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Medicine

Targeting tumor-associated macrophages: Novel insights into immunotherapy of skin cancer

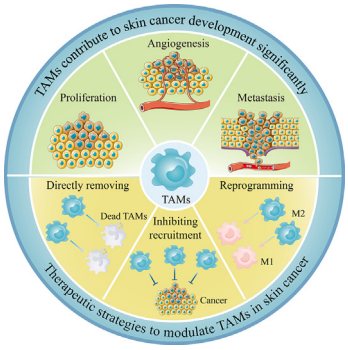
Jun Liu [a,c,1], Jiaye Lu [b,c,1], Ling Wu [a,c], Tingrui Zhang [a,c], Junchao Wu [b,c], Lisha Li [b,c], Zongguang Tai [a,c,*], Zhongjian Chen [a,c,*], Quangang Zhu [a,c,*]

[a] Shanghai Skin Disease Hospital, School of Medicine, Tongji University, 1278 Baode Road, Shanghai 200443, China
[b] School of Medicine, Shanghai University, 99 Shangda Road, Shanghai 200444, China
[c] Shanghai Engineering Research Center of Topical Chinese Medicine, 1278 Baode Road, Shanghai 200443, China

HIGHLIGHTS

- The latest immunotherapeutic strategies for skin cancer are highlighted, with a special focus on tumour-associated macrophages (TAMs).
- Interactions between TAMs and immune cells are discussed, underlining the key role of TAMs in shaping the immunosuppressive microenvironment.
- The paper comprehensively analyzes the origin, classification, and functions of TAMs, shedding light on their crucial role in skin cancer.
- Targeting TAMs as a novel immunotherapy strategy sheds new light on the treatment of skin cancer.
- Immunotherapy strategies centred on TAMs could complement existing

GRAPHICAL ABSTRACT



Abbreviations: **APCs**, antigen-presenting cells; **ARL**, adenosine diphosphate-ribosylation factor-like; **ATC**, anaplastic thyroid cancer; **BCC**, basal cell carcinoma; **BFGF**, basic fibroblast growth factor; **BTC**, biliary tract cancer; **CAF**, scancer-associated fibroblasts; **CCL2**, C–C motif chemokine 2; **CCL5**, C–C motif chemokine 5; **CCR**, CC chemokine receptor; **CCR2**, CC chemokine receptor-2; **CM**, cutaneous melanoma; **COX-2**, cyclooxygenase-2; **CRC**, colorectal cancer; **cSCC**, cutaneous squamous cell carcinoma; **CSF-1**, colony stimulating factor 1; **CTLA-4**, cytotoxic T lymphocyte-associated antigen-4; **CTLs**, cytotoxic T cells; **CX3CL1**, C-X3-C motif chemokine ligand 1; **CX3CR1**, C-X3-C motif chemokine receptor 1; **CXCL2**, C-X-C motif chemokine ligand 2; **DCs**, dendritic cells; **EAF2**, ELL-associated factor 2; **EC**, endometrial carcinoma; **ECM**, extracellular matrix; **EGF**, epidermal growth factor; **EMPD**, extramammary Paget's disease; **EMT**, epithelial-mesenchymal transition; **ERK**, extracellular signal-regulated kinase; **GAB3**, growth factor receptor-bound protein 2-associated binding protein 3; **GIST**, gastrointestinal stromal tumor; **GM-CSF**, granulocyte–macrophage colony stimulating factor; **G-MDSCs**, granulocytic myeloid-derived suppressor cells; **HCC**, hepatocellular carcinoma; **HIF1α**, hypoxia-inducible factor 1α; **HNSC**, squamous cell carcinoma of the head and neck; **ICAM-1**, intercellular adhesion molecule-1; **ICIs**, immune checkpoint inhibitors; **IDO1**, indoleamine 2,3-dioxygenase 1; **IFN-γ**, interferon gamma; **IL**, interleukin; **IL-15Rα**, IL-15 receptor α subunit; **ILC1**, innate lymphoid cells; **IRF4**, interferon regulatory factor 4; **KCs**, keratinocyte carcinoma; **LAG-3**, lymphocyte-activation gene 3; **LIF**, leukocytosis-inducing factor; **LPS**, lipopolysaccharide; **MCC**, merkel cell carcinoma; **MDSCs**, myeloid-derived suppressor cells; **MHC-I**, major histocompatibility complex class I; **MHC-II**, major histocompatibility complex class II; **MIP-1α**, macrophage inflammatory protein-1α; **M−MDSCs**, monocytic MDSCs; **MMP**, metalloproteinase; **MPE**, malignant pleural effusion; **NETs**, neuroendocrine tumors; **NFAT1**, nuclear factor of activated T cells; **NK cells**, natural killer cells; **NMSC**, non-melanoma Skin Cancer; **NSCLC**, non-small cell lung cancer; **OPN**, osteoblastin; **PCA**, pancreatic cancer; **PD-1**, programmed cell death-1; **PDGF**, platelet-derived growth factor; **PD-L1**, programmed cell death-Ligand 1; **PGE2**, prostaglandin E2; **PP-ALL**, plexiformprecursor cell lymphoblastic leukemia-lymphomleukemia; **PROK2**, prokineticin-2; **PTCLs**, peripheral T cell lymphoma; **PVNS**, pigmented villonodular synovitis; **RANK**, receptor activator of nuclear factor-kappa B; **RANKL**, receptor activator of nuclear factor-kappa B ligand; **RCC**, renal cell carcinoma; **ROS**, reactive oxygen species; **SCLC**, small cell lung cancer; **SH2**, src homology region 2; **STS**, soft tissue sarcoma; **TAMs**, tumor-associated macrophages; **TGCT**, tenosynovial giant cell tumor; **TGF-β**, transforming growth factor-beta; **Th**, helper T cell; **TIM-3**, T cell immunoglobulin domain and mucin domain-3; **TLR**, toll-like receptor; **TME**, tumor microenvironment; **TNBC**, triple negative breast cancer; **TNF-α**, tumor necrosis factor-alpha; **Tregs**, regulatory T cells; **TREM-1**, triggering receptor expressed on myeloid cells-1; **TREM-2**, triggering receptor expressed on myeloid cells-2; **VEGF**, vascular endothelial growth factor.

* Corresponding authors at: Shanghai Skin Disease Hospital, School of Medicine, Tongji University, 1278 Baode Road, Shanghai 200443, China.
E-mail addresses: taizongguang@126.com (Z. Tai), aajian818@163.com (Z. Chen), qgzhu@126.com (Q. Zhu).

[1] **Jun Liu** and **Jiaye Lu** contributed equally to this work.

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treatments for skin cancer and show excellent prospects.

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ABSTRACT

Background: The incidence of skin cancer is currently increasing, and conventional treatment options inadequately address the demands of disease management. Fortunately, the recent rapid advancement of immunotherapy, particularly immune checkpoint inhibitors (ICIs), has ushered in a new era for numerous cancer patients. However, the efficacy of immunotherapy remains suboptimal due to the impact of the tumor microenvironment (TME). Tumor-associated macrophages (TAMs), a major component of the TME, play crucial roles in tumor invasion, metastasis, angiogenesis, and immune evasion, significantly impacting tumor development. Consequently, TAMs have gained considerable attention in recent years, and their roles have been extensively studied in various tumors. However, the specific roles of TAMs and their regulatory mechanisms in skin cancer remain unclear.

Aim of review: This paper aims to elucidate the origin and classification of TAMs, investigate the interactions between TAMs and various immune cells, comprehensively understand the precise mechanisms by which TAMs contribute to the pathogenesis of different types of skin cancer, and finally discuss current strategies for targeting TAMs in the treatment of skin cancer.

Key scientific concepts of overview: With a specific emphasis on the interrelationship between TAMs and skin cancer, this paper posits that therapeutic modalities centered on TAMs hold promise in augmenting and harmonizing with prevailing clinical interventions for skin cancer, thereby charting a novel trajectory for advancing the landscape of immunotherapeutic approaches for skin cancer.

Contents

Introduction

In recent years, the incidence of skin cancer has shown a significant increase. Global cancer statistics for the year 2020 reported over 1.5 million new cases of skin cancer worldwide, resulting in approximately 120,000 deaths[1]. Recent predictions by the American Cancer Society estimate that over 100,000 new cases of skin cancer will be diagnosed, with the number of related deaths exceeding 12,000 in the United States in 2023, based on the most recent data available for the country in 2022[2]. The escalating incidence of skin cancer, as indicated by these alarming figures, undoubtedly reflects a concerning upward trend, posing substantial challenges to human life and healthcare systems worldwide[3].

In general, skin cancer can be broadly categorised into two main groups: Cutaneous Melanoma (CM) and Non-melanoma Skin Cancer (NMSC) [4,5]. NMSC includes the two most common types, Basal Cell Carcinoma (BCC) and Cutaneous Squamous Cell Carcinoma (cSCC), originating from the keratinocytes in the epidermis. To differentiate them from other skin cancer types like Merkel cell carcinomas (MCC), Paget's disease, cutaneous lymphomas, and cutaneous adnexal tumors, the collective term "keratinocyte carcinoma (KCs)" is increasingly used to refer to BCC and cSCC. This terminology aids in distinguishing BCC and cSCC from other primary NMSCs[5,6]. Noteworthy is the rising trend in the prevalence of KCs, particularly BCC and cSCC, despite their already high occurrence. BCC has shown a significant increase, and some studies predict further rises at rates of 23 % in males and 29 % in females in the coming years. This underscores the importance of sustained efforts in the prevention, early detection, and effective management of these skin cancer[7–10]. In contrast to the relatively low incidence, accounting for only 4 % of all skin cancer, CM is responsible for a disproportionate number of skin cancer deaths, constituting approximately 75 % of such deaths [11]. Estimates from the American Cancer Society project that around 97,610 individuals may be diagnosed with new cases of CM in the United States alone in 2023, with approximately 7,990 deaths attributed to CM in the same year[2].

For skin cancer, the conventional treatment options include surgical procedures, radiotherapy, and chemotherapy. Among these, surgical treatment is generally regarded as the primary standard of care for curing early-stage, non-metastatic skin cancer[12–14]. However, for metastatic and advanced CM, the efficacy of surgical treatment is limited[12]. Indeed, for patients deemed inoperable or unable to undergo surgery, traditional therapies may prove insufficient for disease management. Fortunately, there is promising progress in the field of immunotherapy, specifically with the development of immune checkpoint inhibitors (ICIs), such as programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors. These ICIs have ushered in a new era for skin cancer patients, providing novel treatment options, prolonged survival rates, and improved quality of life[15–17]. It is true that among various types of tumors, skin cancer have demonstrated remarkable sensitivity to immunotherapy. This can be attributed to their distinctive immunogenicity, which encompasses several factors: a prominent tumor mutation load, heightened expression of tumor antigens, or the presence of viral antigens. The unique immunogenicity of skin tumors, particularly CM, has made them a paradigm for studying tumor-immunity interactions[15,17]. However, the intricate tumor microenvironment (TME) within tumor tissues exerts a potent immunosuppressive effect, making it challenging to achieve desired therapeutic outcomes with existing immunotherapeutic drugs. This difficulty arises from the limited efficacy of these drugs or the development of resistance against them, significantly hampering the attainment of satisfactory results in treatment [18,19].

It is widely acknowledged that macrophages, essential components of the innate immune system, possess the capability to engulf foreign substances and play a pivotal role in defending against microbial infections, maintaining internal homeostasis, and safeguarding the body. However, within the TME, macrophages undergo functional and phenotypic transformations, giving rise to tumor-associated macrophages (TAMs), a significant component of the TME[20,21]. Numerous research studies have provided compelling evidence suggesting a strong correlation between the presence and activity of TAMs and tumor progression. High levels of TAMs infiltration are frequently associated with unfavorable prognoses in malignant tumors. Therefore, investigating the origins and functions of TAMs to modify their activity and function becomes imperative for reshaping the regulatory mechanisms of the TME and developing effective antitumor therapies [20,21]. In recent years, our understanding of the mechanism and regulation of TAMs in various malignancies has grown, particularly in breast cancer, hepatocellular carcinoma and lung cancer, where the role of TAMs has been extensively elucidated[22–25]. So, in what way exactly do TAMs exert their influence in skin cancer?

With such queries in mind, this article aims to provide a concise overview of the origin and types of TAMs and their intricate interaction with other immune cells. Additionally, it will outline the role of TAMs in various skin cancer, while also delving into novel therapeutic approaches, including immunotherapy strategies targeting TAMs, for the treatment of skin cancer.

The origin and classification of TAMs

Origin of TAMs

As scientists explore the origins of cells, the long-standing notion that macrophages are continually regenerated by monocytes in the bone marrow has been debunked. Instead, recent research indicates that several tissue-resident macrophages originate from embryonic precursor cells such as yolk-sac-derived macrophages, which function to maintain normal life activities across a wide range of tissues[26–29]. Regarding TAMs, it is generally accepted that they primarily originate from peripheral inflammatory monocytes. These monocytes are stimulated by tumor-secreted cytokines (such as colony stimulating factor 1 (CSF-1) and vascular endothelial growth factor (VEGF) family members) and chemokines (such as C–C motif chemokine 2 (CCL2) and CCL5). Subsequently, they traverse the bloodstream and infiltrate tumor tissues, where they undergo further differentiation into TAMs[30–33]. CSF-1 plays a pivotal role in attracting monocytes to the tumor tissue, enhancing macrophage viability, and driving the polarisation of TAMs towards an immunosuppressive phenotype[34]. Unlike CSF-1, granulocyte–macrophage colony stimulating factor (GM-CSF) not only facilitates macrophage proliferation but also triggers the activation of macrophage functions associated with anti-tumor activity[35,36].

Recent studies have highlighted that TAMs can also emerge from the significant expansion of macrophages inhabiting healthy tissues. A subset of these macrophages already exists in the tissue surrounding the tumor and, upon stimulation by tumor-associated elements, proliferate and differentiate into TAMs that function within the TME[37,38]. Despite the recognition of TAMs' dual cellular origins, i.e., from both monocyte and embryonic precursor cell sources, their distinct roles in tumorigenesis and progression are still not well understood[30].

Moreover, a significant class of peripheral precursor cells for TAMs has been identified as monocyte-related myeloid-derived suppressor cells (M−MDSCs). These myeloid leukocytes possess immunosuppressive properties and play a crucial role in

modulating immune responses[39]. MDSCs can be divided into two primary groups: monocyte-associated MDSCs and granulocyte-associated MDSCs. This classification is based on distinct surface markers, $Ly6C^+/Ly6C^-$ and $Ly6C^-/Ly6G^+$. Similar to other major TAMs populations, M−MDSCs have the potential to undergo differentiation into TAMs in response to various chemokines[40]. The downregulation of the transcription factor STAT3 plays a crucial role in facilitating the transition of M−MDSCs into fully mature TAMs[41].

In summary, it is evident that the origins of macrophages and TAMs are intricate and not fully comprehended, necessitating further comprehensive studies for a clearer and unambiguous understanding.

Classification of TAMs

Macrophages, pervasive in vivo, delineate into two principal activation phenotypes: classically activated macrophages (M1-like macrophages) and alternatively activated macrophages (M2-like macrophages), based on their functionality and phenotype. Toll-like receptor (TLR) agonists, exemplified by bacterial products such as lipopolysaccharide (LPS) and Th1-type cytokines like interferon-gamma (IFN-γ), elicit the polarisation of TAMs towards M1-like macrophages. The polarised M1-like macrophages assume a role in instigating a Th1-type immune response for innate host defence functions, inclusive of inflammatory response, pathogen clearance, and antitumor immunity. This is realised by (i) expressing copious major histocompatibility complex class I and II molecules (MHC-I and MHC-II), CD80, and CD86 for efficient antigen presentation; (ii) generating an array of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-12, IL-23, and tumor necrosis factor-alpha (TNF-α); and (iii) liberating inflammatory mediators like reactive oxygen species (ROS) and nitric oxide[42–44].

In contrast, M2-like macrophages predominantly undergo polarisation in response to Th2 cytokines (e.g., IL-4, IL-10, and IL-13), pivotal for Th2-mediated immune responses. This polarisation significantly influences various physiological processes, encompassing angiogenesis, anti-inflammatory mechanisms, wound healing, tissue remodelling, and immune modulation[44]. M2-like macrophages are demarcated by their expression of the mannose receptor (CD206), scavenger receptor, and diminished levels of MHC-II, among other markers. They secrete an array of molecules, including matrix metalloproteinase-9 (MMP-9), arginase-1, VEGF, PGE2, and several anti-inflammatory cytokines (e.g., IL-10, IL-13, and transforming growth factor-beta (TGF-β)), and assume a pivotal role in tumorigenesis via diverse mechanisms[43,44]. Consequently, M1-like macrophages are commonly conceptualised as "beneficial cells" proficient in anti-tumor functions, whereas TAMs, epitomised by M2-like macrophages, are perceived as a subset of "detrimental cells" contributing to the promotion of tumor development.

Notably, in recent years, there has been growing evidence suggesting that cellular metabolic processes play a significant role in inducing phenotypic changes in TAMs, consequently impacting their function. Specifically, glucose metabolism, lipid metabolism, and mitochondrial metabolism have emerged as key players in this context[45–47]. For instance, M2-like TAMs have been shown to exhibit heightened intracellular glucose metabolism and secrete substantial amounts of arginase-1, both of which contribute to tumor development[48,49]. However, the precise mechanisms through which these metabolic processes influence the phenotype and function of TAMs remain unclear, necessitating further investigation. It is imperative to underscore the considerable plasticity exhibited by TAMs. The two macrophage subtypes manifest adaptability, undergoing transformations reciprocally in response to alterations within the TME or therapeutic interventions. Consequently, TAMs seldom manifest a singular M1 or M2 phenotype. Hence, a simplistic classification into the two aforementioned primary categories proves inadequately comprehensive to fully encapsulate the intricacies of TAMs behaviour[50]. Consequently, concerted efforts by researchers have been directed towards refining the classification of M2-like macrophages into subtypes such as M2a, M2b, M2c, and M2d. Specifically, macrophages stimulated by Th2 cytokines such as IL-4 and IL-13 tend to transition into the M2a phenotype, thereby exhibiting Th2 immune functions. Conversely, the presence of TLR ligands and immune complexes induces the generation of M2b macrophages, which play a role in immunomodulation. Furthermore, stimulation by IL-10 and TGF-β promotes the development of M2c macrophages, responsible for tissue remodelling and immunomodulation. Finally, M2d macrophages, activated by IL-6, Leukocytosis-Inducing Factor (LIF), and various cytokines and growth factors within the TME, demonstrate immunosuppressive and tumor-promoting effects[44,50]. In consideration of the functional parallels shared between M2-like macrophages in tumor tissues and the M2d phenotype, it has been posited that M2-like macrophages present at the tumor site could be identified as the M2d subtype[44,50] (Fig. 1). Unfortunately, despite these refinements augmenting our understanding of TAMs, the intricate dynamics of TAMs indicate that the extant classification falls short of fully encompassing their characteristics. Consequently, more sophisticated methodologies are requisite to unravel the diverse subtypes and functions of TAMs[51,52]. Taking into account all these factors, this paper will adhere to the conventional dichotomy and classify TAMs into M1-like and M2-like macrophages.

Interactions between TAMs and immune cells

TAMs and $CD8^+$ T cells

$CD8^+$ T cells, also known as cytotoxic T cells (CTLs), play a critical role as immune effector cells in the immune system. They are crucial for effectively combating infectious pathogens, controlling tumor growth, and maintaining immune homeostasis. However, within an immunosuppressive TME, $CD8^+$ T cells often face challenges in executing their original cytotoxic functions. Notably, TAMs, which are major components of the TME, significantly contribute to its immunosuppressive properties. Hence, it is essential to address the impact of TAMs on the functionality of $CD8^+$ T cells within the TME.

TAMs exert interference on the normal functioning of $CD8^+$ T cells through direct contact. They express ligands for immune checkpoints, such as PD-1, CTLA-4, T cell immunoglobulin domain and mucin domain-3 (Tim-3), and Lymphocyte-activation gene 3 (LAG-3). Once these ligands engage their corresponding receptors on the surface of $CD8^+$ T cells, they trigger apoptosis or functional impairment by negatively regulating signalling pathways associated with immune cells. As a result, the immune response is suppressed. Binding of these ligands to T cell receptors leads to the negative regulation of immune cell-related signalling pathways, inducing apoptosis or functional loss of $CD8^+$ T cells and ultimately dampening the immune response [53–55]. In an endeavour to revive the dormant $CD8^+$ T cells and restore their immune cytotoxicity against tumor cells, researchers have developed diverse monoclonal antibody drugs targeting immune checkpoints. These interventions aim to counteract the inhibitory signals imposed on $CD8^+$ T cells. However, it is important to note that the effectiveness of ICIs is limited to tumors infiltrated by a substantial number of $CD8^+$ T cells, and their usage may lead to unintended consequences such as uncontrolled inflammation and drug resistance. Consequently, there is a growing emphasis on comprehending the specific impact of TAMs on $CD8^+$ T cells within the TME. This research direction holds significant promise in advancing our understanding of the complex interplay between

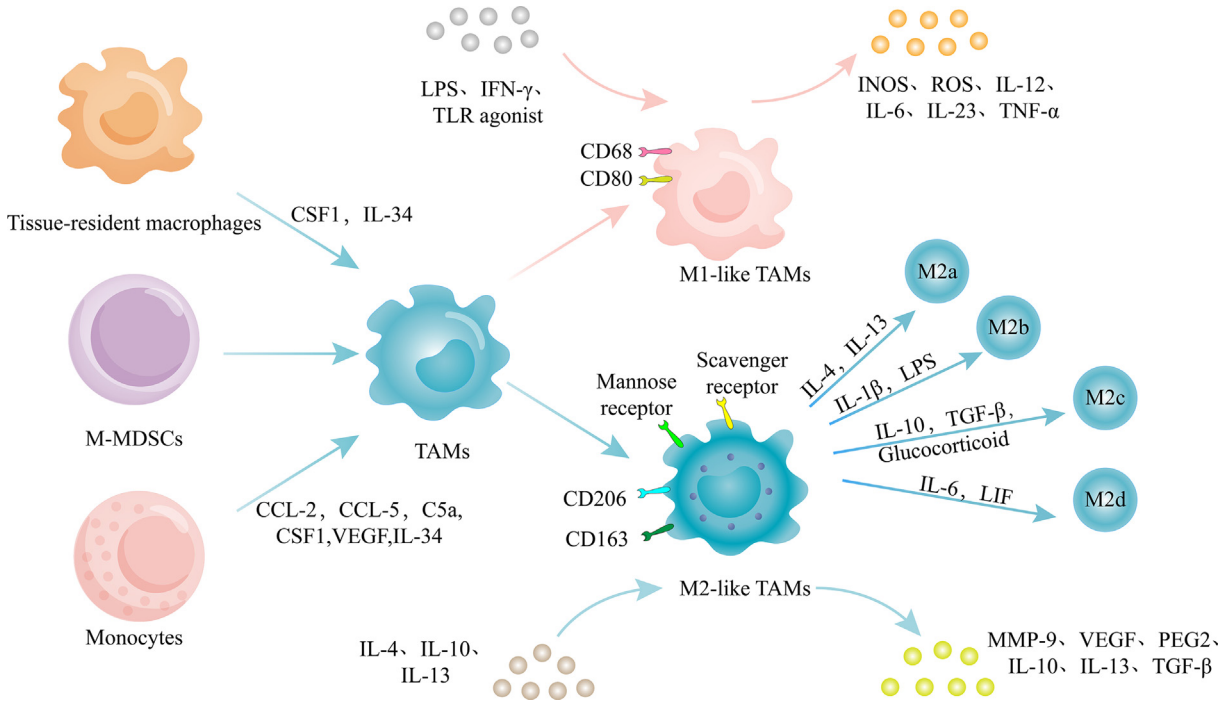

Fig. 1. Schematic representation illustrating the origin and categorization of TAMs. TAMs originate from three primary sources: tissue-resident macrophages, MDSCs, and monocytes. Upon stimulation by cytokines or chemokines, such as CSF-1, IL-34, CCL-2, etc., these cells undergo a transformation into TAMs. Subsequently, TAMs manifest diverse phenotypes influenced by polarisation, specifically differentiating into M1-like and M2-like macrophages, each assuming distinct roles. Moreover, M2-like macrophages can be further subdivided into four subtypes: M2a, M2b, M2c, and M2d.

TAMs and $CD8^+$ T cells[56]. Apart from the aforementioned molecules, there potentially exist numerous undiscovered mechanisms that facilitate direct interactions between macrophages and $CD8^+$ T cells. Consequently, targeting specific surface markers involved in the interaction between TAMs and $CD8^+$ T cells has emerged as a promising strategy to counteract the immunosuppressive microenvironment. This approach holds significant potential for reversing the inhibitory effects and fostering a more favourable immune response against tumor cells.

On the flip side, TAMs establish indirect interactions with $CD8^+$ T cells through the secretion of diverse cytokines and modulation of metabolic pathways. This indirect association effectively hampers the activation, proliferation, and tumor-killing capacity of $CD8^+$ T cells. A notable example is the substantial release of arginase-1 by TAMs. As its name implies, arginase-1 breaks down and metabolises arginine, an essential amino acid necessary for T-cell activation and proliferation. Consequently, augmented expression of arginase-1 actively impairs the function of activated $CD8^+$ T cells, further diminishing their effectiveness in combating tumor cells[57,58]. Simultaneously, tumor cells stimulate the upregulation of IL-15 receptor α subunit (IL-15Rα) in macrophages. Subsequently, IL-15Rα-expressing TAMs impede the recruitment of $CD8^+$ T cells from tumor tissues through the release of the IL-15/IL-15Rαcomplex. Additionally, TAMs, under the mediation of hypoxia-inducible factor 1α (HIF-1α), reduce the protein level of C-X3-C motif chemokine ligand 1 (CX3CL1) in tumor cells. This concerted action further contributes to the inhibition of $CD8^+$ T cell infiltration into the TME[59]. Likewise, within the hypoxic TME, the HIF1α triggers the upregulation of triggering receptor expressed on myeloid cells-1 (TREM-1) present in TAMs. This subsequent surge in TREM-1 expression leads to a reduction in the release of granzyme B and perforin from TREM-1^+ TAMs. As a result, apoptosis is induced, and the cytotoxic function of $CD8^+$ T cells becomes impaired[60]. Fortunately, the field of epigenetics has brought forth fresh research perspectives regarding the interplay between TAMs and $CD8^+$ T cells. Notably, recent studies have indicated that interfering with RNA N6-adenosylmethyltransferase in TAMs results in the dysfunction of $CD8^+$ T cells. This discovery offers new avenues for exploration and sheds light on the intricate relationship between these immune cell populations[61]. Consequently, the pursuit of molecules in TAMs responsible for inducing $CD8^+$ T cell suppression holds immense promise as a viable immunotherapeutic strategy. Such an approach may prove efficacious in breaking the immune tolerance induced by TAMs and reviving $CD8^+$ T cell-mediated tumor clearance.

Overall, TAMs possess the ability to impede $CD8^+$ T cell function through both direct physical interactions and indirect means such as cytokine secretion and metabolic pathway modulation. However, the precise mechanisms underlying $CD8^+$ T cell inhibition by TAMs remain elusive. Unravelling the impact of TAMs on $CD8^+$ T cell functionality is crucial for comprehending tumor immune evasion mechanisms and guiding the advancement of effective immunotherapeutic approaches against cancer.

TAMs and $CD4^+$ T cells

$CD4^+$ T cells, distinguished by the CD4 surface marker, play a crucial role in the immune system by assisting in the activation of B cells and $CD8^+$ T cells through recognition and binding of antigens and MHC-II molecules on antigen-presenting cells (APCs) [62,63]. Upon activation, $CD4^+$ T cells can differentiate into various subpopulations, including helper T cells (Th1, Th2, Th17, etc.) and regulatory T cells (Tregs), each with distinct functions such as promoting cellular immune responses, modulating inflammatory responses, and maintaining immune homeostasis[62,63].

The presence of infiltrating $CD4^+$ T cells in the TME indicates a favorable prognosis, while an increase in M2 macrophages suggests a poorer prognosis[64], prompting focused research on elucidating the specific roles of these cell types and their underlying mechanisms. Interactions between TAMs and $CD4^+$ T cells involve direct cell–cell contact as well as indirect interactions through secreted signalling molecules. Co-culturing M2 macrophages with

$CD4^+$ T cells demonstrated a significant inhibition of activated $CD4^+$ T cell proliferation[65]. Enhanced interactions between macrophages and naive $CD4^+$ T cells in hepatocellular carcinoma suggest an inherent influence on tumor status. TAMs can interact with $CD4^+$ T cells through MHC-II molecules, affecting the activation profile of $CD4^+$ T cells[66]. In specific cases, such as laryngeal squamous cell carcinoma, $CD206^+$ TAMs were found to interact with $CD4^+$ T cells through the MHC-II axis, contributing to an immunosuppressive microenvironment and tumor progression[67]. Additionally, TAMs can secrete various regulatory factors that regulate the activation, proliferation, and differentiation of $CD4^+$ T cells. For instance, TAMs in breast cancer induce the conversion of naive $CD4^+$ T cells into Tregs by secreting the chemokine CCL18, leading to an immunosuppressive TME[68].

The interaction between TAMs and $CD4^+$ T cells is also regulated by multiple signalling pathways. A Triggering receptor expressed on myeloid cells-2 (TREM-2) signalling pathway, for example, performs an instrumental role in regulating the phagocytosis of TAMs and the expression of MHC-II molecules, which influences the interaction between TAMs and $CD4^+$ T cells. TREM-2 is highly expressed in various macrophage subtypes, and its deficiency impairs the phagocytic capacity of myeloid cells, reduces MHC-II expression, and subsequently decreases $CD4^+$ T cell levels[69]. The PD-L1/PD-1 signaling pathway affects the activation and function of $CD4^+$ T cells, and the expression of PD-L1 in TAMs contributes to their immunosuppressive effect on $CD4^+$ T cells, leading to immune escape and resistance to current ICIs[70,71]. The regulation of these signaling pathways modulates the crosstalk between TAMs and $CD4^+$ T cells.

The interplay between TAMs and $CD4^+$ T cells profoundly impacts tumor development and therapy. The polarization state and functional regulation of TAMs affect the immune properties of the TME, impacting the tumor development process. Similarly, the activation state and function of $CD4^+$ T cells directly determine the immune surveillance and anti-tumor immune response in the TME. Therefore, an in-depth understanding of the interaction mechanism between TAMs and $CD4^+$ T cells is crucial for unraveling TME regulation, discovering potential tumor therapeutic targets, and developing new tumor immunotherapy strategies. Future studies will continue to explore the interaction mechanism between TAMs and $CD4^+$ T cells in depth, providing a theoretical foundation and experimental basis for further advancements in tumor immunotherapy.

TAMs and NK cells

Natural killer cells (NK cells), a type of innate lymphocyte prominently characterized by their potent cytotoxic activity, have emerged as a promising class of anticancer therapeutics. Nonetheless, preclinical and clinical studies have revealed that the effectiveness of NK cell infusion in treating solid malignant tumors is hindered by several factors. In particular, TAMs have been identified as a significant bottleneck responsible for the failure of NK cell therapies to attain full therapeutic efficacy[72]. The focus of this paper will revolve around elucidating the impact of TAMs on the functionality of NK cells.

TAMs exhibit the capacity to secrete a variety of cytokines, such as TGF-β and IL-10, which can disrupt NK cells functionality. Significantly, investigations indicate that M2-like TAMs, originating from spontaneous mouse mammary carcinomas or generated in vivo from the peritoneum or bone marrow of healthy mice, exert a pronounced inhibitory impact on NK cells cytotoxicity through direct contact. Moreover, it has been observed that M2-like TAMs induce a distinctive $CD27^{low}CD11b^{high}$ phenotype in NK cells in a TGF-β1-dependent manner[73]. Noteworthy are earlier studies that have documented TGF-β's capacity to influence NK cells function through various mechanisms. TGF-β impedes the T-bet-IFN-γ pathway by targeting transcription factors, thereby impeding NK cells function and adversely affecting cellular metabolism, ultimately obstructing cell activation. Additionally, TGF-β utilises miRNAs to downregulate activation receptors, receptor-associated signalling molecules, and chemokine receptors, consequently inhibiting NK cells cytotoxicity and impairing their recruitment in tissues. Furthermore, TGF-β-induced epigenetic modifications have been found to convert NK cells into innate lymphoid cells (ILC1), exhibiting diminished killing efficacy against tumor cells, thereby significantly attenuating their cytotoxic effects[74]. Concurrently, the abundant secretion of IL-10 by TAMs serves a dual purpose: it leads to the depletion of $CD8^+$ T cells and induces a state of immaturity in NK cells, impairing their ability to perform essential immune functions. This deleterious effect creates an advantageous environment for bladder tumor cells to evade immune-mediated killing[75]. It is intriguing to note that cancer-associated fibroblasts (CAFs) have been identified as key players in the progression of colorectal cancer. CAFs demonstrate the capability to attract monocytes through the secretion of IL-8 and facilitate the M2-like polarisation of macrophages. This collaborative action between CAFs and macrophages synergistically hampers the functionality of NK cells, thereby promoting the advancement of colorectal cancer[76]. Finally, it has been demonstrated that monoclonal antibodies targeting scavenger receptors on M2-like TAMs can effectively mitigate the immunosuppressive impact of TAMs. This intervention not only enhances NK cells activation but also promotes NK cell-mediated killing in both human and mouse melanoma models. Such an approach holds great promise as a complementary strategy to address the limited efficacy of current ICIs, offering a potential avenue for combinatorial immunotherapy in the treatment of cancer[77]. In recent years, the study of extracellular vesicles has garnered considerable attention. Notably, researchers have ascertained that exosomes derived from NK cells possess the ability to effectively induce NK cell-like cytotoxicity on tumor cells. Moreover, when combined with laser irradiation, these exosomes can generate ROS, triggering significant photodynamic therapy. This process not only aids in tumor cell killing but also facilitates the polarisation of TAMs towards anti-tumor phenotypes, resembling M1-like macrophages. Additionally, it promotes the maturation of dendritic cells (DCs), thereby enhancing immune cell activity within the TME. This comprehensive approach aims to fully harness the vitality of immune cells and ultimately achieve tumor eradication[78].

It is crucial to recognise that, despite investigations into the mechanisms governing the interaction between NK cells and TAMs, our current comprehension remains incomplete. This is principally attributable to the intricate nature of tumors and the limitations imposed by extant studies. Consequently, future research is imperative to unveil the intricacies of the interactions between these two immune cell types, yielding a more comprehensive understanding of their dynamics.

TAMs and DCs

As the primary APCs in the immune system, DCs play a pivotal role in capturing, processing, and presenting antigens to activate a targeted immune response in naive $CD8^+$ T lymphocytes. This fundamental function has prompted extensive research into technologies such as DC cell vaccines and other immunotherapies for their potential applications in the field of tumor therapy[79]. Additionally, recent studies have revealed that macrophages possess the ability to cross-present antigens in a manner akin to DCs[80]. Therefore, it is essential to explore the interconnections and roles of these two cell types within the TME.

The preferential differentiation of monocytes into immunosuppressive TAMs rather than immunostimulatory DCs in the TME remains a perplexing phenomenon. Although well-established that monocytes can differentiate into both macrophages and DCs, the underlying reasons for this bias are not fully understood. Recent studies conducted in a mouse sarcoma model have shed light on this issue. These studies have demonstrated that the TME induces tumor cells to produce retinoic acid, which, in turn, inhibits the DC-promoting transcription factor IRF4. Consequently, intratumoral monocytes are driven to differentiate into immunosuppressive TAMs rather than immunostimulatory DCs. However, further research is required to fully comprehend the complex mechanisms involved[81]. This may provide a potential explanation for the observation that the number of infiltrated DCs within the TME is often significantly lower compared to that of TAMs. Additionally, the cytokines and signalling molecules produced by TAMs have the ability to influence the maturation and function of DCs. For instance, immunosuppressive factors like IL-10 and TGF-β, secreted by TAMs, can impede the maturation and antigen-presenting capacity of DCs, thereby weakening the immune response. More specifically, IL-10 down-regulates the expression of MHC-I and MHC-II molecules, co-stimulatory molecules (e.g., CD80 and CD86), as well as intercellular adhesion molecules (e.g., ICAM-1) on the surface of DCs. This deterioration in antigen-presenting properties interferes with the maturation process of monocytes into DCs[82,83]. Regarding TGF-β, it has been found to substantially diminish the antigen-presenting ability of DCs in vitro by decreasing the expression of MHC-II genes. Additionally, TGF-β signalling can trigger the production of immunosuppressive molecules such as IDO and arginase, which play a critical role in the immune tolerance program of DCs. Furthermore, TGF-β signalling is involved in the immune evasion of tumors by enhancing the expression of immune tolerance-inducing factors, such as IDO and the chemokine CCL22, in DCs[84]. Recent studies have revealed intriguing insights into the impact of TAMs and DC immunotherapy on the survival of mice in mesothelioma mouse models. Interestingly, solely reducing the number of TAMs did not result in an improved survival rate for the mice. However, when combined with DC vaccine treatment, a remarkable decrease in TAMs was observed, accompanied by an augmentation in both the quantity and functionality of $CD8^+$ T cells. This synergistic approach significantly enhanced the survival rate of mice, suggesting that the combination of TAMs-mediated immunosuppression and DC immunotherapy can successfully generate a powerful and durable anti-tumor immune response[85]. Furthermore, in tandem with the rapid advancements in nanotechnology, researchers have successfully devised an innovative nanodelivery system. This system leverages iron oxide nanoparticles to activate macrophages, which are harnessed as carriers of tumor antigens. Rather impressively, this approach not only acts as a "cytokine microfactory," leading to a substantial increase in the expression of GM-CSF, TNFα, and macrophage inflammatory protein-1α (MIP-1α), but also enables efficient delivery of tumor antigens to DCs via cell-to-cell transfer. As a result, DC maturation is stimulated, and the pro-angiogenic activity of anti-tumor TAMs is effectively attenuated. Furthermore, this technique holds the potential to enhance anti-tumor T-cell responses by enriching the therapeutic strategy that focuses on initiating anti-tumor immunity. By facilitating antigen delivery and remodelling the immune environment within tumors, it offers a promising avenue for further advancing anti-tumor treatment strategies[86].

Significantly, the intricate mechanism of interaction between TAMs and DCs remains a subject of extensive investigation, with numerous aspects yet to be thoroughly explored. Currently, studies primarily concentrate on unravelling the intricate modulatory effects of their interactions on tumor immune responses. The ultimate goal is to uncover essential insights that pave the way for the development of innovative immunotherapeutic strategies.

TAMs and Tregs

The mechanism underlying the interaction between TAMs and Tregs holds significant importance within the realm of tumor immunology research. While investigations in this field are still ongoing, there have been noteworthy findings that offer insights into their interactions. Within the TME, a dynamic equilibrium exists between TAMs and Tregs. These two cell types intricately regulate anti-tumor immune responses through their mutual interactions, thereby playing a pivotal role in shaping the immune landscape[87]. The secretion of cytokines by TAMs plays a crucial role in promoting the growth and functionality of Tregs, enabling them to effectively inhibit and eliminate tumors. In turn, Tregs exert an influence on the function of TAMs, augmenting their immunosuppressive properties and thereby regulating both tumor growth and the microenvironment. Moreover, TAMs possess the ability to modulate the infiltration levels of Tregs within tumor tissues, further contributing to the intricate interplay between these cell types[87,88]. Research has provided compelling evidence that TAMs, via the activation of the extracellular signal-regulated kinase (ERK)/NF-κB pathway, produce CCL20. This chemokine plays a pivotal role in fostering the infiltration of Tregs into the TME, amplifying their presence at the site of tumorigenesis[21]. In addition to their aforementioned functions, TAMs significantly impact Tregs proliferation, migration, and functionality via multiple pathways. Notably, chemokines such as CCL-2, CCL-3, CCL-4, CCL-5, and CCL-20, as well as cytokines like IL-10 and TGF-β, which are produced by TAMs within the TME, can induce Tregs expansion and recruitment. This not only disrupts local immunosurveillance at the tumor site but also promotes tumor growth, consequently playing a pivotal role in maintaining an immunosuppressed TME [89,90]. Moreover, within the hypoxic TME, tumor-activated HIF1α triggers TAMs to secrete IL-23, which in turn facilitates the proliferation of Tregs[91]. In malignant pleural effusion (MPE), Tregs play a substantial role in promoting the differentiation of monocytes into immunosuppressive TAMs, thereby contributing to the establishment of an immunosuppressive microenvironment. Furthermore, TAMs express CCL22, which facilitates the recruitment of Tregs. Additionally, Tregs secrete IL-8, which induces TAMs to produce TGF-β. This creates a detrimental cycle that modifies the immune microenvironment within MPE, ultimately enhancing the tumor's ability to evade immune surveillance[92]. Conversely, Tregs have the ability to influence the polarisation of TAMs towards an M2-like phenotype by interfering with TAMs' metabolism. In particular, Tregs impact the synthesis of fatty acids in M2-like TAMs, thereby modulating their metabolic adaptations. These effects on macrophage polarisation by Tregs contribute to tumor progression[93]. IFN-γ interferes with the metabolism, mitochondrial integrity, and survival of TAMs, and Tregs act as a regulator of TAMs by inhibiting IFN-γ secretion from $CD8^+$ T cells[94].

Indeed, the examples provided offer only a glimpse into the complex mechanisms of interaction between TAMs and Tregs. As research progresses, we can anticipate more comprehensive insights and novel discoveries regarding their intricate interplay. It is an ongoing process that holds promise for expanding our understanding of these cellular interactions in the TME.

TAMs and MDSCs

MDSCs represent a category of immature, pathologically activated myeloid cells further classified into M−MDSCs and granulocytic MDSCs (G-MDSCs)[40]. Despite their distinct phenotypic and functional characteristics, both subpopulations of MDSCs serve as

potent suppressors of the immune response. This immune suppression plays a crucial role in facilitating immune evasion by tumor cells[40,95].

As previously mentioned, MDSCs constitute a significant source of TAMs[40]. Recent studies have revealed that the immunosuppressive activity of macrophages derived from M−MDSCs relies on the persistent expression of the S100A9 protein within these cells. Interestingly, this protein not only facilitates the polarisation of macrophages into M2-like TAMs but is also absent in macrophages originating from tissue-resident macrophages and monocyte-derived macrophages[96].

Meanwhile, TAMs and MDSCs exhibit a close interplay within the TME. On one hand, MDSCs disrupt the effectiveness of macrophages as antigen-presenting cells by secreting IL-10, leading to a notable reduction in the expression of MHC-II molecules on macrophage surfaces. Consequently, this dampens T cell activation and reinforces the immunosuppressive capacity of macrophages[97]. On the other hand, the secretion of IL-10 by MDSCs diminishes the production of proinflammatory factors, particularly IL-6 and IL-12, in macrophages. Remarkably, macrophages themselves also release IL-6, which further stimulates the production of IL-10 by MDSCs. Additionally, this IL-6-induced signalling expedites the transformation of macrophages into M2-like TAMs, which possess immunosuppressive characteristics[97]. It is possible that the strong connection between TAMs and MDSCs contributes to the limited efficacy of blocking TAMs through CSF-1R signalling inhibition in restraining tumor progression. Subsequent investigations have indicated an increased presence of CAFs and a substantial upregulation of various chemokines originating from CAFs, notably C-X-C motif chemokine ligand 2(CXCL2), in tumors treated with anti-CSF1Rs[98,99]. CXCL2, a well-known chemoattractant for G-MDSCs, promotes the recruitment of MDSCs to the tumor, resulting in a substantial infiltration of MDSCs within the TME. Therefore, the elimination of TAMs may trigger a compensatory increase in the population of MDSCs. To enhance the immunotherapeutic efficacy of the tumor, researchers have proposed simultaneous targeting of both TAMs and MDSCs to reduce the number of these cell types[98,99]. Moreover, it has been discovered that the continual expansion of MDSCs hampers CD40/IL-27 signalling in macrophages, thereby fostering melanoma growth and provoking autoimmune responses[100]. Furthermore, the activation of Notch signalling may regulate lactate metabolism and contribute to the differentiation of MDSCs as well as the maturation of TAMs in tumor tissues experiencing abnormal glucose metabolism[101]. Additionally, the activation of Notch signalling in macrophages leads to increased secretion of CCL2, thereby amplifying the recruitment and accumulation of MDSCs in tumor tissues[102]. Encouragingly, entinostat, an oral histone deacetylase inhibitor, exhibits the ability to not only modify the phenotype of MDSCs but also epigenetically reprogram M2-like TAMs into M1-like TAMs. This transformative effect significantly enhances the

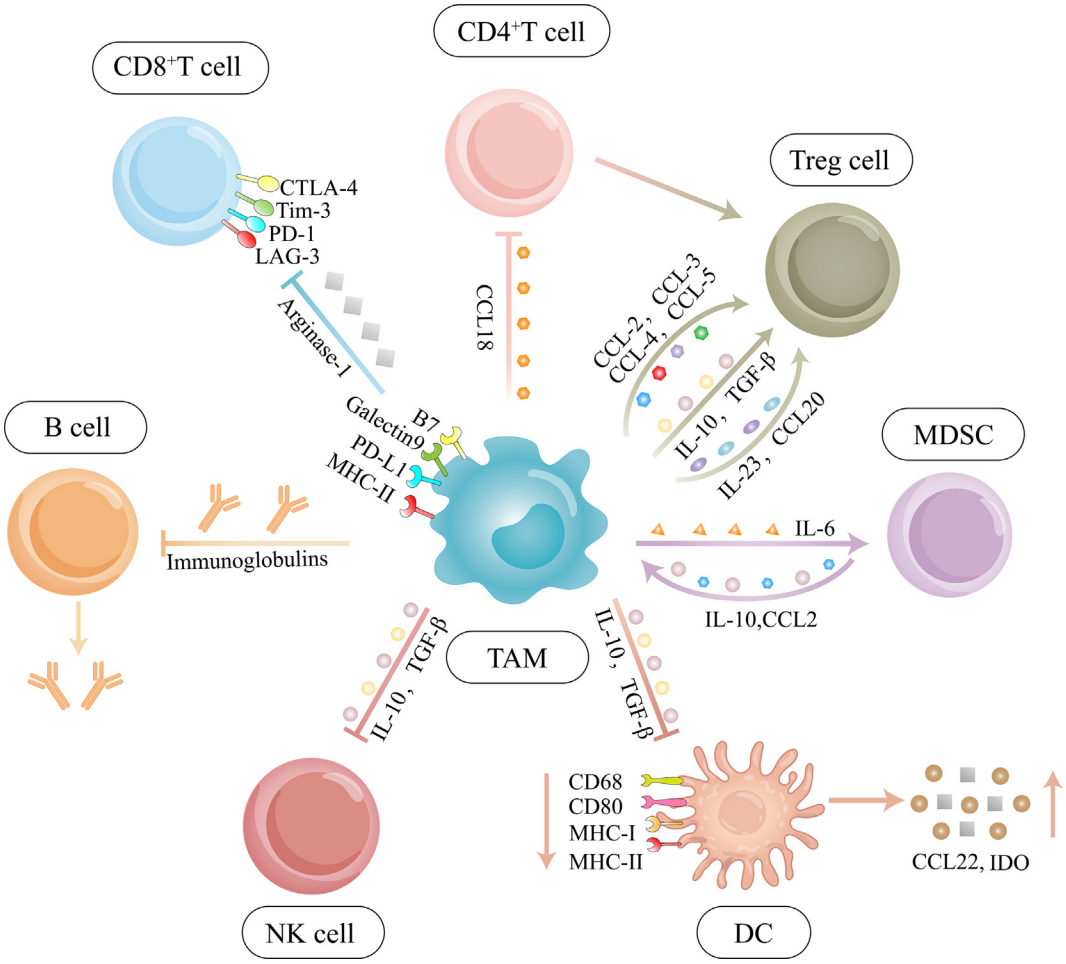

Fig. 2. TAM engage in interactions with other immune cells in skin cancer. TAMs not only function as inhibitors for the cytotoxic effects of $CD8^+$ T cells by expressing various immune checkpoint ligands in direct contact with them, but they also release a range of cytokines, particularly TGF-β and IL-10, which impact the functions of $CD8^+$ T cells, NK cells, DCs, and Tregs. Additionally, TAMs collaborate with MDSCs and Tregs to exert immunosuppressive effects. Ultimately, TAMs play a central role in shaping an immunosuppressive TME that aids in the tumor's ability to evade the immune system.

immune-suppressive TME, offering newfound hope for patients with cancer[103].

Taken together, the interplay between TAMs and MDSCs is known to exert a significant influence on tumor progression and immune regulation. Their collaboration establishes an immunosuppressive TME that facilitates tumor growth, invasion, metastasis, and hinders effective immune responses against the tumor. Therefore, delving into the mechanisms underlying TAM-MDSC interactions can unveil the mechanisms of tumor immune evasion, offering a valuable foundation for the development of novel immunotherapeutic strategies.

In summary, TAMs engage in interactions with various immune cells, particularly MDSCs and Tregs, which collectively contribute to the immunosuppressive nature of the TME. Additionally, TAMs secrete a range of cytokines, notably including IL-10 and TGF-β, which disrupt the functioning of normal immune effector cells (Fig. 2). Consequently, achieving a balance in the interactions between TAMs and other immune cell types is crucial for both current and future treatment strategies against malignant tumors.

Functions of TAMs in skin cancer

In general, TAMs can contribute to tumor development through various mechanisms, including, but not limited to: (1) TAMs play a pivotal role in promoting tumor cell growth and proliferation by secreting a diverse array of growth factors and cytokines, including epidermal growth factor (EGF), VEGF, platelet-derived growth factor (PDGF), TGF-β, and basic fibroblast growth factor (BFGF), among others. These growth factors activate cellular proliferation pathways and create a conducive growth environment for tumor cells[104,105]. (2) TAMs generate pro-angiogenic factors, including VEGF, cyclooxygenase-2(COX-2), PDGF, and MMPs, to promote tumor angiogenesis. Subsequently, increased vascularisation facilitates adequate oxygen and nutrient supply to tumor cells, thereby promoting their growth and dissemination[93,106,107]. (3) Additionally, TAMs exert influence on tumor cell invasion and metastasis by modifying the composition and structure of the extracellular matrix (ECM). They accomplish this by releasing enzymes, including MMP-2, MMP-7, MMP-9, MMP-12, among others, which facilitate ECM dissolution. This alteration in the ECM aids in promoting tumor cell invasion and metastasis[108,109]. Furthermore, TAMs can induce the activation of epithelial-mesenchymal transition (EMT) through interactions with tumor cells. This process equips tumor cells with heightened invasive and metastatic capacities, further contributing to tumor progression[110–112]. (4) TAMs secrete immunosuppressive cytokines, including TGF-β, IL-10, and indoleamine 2,3-dioxygenase 1 (IDO1). These cytokines upregulate the expression of immune checkpoints such as PD-L1, CTLA-4, TIM-3, and LAG-3. As a result, T cell activation and function are inhibited, and the activity of NK cells is diminished, leading to a weakened anti-tumor immune response. The presence of CTLA-4, TIM-3, and LAG-3 further hampers T cell activation and function, while also suppressing the activity of NK cells, ultimately enabling the tumor to evade the body's immune defence system[113–117]. In skin cancer, scientists are exploring whether TAMs exhibit similar roles or if there are distinct mechanisms driving tumor growth. To address this question, continuous research efforts have been focused on unravelling the intricacies between TAMs and skin can-

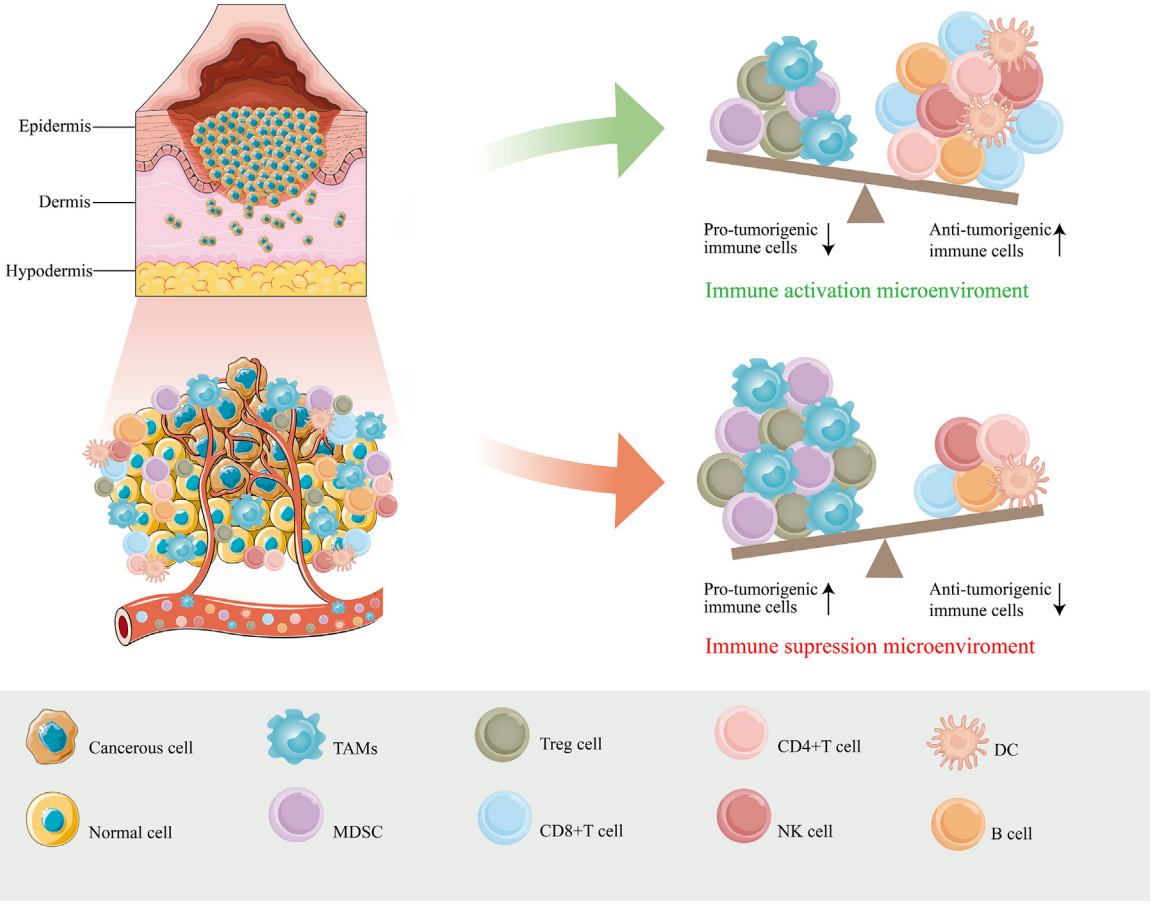

Fig. 3. Role of TAMs in the immune microenvironment of skin cancer. TAMs play a pivotal role as a core cell population in the immune microenvironment of skin cancer. Immunosuppressive cell populations orchestrated by TAMs facilitate tumor progression while dampening the immune response. Conversely, an augmented presence of immune cells, such as cytotoxic T lymphocytes, is correlated with an improved clinical prognosis.

cer. This paper aims to provide a comprehensive synthesis of recent studies, outlining the functions and underlying mechanisms of TAMs in various types of skin cancer, including CM, BCC, cSCC, MCC, and extramammary Paget's disease (EMPD) (Fig. 3).

TAMs and CM

CM stands out as an exceptionally aggressive form of skin cancer, responsible for the majority of skin cancer-related fatalities. A distinctive feature of CM is the influx of inflammatory cells into the tumor tissue, notably an abundance of M1-like macrophages. The heightened infiltration of these M1-like macrophages is linked to a more favourable prognosis for CM patients, serving as a potential indicator of improved clinical outcomes[118]. This notion gains support from studies demonstrating increased expression of growth factor receptor-bound protein 2-associated binding protein 3 (GAB3) and ELL-associated factor 2 (EAF2) in CM tissues. These proteins have been shown to enhance the infiltration of various immune cells, including macrophages, into the TME. Consequently, this augmented immune cell infiltration stands as a reliable prognostic marker for favourable outcomes in CM patients[119,120]. Moreover, in instances of metastatic CM, macrophages display a notable overexpression of the transcription factor known as CEBPB. This heightened CEBPB expression is strongly correlated with increased inflammatory responses and activation of immune response pathways[121]. Hence, these findings suggest that metastatic CM may confer a more favourable prognosis. Based on these observations, it is plausible to speculate that M1-like macrophages could serve as potential prognostic indicators for CM in the future.

In contrast to M1-like macrophages, an increased abundance of M2-like macrophages exerts a promotive effect on tumor development. In CM, for example, cancer cells demonstrate elevated expression levels of the anti-apoptotic protein BCL-2. This triggers the IL-1β pathway, inducing a phenotypic shift in macrophages and transforming TAMs into M2-like macrophages. Consequently, this conversion diminishes the population of IFN-γ and effector memory T-cells, compromising the immune response mediated by T-cells. Ultimately, this establishes a TME conducive to the progression of CM[122]. Additionally, heightened expression of nuclear factor of activated T cells (NFAT1) in CM significantly contributes to the polarisation of TAMs towards the M2 phenotype, amplifying the growth and metastatic potential of TAMs, and exerting enhanced effects on CM cells[123]. An intriguing observation is that exosomes derived from CM contain miR-125b-5p, a non-coding RNA critically regulating TAMs in CM. This RNA molecule targets lysosomal acid lipase A, promoting TAM polarisation towards a pro-tumorigenic phenotype[124]. Evidence also suggests that MFG-E8, an angiogenic factor secreted by pericytes, plays a role in facilitating the polarisation of TAMs towards the M2-like phenotype, thereby promoting angiogenesis and facilitating the growth of CM[125]. Furthermore, TAMs can orchestrate the formation of the angiogenic network and contribute to CM development by secreting osteoblastin (OPN), prostaglandin (PGE2), and MMP-9, with these specific molecules playing a crucial role in regulating the TME[126].

Throughout the dynamic process of CM, where CM cells recruit monocytes/macrophages and transform them into TAMs, activin A emerges as a key player. This molecule, secreted by both CM cells and TAMs, modulates the expression of various cytokines and chemokines. Notably, it enhances the production of immunosuppressive factors such as COX-2/PGE2 and IDO1, as well as pro-angiogenic factor VEGF-A and pro-proliferative factor CCL20. These alterations ultimately bolster the pro-tumorigenic and immunosuppressive functions of TAMs. Tragically, these changes in the TME contribute to a worse prognosis for patients affected by CM [127]. Significantly, the chemokine CCR6/CCL20 axis actively participates in the progression of various malignant tumors and chronic inflammatory skin diseases, such as CM. It assumes a pivotal role in the pathogenesis of skin-related disorders[128]. Some researchers have made an intriguing discovery of a distinct subset of pre-tumor TAMs in metastatic primary CM, which operates independently of the traditional M1-like and M2-like TAM classifications. These TAMs are found to produce CCL20, thereby facilitating tumor growth and metastasis[129]. Furthermore, in metastatic primary CM, TAMs exhibit heightened secretion of CCL20 and VEGF-A, a phenomenon regulated by the p53/NF-κB signalling pathway[130].

However, in contrast to the previously documented pro-tumorigenic role of M2-like macrophages in CM, it is now evident that these macrophages can also exhibit anti-tumorigenic effects. Interestingly, studies have revealed that in CM cases characterized by high expression levels of the membrane transport regulator adenosine diphosphate-ribosylation factor-like (ARL) proteins, particularly ARL11, there is a notable increase in the infiltration of various immune cells, including $CD8^+$ T cells and M2-like macrophages. This phenomenon leads to the remodelling of the immune microenvironment in CM and enhances the immune response. Consequently, it has a positive impact on the prognosis of CM patients, ultimately contributing to improved outcomes [131].

Therefore, the increase in M1-like macrophages is evidently of significant importance for CM prognosis. However, the specific mechanisms through which M1-like macrophages exert anti-tumor effects in CM remain unclear and necessitate further investigation. While existing studies predominantly highlight the pro-tumorigenic effects of M2-like macrophages in CM, encompassing the promotion of tumor cell growth, proliferation, angiogenesis, invasion, metastasis, and immunosuppression, there have been isolated findings suggesting that M2-like macrophages may also exhibit some anti-tumor effects in CM. It is plausible that these divergent results stem from the complexity surrounding the categorisation of M2-like macrophages. Nevertheless, it is undeniable that the current understanding of M2-like macrophages in CM is incomplete and lacks a cohesive perspective. Further research is needed to fully elucidate this intricate relationship.

TAMs and BCC

BCC stands as the prevailing type of skin cancer. While the majority of BCC cases are localised and effectively managed, patients with advanced BCC face limited treatment options[132]. The progression of human BCC is primarily governed by the host immune response and the presence of inflammatory cells in the TME. Among these inflammatory cells, macrophages play a crucial role. Previous research has demonstrated a positive correlation between the number of TAMs and the extent of infiltration, microvessel density, and COX-2 expression levels in human BCC cells. It has also been observed that TAMs stimulate BCC cells to secrete BFGF, VEGF-A, and MMP-9 in a COX-2-dependent manner, thus promoting BCC invasion and angiogenesis[133].

Subsequent studies, however, have presented conflicting findings that challenge these notions. In a mouse model of BCC, it was discovered that reducing the population of macrophages and DCs actually facilitated tumor growth[134]. Since then, several researchers have explored the association between BCC characterised by limited nodular and infiltrative fibrosis and TAMs. Surprisingly, these studies have revealed that the presence of infiltrative TAMs in BCC tissues does not seem to be correlated with the invasion of BCC[135]. Meanwhile, a study aimed at comparing the correlation between the overall quantity of macrophages and their M1 and M2 subtypes in patients who experienced recurrent and non-recurrent nodular BCC following

Mohs micrographic surgery yielded interesting results. The study revealed no significant differences between the groups concerning the average percentage of M1 macrophages, M2 macrophages, and total cells. As a result, it was concluded that there is no apparent association between TAMs and tumor recurrence in these cases [136]. Fortunately, a recent study has put forth a fascinating proposition that highlights the significant role of brain-derived neurotrophic factor proBDNF and its receptor p75NTR in promoting the recruitment of M1-like macrophages and T-cells. This overexpression of proBDNF and p75NTR was found to regulate the immune microenvironment of BCC through the necroptosis apoptosis signalling pathway in a mouse model. These findings offer a fresh perspective for further exploration into the study of BCC [137].

In conclusion, a debate persists concerning the direct correlation between tumor-infiltrating TAMs and the development of BCC, and a consensus has yet to be reached. Consequently, the precise role of TAMs in BCC and the underlying mechanisms involved require further investigation by scientists in the future.

TAMs and cSCC

While cSCC ranks as the second most prevalent skin cancer, its precise pathogenesis remains elusive. In comparison to normal skin tissues, cSCC exhibits an elevated presence of TAMs, which display heterogeneous activation and can be classified into three primary subtypes: TAMs expressing M1-like markers, TAMs expressing M2-like markers, and TAMs expressing a combination of both M1-like and M2-like macrophage markers[138]. An important characteristic of the TME in human cSCC is the heightened density of lymphatic vessels. TAMs play a crucial role in this process as they facilitate lymphangiogenesis and promote cSCC metastasis by producing VEGF-C[139,140]. On the other hand, within cSCC, TAMs secrete a range of matrix metalloproteinases, including MMP-9, MMP-11, and MMP-13. These enzymes play a crucial role in promoting cSCC invasion, thereby influencing prognosis [141,142]. Furthermore, the targeted and specific inhibition of MMP-13 expression has demonstrated effective suppression of the growth and invasion of SCC. Therefore, targeting and inhibiting MMPs presents a promising therapeutic strategy for the treatment of SCC[143].

In a study investigating the density and polarisation status of TAMs in SCC and BCC, notable findings were observed. The density of $CD68^+$ TAMs was found to be higher in SCC compared to BCC, and SCC exhibited increased expression of TAMs-related markers, including arginase-1, MMP-9, CD40, and CD127. These differences in TAMs suggest that SCC may possess distinct clinical characteristics from BCC. Additionally, SCC demonstrated higher levels of lactate compared to BCC, indicating that soluble factors like tumor-derived lactate play a significant role in the polarisation of TAMs in SCC[144,145]. Furthermore, activin is notably up-regulated in human NMSC, particularly in BCC and cSCC. This up-regulation of activin can attract blood monocytes, increase the number of macrophages in the skin, and reprogram the phenotype of TAMs. Consequently, TAMs induced by activin express various tumor-associated factors like OPN, arginase 1, MMP-12, MMP-13, and MMP-14. Ultimately, this leads to the promotion of tumor site angiogenesis and enhances the migratory capabilities of tumor cells[146].

CD200 is a cell surface glycoprotein that, upon specific binding to its receptor CD200R, serves as an inhibitor of autoimmune and alloimmune functions. While crucial for maintaining normal tissue homeostasis, this interaction may also lead to the suppression of immune surveillance against tumors. As a result, CD200 plays a significant role in the etiology of cancer development and metastasis across various malignancies[147–149]. It has been observed that in SCC, there is an upregulation of CD200 expression in the vascular endothelium surrounding tumor cells. Additionally, CD200R expression has been detected on various immune cell types, including TAMs, MDSCs, NK cells, and T cells[150]. Moreover, in cSCC, the expression of CD200 by cSCC cells, facilitated by histone K derived from these cells, enables an interaction with CD200R on immune cells. This interaction, in turn, facilitates the promotion of cSCC invasion and metastasis[151,152].

Interestingly, it has been observed that the presence of resident Langerhans cells in the skin and macrophages in the dermis has minimal impact on the development of cSCC. However, it has been found that mice lacking circulating monocytes exhibit complete resistance to UV-induced cSCC, highlighting the crucial role of monocytes in the early stages of cSCC development[153].

In conclusion, while cSCC and BCC share certain similarities as prevalent skin cancer, it is evident that there exist notable distinctions in the specific mechanisms involving TAMs in these two malignancies. Furthermore, our findings suggest a relative uniformity in the existing studies pertaining to TAMs in cSCC, where M2-like macrophages have been recognized as promoting tumor progression. In contrast, investigations into the role of M1-like macrophages in cSCC remain comparatively limited.

TAMs and MCC

MCC is an infrequent neuroendocrine carcinoma of the skin that predominantly affects older individuals and those with weakened immune systems. The disease is characterised by its exceptionally aggressive nature, often leading to rapid progression. Once metastasis takes place, patients encounter significant challenges in terms of treatment. It is noteworthy that Merkel cell polyomavirus is the primary pathogen associated with the majority of MCC cases[154]. Currently, there is a scarcity of research focused on delineating the precise mechanisms of TAMs in the pathogenesis of MCC. Nevertheless, available studies have highlighted the significance of TAMs in MCC. Within the TME of MCC, a substantial presence of diverse inflammatory cells, including macrophages, has been observed [155]. Meanwhile, it has been observed that the expression of prokineticin-2 (PROK2) is markedly elevated in Merkel cell polyomavirus-positive MCC. This upregulation of PROK2 leads to an increased infiltration of TAMs, including $CD68^+$ and $CD163^+$ macrophages, within tumor tissues. Consequently, this modulation of the immune response plays a crucial role in MCC. Moreover, it has shown potential in enhancing patient survival rates[156]. Nevertheless, the small T antigen of Merkel cell polyomavirus facilitates immune evasion in MCC by regulating the expression of CD47 surface antigen and impeding macrophage phagocytosis through the interaction between CD47 and SIRPα. This mechanism aids MCC in evading immune surveillance and clearance by macrophages[157]. MCC can induce the transformation of TAMs to immunosuppressive M2-like macrophages through the high expression of CD200, an immunomodulatory ligand, while increasing the infiltration of Tregs and generating an immunosuppressive TME[158].

TAMs and EMPD

EMPD is an uncommon malignant skin cancer, the precise pathogenesis of which remains elusive. While the aberrant activation of signalling pathways in tumor cells and lymphangiogenesis contributes to the progression of EMPD, the involvement of other cellular immune components, particularly TAMs, in the TME of EMPD, remains uncertain[159].

Receptor activator of nuclear factor-kappa B ligand (RANKL) plays a crucial role in preserving a balanced immune response in the skin by regulating the population of Tregs. This regulation is

essential for suppressing autoimmune reactions and preventing detrimental immune responses to both self-antigens and harmless foreign antigens. Notably, about sixty percent of $CD163^+$ macrophages in EMPD express Receptor activator of nuclear factor-kappa B (RANK), while the lesional skin of EMPD exhibits substantial secretion of soluble RANKL[160]. Upon stimulation by RANKL/RANK signalling, M2-like macrophages secrete CCL17 to recruit $Foxp3^+$ Tregs into the TME of EMPD, thereby inducing an immunosuppressive microenvironment[161]. In addition, one of the hallmarks of many cancers, including EMPD, is the enhancement of aerobic glycolysis, a metabolic process, and the lactic acid generated increases the number of immunosuppressive cells, such as $CD163^+$ M2-like macrophages and $Foxp3^+$ Tregs, mediated by IL-6, which enhances immune escape in EMPD[162]. As expected, in EMPD, M2-like TAMs exert their influence on immune cell functionality through interactions involving RANKL/RANK signalling pathways and metabolic processes. These combined mechanisms contribute to the creation of an immunosuppressive TME that ultimately results in a detrimental prognosis for individuals with EMPD.

In summary, the study of TAMs in skin cancer introduces several ambiguous and controversial aspects. However, in comparison to other skin cancer, the research on TAMs in CM is the most extensive and comprehensive. Nevertheless, the specific mechanisms and points of contention concerning TAMs in BCC, cSCC, MCC, and EMPD still require thorough exploration. Particularly, for rare NMSC like EMPD, there is ample research space available to investigate the specific functions and related mechanisms of TAMs. It is important to note that despite the observed heterogeneity among different tumors, TAMs generally contribute to skin cancer by promoting tumor cell proliferation and survival, facilitating tumor angiogenesis, suppressing immune responses, and supporting tumor invasion and metastasis. Gaining a comprehensive understanding of these mechanisms will enhance our knowledge of the development of skin cancer and provide novel insights for the development of therapeutic strategies targeting TAMs in the treatment of such conditions.

Therapeutic strategies to modulate TAMs in skin cancer

Due to their significant involvement in the initiation and progression of skin malignant tumors, TAMs have garnered considerable attention from researchers seeking to explore their regulation for therapeutic purposes. Currently, the primary strategies employed in the field of skin cancer treatment to target TAMs include direct elimination of TAMs, inhibition of TAMs recruitment, and reprogramming of TAMs, among others.

Directly removing TAMs

Directly targeting TAMs for removal is indeed a straightforward approach to counteract the detrimental effects of TAMs. Bisphosphonates, known for their ability to inhibit excessive bone resorption by osteoclasts (a type of macrophage), are commonly employed in the treatment of osteoporosis and cancer-induced bone metastasis. Therefore, they have emerged as a potential therapeutic option for modulating TAMs activity[163]. Consequently, this has sparked the interest and vigorous investigation of scientists regarding the potential application of these drugs in targeting TAMs for tumor treatment. Researchers have made significant progress by developing various liposomal formulations capable of encapsulating bisphosphonates. Upon phagocytosis by macrophages, these liposomes release the drugs, leading to the direct elimination of TAMs, inhibition of tumor site angiogenesis, and remarkable anti-tumor effects[164–167]. Nonetheless, a significant challenge associated with this therapeutic strategy lies in the fact that bisphosphonates may not exclusively deplete TAMs but rather affect tissue-resident macrophages as a whole. This raises concerns about potential disruption to normal immune function within the body.

Hence, scientists are actively exploring novel therapeutic strategies that can effectively eliminate TAMs with immunosuppressive functions. For instance, researchers have developed a new synthetic peptide called bee toxin dKLA, which has been shown to selectively target M2-like macrophages and induce the expression of caspase3 to promote apoptosis in these cells. As a result, dKLA treatment has demonstrated significant anti-tumor effects in CM models[168]. Furthermore, some researchers have developed a dual-targeting nanoparticle capable of targeting M2-like TAMs and efficiently delivering anti-CSF-1R siRNA to these cells. This approach has resulted in a remarkable reduction of TAMs, reversal of tumor immunosuppression, and inhibition of CM growth[169].

Inhibiting the recruitment of TAMs

Alongside the direct removal of TAMs, targeting the recruitment of TAMs as a means to reduce their presence has emerged as a promising therapeutic strategy.

The CCL2/CCR2 signalling pathway plays a crucial role in mediating the recruitment and infiltration of circulating monocytes into the TME. Tumor cells release CCL2, which attracts monocytes expressing CCR2 from the peripheral blood to the tumor site. Hence, disrupting this signalling pathway presents a compelling therapeutic approach for targeting TAMs[170–172]. Multiple studies have demonstrated that the use of neutralising antibodies against CCL2 and inhibitors of CCR2 effectively diminishes the recruitment of circulating monocytes, leading to reduced TAMs numbers in various tumor types, including esophageal SCC, hepatocellular carcinoma, and more. Additionally, this approach enhances the functionality of $CD8^+$ T cells and NK cells within the TME, resulting in TME remodelling and a potent anti-tumor effect[173–175]. As a result, there is a range of drugs targeting the CCL2/CCR2 signalling pathway that are currently undergoing clinical trials[172]. It is evident that the development of drugs targeting the CCL2/CCR2 signalling pathway in skin cancer is relatively limited, highlighting the broader potential for their development in this context. In recent years, attention has also been drawn to the CX3CL1/CX3CR1 axis, which similarly facilitates the recruitment and polarisation of TAMs. This axis is known to secrete factors such as VEGF, Wnt3a, IL-1, and TNF-α, which promote skin carcinogenesis[176]. Hence, the inhibition of TAMs recruitment through targeting the CX3CL1/CX3CR1 axis offers novel possibilities for effectively combating skin cancer.

Of course, it is important to recognise that TAMs can also originate from tissue-resident macrophages. Simply targeting the recruitment of TAMs may not be sufficient to achieve a comprehensive anti-tumor effect, as it does not address this population of TAMs. Therefore, a more comprehensive therapeutic approach should consider strategies to target both recruited TAMs and tissue-resident macrophages to maximise the anti-tumor potential.

Reprogramming the TAMs

Both the direct removal of TAMs and inhibition of TAM recruitment fail to address a key aspect—the high degree of plasticity exhibited by TAMs, particularly the M1-like macrophages. These M1-like macrophages possess immune properties such as phagocytosis and antigen presentation, enabling them to exert anti-tumor effects. Recognising this, the therapeutic strategy of repro-

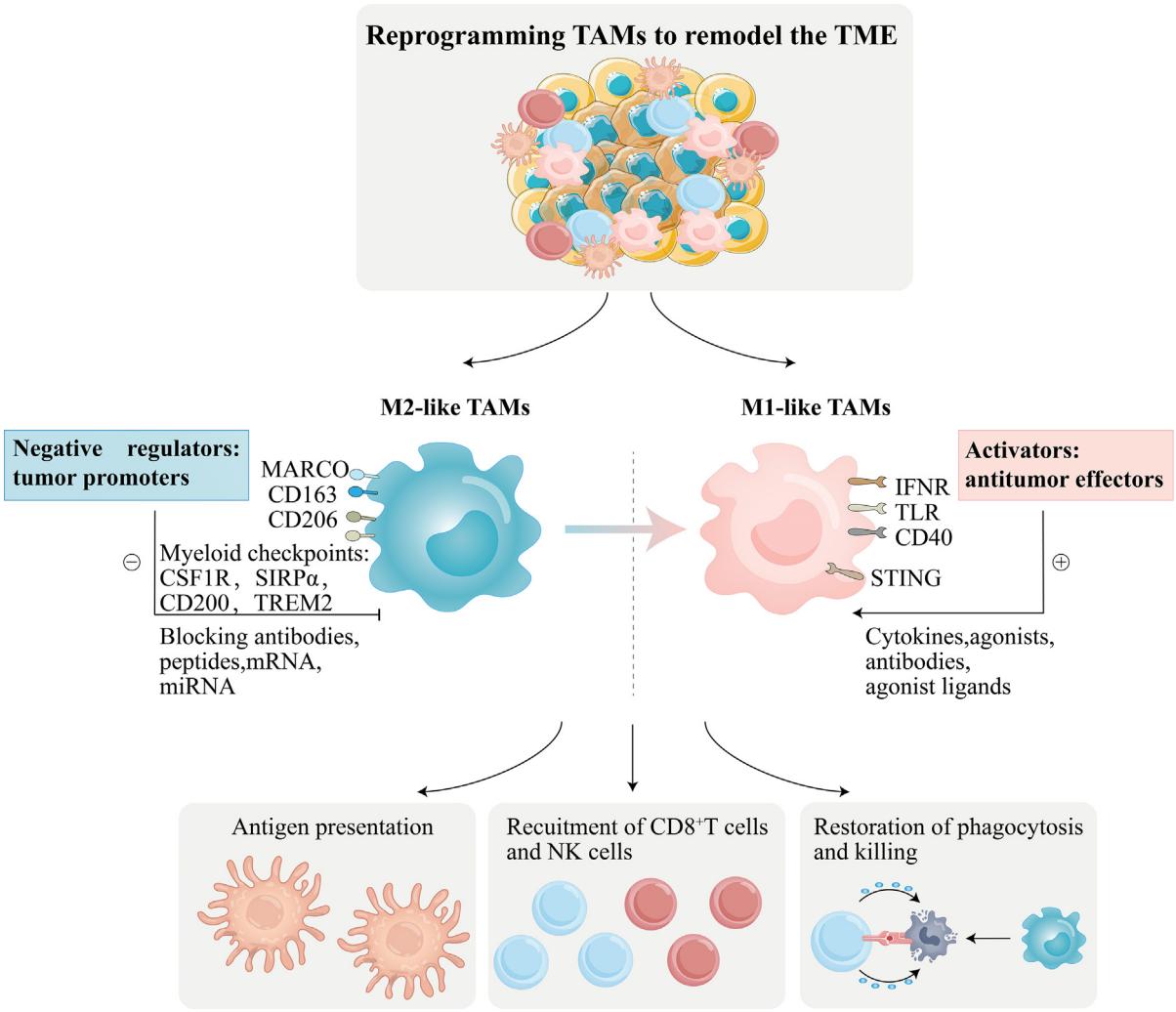

Fig. 4. Reprogramming TAMs enhances both adaptive and intrinsic immunity. Among the strategies for TAM reprogramming, five major approaches have emerged, including interfering with CSF-1/CSF-1R signalling, agonising CD40, inhibiting PI3Kγ, agonising TLR, and blocking CD47/SIRPα interaction. These approaches restore the original functions of macrophages, such as phagocytosis and antigen presentation, while also enhancing the tumor-killing capabilities of NK cells and $CD8^+$ T cells, thereby achieving a dual antitumor effect through innate and adaptive immunity. Numerous small molecule drugs and biologics based on these therapeutic strategies are currently either available on the market or undergoing clinical trials, highlighting the prominent position of TAM reprogramming as a promising therapeutic approach.

gramming TAMs from immunosuppressive M2-like macrophages to M1-like macrophages has emerged, capitalising on the inherent plasticity of TAMs (Fig. 4).

Interference with CSF-1/CSF-1R signaling axis

The CSF-1/CSF-1R signalling axis plays a crucial role in TAMs, as the upregulation of CSF-1 promotes the infiltration, survival, proliferation, and immunosuppressive functions of $CSF\text{-}1R^+$ TAMs within the TME. Consequently, this contributes to tumor growth. Therefore, targeting the CSF-1/CSF-1R signalling pathway has emerged as an appealing strategy to reprogram TAMs and disrupt their immunosuppressive functions, presenting a potential avenue for therapeutic intervention[177–179]. Currently, several small molecule compounds and monoclonal antibodies are available in the market or being investigated in clinical studies that effectively inhibit the CSF-1/CSF-1R signalling axis, as indicated in Table 1 and 2. Extensive research has demonstrated that blocking the CSF-1/CSF-1R signalling axis significantly enhances the efficacy of various tumor therapies, including ICIs, chemoradiation, and radiotherapy, among others. These findings highlight the potential of targeting the CSF-1/CSF-1R signalling axis to improve the outcomes of diverse treatment modalities for tumors[180,181]. Perhaps for this reason, there has been relatively less focus on the development of CSF-1R inhibitors as standalone treatments in recent years. Instead, there has been a growing emphasis on conducting clinical studies of CSF-1R inhibitors in combination with other antitumor agents, particularly ICIs. This approach highlights the potential synergistic effects of combining these therapies to enhance their overall therapeutic efficacy and improve outcomes for cancer patients.

CD40 agonists

The immune response relies on various ligands of the tumor necrosis factor superfamily and their corresponding receptors, among which CD40/CD40L is a crucial component. Antigen-specific T cells require the presence and proper functioning of APCs for effective recognition and elimination of antigens. CD40, predominantly expressed by APCs like monocytes, macrophages, and DC cells, plays a significant role in this process. The interaction between CD40L and CD40 triggers the activation of anti-tumor T cells by DC cells, subsequently instructing macrophages to eradicate the tumor stroma. Hence, CD40 holds immense importance in orchestrating immune responses[187]. Compared to normal tissues, CM showed significantly reduced expression of CD40, partic-

Table 1
Development of inhibitors targeting the CSF-1/CSF-1R axis.

Type	Target	Name	Status	Country	Applications	Ref./NCT
Small Molecule Drugs	CSF-1R	Pexidartinib (PLX-3397)	Available in 2019	USA	TGCT	[182]
			Phase 2	USA	Recurrent glioblastoma	NCT01349036
			Phase 1	USA	Neurofibroma, promyelocytic, acute sarcoma, PP-ALL	NCT02390752
			Phase 1/2	China	Melanoma	NCT02975700
			Phase 3	China	TGCT	NCT04488822
			Phase 1	China	Advanced solid tumors	NCT02734433
		Regorafenib	Available in 2012	USA	Refractory metastatic CRC, advanced GIST, unresectable HCC	[183–185]
			Phase 2	USA	HCC	NCT04476329
			Phase 2	Italy	Melanoma, Ovarian Cancer, Sarcoma, Thymic Carcinoma, PCA	NCT02307500
		C019199	Phase 1	China	TGCT and other advanced solid tumors	CTR20202045
		ARRY-382	Phase 1	USA	Metastatic cancer	NCT01316822
		Surufatinib	Available in 2020	China	Neuroendocrine tumors and other solid tumors	[186]
			Phase 2	China	BTC, HCC	NCT02966821 NCT05171439
			Phase 2	USA	NETs, intestinal NET	NCT04579679
			Phase 1/2	Japan	NETs, non-hematologic malignancy	NCT05077384
	CSF-1	Simmitinib	Phase 1	China	Advanced solid tumors	NCT04058587
Monoclonal Antibody	CSF-1R	Cabiralizumab	Phase 1/2	USA	PVNS, TGCT	NCT02471716
			Phase 1	Japan	Advanced malignancies	NCT03158272
	CSF-1	LY3022855	Phase 1	USA	Neoplasm and metastatic neoplasm	NCT02265536 NCT01346358

ularly in patients with RAS mutations. Conversely, tumors with elevated CD40 expression tended to be associated with better patient prognosis[188,189]. Numerous monoclonal antibodies that agonise CD40 are being investigated in combination with pharmacologic oncology strategies targeting CSF-1R, PD-1, PD-L1, and VEGF in clinical or preclinical studies. These endeavours have yielded promising outcomes across various tumor types, including CM[190]. Therefore, CD40 agonists are gaining momentum as promising immunotherapy strategies for cutaneous malignancies.

PI3Kγ inhibitors

PI3Kγ functions as a crucial molecular switch that regulates immune responses within cells, concurrently disabling normal immune functions and activating immunosuppressive functions. In macrophages, the absence of PI3Kγ not only increases the expression of MHC-II and pro-inflammatory cytokines like IL-12 but also enhances adaptive immune functions, such as improved recruitment and cytotoxicity of $CD8^+$ T cells. Additionally, it reduces immune-suppressing molecules like IL-10 and arginase, which consequently play a significant role in inhibiting tumor progression[191,192]. Furthermore, specifically targeting and inhibiting PI3Kγ holds great potential in the treatment of tumors that are resistant to ICIs[191,193]. Studies have also explored the potential of co-targeting M2-like macrophages by utilising nanocellular micelles to deliver PI3Kγ inhibitors along with siRNA targeting CSF-1R. This approach aims to remodel the TME and elicit a favourable anti-tumor response[194]. Meanwhile, studies have reported that baicalein could be a promising PI3Kγ inhibitor that induces the polarisation of TAMs to M1-like macrophages via the NF-κB/TNF-α signalling pathway. Furthermore, it has demonstrated notable anti-tumor effects in a murine model of CM[195]. In BRAF-mutated CM, the development of resistance to MEK1/2 inhibitors has been shown to be inhibited by the administration of PI3Kγ inhibitors[196]. Nevertheless, the majority of ongoing studies regarding this category of drugs for skin cancer are currently in the clinical trial phase. Therefore, further assessment of their effectiveness and safety is necessary.

Toll-like receptor agonists

TLRs are pattern recognition receptors present in macrophages and DCs. They facilitate the identification and response to foreign pathogens, playing a crucial role in inflammation and regulation of immune cells. Among them, MyD88 acts as the principal adaptor protein in the TLR signalling pathway[197]. In a mouse model of CM, the polarisation of TAMs from an M2-like to an M1-like phenotype, facilitated by the TLR-MyD88 signalling axis, was observed to play a significant role in restraining CM growth[198]. Nonetheless, it has also been proposed that the MyD88/IL1R axis can upregulate PD-1 expression on TAMs, which is crucial for sustaining the immunosuppressive function of TAMs in CM[199]. Therefore, a comprehensive investigation into the specific effects of the TLR-MyD88 signalling axis on TAMs and tumors is necessary to facilitate the precise development of this drug class in the future.

Blockade of CD47-SIRPα interaction

CD47 molecules on tumor cells interact with SIRPα on TAMs to impede the phagocytosis of tumors by macrophages, effectively acting as an "accomplice" in immune evasion. SIRPα serves as a docking protein that activates the Src homology region 2 (SH2) structural domain phosphatases SHP1 and SHP2. The expression of CD47 is notably elevated in skin cancer compared to normal tissues, resulting in immune suppression and often serving as an indicator of a poor prognosis for the patient. In skin cancer, the expression of CD47 is significantly increased compared to normal tissues, leading to immune suppression and frequently implying an unfavourable prognosis for the patient[200,201]. In a CM mouse model, the simultaneous inhibition of CSF-1R and SHP2 demonstrated notable outcomes. It not only successfully reprogrammed M2-like macrophages into an active M1 phenotype but also significantly augmented TAMs' phagocytic activity. These findings underscore the benefits of employing a combination of CSF-1R inhibitors and SHP2 inhibitors in the treatment of CM[202]. Likewise, the inhibition of CD47 has been observed to enhance the sensitivity of CM to anti-PD-1 drug therapy. This combination approach not only improves treatment efficacy but also reduces tumor burden. These findings indicate the promising potential of combining CD47 inhibitors with PD-1 inhibitors in the management of CM[203]. Naturally, the development of drugs targeting

Table 2
R&D targeting the CSF-1/CSF-1R axis in combination with other therapies.

Type	Target	Name	Combination drugs	Status	Country	Applications	NCT
Small Molecule Drugs	CSF-1R	ARRY-382	Pembrolizumab	Phase 1/2	USA	Advanced solid tumors	NCT02880371
		Pexidartinib (PLX-3397)	Placebo	Phase 3	USA	PVNs, TGCT	NCT02371369
			Pembrolizumab	Phase 1/2	USA	Melanoma, Ovarian cancer, NSCLC, HNSC, GIST	NCT02452424
			Temozolomide, Radiation Therapy	Phase 1/2	USA	Newly diagnosed glioblastoma	NCT01790503
			Paclitaxel	Phase 1	USA	Solid tumors	NCT01525602
			Binimetinib	Phase 1	USA	GIST	NCT03158103
			PLX9486, Sunitinib	Phase 1/2	USA	GIST	NCT02401815
			Durvalumab	Phase 1	France	CRC, PCA, metastatic cancer, advanced cancer	NCT02777710
		Regorafenib	Camrelizumab, Toripalimab, Pembrolizumab	Phase 2	China	HCC	NCT05048017
			Sildenafil Citrate	Phase 1	USA	Solid tumors	NCT02466802
			Nivolumab	Phase 1/2	Japan	Advanced and metastatic solid tumors	NCT03406871
		Surufatinib	Tislelizumab	Phase 1/2	USA	Metastatic solid tumors, gastric cancer, NETs, SCLC, STS, ATC, CRC	NCT04579757
			Temozolomide, S-1	Phase 1/2	China	Neuroendocrine tumors	NCT06038461
			Sintilimab	Phase 1	China	Advanced or metastatic solid tumors	NCT04427774
Monoclonal Antibody		Cabiralizumab	Nivolumab	Phase 1	USA	Advanced solid tumors, head and neck cancer, malignant glioma, ovarian cancer, PCA, RCC, NSCLC	NCT02526017
			Nivolumab, APX005M	Phase 1	USA	Advanced melanoma, NSCLC, RCC	NCT03502330
			Nivolumab	Phase 2	USA	PTCLs	NCT03927105
			Nivolumab	Phase 2	USA	HCC	NCT04050462
			Nivolumab, stereotactic body radiotherapy	Phase 2	USA	PCA	NCT03599362
			Nivolumab, Gemcitabine	Phase 3	USA	PCA	NCT03697564
			Nivolumab, Paclitaxel, Carboplatin	Phase 1/2	USA	TNBC	NCT04331067
		LY3022855	Durvalumab, Tremelimumab	Phase 1	USA	Solid tumors	NCT02718911
			Vemurafenib, Cobimetinib	Phase 1/2	USA	Melanoma	NCT03101254
			Pembrolizumab, Cyclophosphamide, GVAX	Early Phase 1	USA	PCA	NCT03153410
	CSF-1	Lacnotuzumab (MCS-110)	Gemcitabine, Carboplatin	Phase 2	USA	Advanced TNBC with high TAMs	NCT02435680
			Placebo	Phase 2	USA	PVNS, TGCT	NCT01643850
			PDR001	Phase 1/2	USA	Melanoma, TNBC, PCA, Endometrial Carcinoma	NCT02807844
			Dabrafenib, Trametinib	Phase 1/2	USA	Melanoma	NCT03455764
			Spartalizumab, LAG525, NIR178, Capmatinib, Canakinumab	Phase 1	USA	TNBC	NCT03742349

ATC: anaplastic thyroid cancer; BTC: biliary tract cancer; CRC: colorectal cancer; EC: endometrial carcinoma; HCC: hepatocellular carcinoma; HNSC: squamous cell carcinoma of the head and neck; GIST: gastrointestinal stromal tumor; NETs: neuroendocrine tumors; NSCLC: non-small cell lung cancer; TGCT: tenosynovial giant cell tumor; TNBC: triple negative breast cancer; PCA: pancreatic cancer; PP-ALL: plexiformprecursor cell lymphoblastic leukemia-lymphomleukemia; PTCLs: peripheral T cell lymphoma; PVNS: pigmented villonodular synovitis; RCC: renal cell carcinoma; SCLC: small cell lung cancer; STS: soft tissue sarcoma.

CD47/SIRPα is progressing rapidly, as they have the ability to revive TAMs' phagocytic activity towards tumors and fully leverage the innate immune function of macrophages. This class of drugs holds vast potential for further development.

Otherwise

Indeed, the rapid advancements in nanotechnology have presented novel research avenues for modulating TAMs in the treatment of skin cancer. For instance, utilising TAMs or their extracellular vesicles such as exosomes and cell membranes derived from macrophages as carriers to deliver diverse classes of drugs directly to the tumor site holds great promise. This targeted drug delivery approach has the potential to effectively eliminate tumors. As a result, there is substantial room for the development of macrophage-mediated drug delivery systems, which will significantly improve the current treatment landscape for various malig-

nant solid tumors, including drug-resistant and metastatic tumors. These advancements bring forth renewed hope and countless possibilities[204,205].

In conclusion, our investigation reveals that the predominant therapeutic strategies targeting TAMs, in both preclinical investigations and clinical trials, have been amalgamated with ICIs, such as anti-PD1, anti-PDL1, and anti-CTLA4 antibodies for managing diverse categories of skin cancer, encompassing CM. This underscores the widespread acknowledgment of remodelling the TME by specifically addressing TAMs with immunosuppressive attributes. The amalgamation of strategies for modulating TAMs with prevailing immunotherapeutic agents holds considerable promise for the future and imparts renewed momentum to the realm of immunotherapy.

Conclusion and outlook

Presently, the escalating incidence of skin cancer constitutes a substantial menace to human health and well-being. Conventional treatment modalities have proven inadequate in meeting the requisites for effective management. Despite the emergence of tumor immunotherapy as a promising avenue in recent years, impediments such as drug resistance and adverse reactions often thwart its success. This study centres on scrutinising the role of TAMs within the TME, presenting a methodical overview of their origins and classifications. In contrast to other reviews[206,207], this paper delves into the intricate interactions between TAMs and diverse immune cells, highlighting the central role of TAMs. Moreover, we systematically summarise the mechanisms through which TAMs contribute to various skin cancer, including CM, BCC, cSCC, MCC, and EMPD. Besides, we discuss prevailing therapeutic strategies and pharmaceutical agents designed to modulate TAMs for skin cancer treatment, providing valuable insights into this domain. Our findings indicate that, among therapeutic strategies targeting TAMs, reprogramming holds greater theoretical promise and rationale compared to the direct removal of TAMs or inhibition of their recruitment. Additionally, research on TAMs reprogramming is more comprehensive, with several therapeutic agents targeting skin cancer undergoing clinical trials or having already obtained market approval. These agents demonstrate considerable potential in addressing the shortcomings of current ICIs, thereby introducing innovative immunotherapy approaches for a diverse spectrum of tumors, including skin cancer, with widespread applicability. Furthermore, ongoing progress in nanotechnology continually enhances drug delivery systems, consistently supporting the development of TAMs modulation therapies for skin cancer treatment.

Nevertheless, ongoing research on TAMs lacks the depth required for comprehensive understanding. Notably, TAMs exhibit a high degree of complexity and manifest diverse classes and functions in response to varied physiological and pathological conditions, alongside different measures of drug administration. Regrettably, extant classification methods prove inadequate in capturing this nuanced aspect of TAMs. Furthermore, the investigation of TAMs in skin cancer, taken as a whole, is still in its early phases, with a considerable proportion of studies concentrating solely on CM. Consequently, there exists a substantial void in elucidating TAMs' roles in other skin cancer, presenting extensive opportunities for subsequent investigations. Additionally, TAMs demonstrate heterogeneity across various skin cancer, frequently showcasing distinctive phenotypes and functions. Even within the confines of the same cancer, their functionality remains a subject of contention, underscoring the imperative need for more thorough exploration to unravel their intricate biological mechanisms.

Author statement

Chen Zhongjian & Quangang Zhu: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Zongguang Tai:** Writing – review & editing, Supervision, Project administration, Formal analysis. **Jun Liu:** Conceptualization, Writing – original draft, Writing – review &editing, Visualization, Investigation, Validation. **Jiaye Lu:** Conceptualization, Data curation, Writing – original draft, Writing – review &editing, Visualization, Methodology, Resources. **Ling Wu & Tingrui Zhang:** Investigation, Validation, Formal analysis, Methodology, Supervision. **Junchao Wu & Lisha Li:** Supervision, Resources, Project administration and Software.

Declaration of competing interest

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.

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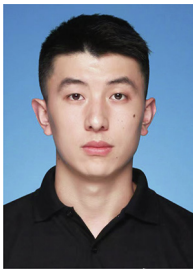
Jun Liu is a joint Master Student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University. Jun Liu current research focuses on the immunotherapy of skin cancer.

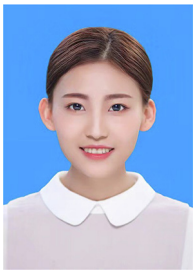
Jiaye Lu is a joint Master Student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University and Shanghai University. Jiaye Lu current research focuses on the therapeutic effect of nanodrug delivery systems for tumors in melanoma.

Ling Wu is a joint Ph.D student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University. Her main research interests include design of cancer drug delivery as well as pharmacological mechanisms.

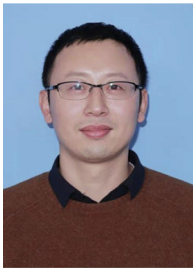


Tingrui Zhang is a joint Master Student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University and Shanghai University. Tingrui Zhang current research focuses on repairment of skin tissue.

Junchao Wu is a joint Master Student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University and Shanghai University. Junchao Wu current research focuses on pathogenesis and intervention treatment of atopic dermatitis.



Lisha Li is a joint Master Student in both Department of Pharmacy at Shanghai Skin Disease Hospital, School of Medicine, Tongji University and Shanghai University. Lisha Li current research focuses on ionic liquids and their application in the field of medicine.



Zongguang Tai is an associate chief pharmacist of Shanghai Skin Disease Hospital, School of Medicine, Tongji University. He received his PhD from Naval Medical University. His research interest includes innovative drugs for dermatology, emerging immunotherapy, and drug delivery system.

Zhongjian Chen is the vice president of Shanghai Skin Disease Hospital, School of Medicine, Tongji University. He holds a Ph.D of Medicine and is also a professor of Pharmacy at Tongji University School of Medicine. His research activity includes pharmacology of skin, topical drugs, nanomedicine and novel drug delivery systems.

Quangang Zhu is the Director of Department of Pharmacy and GCP (Good Clinical Practice) Office of Shanghai Skin Disease Hospital, School of Medicine, Tongji University. He holds a Ph.D. of Pharmacy and is also a Professor of Pharmacy at Tongji University School of Medicine. His research activity includes pharmacology of skin, topical drugs, nanodelivery systems, and novel drug delivery systems.