Moreover, considering that immunologic adjuvants applied in clinical and laboratory are essentially exogenous "danger signals", administrating inducers of "danger signals" to directly generate and release endogenic DCs-stimulating molecules (mainly DAMPs) could also theoretically manipulate chemokine receptors-mediated emigration behavior in DCs. Actually, DAPMs will be exposed or released within inflammatory tissues by stressed, damaged, dying, or apoptotic cells, after the local tissues or cells are under laser, hypoxia, redox imbalance, acidosis, hypertonic/hypotonic stress and intracellular ion or cytoskeleton perturbations[132].

Accordingly, felicitously utilizing inducers of DAMPs would be an available attempt to in situ recruit, stimulate and activate DCs as well as increase SLOs-homing capacity. Schineis et al. co-encapsulated a photosensitizer together with Ags in PLGA microspheres to promote photochemical internalization (PCI)-mediated Ag cross presentation and CCR7-based LNs chemotaxis in DCs, which may be a promising strategy for therapeutic cancer vaccinations, though PCI-based PLGA microspheres-immunization indeed provoked a transient skin inflammation[104]. Similarly, Machado et al. implied that combining epicutaneous immunization via laser microporation with DCs-targeting mannan neoglycoconjugates could synergistically elicit preferential humoral and cellular immune responses compared with intradermal vaccine inoculation[105].

Specially, the DAMPs and TAAs/TSAs during tumor therapy, such as γ-irradiation-based radiotherapy (RT) [133], [134], chemotherapy (CT) (e.g. anthracyclines and oxaliplatin)[135], photosensitizer-and laser-mediated photo-thermotherapy (PTT) and photodynamic therapy (PDT)[136], are massively released due to ICD of tumor cells. Importantly, most of the first-line treatments for cancer patients are CT or RT, which stand a good chance to become valuable ICD inducers to trigger tumor immunogenicity in clinical. Actually, the DAMPs featuring main immunogenic characteristics of ICD, include adenosine triphosphate (ATP), surface-exposed calreticulin (CRT), heat shock protein (Hsp70 and Hsp90), ANXA1, high mobility group protein B1 (HMGB1), soluble F-actin as well as micronuclei and mitochondrial DNA (mtDNA), which intercommunicate with purinergic receptor, phagocytic receptor, FPR1, TLR4, C-type lectin domain containing 9 A (CLEC9A)[137] and endosomal TLR3[138] respectively, leading to a cascaded process composed of recruitment, mature and LNs-migration of DCs[139].

For instance, Ghiringhelli et al. employed tumoricidal activity of oxaliplatin to foster the release of ATP from EL4 thymomas cells, and released ATP could function on P2X7 purinergic receptors in neighboring DCs and subsequently triggered pyrin domain containing-3 protein (NLRP3) (belonging to NLR family) inflammasome activation-dependent DCs maturation[106]. Lu et al. utilized tumor cell or their intracellular substances to co-culture with *ex vivo*-generated mo-DCs, which endowed these mo-DCs with accomplished capacity to identify intricate TME and locomote towards tumors in vivo and in vitro[27]. Pfirschke et al. combined clinically approved chemotherapeutic drugs (oxaliplatin and cyclophosphamide) to engender ICD in Kras/Trp53 mutant lung tumor models, which activated intratumoral/peritumoral DCs via a TLR4-stimulated manner and subsequently made resistant tumors sensitive to ICB immunotherapies due to the

mature DCs-based CTLs influx[107].

3.1.2. Gene engineering

As mentioned above, migratory dynamics of DCs towards inflammatory locus or SLOs are exquisitely and elaborately modulated by the coordination of paired chemotactic cues in destination and corresponding chemokine receptors on DCs. However, considering that **1)** *ex vivo*-derived mo-DCs vaccines may exhibit inherent deficiencies in immune activation characteristics compared with naturally in vivo-developed DCs (mainly refers to cDCs), such as suboptimal CCR7 expression and inferior IL-12 and interferon (IFN) I/III secretion, leading to defective LNs homing competence (including intradermal (i.d.), intravenous (i.v.) and intranodal (i.n.) routes) and insufficient T-cell initiation[27], [140], [141]; **2)** immunosuppressive TME conspires to pose multifarious challenges that impede the tumor infiltration and immunological activity of DCs, such as downregulating tumor-chemotaxis chemokine receptors (e.g. CCR5) on DCs to rust DCs' migration capacity towards TME[85]. Predictably, with the satisfactory progress and harvest accumulated in the development of gene engineering or nucleic acid delivery, it would be a practicable and impactful attempt to directly elevate (or change) the expression of chemokine receptors on DCs in vivo and *ex vivo*, for intelligently manoeuvre the tumor- and/or LNs- chemotaxis.

Adoptive transfer of in vitro genetically engineered DCs could display a manipulated motility. For instance, Okada et al. found that intradermal reinfusion of DCs vaccine transduced with CCR7 and TAA/TSA (gp100/OVA) gene through a fiber-mutant adenovirus (Ad) vector, elicited a more robust Ag-specific immune response in melanoma-bearing mice with a lower dosage than DCs vaccine only genetically engineered by Ag alone[108]. Similarly, Chen et al. adoptively transferred genetically recombined DCs vaccines co-transfected by TAAs gp100- and CCR7-coding plasmid in B16BL6 melanoma-bearing mice, promoting an increased influx of gp100-crosspresenting DCs into SLOs, which promised a DCs-vaccines-unleashed anti-melanoma immunity in vivo[109]. Robert et al. genetically modified DCs in vitro by retroviral transduction to express a novel receptor for peripheral node addressin (PNAd) called chimeric E/L-selectin, and such engineered DCs could directly extravasate from the peripheral blood into the LNs after venous reinfusion[110]. What's more, Yang et al. intradermally administrated a OVA- and CCR7 pDNA-co-loaded micelles (M-COSA) to support DC mobilization to LNs and boost MHC I-restricted Ag presentation in B16-OVA melanoma models[112].

Besides, CCR5 is also expressed on immunoregulatory and tumor-promoting cells (e.g. M2 polarization macrophages, Treg and MDSCs) and anti-CCR5 mAb therapeutics to decrease the abundance of immunosuppressive cells mentioned above may be a promising strategy in anti-carcinoma of large intestine. Hence, directly applying nonselective or indiscriminate gene engineering therapy to improve the CCR5 expression in vivo, may lead to enhanced accumulation of pro-tumor cells instead of anti-tumor DCs within TME[142]. On the other hand, reinfusion of DCs-based vaccines with high CCR5 expression, may be beneficial to trafficking DCs into canceration regions. For instance, Lu et al. elevated the CCR5 expression on adoptively transferred DCs vaccines through co-culturing in vitro-derived mo-DCs with tumor cells or their

intracellular components, which polished up the in vivo chemotaxis towards TME[27].

Conversely, given that DCs can functionally elicit either immunogenic or tolerogenic immunity heavily lying on their maturational state and positioning, consequently, during malgenic autoreactive immune response or allografts, elevating SLOs-homing chemokine receptors on tolerogenic or immature DCs could contribute to amplification the abundance of “tolerance executor” Treg in SLOs rather than that of “immune effector” subsets. For example, Xin et al. co-overexpressed CCR7 and B and T lymphocyte attenuator (BTLA) on immature DCs via an Ad-based delivery, which simultaneously enhanced motility potential and tolerance induction of DCs and provided a feasible choice for transplant recipients suffering from overwhelming graft rejection[111]. Besides, Garrodr and colleagues indicated that reinfusing immature DCs co-expressing CCR7 and immunomodulatory molecule viral IL-10 could significantly extend cardiac allograft survival (mean survival time even >100 days) in an immunoregulatory Treg subset expansion-dependent fashion[113].

3.1.3. Epigenetic reprogramming

Immunosuppressive TME function as an instrumental part in tumorigenesis, aggressive progression and therapeutics response/resistance. Particularly, the epigenetic landscape within tumors is deregulated, including the epigenetic regulation of tumor cells as well as immune cells present in the TME[143]. Despite the specific mechanisms modulating the development and function of DCs in tumor-bearing hosts still remain inadequately understood, complicated TME seems indeed to transcriptionally and epigenetically alter biological activities and immunological phenotypes of DCs to hinder their multifunctional orchestration in boosting anti-tumor immune responses (e.g. crippling tumor infiltration of DCs).

For instance, tumor-derived transforming growth factor β (TGF-β) could manipulate the H3K4 trimethylation (H3K4me3) and H3K27 trimethylation (H3K27me3) modification of transcription factors associated with expression of certain costimulatory molecules, cytokines/chemokines as well as receptors in DCs, to force tolerance and dysfunction of DCs[144]. The relatively insufficient expression of CCR7 on mo-DCs mainly due to the Ccr7 promoter in mo-DCs enriched transcriptionally repressive histone modification H3K27me3, compared to cDCs[145]. Besides, microRNA (miR)− 146a and miR-146b could provoke intratumoral DCs apoptosis and block IL-12 and TNF-α production by modulating TRAF6 and IRAK1, and miR-146a always aberrantly elevated in TIDCs within several types of tumor[146], [147]. Furthermore, miR-155 targets special AT-rich binding protein 1 (Satb1, a master genomic coordinator for gene expression) in ovarian cancer-associated DCs, driving differentiated DCs into an immature, hyporesponsive and tumor-promoting regulatory phenotype[148]. Hence, a more comprehensive understanding about how tumors negatively affected immunological migration and competent capacity of DCs though epigenetic regulations may be heavily beneficial to convert immunosuppressive TME into immunoresponsive types.

In these regards, epigenetic reprogramming tumor cells and/or immune cells within neoplasm regions to heighten the expression of chemokine receptors on DCs appears to be an impactful way to reconstruct tumor-reactive immune contexture. In fact, epigenetic modifying agents have been deemed as versatile and booming therapeutics to restore endogenous tumor-killing immune responses[149] by reprogramming

expression profiles of chemotactic factors- chemokine receptors and cytokines-cytokine receptors[150]. For example, Fragale et al. combined IFN-α2b, romidepsin and 5-azacytidine (a type of DNA methyltransferase inhibitors) to reactivate malfunctioned DCs in colorectal cancer-bearing mice targeting specific epigenetic modifications, triggering upregulation of CXCR4-mediated pronounced navigation of DCs towards tumor region[114]. Besides, Tu et al. manufactured a chidamide (CHI, a novel subtype-selective histone deacetylase inhibitor)- and Bristol-Myers Squibb (BMS, chemical small-molecule inhibitors of PD-1/PD-L1 pathway)–202-co-delivered liposome system for the treatment of 4T1 triple-negative breast cancer (TNBC), boosting a powerful anti-tumor immune response against TNBC by CHI-mediated amelioration of DCs immunological function and enhanced tumor immunogenicity as well as BMS-202-based PD-L1 restriction[115]. A recent clinical trial I demonstrated that tumor NY-ESO-1 vaccine (CDX-1401 + adjuvant (poly(I:C) in combination with azanucleoside decitabine could abate the abnormal elevated promoter methylation levels in DCs, augment the intratumoral/peritumoral CD141 + cDC1 frequency and enhance the maturity of CD141 + cDC1, from patients suffering from malignant myelodysplastic syndromes[116].

3.1.4. Promoting CCR7 oligomerization

After activated by inflammatory stimulus, DCs upregulate the expression of CCR7 and subsequently form CCR7 oligomers before or during their SLOs-targeting movement[117], and the hindered CCR7 oligomerization on DCs will remarkably depress DCs' response degree or sensitiveness to the established concentration gradient of CCL19/CCL21, provoking impaired SLOs homing competence on DCs[18]. Accordingly, pharmacologically promoting CCR7 oligomerization may be beneficial to DCs-based T-cell immunoresponsive initiation in SLOs and inhibit the progression of immunodeficiency diseases (i.e. cancers, some infections), and instead pharmacologically blocking the formation of CCR7 oligomer may suppress the development of DCs-dependent autoimmune diseases, graft rejection or allergy.

For instance, Hauser and colleagues found that cholesterol-lowering drugs as well as Prostaglandin E2 (PGE2) could orchestrate inflammatory signals to further increase CCR7 oligomerization on DCs, which positively modulated DC migration to LNs[117]. Interestingly, Angeli et al. discovered that dyslipidemia associated with atherosclerosis may greatly crippled DCs' homing capacity, leading to activated skin DCs remained in situ and locally boosting dermal inflammation, and actually atherosclerosis is a common clinical feature in autoimmune disorders (e.g. SLE, rheumatoid arthritis, and psoriasis) with local inflammation[118]. In these regards, cholesterol accumulation or atherosclerosis-associated dyslipidemia may alter or impair DCs mobilization ability to LNs, and the retention of activated DCs populations may be an important pathogenesis of autoimmune disorders mentioned above, and cholesterol-lowering drugs may relieve symptoms caused by local inflammatory DCs with restricted mobilization.

Moreover, the exquisite metabolic transition from oxidative phosphorylation to glycolysis is indispensable in forming and maintenance of CCR7 oligomer, in accordance with DCs maturation[18]. Therefore, promoters of glycolytic metabolism may boost CCR7 oligomerization as well as SLOs-homing competence, and inhibitors of that may function oppositely. Guak et al. utilized 2-Deoxy-D-glucose (2-DG) to block DCs

glycolysis metabolism, which markedly decreased the DCs' migration from the lung to the mediastinal LNs in HDM-induced allergic asthma models[18].

3.1.5. Activating motion-related proteins/axis

Activation and maturation of DCs by stimuli such as multifarious DAMPs and PAMPs exposed during bacterial invasion and malignant mutation always lead to exquisite transition in migratory patterns and dramatic metabolic reprogramming. Migration of mature DCs is based with a continuous, motivated and directional manner, rather than the random and patrol-like locomotion behaviors of immature DCs that alternate their migration between fast and slow phases[151]. And such captivating change or difference in motility patterns of DCs is mainly regulated and controlled by actin nucleation after sensing stimulus. Actually, in several types of human and murine cancers, the actin organization-mediated DCs mobilization is frequently damaged. For instance, DCs in chronic myeloid leukemia (CML) patients are featured with distempered actin organization capability, which also characterize crippled migration talent and insufficient Ag-crosspresentation competence, due to the altered actin organization[152]. Thus, the regulation or stimulation of DCs' motion-related functional proteins/axis to alternate cytoskeletal organization may be a fascinating strategy to dominate motility manners and chemotaxis of DCs.

For example, Bretour et al. pharmacologically stimulated lysosome-associated TFEB-TRPML1 (transcription factor EB- transient receptor potential cation channel, mucolipin subfamily, member 1) pathway to reorganize actin cytoskeleton and enhance the expression ratio of front:rear filamentous actin (F-actin) in DCs to triggering a fast and mature-DCs-like locomotion manner, based with the fact that immature DCs employ the F-actin at front to facilitate micropinocytosis and mature DCs concentrate F-actin at their rear to boost cell motility[22]. Oliveira et al. found that Wiskott-Aldrich syndrome protein (WASp) could act as an effective actin regulator to coordinate several cytoskeletal reorganization-dependent behaviors such as migration and cell-cell intercommunication in DCs via regulating the formation of DCs' podosomes, and in WAS patients featuring defective function WASp mutations usually suffered from immunodeficiency partially due to the dysfunctional migratory capacity of DCs[153]. Besides, the carriers of an ASAP1 gene variant have been proved possess an enhanced susceptibility to tuberculosis, for people with mutational or defective ASAP1 gene exhibit migration deficiency of DCs and insufficient T-cell generation to deal with Mycobacterium tuberculosis infection[154]. Diao et al. utilized low dose PGE2 to support the F-actin cytoskeleton reorganization- and CCR7 expression-based DCs mobilization towards LNs[119]. Additionally, Ufer et al. indicated that activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1 (Arc/Arg3.1) pathway specifically determined the transformation from a steady and immature resting state to accelerated and activated DC motility after migratory skin DCs encountered stimulus or inflammation, and the genetic downregulation of Arc/Arg3.1 axis devoted a lot to the remission of allergic contact dermatitis reaction and experimental autoimmune encephalitis, which implied Arc/Arg3.1 could be a therapeutic target to modify DCs-based immunotherapy[23]. Furthermore, Eps8, fascin-1, formin mammalian Diaphanous-related 1 (mDia) and actin-nucleating complex Arp2/3 all could act as modulators for DCs locomotion-manners that are regulated by actin dynamics or meshwork architecture, whose

pharmacological activation and/or inhibition may contribute to the remission in immunologic deficiency and/or immunologic overreaction diseases[120], [121].

3.2. Regulation of chemokine concentration in destinations

It's well known that "tricky" tumors always establish overlapping mechanisms for immune privilege and uncontrolled tumor progression. In fact, tumors could modify or change their chemokine expression profiles and/or downregulate corresponding chemokine receptors in tumor-reactive immune cells to exclude immunoresponsive populations. For instance, direct downregulation of chemokines CCL5, CXCL1 and CXCL2 in melanoma by expressing intrinsic β-catenin signal in melanoma[85] and adenocarcinoma of the uterine cervix[155], altered the TIDCs (especially cDC1) landscape in TME as well as led to immune evasion. Consequently, polishing up the immune-microenvironment of destination (e.g. cancer lesions with immune-boosting chemotactic factor insufficiency) via direct delivery of chemokines or their nucleic acids, enhancement of NK-DCs-based cascaded infiltration, and administration of DCs-stimulating or development factors, may possess certain therapeutic value for ameliorated anti-tumor effectivity (Table 3**,** Fig. 4**B**).

3.2.1. Direct delivery of chemokines or their nucleic acids

DCs' trafficking into neoplasm sites is elaborately managed by multiple complicated chemoattractants-chemokine receptors systems, and one of the simplest ways to interfere intratumoral/peritumoral deployment of functional DCs is reducing supplies or production of chemoattractants attracting DCs into tumor. Thus, direct delivery of potent chemotactic factors (e.g. CCL5, XCL1, CXCL12 and CCL19, CCL21) into tumor regions, or forcing tumors themselves to produce and secrete guidance cues via delivering mRNA or DNA of chemokines, may be an impactful strategy for chemotactic recruitment of DCs into TME.

3.2.1.1. XCL1

The chemokine receptor XCR1 is exclusively expressed on a cDC1 subpopulation involved in Ag cross-presentation, and XCR1 + cDC1 subtype is a critical or even indispensable component of mobilizing and amplifying adaptive and innate immunity against malignancies[11]. In addition, the only two ligands currently found for XCR1 are XCL1 and XCL2 (specific exists in human), both of which could engender potent and highly specific chemotaxis of XCR1 + DCs, but not of any other activated or resting DC subsets, B cells, T cells, or NK[79]. Therefore, targeted delivery of XCR1 ligands into tumor lesions may be an available and efficacious approach to lead cDC1s into the TME.

Hartung et al. immunized mice with XCL1-OVA along with adjuvant LPS, which prevented tumor progression of E.G7-OVA lymphadenoma via a OVA-specific CTLs immunity[156]. Matsuo et al. generated a variant and stabilized form of XCL1 entitled mXCL1-V21C/A59C, which even possessed more potent chemotactic and calcium-mediated cDCs mobilization competences after intradermal injected (along with OVA) compared to wild type of XCL1[157].

Moreover, Chen et al. immunized hepatocellular carcinoma-bearing mice with XCL1/Glypican-3 fusion pDNA vaccine, with amplified concentration of several functional cytokines and chemokines (e.g. XCL1, CXCL19, CCL5, IFN-γ and granzyme B) in liver, which aroused potent Glypican-3-specific anti-tumor cellular immunity and ameliorative anti–PD-1 efficacy[158]. Gao et al. transfected chemokines CCL19 or XCL1 cDNA into several cancers via a recombinant Ad vector, and found that both XCL1 and CCL19 transfection delayed murine lung cancer A549 and melanoma B16 progression[159]. However, another similar study demonstrated that although both CCL19 and XCL1 were efficacious motif chemokines for DCs, impressively, CCL19 transfection into ovarian carcinoma displayed a prominent tumor-suppressive efficacy, whereas XCL1 did not[160], which may closely related to that CCL19 expression tumor could attracted CCR7 + mature DCs into TME or TLS and XCL1 could recruit immature XCR1 + DCs that may malfunction in immunosuppressive TME[3], [11], [18].

3.2.1.2. CCL19/CCL21

The dynamics of cDC1 trafficking within tumors remains largely incomprehension, and it's still unclear whether cDC1s infiltrating into TME will eventually leave and migrate to TDLNs[183]. Furthermore, considering the evidence recently found that promising naïve T cells and mature DCs actually could live and intercommunicate in TLS[67], intratumorally administration of CCL19/CCL21 proteins/polypeptides or their nucleic acid modes to boost a robust immune response to tumor may be a potential therapeutics to promote mature DCs' infiltration to immune-hostile TME. Because, such measure may massively heighten the intratumoral/peritumoral frequency of CCR7 + DCs with activated biological activity as well as DC-T crosstalk within tumor.

Wimalachandra synthesized folate-modified CCL21-loaded upconversion nanoparticles (UCNPs) (CCL21-FA-UCNPs) for chemotactic recruitment of CCR7 + DCs and T cells from the vascular compartment into the neoplastic lesions, augmenting the crippled host immune response in ovarian cancer[161]. Fenton et al. fabricated a tunable and injectable biomaterial hydrogels constituted by CCL21-loaded self-healing and shear-thinning polymer–nanoparticle (PNP), whose minimally invasive subcutaneous administration professionally recruited DCs to injection site[162]. Intriguingly, Jorgensen et al. found that CCL21 exhibited suboptimal chemotactic potency compared to CCL19 in provoking DCs migration, and CCL21 with removed tail could display enhanced competence in glycosaminoglycan binding with CCR7 + DCs and orchestrating initial cross-talk between DCs and naïve T cells in LN T-cell zones[62]. Besides, Zhao et al. generated a CCL21/IL-15 bicistronic Ad carrier (Ad-CCL21-IL-15), whose intratumoral injection into CT-26-carrying mice triggered chemotactic recruitment and stimulation of DCs, T cells and NK cells[163]. Liu et al. utilized folate-modified cationic nanoparticles to deliver CCL19 plasmid DNA (pDNA) into colon carcinoma, resulting in activated immune system-mediated anti-tumor potency[164]. Analogously, Hisada et al. co-transfected murine colon cancer cells CT-26 with chemokine CCL21 and costimulatory molecule LIGHT, which synergistically promoted co-localization of mature DCs and T cells within tumor nodules and elicited a colon carcinoma-specific CTLs immunologic activity[165].

3.2.1.3. CXCL12

Besides, some studies suggested that intratumoral upregulation of CXCL12 may devote to CXCR4 + DCs locomotion into TME and correlate positively with suppressive tumor progression. For instance, Fushimi et al. utilized adenoviral gene transfection of CXCL12 in A549 lung carcinoma, CT26 colon cancer and B16 melanoma, and expressed CXCL12 could function as a chemotactic factor for facilitating an influx of immature CXCR4 + DCs into TME and succedent inflammatory enlargement of TDLNs and tumor regression[166]. Analogously, Chen and colleagues generated CXCL12-loaded gold nanoparticles, which evidently driven DCs to express CXCR4 and secrete more CXCL12 to further intercommunicate with nearby DCs, contributing to migratory potential of mature DCs and initiation of acquired immune response[167]. Besides, Garnica et al. indicated that systematic administration of small amounts of CXCL12 supplementation could direct CXCR4 + DCs homing to spleen, where DCs initiated T cells into diversified subtypes, accordingly augmenting the control against *Plasmodium berghei* malaria[168].

However, CXCL12/CXCR4 can be a two-edged sword in tumor progression. Under normal circumstances, the expression of CXCL12 are upregulated during malignancy development under hypoxia, and large-scale hyporesponsive and immunosuppressive Treg and myeloid derived suppressor cells (MDSC) (rather than tumor-suppressive DCs) could accumulated into TME in a CXCR4-based manner consequently. Then, the increased tumor-infiltrating Treg and MDSC may even be positively intertwined with promoted neoangiogenesis, invasion and metastasis[184], [185]. In brief, in clinical practice, CXCL12/CXCR4 over-expression predicts unfavorable overall survival and poor prognosis in malignancies, and the administration of CXCR4 antagonist has been gradually regarded as a powerful weapon of recruiting intratumoral CD103 + cDC1 and augmented anti-cancer immunity[185], which indicates that supplement of CXCL12 or its nucleic acid modes needs to face the risk of potential tumor-promoting effect.

3.2.2. Augmentation of NK-DCs cascaded tumor-infiltration

It is worth a whistle that immune cells boosting the development, recruitment, Ag cross presentation and maturation of DCs can be deemed as “DCs helper cells”[19]. In these regards, NK cells could be regarded as such so called “DCs helper cells”. As the crucial force of innate immune system against malignancies, NK cells usually precede cDC1s recruitment in several cancer models, and NK are the main producer of XCL1 and cytokine Flt3L associated with mobilization and generation of cDCs as wells. Hence, molecular modulators regulating NK tracking and infiltration into TME could be significant determinants of intratumoral/peritumoral cDC1s abundance or cascaded NK-DCs infiltration[11], [186]. In addition, accumulated evidence demonstrates that intratumoral NK–DCs interaction axis defines the responsive mode or efficacious degree of immunization therapies (including ICBs therapy) to cancers[186], whereas tumors pose diversified suppressive challenges to exclude NK and DCs to interrupt such immunoreactive crosstalk[169]. Therefore, facilitating tumor-infiltration of activated NK cells with biological capacity could be a significant contributor to expansion and stimulation of DCs (especially cDC1) within TME.

3.2.2.1. COX-2 restriction

Notably, some researchers declared that metabolites of arachidonic acid (particularly PGE_2) could act as a proinflammatory mediator supporting DCs activation and adequate migration in prostate cancer, for low concentration PGE_2 could stimulate CCR7 oligomerization-based [187] and F-actin polymerization[119] LNs-homing of mature DCs as well as enhance the expression of C5aR on mo-DCs and secretion of membrane-bound metalloproteinases (MMPs)[188]. Quite the contrary, other studies demonstrated that in several types of cancer (e.g. melanoma, mammary cancer and carcinoma of colon), the rare distribution frequency of TIDCs may be in part due to a tumor-derived high-concentration PGE_2-mediated downregulation of XCR1 and dampened tumor-towards emigration of NK cells as well as the diminished production of NK-associated XCL1 and CCL5[11], and PGE2 also appeared to be intertwined with the generation of immunosuppressive indoleamine 2,3-dioxygenase (IDO)[189] and tumor growth via immunity evasion[169]. As a consequence, Böttcher et al. decreased the concentration of tumor-derived PGE_2 through cyclooxygenase(COX)− 2 blockade to reinstate the tumor infiltration of functionally competent NK, which stimulated XCR1-and CCL5- mediated chemotactic recruitment of cDC1 into TME to further synergistic activation of the immune control against tumor[11]. Analogously, Zelenay et al. combined ICBs and selective depressant of COX (aspirin) to effectually reverse tumor immune privilege via a cascaded NK-DCs tumor-infiltration and the reinforced immune-promoting intercommunication between NK and DCs, implying the COX-2 restriction may constitute efficacious additions to the arsenal of current anti-tumor immunization therapies[169].

3.2.2.2. Chemotactic factor receptor upregulation

Additionally, Maghazachi et al. used drugs for treating multiple sclerosis (such as glatiramer acetat, monomethyl fumarate and dimethyl fumarate) to upregulate the expression of CCR10 on IL-2-activated NK cells, which could respond to the concentration gradients of CCL27 and CCL28 that were secreted by selective tumor types such as malignant melanoma, squamous cell carcinomas, and colorectal cancer, respectively[170].

3.2.2.3. Chemokines replacement therapy

For example, supplying extra chemerin and its synthetic derivatives could biologically recruit DCs and NK cells in vivo, leading to strengthened anti-tumor defense in multiple tumors (including melanoma, mammary cancer and hepatocellular carcinoma)[81], [82], [83], [84]. Wendel et al. exogenously applied IFN-γ–induced protein 10 (IP-10, or CXCL10) or forced tumor cells to ectopically produce CXCL10 via a retroviral vector-delivered CXCL10 cDNA expanded intratumoral CXCR3 + NK population and prolonged NK cell–dependent survival[171]. Specially, a phase II clinical trial results implied that the orally active antitumor agent ONC201 could upregulate endogenous TNF-related apoptosis-inducing ligand (TRAIL) both in tumor cells and engender CXCL10-modulated CXCR3 + NK cells accumulation in tumor regions, arousing robust NK- and CTLs-based immunity against tumor migration/invasion and metastasis[172].

3.2.2.4. Pro-inflammation cytokines

Wong et al. found that reinfusion of IL-18-primed “helper” NK cells could function as the prominent

inducers of local immunoreactive immune cell accumulation, mobilizing the CCR5-modulated chemotactic recruitment of immature DCs and inducing subsequent DCs secretion of CXCL9, CXCL10, and CCL5 to further attract effector CTLs in hosts-bearing malignant caners[173]. Moreover, IL-17D replacement therapy or doxycycline-pre-treated regressed cancer types with high IL-17D expression may stimulate production of monocyte chemotactic protein-1 (MCP-1, aka CCL2) and indirectly recruit NK cells into TME[174].

3.2.3. Administration of DCs-stimulus

The immunoreactivity and immunoresponse-mediated by Ag-carrying DCs are closely interrelated to total number of available DCs, the chemotaxis of DCs (especially towards tumors and LNs), and the maturation state or immunologic function of DCs in vivo[19]. In fact, all these immunological features could be remarkably modulated by diversiform cytokines and transcription factors (e.g. IFN I, IFN III, IL-1β, TNF-α, Notch ligand, Flt3L and GM-CSF) [190], [191]. On the contrast, the exist of anti-inflammatory cytokines, such as IL-10 and TGF-β, negatively impact the biological activities and lead to tolerogenic properties, leadng to diminished CTLs mobilization[144], [192]. Accordingly, exogenous application of other factorsclosely associated with the development and maturation of DCs or triggering ectopic synthesis of these factors in tumor cells or (adoptive transfer) immune cells would be attractive therapeutic means of eliciting immune response against tumors as well.

3.2.3.1. Cytokines supplement

Interestingly, Oh et al. utilized gelatin-based hydrogel to co-deliver oncolytic adenovirus (Ad) co-secreting IL-12 and GM-CSF and immature DCs for optimally long-term release of both therapeutics within immune-hostile tumor lesions[175]. Administration of cGAMP or cGAMP–like agonists (e.g. cyclic seven-membered ring (PC7A)) of STING (stimulating expression of IFN) seemed to stimulate the generation and secretion of IFN I[176], as well as facilitating synergistic infiltration and activation of DCs and NK cells in TME[177], [178]. Intriguingly, Haabeth et al. employed a CART delivery vehicle (BDK-CART)-mRNA delivery platform to simultaneously provoke local expression of various immunomodulatory molecules (including IFN-γ, IL-12, CD86, CD70, OX40L and CD80) in tumor cells or stoma cells, which reactivated a systemic immune response to repress tumor invasion both in proximal (treated) and distal (untreated) tumors[180]. In addition, supplying tumor necrosis factor (TNF)-α and RANTES are the main chemoattractants for attracting murine LCs into LNs[193]. A recent phase I clinical research demonstrated that a personalized precision vaccine composed of autologous tumor tissue that was transfected a pDNA encoding GM-CSF and bi-shRNA-furin to attract DCs as well as suppress TGF-β expression, manifested a significant overall survival advantage in advanced-stage ovarian cancer patients[179].

Moreover, Lai et al. adoptively transferred Flt3L-releasing T cells along with adjuvant poly (I:C) and anti-4–1BB, which augmented the amount of intratumoral endogenous cDCs with robust Ag cross presentation ability and substantially enhanced DC-T cell synergistic activation[181]. Kirkling et al. demonstrated co-culture system containing Flt3L and OP9 stromal cells expressing the Notch ligand Delta-like 1 (OP9-DL1) could engender optimal development of interferon regulatory factor 8 (IRF8)-dependent cDC1s with

optimizational competent properties in human and murine, which possessed a superior CCR7-based LNs-homing behavior that caused a preferential T cell cross-priming talent and antitumor efficacy in vivo[194]. Importantly, a recent phase I/II clinical trial combined intratumoral Flt3L and poly (I:C) administration as well as low-dose radiotherapy to convert low-grade B cell lymphomas into a Flt3L-primed in situ vaccine manufacturing factories for DCs-development, recruitment and activation[182].

3.2.3.2. ICD inducers

Actually, apart from exposing immunologic adjuvant-like exogenous "danger signals" (such as ATP, HMGB1 and soluble F-actin mentioned above) to manipulate upregulated CCR7-based DCs mobilization behavior, ICD inducers could also directly release chemoattractants for in situ recruitment of DCs. For instance, ICD, not tolerogenic cell death, could massively chemokines (e.g. CXCL1, CXCL2, CCL2, and CXCL10), boost NK-DC-T cascaded tumor-infiltration and synergetic stimulation[195]. Besides, tumor cells succumbing to CTs triggering ICD (such as anthracyclines), would massively expose the chemotactic cue ANXA1 expressed on their cell membrane. Then, the released ANXA1 could grant FPR1 + DCs entry into neoplastic lesions and allowed FPR1 + DCs to cross-present TAAs/TSAs belonging to nearby dying cancer cells[28]. As a consequence, breast and colorectal carcinoma patients characterizing a deficiency-of-function single-nucleotide polymorphism (SNP) in FPR1 seemed to possess poor prognosis after anthracycline or oxaliplatin-based chemotherapy[28].

3.3. Modulating monocyte precursors infiltration and DCs differentiation

DCs as well as their monocyte precursors are both endowed with functional plasticity or flexibility to handle with diversiform diseases. In brief, monocytes, as phagocytic effectors and short-lived transient intermediates, could serve as BM-resident heterogeneous progenitors to seed peripheral tissues (inflammatory sites mainly) with their progeny (including monocytes-derived DCs and macrophages) to significantly mobilize innate and adaptive immune responses. Under normal circumstances, after egress from BM, Ly6C^{hi} CCR2 +[196] and/or Ly6C^{hi} CCR6 +[41] inflammatory monocytes could provide a transient functionally versatile complement to mo-DCs possessing Ag-cross-presenting capacity and tissue-resident macrophage compartments to unleash immune defenses against microbes infection[196], [197], amplify vaccine-sculptured immune responses[41], provoke inflammatory diseases[43], [198], and/or establish peripheral tissues' immune homeostasis[199]. Beside, Ly6C^{low} CX3CR1 + monocytes, which seem to be differentiated by Ly6C^{hi} monocytes returning to BM in the absence of inflammation[200], are apt to freely patrol blood vessels and extravasate spontaneously to non-inflamed tissues to prepare for potential infections, and Ly6C^{low} CX3CR1 + monocytes participate in the initial inflammatory response in infection regions before Ly6C^{hi} monocytes arrive in[201].

1) As a matter of fact, in comparison to infrequent progeny DCs subgroups, mononuclear precursors possess a massive amount in vivo. Prior studies have established that the peripheral tissues are imbued with circulating monocytes or their progenies owing to the exquisite deployment of monocytes populations[202]. For example, Ly6C^{low} CX3CR1 + monocytes can give rise to CX3CR1 + DCs to preserve

internal homeostasis by eliminating pathogenic bacterium/virus or triggering tolerance to food-Ag and SI symbiodinium in gastrointestinal tract[203]. Furthermore, elegant studies about migration kinetic and differentiation kinetic of adoptively transferred monocytes have illustrated that, Ly6C^{hi} monocytes are more potential to give rise to CD103 + DCs, whereas LY6C^{low} monocytes are more likely to generate CD11b+ DCs in lung[204], [205].

2) In addition, monocyte precursor cells (especially Ly6C^{hi}) instinctively feature more potent inflammatory chemotaxis in vivo, no matter towards common inflammatory locus (e.g. pathological infection regions), or towards neoplastic lesions or vaccine inoculation sites. For instance, after antineoplastic therapeutics induce ICD, the intratumoral infiltration abundance of mononuclear progenitors is fairly more than that of DCs, which may be attributed to the fact that disparate DAMPs including soluble fragments of fractalkine (CX3CL1), the lipid lysophosphatidylcholine (LPC), S1P and the nucleotides ATP and UTP all could provide "find-me" signals exposed by cancer cells for monocytes[206].

3) Furthermore, as a nonconventional and highly plastic DCs subtype, it remains unknown whether mo-DCs are generated elsewhere to be advisedly attracted to the inflammatory regions in response to chemoattractants for DCs' recruitment, or they are developed from inflammation-infiltrating progenitor monocytes and activated in situ. But whether or not, it displays better practicability or simplification to recruit monocyte precursors that characterize robust inflammatory chemotaxis as well as differentiation potential and then to facilitate monocytes' in situ differentiation into multifunctional DCs, compared to directly attracting rare DC populations. Generally, administration of ICD inducers and adjuvant components, and chemokine supplement may be efficacious approaches for trafficking Ly6C^{hi} monocytes into the destinations (Fig. 4**C**).

3.3.1. ICD inducers

Ma et al. found that the anthracyclines could effectually boost large-scale CD11c+CD11b+Ly6C^{hi} cells accumulation in tumor bed, and these Ly6C^{hi} cells characterized with monocytic precursors together with some differentiated inflammatory DCs, which could efficiently engulf exposed TAAs/TSAs after ICD and then successfully cross presented captured-Ags to T lymphocytes[207]. Specially, ATP seemed to favor monocytes' tumor infiltration and their succedent differentiation to DCs during anthracyclines-triggered ICD[207]. Besides, massive CCL2 that released during tumor ICD also participated in trafficking monocytic precursors into TME[195], despite depletion of tumor-derived CCL2 could block breast-tumor metastatic seeding and CCL2-CCR2 recruited inflammatory monocytes may sometimes support metastasis because monocytes also could develop into immunosuppressive M2 as well[208].

3.3.2. Adjuvant administration

Several established studies demonstrated that intramuscular immunization of MF59 (a FDA-approved emulsion-based vaccine adjuvant) as well as adjuvant System AS03[209] could construct an "immunocompetent environment" in situ by producing manifold guidance cues (such as CCL2, CCL4, CCL5

and CXCL8), directly conferring the capacity to enter injection sites on CCR2 + CCR5 + inflammatory monocytes, which could further differentiate into mo-DCs to elicit vaccine-specific immune responses[210], [211]. Similarly, Lian et al. generated an oil formulation loading adjuvants and Ags to attract monocytes and endow them with the capacity to migrate into interfollicular regions (IFRs) of LNs, where they developed into Ag-presenting mo-DCs and further recruited and initiated CD4 + T cells[212].

3.3.3. Chemokine supplement

What's more, monocytes, serving as precursors of mo-DCs, after transepithelial or transdermal immunization could navigate to the vaccine inoculation sites with the guidance of CCR6-CCL20 axis, and in situ development into DCs that are accomplished in Ag-Specific CD8 + T cell priming[41]. Cao et al. administrated recombinant macrophage inflammatory protein 1α (MIP-1α) could mobilize CCR2 + or CCR6 + DCs precursors into circulation, and further adoptive transfer of human melanoma-associated gene (MAGE)− 1-transfected DCs-derived from MIP-1α–mobilized circulating precursors could trigger CTLs expansion and abolish tumor development[213].

In summary, despite there exist a large number of practicable approaches for chemotactic or inflammatory recruitment of monocytic precursors into tumor lesions and monocytes indeed greatly possess latent capacity to differentiate into DCs that feature with expert Ag-cross-presentation competence, inflammatory monocyte precursor cells pose more potential to develop into macrophages (particularly immune-hostile M2) in immunosuppressive TME, leading to tumor immune privilege and metastasis of tumor[208], [214], [215]. In these regards, to avoid recruited monocytes in situ transform into tolerogenic M2 instead of tumor-infiltrating mo-DCs, appropriate combination with immunotherapies mentioned above that favor development and maturation of DCs may be a valuable strategy, for example ectogenic complementarity or genetic transfection of Flt3L and GM-CSF[175], [181], [182], [194].

3.4. Physical method-manipulated DCs locomotion

Except for physiological chemokine-chemokine receptor systems-regulated DCs chemotaxis in vivo, some recent reports manifested that physical methods could participate in manipulating DCs directional migration and tracking DCs' motility without invasiveness as well (Fig. 4**D**).

For instance, Jin et al. utilized fluorescent magnetic nanoparticles (α-AP-fmNPs consisted of Ag gp100, iron oxide nanoparticles, and indocyanine green (ICG)) together with magnetic pull force to manipulate DCs directional motility in vivo and *ex vivo*, and reinfused mo-DCs with internalizationof α-AP-fmNPs could favorably position LNs under the guidance of magnetic pull force and inflammatory stimulation of tumor necrosis factor (TNF)-α, which boosted amplified anti-melanoma immunity[216]. Similarly, Schreiber et al. reported a fluorescent carbon magnetic nanoparticles (CMNPs) along with TLR9 agonist CpG to stimulate DCs that endocytosed CMNPs, and these activated DCs could be enriched into either SLOs or chronic inflammation sites in vivo by an external magnet-based magnetic pull force[217].

Therefore, physical method may be an effective alternative to mediate DCs enrichment into SLOs to elicit multiplicate T-cell subsets-based immune responses or immunological tolerance as well as into inflamed foci to capture Ags and subsequently (re)stimulate and expand T cells.

4. Clinical applications of manipulating DCs chemotaxis for immune amplification and immune tolerance

Emerging evidence from clinical trials or practices exhibits that immunization therapies based on modulating DCs chemotaxis to SLOs or peripheral inflammation foci (especially neoplastic lesions) could be efficacious contributors to repress malignancies progression and attenuate infections via boosting adaptive and innate immunity, or relieve inflamed diseases (an extensive term, including tissue inflammations and autoimmune diseases) via inducing immunological tolerance. Generally, DCs-based immunotherapies to amplify immune responses are mainly composed of protein-based vaccines, nucleic acid-based vaccines (including mRNA and DNA) and reinfused DCs-based vaccines, whose robust potencies actually are positively correlated with their competence in regulating migratory behavior and in vivo positioning either in hosts' intrinsic DCs or adoptively transferred DCs generated in vitro. Oppositely, clinically therapeutic regimens for organ inflammation and autoimmune diseases, are mainly constituted of immune inhibitors to prevent maturation and SLOs-homing of DCs (Table 4, Table 5).

Table 4. Clinical trials to regulate DCs migration for immune amplification.

Indication	Research phase	Strategies related toFig. 4	Specific measures	Targeted DC subsets	Chemotaxis directions	Results	Ref.
			Protein-based vaccines				
cervical carcinoma, vagina carcinoma, anogenital and oropharyngeal carcinomas	listed on the market	Strategy A + C	DNA-free multivalent HPV VLP + adjuvants (AS04 or aluminiumhydroxide or aluminiumhydroxy-diphoshosulfate)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	persisted protection from multiple types HPV induced carcinomas and genital warts	[218]
melanoma	phase I	Strategy A	13–20 IMP + poly (IC:LC) ± PD-1 mAb	all DC subsets	LNs	4/6 patients had no recurrence at 25 months after vaccination	[219]
	phase II	Strategy A + B + C	12 IMP + incomplete Freund's adjuvant ± GM-CSF	all DC subsets (mo-DCs	LNs	patients without GM-CSF had better immune	[220]

				especially)		responsiveness	
	phase I	Strategy A + B	7 IMP + 2 gp100-derived peptides + IL-12p70	all DC subsets	LNs	mutant peptides-specific T cells expanded	[221]
acute myeloid leukemia	phase I	Strategy A	NY-ESO-1 (CDX-1401 + poly (IC:LC)) + decitabine	CD141 + cDC1	tumor sites and LNs	4/7 and 6/7 patients elicited Ag-specific immunity	[116]
lymphomas	phase I/II	Strategy A + B + C	CDX-301 (Flt3L+poly(IC:LC)) + local RT + PD-1 mAb	CD141 + cDC1 mainly	tumor sites and LNs	expansion of DC subgroups and regressions of distant tumors	[222]
	phase I/II	Strategy A + B + C	CDX-301 (Flt3L+poly(IC:LC)) + low-dose RT	CD141 + cDC1 mainly	tumor sites and LNs	expanded intratumoral cDC1	[182]
prostate and endometrial cancer	phase II	Strategy B	oral ONC201 + PD-1 mAb	XCR1 + or CCR5 + DCs	tumor sites	NK-based regression of metastatic lesions	[17 2], [223]
glioblastoma	phase I	Strategy A + B + C	20 IMP + poly (IC:LC) + GM-CSF	all DC subsets (mo-DCs especially)	LNs	aroused Ag-reactive Th1 immune response	[224]
lung adenocarcinoma	phase I/II	Strategy B + C	bystander cells (expressing GM-CSF+CD40L) + CCL21	mature DCs	LNs and injection sites	safe biocompatibility and increased DCs infiltration	[225]
ovarian cancer	phase I	Strategy A	NY-ESO-1 + poly (IC:LC)	all DC subsets	LNs	biosafety, induced synergetic immunity	[226]
	phase I	Strategy A + B	cisplatin + Rintatolimod + oral celecoxib ± IFN-α	all DC subsets (cDC1)	LNs and tumor sites	safe, tolerable and favored CTLs chemoattraction	[227]
	phase II	Strategy A	Motolimod + PLD	all DC	LNs and	1/13 achieved a	[22

		+ B		subsets	tumor sites	complete response	8]
mCRC	phase Ib	Strategy A	PolyPEPI1018 and Montanide ISA51VG	all DC subsets	LNs	80% patients triggered anti-tumor response	[229]
melanoma, sarcoma, ovarian, colorectal and non-small cell lung cancers	phase I	Strategy A + B	CDX-1401 (NY-ESO-1 + DEC205 mAb) + resiquimod + poly(IC:LC) + PD-1 mAb	mo-DCs, dermal cDCs and LCs	injection sites and LNs	6/8 patients accepted PD-1 had objective tumor regression	[230]
		Nucleic acid-based vaccines					
COVID-19	listed on the market	Strategy A	BNT162b2 (Pfizer-BioNTech)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	high humoral responses for enhanced protection against COVID-19	[231]
	listed on the market	Strategy A	mRNA-1273 (Moderna)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	high humoral responses for enhanced protection against COVID-19	[231]
cervical carcinoma	phase IIb	Strategy A	VGX-3100 (E6 pDNA + E7 pDNA)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	more likely to clear in vivo HPV 16/18 compared to control	[232]
	phase II	Strategy A	GX-188E (HPV pDNA)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	35/52 patients presented histopathologic regression	[233]
gastrointestinal cancer	phase I/II	Strategy A	mRNA-4650 (encoding 20 IMP)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	safe, and potential future combination of ICBs	[234]
melanoma	phase I	Strategy A	mRNA encoding 2 mutant peptide	mo-DCs, dermal	injection sites and	a sustained progression-free	[235]

				cDCs and LCs	LNs	survival	
Zika virus	phase I	Strategy A	GLS-5700 (DNA encoding premembrane and envelope proteins)	mo-DCs, dermal cDCs and LCs	injection sites and LNs	triggered Zika virus-specific antibodies	[236]
		DCs-based vaccines					
glioblastoma	phase I	Strategy A	tetanus toxoid + CCL3 + mo-DCs pulsed with cytomegalovirus pp65 RNA	mo-DCs	LNs	enhanced bilateral DCs migration and improved survival	[237]
	phase III	Strategy A + B	autologous tumor lysate-pulsed mo-DCs + CT	mo-DCs	LNs and tumor sites	prolonged survival	[238]
	phase II	Strategy A + B	autologous tumor lysate-pulsed mo-DCs + CT + RT	mo-DCs	LNs and tumor sites	11/27 patients elicited TAAs/TSAs-specific immunity	[239]
	phase II	Strategy A + B	IFN-γ, LPS, and Audencel-pulsed autologous mo-DCs	mo-DCs and maybe cDC1	LNs and tumor sites	up-regulated Th1-associated immunovariables	[240]
	phase II	Strategy A	mo-DCs pulsed with autologous tumor lysate	mo-DCs	LNs	no evident effect on overall and progression-free survival	[241]
NSCLC	phase I	Strategy B	CCL21 overexpressed autologous mo-DCs (i.t.) + pembrolizumab	mature DCs	tumor sites	inducing systemic tumor Ag–specific immune responses	[242]
melanoma	phase II	Strategy A	autologous mo-DCs electroporated with synthetic mRNA	mo-DCs	LNs	6-month disease control rate was 51%, the overall	[243]

			(TriMixDC-MEL) + ipilimumab			tumor response rate was 38%	
	phase II B	Strategy A	autologous tumor lysate-pulsed mo-DCs	mo-DCs	LNs	no benefit was found in patients receiving up to three doses	[244]
	phase III	Strategy A	autologous mo-DCs pulsed with multiple IMP + DTIC	mo-DCs	LNs	no extra superiority was found than DTIC in advanced melanoma patients	[245]
	phase I B	Strategy A	autologous mo-DCs-transfected with mRNA (CD70 + CD40L + several IMP)	mo-DCs	LNs	all melanoma free between 2 and 4 years after study initiation	[246]
cervical carcinoma	phase I	Strategy A + B	autologous tumor lysate-pulsed mo-DCs + bevacizumab + cyclophosphamide	mo-DCs	LNs and tumor sites	enhanced neoepitope-specific T cell response	[247]
lymphoma	phase I	Strategy A + B	RT + immature autologous mo-DCs + low-dose rituximab	immature mo-DCs, other DCs in vivo	tumor sites and LNs	5/14 patients (36%) displayed objective clinical responses	[248]
	phase I	Strategy A + B	autologous tumor lysate-pulsed IFN-DC + low doses of rituximab	IFN-DC, other DCs in vivo	tumor sites and LNs	IFN-DC could engender anti-tumor responses	[249]

VLPs: virus-like particles; HPV: human papillomavirus; IMP: immunizing long peptides; PLD: pegylated liposomal doxorubicin; NSCLC: non-small cell lung cancer; pp65: phosphoprotein 65; mCRC: metastatic colorectal cancer; i.t.: intratumorally injected; DTIC: Dacarbazine; mAb: monoclonal antibody

Table 5. Clinical trials to regulate DCs migration for immune tolerance.

Indication	Research phase	Strategies related toFig. 4	Specific measures	Targeted DC subsets	Chemotaxis directions	Results	Ref.

		reinfusion of tolDCs					
type 1 diabetes	phase I	Strategy A	proinsulin peptide C19-A3 alone (without adjuvant) pulsed autologous tolDCs	autologous tolDCs	LNs and pancreatic island	Treg expansion-based protection β cells from autoimmune destruction	[123]
	phase I	Strategy A	antisense ODN targeting CD40, CD80, and CD86 in autologous mo-DCs	autologous tolDCs	pancreatic island	safe and tolerated. Upregulating the frequency of beneficial cells	[263]
refractory Crohn's disease	phase I	Strategy B	Dex-engendered autologous tolDCs (i.p.) + low doses of corticoids	autologous tolDCs	Inflamed colon	improvement of life quality in 3/9 patients	[264]
rheumatoid arthritis (RA)	phase I	Strategy A + B	Dex- and TLR4 ligands-induced autologous tolDCs	autologous tolDCs	Inflamed arthrosis and LNs	Safe, but no systemic clinical effects	[265]
	phase I	Strategy A + B	4 citrullinated peptide Ags pulsed autologous tolDCs modified with an NF-κB inhibitor	autologous tolDCs	Inflamed arthrosis and LNs	enhances the ratio of Treg to effector T cells	[266]
Neuromyelitis opticaspectrum disorders	phase Ib	Strategy A	aquaporin-4 pulsed autologous tolDCs	autologous tolDCs	CNS and LNs	eliciting Ag-specific IL-10 production in Treg	[267]
Multiple sclerosis	phase Ib	Strategy A	myelin-derived peptides pulsed autologous tolDCs	autologous tolDCs	CNS and LNs	Promoting Treg – based IL-10 secretion	[267]
		Administration of immunosuppressive drugs					
relapsing multiple sclerosis	phase III	Strategy A	oral fingolimod (FTY7200) to reduce DCs maturation and migration	All DCs	LNs ↓	reduced the annualized relapse rate in 2 years	[39], [40], [268]
	listed on the	Strategy A + C	Glatiramer Acetate	Th2-inducing	LNs	DCs initiating Th2 immunity rather	[269]

	the market	+ C		inducing DCs		immunity rather than malgenic Th1	9], [270]
	phase III	Strategy A	Laquinimod	Th2-inducing DCs	LNs	Promoting IL-10, IL-4 and TGF-β rather than IL-12 secretion	[271]
	listed on the market	Strategy A + C	IFN-β1b to reduce CXCL12-CXCR4 axis-based mo-DCs and monocyte progenitors migration	Especially mo-DCs or CXCR4 + DCs	CNS↓ and LNs ↓	Decreasing the CXCR4 mRNA transcription on mo-DCs and monocytes	[168], [269], [272]
GvHD	phase II	Strategy A	extended CCR5 blockade	CCR5 + DCs	allografts↓	Prevented acute and chronic GvHD	[57], [273]
rheumatism	listed on the market	Strategy A	hydroxychloroquine and chloroquine	All DCs	LNs ↓	Restricting TLR signal stimulating-based DCs activation	[274]

GvHD: graft versus host disease; Tolerogenic DCs: tolDCs; vitD3: vitamin D3; Dex: dexamethasone

4.1. Immune amplification

Clinical researches involved in manipulating DCs positioning in vivo for amplifying immune responses in anti-tumor and anti-virus (Table 4, Fig. 5) are shown as bellow.

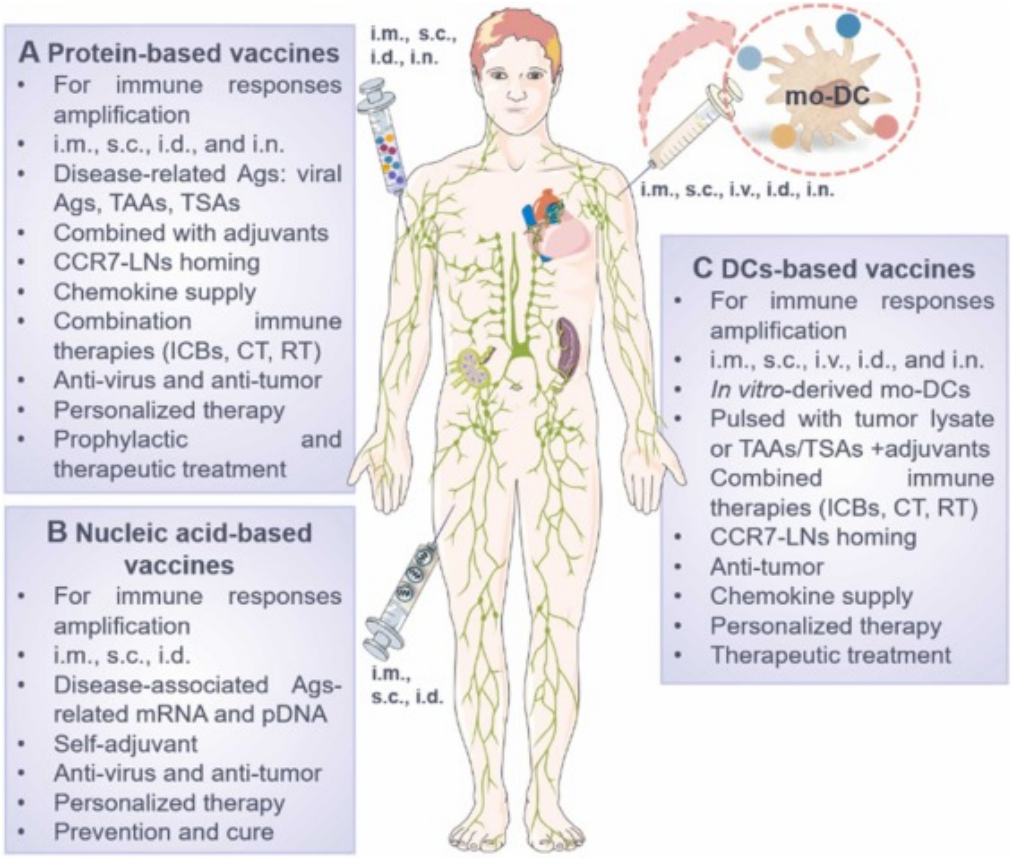

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Fig. 5. Clinical applications of manipulating DCs chemotaxis for amplified immunity. **(A)** Protein-based vaccines. As one of the most widely utilized vaccine types in clinical practice, protein/peptide-based vaccines, which are composed of antigenic disease-associated proteins/peptides and immunogenic adjuvants and are mainly delivered via i.m., i.d., s.c., and i.n., are used in anti-tumor and anti-virus therapies for both prevention as well as therapeutics via boosted immune responses. **(B)** Nucleic acid-based vaccines. As a novel and effective vaccine kind, nucleic acid-based vaccines, which include disease-related Ags-encoding pDNA or mRNA with robust self-adjuvant effect, could be administrated by i.m., i.d. and s.c. routes, for either prophylactic or therapeutic strategies through magnified immune responses. **(C)** DC-based vaccines. The massive reinfused DCs vaccines, which are mainly composed of in vitro-generated mo-DCs that are pulsed with individualized TAA/TSAs (with adjuvants) compounds or autologous tumor lysates prior to localized or systemic administration (i.m., i.d., s.c., i.v. and i.n.), could be employed in anti-cancer treatment. i.v.: intravenous injection; s.c.: subcutaneous injection; i.n.: intranodal injection; i.m.: intramuscular injection; i.d.: intradermal injection; ICBs: immune checkpoint blockades; CT: chemotherapy; RT: radiotherapy; TSA: tumor specific antigen; TAA: tumor associated antigen.

4.1.1. Protein-based vaccines

Modern vaccines are one of the most important weapons for humans against pathogenic attack[250] and malignancy progression[27]. Prominently, considering peptide- and/or protein-based vaccines feature safe biocompatibility, storage stability and well maneuverability (or simplification) to manufacture at quantity between the batch, they are nearly the most commonly used vaccine types in clinical research and practice. In addition, just as mentioned above, the immune adjuvants usually are the indispensable components in the most protein-based vaccines in clinical applications for amplified immune responses by polishing up the diversified costimulatory molecules and p-MHC molecules, and the appropriate administration of adjuvants could upregulate chemokine receptor CCR7-based directional SLOs-towards chemotaxis by ameliorating the maturity of DCs[73], [98]. Besides, after localized injection, adjuvants, the analogues of DAMPs and PAMPs, could recruit massive pre-DCs and rapidly promote the precursor cells' differentiation into multifunctional DCs in situ[209], [212]. Hence, the protein-based vaccines containing potent adjuvant components are significant measures to manipulate DCs trafficking.

Specially, among a large number of prophylactic or therapeutic vaccines against malignancies, the multivalent (including bivalent vaccines (2vHPV, Cervarix), tetravalent vaccines (4vHPV, Gardasil) and nine-valent vaccines (9vHPV, Gardasil 9)) vaccines, is first and currently the only one successfully prevented cancers[218]. In detail, this vaccine is composed of DNA-free HPV virus-like particles (VLP) with "high risk" (such as HPV16 and HPV18) or "low risk" (such as HPV6 and HPV11) and immunogenic adjuvants (such as AS04, aluminum hydroxide and aluminum hydroxy diphosphosulfate). In fact, the past decade has witnessed that large-scale vaccination of the DNA-free HPV VLP-based vaccine has almost eliminated cervical carcinomas in 14 high-income countries, as well as eased the burden of HPV-provoked other carcinomas (e.g. cervical carcinoma and vagina carcinoma) and genital warts[251]. Accordingly, viral cancers containing HPV-engendered cervical carcinoma and Kaposi sarcoma herpesvirus (KSHV or HHV8)-induced Kaposi sarcoma, have been gradually characterized as the "low-hanging fruit", for which could potentially be prevented via an appropriate immunization[252].

Besides, other clinical research involving immunizing long peptides (IMP)-based anti-neoplasm vaccines also harvested some delectable progress. For instance, a phase I/II clinical trial of combining CDX-301 (composed of Flt3L and poly(IC:LC)) and local radiotherapy (RT) as well as PD-1 monoclonal antibody (mAb), significantly expanded intratumoral CD141 + cDC1 subgroup with activated immunological function, leading to the regressions of distant (untreated) lymphomas[222]. Therapeutic lung adenocarcinoma vaccine utilized the combination of chemotactic factor CCL21 and bystander cells expressing GM-CSF and CD40L, prominently increased mature DCs' accumulation in adenocarcinoma foci[225]. In addition, another phase I clinical research exhibited that CDX-1401 (constituted of DCs-targeting DEC205 mAb fused TAA NY-ESO-1) together with resiquimod and poly(IC: LC) and PD-1 mAb, promoted robust humoral and cellular immunity in patients bearing diversified solid tumors, and even induced objective tumor regression in 6/8 patients that received PD-1 mAb therapy[230]. Interestingly, an oral anti-carcinoma drug ONC201 along with PD-1 mAb augmented cascaded or synergic tumor-infiltration and stimulation of NK-DC-T cells, and regressed partial metastatic lesions in individuals suffering from prostate and endometrial cancers[172], [223].

In sum, for Ag-reactive immune responses amplification, several principles in protein-based vaccine design include: **1)** as a cardinal part of a potent and targeted vaccine, the carefully screened Ags (from virus or cancer) should possess high antigenicity, extensive and specific expression in targeted foci, and immunogenicity[219]; **2)** as described above, antigenic protein or peptide-based vaccines need the combination of immunogenic adjuvants (TLR-3 agonist poly(IC: LC) in clinical particularly) to improve the sufficient persistence, efficiency, and breadth in Ag-reactive immune responses[116]; **3)** considering the restricted in vivo migration of DCs in tumor-bearing individuals, it's necessary to ensure DCs or their mononuclear precursors could reach the immunization sites and then the activated DCs carrying Ag-epitopes could rapidly migrate to SLOs where they share antigenic information and orchestrate Ag-specific immune responses[182], [225]; **4)** considering the differential chemotactic responses and bio-distribution under different injection routes and the diversified strength and duration of immune responses under different vaccination dosage and frequency, appropriate administration routes, dosage and frequency of vaccine inoculation need to be further explored or unified to ensure an optimum induction of DCs-based immunity[253], [254]; **5)** given the involute TME provided variegated immunosuppressive molecules, thus, in therapeutic vaccines (to defense tumor especially), combining with other (immune)therapies (e.g. CT, RT, ICBs, chemokine supplementation and cytokine therapies) may be an essential strategy[227].

4.1.2. Nucleic acid-based vaccines

As described above, in comparison with protein subunit vaccines in insufficient immunogenicity, nucleic acids (including DNA and RNA)-based vaccines are characterized with self-adjuvant effect via their PAMPs-like molecular structure to adequately stimulate PRRs (such as TLR-3/−7/−8/−9) on/within DCs, which could directly attract and subsequently activate neighboring monocyte progenitors as well as dermal cDCs and LCs, inducing immune responses amplification via plenty of Ag-carrying DCs homing to LNs in a CCR7-dependent manner[102]. Furthermore, recently highlighted advances in the design, modification, purification, production, storage and in vivo delivery of nucleic acids have endowed the progression of nucleic acid-based prophylactic and/or therapeutic treatments for extensive applications in clinical.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), features a high infection rate and complex and highly variable disease pathology[255]. Specially, due to the approval of several mRNA-based vaccines in the COVID-19 pandemic, nucleic acids (particularly mRNA)-based vaccines enter a rapidly emerging or development stage, or a new era in vaccinology[131], for which promise a versatile, efficacious and self-adjuvant novel vaccine-platforms[231]. Actually, mRNA is transiently expressed and theoretically won't integrate into the genome of the hosts, and mRNA can be optimized for enhanced serum stability and translation/transfection efficiency under appropriate delivery carrier[255]. It deserves to be mentioned, mRNA-based BNT162b1, one of the most advanced lipid nanoparticle (LNP)-encapsulated mRNA vaccine candidates against COVID-19, encodes the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, which acts as a critical target of neutralizing antibodies. And the results from clinical trials and subsequently large-scale vaccination manifested several LNP-loaded mRNA vaccine candidates (especially the advanced one BNT162b1 from Pfizer and mRNA-1273 from

Moderna) with endurable or slight side effect could orchestrate both cellular immunity and humoral immunity after multiple vaccination, consequently, providing a durable protection against severe disease, hospitalization, and death caused by COVID-19[231], [255]. Additionally, a clinical phase I trial against melanoma as well as a clinical phase I/II trial against gastrointestinal cancer both employed mRNA-based vaccines that encoded less than 20 individual IMP or mutant peptides of the hosts, which seemed to display a sustained progression-free survival in immunized patients[234], [235].

Back in the early 1990 s, DNA-based vaccines show up prominently and suddenly develop into the scientific limelight. Similar to mRNA vaccines, Ag-encoded DNA-based vaccines could transfect both APCs (mainly refer to dermal cDCs, LCs and mo-DCs as well as undifferentiated monocyte progenitor cells) and somatic cells (such as keratinocytes and myocytes) after local administration, and unleash robust Ag-reactive humoral immunity and cellular immunity with the participation of exquisite antigenic information transfer or share in situ and in SLOs[7]. Despite up to now there exists no DNA-based vaccine has been listed on market, because of people's concerns about the potential risks of genome integration caused by delivered ectogenic DNA, the past decades witnessed massive clinical researches about DNA vaccines involving diversified causative/pathogenic agents and TAAs/TSAs[256]. For example, two phase II trials in cervical carcinoma patients both used pDNA encoding proteins (E6, E7) from high risk HPV16 and/or HPV18 subtype, eliciting efficacious Th1 immunity, which showed more possibility to eliminate HPV 16/18 and induce histopathologic regression carcinoma of compared to placebo group[232], [233]. Furthermore, GLS-5700 in phase I trial I was also a DNA vaccine encoding premembrane and envelope proteins of Zika virus, which could provide virus-specific antibodies for defensing from Zika virus infection[236].

In brief, for well biosafety and boosting immune responses, rules in nucleic acid-based vaccine design should include: **1)** optimized encoding associated with target proteins/peptides featuring high specificity, biocompatibility and immunogenicity, just similar to the "principle 1)" in protein subunit vaccine; **2)** optimizational delivery or encapsulation technology for better stabilization and transfection efficiency; **3)** considering stroma cells without costimulatory molecules and pro-inflammatory cytokine-secreting competence, also could capture the nucleic acids, translate corresponding Ag and present on their MHC I molecules to serve as tolerogenic "APCs-like" cells, which may lead to Ag-responsive T cell exhaustion or initiate Treg-dependent tolerance induction, thus，appropriate adjuvants (if necessary) and administration dosage, frequency and routes are indispensable to avoid unnecessary (but overwhelming) inflammatory reaction in injection sites and acquire robust Ag-specific responses; **4)** as the complexed and immunosuppressive state in TME, combination immunotherapies should be carefully considered.

4.1.3. DCs-based vaccines

Despite DCs, especially cDC1, are adept at Ag cross presentation and polyfunctional T cell priming, they are regularly excluded in the very early stage of progressive tumor development. Besides, DCs' in vivo generation, migration and maturation are obstructed by the systematic immune tolerance induced by tumor, leading to inadequate tumor-infiltration of immunoreactive cell populations (DCs, NK and CTLs) and

poor clinical outcomes[10], [11]. In fact, according to the meta-analysis results from various human cancers, the pre-existing immune contexture within TME, heterogeneous across patients, may be of significant prognostic value in multiple types of human malignancy[67]. Immunological landscape within TME is gradually regarded as a predictive biomarker of response and sensitivity to several immunotherapies, including immune checkpoint blockade (ICB, e.g. PD-1 mAb) and multiple protein- or T cell-based vaccines therapeutics[3], [27]. In addition, although cancer immunotherapy is an emerging and boomingly evolving field and still making progress, its long-term response rates keep in a modest level around 20–40%[257], which may be largely interrelated to restricted tumor infiltration of tumor-reactive immune cells and their stagnant proliferation in TME during tumor rejection[258]. In these regards, large-scale reinfusion of in vitro expanded and activated DCs that presented diversiform epitopes of TAAs/TSAs, may convert the immunosuppressive immune landscape in TME and favorably facilitate promoted anti-carcinoma responses and rebuild immunological surveillance[3], [243].

In general, the preparation steps of in vitro-generated and -activated DCs vaccines used for adoptive transfer commonly include: **1)** separation and extraction of DC precursor cells, including human allogeneic or autologous $CD34^+$ progenitor cells from BM and $CD14^+$ monocyte progenitors in peripheral blood monouclear cells (PBMCs), which could differentiate into DCs (mainly mo-DCs) via the stimulation of GM-CSF and IL-4[259]; **2)** the pulse of IMP mixture of TAAs/TSAs or autologous tumor lysate (with or without immunogenic adjuvants) to activate immature DCs for cross-presentation of epitopes[241]; **3)** adopting appropriate administration (mainly subcutaneous, intradermal or intravenous injection) to reinfuse the Ags-carrying DCs vaccines (Fig. 6).

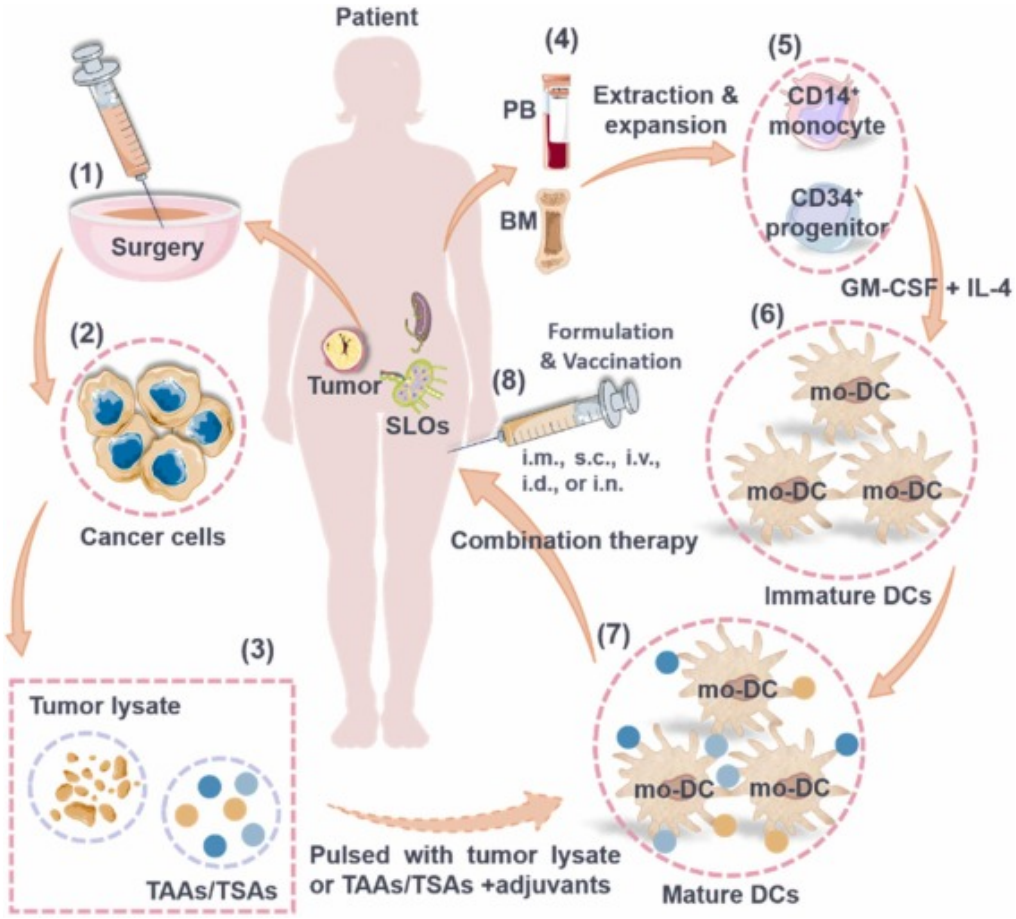

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Fig. 6. Reinfusion of in vitro-derived and activated DCs vaccines. Personalized DCs vaccines employed in anti-cancer therapy are mainly generated from GM-CSF- and IL-4-treated $CD34^+$ progenitors and/or $CD14^+$ mononuclear precursors that extracted from BM and/or PB, and then the differentiated immature mo-DCs would be further pulsed with individualized TAAs/TSAs or tumor lysate for cross presenting more specific Ag epitopes and eliciting tumor-reactive T-cell immune responses. PB: peripheral blood; BM: bone marrow; GM-CSF: granulocyte-macrophage colony stimulating factor.

To be worthy of attention, the antigenic IMP or autologous tumor lysate alone in stimulation DCs and subsequent restoration of the systemic immunity with hyporesponsiveness may be quietly insufficient, because of the complicated immune hostile molecules or cues conspired by tumors to obtain immunologic escape or privilege[153]. For example, the results from a phase III clinical trial and a phase IIb clinical trial associated with mo-DCs respectively pulsed with multiple IMP or autologous tumor lysate in advanced melanoma patients, manifested that no extra superiority or benefit was found compared with the controlled group[244], [245]. Analogously, a phase II research against glioblastoma via reinfusing mo-DCs pulsed with autologous tumor lysate also didn't devote to prolong the overall and progression-free survival

in hosts accepting several doses of indicated DCs vaccines[241]. The dissatisfactory or inadequate anti-tumor curative effect may be partially related to **1)** the inherent deficiency of mo-DCs in CCR7 expression and T cell priming compared the cDCs; and **2)** the systematic immune tolerance or silence[140].

Therefore, to further mobilize adoptive transfer individualized DCs-based vaccines as well as intrinsic or naturally developed DCs in vivo, optimized combinatorial immunotherapy by combining with exogenous chemokines supplement, ICD inducers and ICBs, may be a viable alternative to augment the tumor regression in cancer treatment. For example, intratumoral injection of CCL21-overexpressed autologous mo-DCs could chemotactically attract mature DCs (intrinsic DC subgroups in vivo) entry into TLS within neoplastic lesions and reinstate systemic tumor Ag–specific immune responses in non-small cell lung cancer (NSCLC) patients[242]. Intriguingly, a phase I research against glioblastoma created a novel approach through the pre-condition of potent recall Ags (such as tetanus and diphtheria toxoid) in vaccine sites to heighten the LNs-homing capacity of injected DCs vaccines, and the administration of extra CCL3 further promoted the DC-T crosstalk in LNs, which significantly elevated DCs migration to LNs bilaterally and prominently improved patients' survival[237]. In additional, the combination with ICD inducers (CT and/or RT) could elicite robust TAAs/TSAs- specific immunity in almost half of glioblastoma patients[238], [239], and similar situation happened under the combination therapy composed of IFN-γ, LPS and Audencel-pulsed autologous mo-DCs[240].

In summary, although prospective tolerability, well biocompatibility and immunogenicity profiles, there are still several limitations or insufficiencies in the anti-cancer clinical trials or clinical practices of current DCs-based vaccines[241], [260]. **1)** mo-DCs are the commonest type of DC subset utilized in clinical reinfusion for their relative simplification in manufacturing or expansion in vitro process compared to cDCs, however, their inadequate biological functions in CCR7-modulated SLOs-homing and in vivo IL-12- as well as Ag-cross-presentation-based T cell mobilization, to a great extent, block the initiation of Ag-reactive immunity. As a matter of fact, after local administration (subcutaneous or intracutaneous), most of mo-DCs vaccines would be restricted in injection site and then lose viability or directly undergo apoptosis, which may be eliminated by the inflammatory-infiltrating macrophages soon afterwards[141], whereas some existing Ag transfer behavior may promoting Ag-specific immune responses to a degree[7]. **2)** The *ex vivo* generation process of a pure population of cDCs (particularly cDC1) that characterize robust T cell activation and expansion competence as well as motility ability towards tumor lesions and SLOs, is actually more difficult, expensive, complicated and time-consuming than established manufacturing protocols of mo-DCs, whereas the producing methods of the latter are complexed as well. In fact, the insufficiency of (simply) approaches for the preparation of functional cDC1-like cells has been a significant bottleneck in clinical progression of DCs-based therapeutic cancer vaccines[261]. Besides, it's also quite difficult to guarantee the quality agreement of *ex vivo*-derived DCs between batches. **3)** As an aggressive and progressive immune disorder, cancer could systematically suppress the adaptive as well as the innate immunity via a complex immunosuppressive network composed of tumor cells, tumor stroma cells together with tolerogenic immune cells (including Treg, MDSCs and M2) to provoke dysfunction in DCs and T cells. Consequently, it's hard for exogenous DCs vaccines, nucleic acid vaccines or protein vaccines (even if adjuvants exist) alone to

completely eliminate tumor burden in patients, calling for elaborately orchestrated combinatorial immunotherapies to reactivate malfunctioned DCs and effector cells for synergistically resetting the systemic immune landscape. **4)** Given that immunosuppressive molecules may exist in tumor whole cell lysate, hence, DCs that directly contact with tumor lysate may result in low maturity or tolerogenic phenotypes, and reinfusion of such regulatory DCs vaccine may trigger tumor-reactive effector T cells exhaust and expand the Treg subgroup instead[27], [262].

4.2. Immune tolerance

Conventionally, DCs featuring a stably semi-mature phenotype (anti-inflammatory membrane molecules) as well as immunomodulating attributes (secreting anti-inflammatory products) are termed as tolerogenic DCs (tolDCs), which could amplify the abundance of tolerogenic Treg subtype and delete or exhaust the autoreactive cytotoxic T cells to maintain long-term peripheral tolerance and ameliorate or ease overwhelming autoimmune destruction and GvHD.

Generally, current DCs-participated clinical immunomodulation therapies mainly comprise 1) reinfusion of in vitro-generated tolDCs pulsed with disease-specific Ags with negligible immunogenicity, for further reeducating the immune system in an Ag-specific mode by priming regulatory Ag-specific Treg[123]; and 2) administration of immunosuppressive drugs (such as 1,25-dihydroxyvitamin D3, rapamycin, cyclosporin, tacrolimus, mycophenolate mofetil, and glucocorticoids) to systematically inhibit the maturation of hosts' inherent DCs for reduced LNs-homing and CTLs initiation in vivo.

Clinical trials involving modulating DCs locomotion in vivo for regulatory immunomodulation in anti-inflammation treatment against various chronic-inflammatory or autoimmune diseases as well as GvHD (Table 5, Fig. 7) are displayed herein.

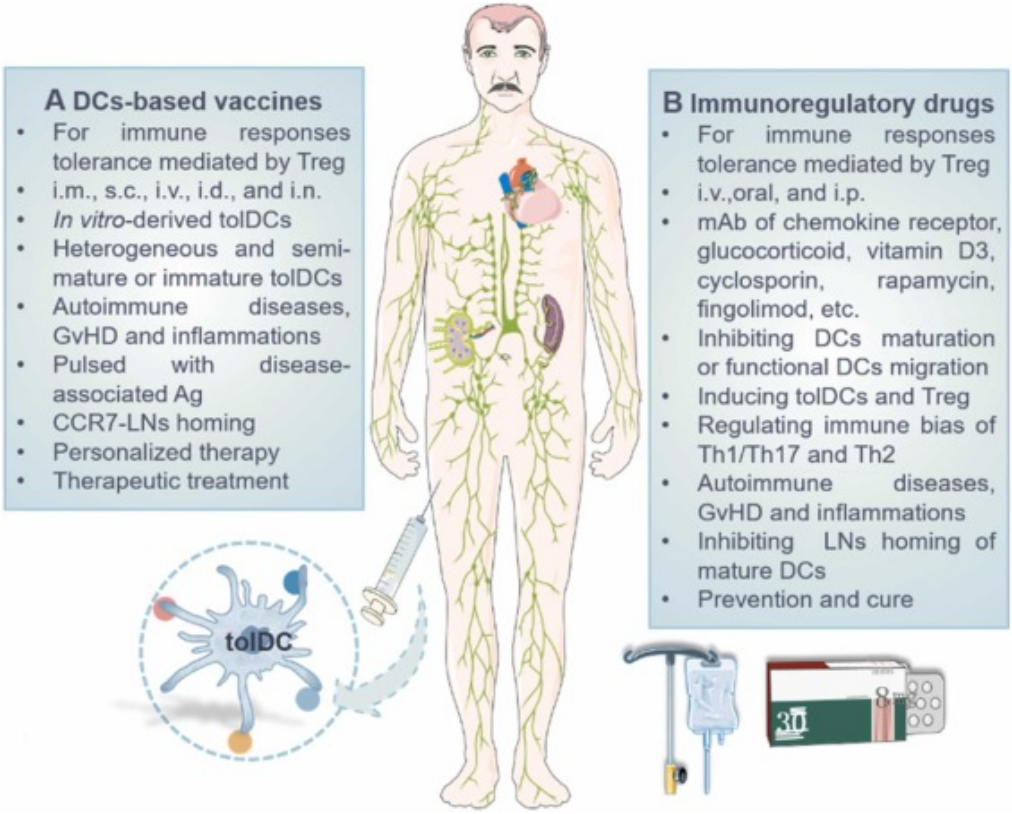

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Fig. 7. Clinical applications of regulating DCs migration for immune tolerance. **(A)** DC-based vaccines. The adoptively transferred DCs vaccines are mainly composed of heterogeneous tolDCs loaded with/without disease-specific Ags for unleashing (Ag-specific) Treg-based tolerance induction and (Ag-specific) effector T cells deletion. Besides, the administration (i.m., i.d. i.v., i.n. and s.c.) of tolDCs could ameliorate the progression of autoimmune diseases, tissue/organic inflammations and GvHD in vivo. **(B)** Immunoregulatory drugs. To 1) inhibit the maturation and migration both towards LNs as well as inflamed focus, 2) induce tolDCs generation in vivo or 3) change the immune bias/balance of Th1/Th17 and Th2 induced by DCs, immunoregulatory drugs are administrated through taking orally, i.v. and i.p. and used to provoke immune tolerance for prevent or treat inflammatory disorders. i.d.: intradermal injection; i.v.: intravenous injection; s.c.: subcutaneous injection; i.n.: intranodal injection; i.m.: intramuscular injection; GvHD: graft versus host disease.

4.2.1. Reinfusion of tolDCs

Direct separation and purification of immature DCs or tolDCs in PBMCs are quite tough, because the infrequent human DC subsets are characterized with immunogenic attributes rather than tolerogenic properties under inflammatory conditions[275]. Fortunately, like the *ex vivo*-derived mo-DCs used in therapeutic anti-tumor vaccines, the protocols to in vitro manufacture tolDCs with hyporesponsiveness

have been described. In brief, during the process of isolated CD14 + or CD34 + mononuclear progenitors differentiate into immature mo-DCs, diversified tolerance-inducing agents or biomolecules are extra added to generate heterogeneous tolDCs, although there exists still no definite consensus on what is the optimal method or how to choose (or combine) complicated immunosuppressive agents to engender superior DC tolerogenicity for optimized anti-inflammation effectiveness[192].

In addition, it is noteworthy that synthetic and endogenous molecules used to trigger tolerogenic features in in vitro-generated mo-DCs, mainly including vitamin D3, rapamycin, minocycline, glucocorticoids, IL-10, TGF-β and ethyl pyruvate[192]. For example, 1,25-dihydroxyvitamin D3 has been recently reported to induce stable and reproducible therapeutic tolDCs via differential DNA methylation modification in DCs' metabolic and immune pathway[276]. Intriguingly, in a phase I clinical research, antisense ODNs targeting co-stimulating molecules (CD40, CD80 and CD86) were employed to pre-treat autologous mo-DCs for a stable and immature phonotype, although the intradermal reinfusion of such DCs-based vaccine seemed to not arouse any significant clinical effect in patients bearing type 1 diabetes[263]. Moreover, intraperitoneal injection of dexamethasone (Dex)-induced autologous tolDCs has been proved to polish up life quality in 3/9 Crohn's disease patients because of the augmentation of circulating Treg and the reduction of IFN-γ concentration[264].

Besides, immunomodulatory tolDCs exposed to specific autoantigens or inflammatory disease-associated Ags could potentiate the ability to suppress persistent inflammation by reeducating the immune system in an Ag-specific manner[123], [266]. For instance, a phase I clinical trial against rheumatoid arthritis (RA) generated a 4 citrullinated peptide Ags pulsed autologous tolDC vaccine that was modified with an NF-κB inhibitor, whose intracutaneous administration evidently enlarged the ratio of regulatory to effector T cells and crippled the concentration of pro-inflammatory IL-15, IL-29, CX3CL1 and CXCL11 (the guidance cue secreted by activated DCs to recruit NK and effector T cells) in serum[266]. Furthermore, without the participant of adjuvants with potent immunogenicity, the tolDCs respectively pulsed with proinsulin peptide C19-A3, aquaporin-4 or myelin-derived peptides could protect the hosts from destructive autoimmunity by eliciting disease-specific Treg-based IL-10 production in patients bearing type 1 diabetes, neuromyelitis opticaspectrum disorders or multiple sclerosis[123], [267].

In summary, opposite to keep immunological function of therapeutic DCs vaccines under systemic immunosuppressive condition in neoplasms, how to maintain the immunomodulatory characteristics in adoptively transferred tolDCs-based vaccines in inflammatory environment is the pivotal role or one of the biggest challenges to ameliorate or cure chronic-inflammation, autoimmune diseases and GvHD[275]. However, mature DCs are the crime culprits in orchestrating persistent Ag-specific inflammation disorders in vivo, and the multifarious inflammatory stimulus in vivo may convert exogenous semi-mature DCs into activated DCs with effector T cells initiation competence, which may face the risk to increase instead of easing the burden of intrinsic inflammation[265]. Consequently, both of understanding the mechanisms that underlie stable immunoregulatory properties in DCs and further optimizing the protocols for yielding disease Ag-specific tolDCs-based vaccines with preserved semi-mature or immature immunological

features even when facing inflammatory stimulations are prominent.

4.2.2. Administration of immunosuppressive drugs

Commonly, the mechanisms of immunosuppressive drugs applied in clinical practice and researches to ameliorate pernicious inflammation-provoked chronic or acute organ-inflammation, autoimmune diseases and GvHD, mainly involve **1)** impeding the inflamed focus-infiltration of activated DCs and effectors to cripple the Ags capture and cross presentation and in situ effectors (re)stimulation and expansion, and **2)** directly hampering the SLOs-homing competence of mature DCs (or inducing generation of semi-mature tolDCs by repressing DCs activation) as well as the succedent effectors' and memory cells' egress from efferent lymphatic. Briefly, such intervention measures include: **1)** multifarious immunosuppressive drugs or molecules to generate heterogeneous tolDCs in vivo, such as ethyl pyruvate, acetylsalicylic acid, glucocorticoid, vitamin D3, cyclosporin, rapamycin, fingolimod[268], [275]; **2)** chemokine receptor blockade or downregulation via administration of mAb and transcriptional interference agents, such as CCR5 mAb and IFN-β1b[168], [269], [272], [273].

For instance, fingolimod, a manufactured analogue of sphingosine and a functional antagonist at all S1PRs, could block S1P- $S1PR_{1-5}$ system-mediated DCs chemotactic migration to LNs and modulate the redistribution of lymphocytes by restricting the egress of T cells from thymus and lymph nodes[39], [40], [277]. And a phase III clinical trial displayed that oral fingolimod (FTY7200) could hinder DCs maturation and migration, thus, abating the annualized relapse rate in 2 years[268]. Moreover, hydroxychloroquine and chloroquine, which are serendipitously and empirically for various rheumatic diseases treatment, could restrain DCs mature and CTLs priming in SLOs and abused tissues though hampering TLR signals transmission and competent cytokines secretion of stimulated DCs[274]. In addition, classical IFN-β1b therapy against relapsing multiple sclerosis has been proved could obstruct significant chemokine receptor CXCR4 mRNA transcription on mo-DCs and monocyte progenitors, hence, disturbing the CXCL12-CXCR4 axis-based inflammatory infiltration within CNS and in situ differentiation of mo-DCs[168], [269], [272]. Considering that the detection of upregulated CCR5 on CD16 + myeloid blood DC subgroup could be deemed as a vital biomarker before the clinical diagnosis of GvHD[57], a phase II research manifested that extended CCR5 blockade could provide an effective protection from acute and chronic GvHD after transplant surgery[273].

Specially, Glatiramer acetate (Copaxone®, co-polymer 1) functions in an attractive and especial fashion, which could regulate the biological phenotypes in activated DCs to manipulate mature DCs (instead of semi-mature tolDCs)-mediated bias or balance of Th1 (or Th17)/Th2 by engendering DCs-based counterinflammatory Th2- partiality immune microenvironment to support Th2 differentiation rather than morbigenous Th1 or Th17, which has been proved to reduce the number of enhancing lesions and lesion volume as well as decrease the recurrence rate in (relapsing) multiple sclerosis populations[270]. Similarly, a phase III trial showed that laquinimod also seemed to transform the activation mode of DCs from Th1/Th17 inducer to relative anti-inflammatory Th2 inducer[271]. Therefore, elegantly manipulating

maturity or mature characteristics of DCs (rather than crudely inhibiting DCs activation) to re-modulate the T cell differentiation rate of Th1(or Th17)/Th2/Treg in inflamed foci, may be a potential contributor to impede the exacerbation of auto-inflammation associated disorders and re-build the immune homeostasis in hosts.

5. Conclusions and prospects

As the cardinal elicitors of T-cell responses, DCs, which inherently feature multifunctional biological properties and diversified migration modes, orchestrate immune amplification and immune tolerance in specific humoral and cellular immunity. DCs' in vivo positioning and migratory behavior toward SLOs or inflamed regions, actually possess a considerable application value in vaccine design or clinical therapy against carcinomas, infections and inflammatory disorders. This paper herein systematically reviews the existing mechanisms and modulation strategies in laboratory as well as in clinical applications (or researches) to regulate chemotaxis of endogenous DCs and exogenously reinfused DCs vaccines, proposes the inadequacy or deficiency of current researches, and also presents certain suggestions for further development or design of clinical practice in regulating DCs in vivo mobilization manner. However, up to now, it has still not completely unveiled the complicated mechanistic understanding that in vivo manipulate DCs diverse mobilization fashions (especially towards inflamed sites, such as TME and autoimmune foci). Consequently, more efforts and attentions are required for more comprehensive understanding in diversiform motility modes and modulators of DCs and their mononuclear precursors under physiological and immunosuppressive or inflammatory pathological conditions, which may devote to a better clinical outcome no matter under malignancies, viral/bacterial infections and chronic or acute inflammation.

Furthermore, to find a better strategy to intelligently modulate DCs' in vivo chemotaxis behavior for various diseases treatment or DCs-based vaccine design, there are several major issues remains unsolved. **1)** Considering mo-DCs are the most frequently-used DC subtype in preclinical researches and clinical applications, for maximize the T-cell activation efficiency in anti-tumor treatment, how to overcome the inherent deficiency of CCR7 expression and T cell priming in mo-DCs? **2)** What is the most precise bio-distribution kinetics of injected exogenous mo-DCs under different route of administration (e.g. i.v., s.c., i.n., i.d.)? **3)** Does all the underlying mechanisms involving different DC subsets directional migration have been revealed, especially towards SLOs specific compartment and multiple inflammatory regions? **4)** How to realize the industrialized manufacture of cDCs with better SLO-homing competence and T-cell initiation ability, for more efficacious anti-tumor and anti-virus therapies? Similarly, how to formulate viable protocols to manufacture tolDCs with maintained hyporesponsiveness in anti-autoimmunity therapies? **5)** How to overcome the influence of immunosuppressive landscape in TME? How to maintain the immunomodulatory features of refused tolDCs and prevent tolDCs converting into self-reactive activated DC species in the pro-inflammatory microenvironment filled with the inflammatory molecules in patients suffering from autoimmune diseases? **6)** How does DCs intercommunicate with either other APCs or non-APCs (mainly somatic cells, e.g. keratinocytes and myocytes) in the localized vaccination sites? Do such

immunological intercommunications impact the immune amplification or tolerance induction?

In these regards, continued research into the detailed biological and immunological mechanisms of diversified DC subgroups chemotaxis in pathological and physiological conditions, may contribute to preclinical studies and clinical transformations in multiple immune-associated disorders treatment.

CRediT authorship contribution statement

Yichao Lu: Conceptualization, Writing – original draft, Writing – review & editing. **Jian You**: Conceptualization, Writing – review & editing, Funding acquisition. All authors participated in the discussions of the results.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81973246, 82003667 and 82273862) and Zhejiang Province Public Welfare Project LGF22H300003.

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