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The immunology of rheumatoid arthritis

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The immunopathogenesis of rheumatoid arthritis (RA) spans decades, beginning with the production of autoantibodies against post-translationally modified proteins (checkpoint 1). After years of asymptomatic autoimmunity and progressive immune system remodeling, tissue tolerance erodes and joint inflammation ensues as tissue-invasive effector T cells emerge and protective joint-resident macrophages fail (checkpoint 2). The transition of synovial stromal cells into autoaggressive effector cells converts synovitis from acute to chronic destructive (checkpoint 3). The loss of T cell tolerance derives from defective DNA repair, causing abnormal cell cycle dynamics, telomere fragility and instability of mitochondrial DNA. Mitochondrial and lysosomal anomalies culminate in the generation of short-lived tissue-invasive effector T cells. This differentiation defect builds on a metabolic platform that shunts glucose away from energy generation toward the cell building and motility programs. The next frontier in RA is the development of curative interventions, for example, reprogramming T cell defects during the period of asymptomatic autoimmunity.

Initial evidence for an autoimmune pathogenesis for RA came from the discovery of autoantibodies against the Fc portion of IgG, the so-called rheumatoid factor (RF) first described by the Norwegian investigator Erik Waaler in 1940. Since then, concepts of autoimmunity have been extensively modified and, accordingly, RA is now understood as a chronic immune-mediated disease in which multiple immune cells types and signaling networks malfunction to elicit a maladaptive tissue repair process that leads to organ damage predominantly in the joints but also in the lungs and the vascular system.

Genetic studies have identified more than 100 polymorphisms conferring disease risk, have confirmed the strong association of RA with MHC class II alleles and have reinforced the central role of adaptive immunity, particularly effector T cells. Twin studies have emphasized the contribution of environmental exposures, which may function as triggers of innate immunity and may contribute to the breakdown of self-tolerance by modifying protein antigens.

Two developments have dovetailed to give new understanding of human autoimmune disease, and both have spearheaded new concepts of RA. Immunology has seen astonishing progress in the definition of cell types, cell–cell interactions, intracellular signaling pathways and the genetic control of immune system components. Recognition that T cell and B cell responses to (auto) antigen are under contextual control has opened understanding of non-antigenic determinants in autoimmunity, ranging from microenvironmental regulation to metabolic control of cell fate. Genomics, proteomics and single-cell technologies have added granularity to the analysis of immune responses. Of equal impact have been epidemiologic studies that have revised the understanding of when and where self-tolerance is lost and how autoimmunity can persist in individuals for decades before it causes clinically apparent disease.

It is now evident that RA is an almost lifelong process in which genetically predisposed individuals lose self-tolerance and begin to produce autoantibodies. A phase of disease risk is followed by a phase of asymptomatic autoimmunity, characterized by prototypic autoantibodies that are reactive against post-translationally modified proteins, often citrullinated antigens. Individuals carrying such antibodies to modified protein antigens are asymptomatic for years to decades. Eventually, some enter a new phase and become symptomatic with synovitis. Often, acute joint inflammation transitions into chronic, destructive synovitis. At this stage of disease, the tissue responds with a maladaptive wound healing response, described as pannus formation, which by itself has destructive features and will lead to irreversible tissue injury targeting tendons, cartilage and bone. The evolution of RA over an individual's lifetime includes distinct transition points at which the disease process takes a transformative step (Fig. 1). At each checkpoint, the immune system fails to maintain tolerance, and protective immunity switches to pathogenic immunity in a disease-specific manner.

The immunology of preclinical RA

As a clinical entity, RA is a disease of the sixth decade of life[1]. As an immunological entity, RA begins years to decades earlier (Fig. 1)[2]. Genetic polymorphisms contribute 30–60% of the overall risk[3,4]. HLA class II alleles confer the strongest risk; specifically, *HLA-DRB1* alleles containing a particular sequence at amino acid residues 71–74 of the β-chain[5,6]. This sequence ('shared epitope'), together with amino acid residues 11 and 13, forms an antigen-binding pocket, pocket 4, implicating the HLA antigen–T cell receptor complex in disease risk. Among the >100 non-HLA genes predisposing to RA, many are involved in shaping the selection, maturation and function of T cells[7,8].

The conversion of immune health to autoimmunity and the transition to relentless tissue inflammation develops over decades, consistent with progressive immune system remodeling. The functionality of the T cell compartment is highly time-dependent, with profound restructuring as the host ages. Dominated by thymic generation during the prenatal period and childhood, T cell production switches to alternate processes thereafter, when homeostatic proliferation takes over as the dominant replenishment mechanism and peripheral tolerance mechanisms trump thymic selection[9]. The repertoire of protective and pathogenic T cells in a 20-year-old is fundamentally different from the repertoire in a 55-year-old with clinically apparent RA[10]. This time dependence implicates immune system and tissue aging as critical in all stages of RA. A temporal separation of tolerance breakdown and immune-mediated tissue destruction and the recognition that autoantibodies precede clinical

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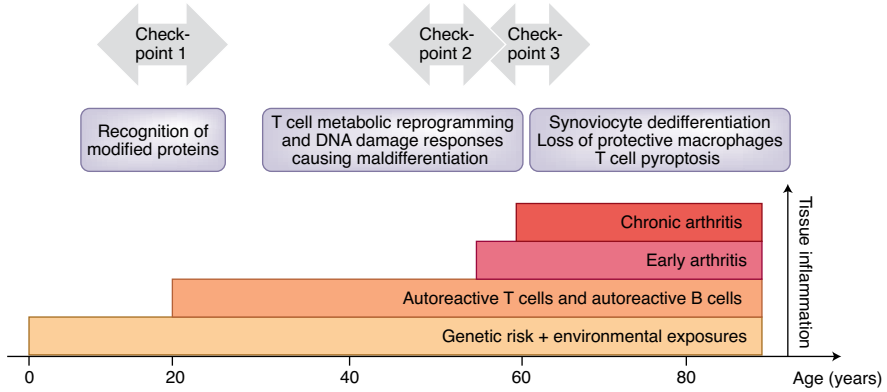

Fig. 1 | Evolution of rheumatoid arthritis over an individual's lifetime. The disease process of RA begins with an individual transitioning from being at risk to having overt autoimmunity. Recognition of modified protein antigens and the emergence of autoantibodies mark the loss of self-tolerance (checkpoint 1). The timing and location of this tolerance defect are not precisely identified, but autoantibodies appear years to decades before obvious joint disease. The individual with overt autoimmunity is clinically asymptomatic. A cell-intrinsic shift in metabolic networks and DNA instability drive T cell maldifferentiation toward tissue-invasive short-lived effector T cells. The failure of tissue tolerance manifests as early synovitis during the sixth decade of life (checkpoint 2) and transitions relatively quickly into chronic synovitis (checkpoint 3). Autoaggressive dedifferentiated synoviocytes, loss of tissue-protective macrophage populations and T cell pyroptosis drive joint damage. The loss of tissue tolerance is irreversible in the majority of cases.

disease by years to decades are generalized rules in human autoimmune disease. Prospective studies of children at risk for type 1 diabetes mellitus (T1DM) revealed antibodies reactive against pancreatic beta-cell antigens long before target tissue destruction. Autoantibodies against nuclear antigens are present years before the diagnosis of systemic lupus erythematosus (SLE), and the spectrum and number of autoantibody specificities progressively increases until the presentation of clinical disease[11,12].

Checkpoint 1—systemic breakdown of self-tolerance

The initial tolerance breakdown and causally relevant upstream events occur outside the joint. Epidemiologic studies in the early 1990s revealed the presence of RFs long before synovitis developed[13]. Subsequent reports of autoantibodies to citrullinated and carbamylated antigens in the presynovitic stage documented that tolerance breakdown precedes clinically apparent RA[14]. In contrast to T1DM, there is no clear temporal or functional relationship between the different antigenic systems in RA. Citrullination and carbamylation (resulting in homocitrulline formation) are post-translational protein modifications[15]. Similarly, RFs can recognize glycation-modified IgG Fc fragments[16]. Thus, RA autoimmunity is not directed against native peptide sequences but rather, as a rule, against post-translationally modified proteins, introducing a high degree of multireactivity. Since thymic selection does not purge T cells recognizing protein modifications, a peripheral tolerance defect is believed to be dominant in RA[17].

Evidence suggests that the major genetic risk factors for RA promote autoantibody production. Shared-epitope-positive HLA-DRB1 alleles and the PTPN22 variant are associated with the production of RFs and anti-citrullinated protein antibodies (ACPA). T cells can recognize citrullinated antigens in the context of HLA-DRB1*04, and the autoimmune B cell response encompasses a large spectrum of citrullinated proteins, consistent with primary T cell responses to citrullinated peptides presented by B cells[18–21].

Aside from genetic risk factors, the maintenance of peripheral tolerance of post-translational modifications is context dependent. Citrullination and carbamylation are distinct chemical reactions, both universal and physiological, with no clues for a common denominator to explain disease specificity[21]. Carbamylation is an enzyme-independent derivatization of lysine, requires the reactive metabolite cyanate and is essentially irreversible. By contrast, citrullination is an enzyme-mediated deimination of an arginine residue. Tissue inflammation and smoking upregulate peptidyl arginine deiminase expression[22]. Although intuitive, self-antigen abundance appears to not be important in the process of quorum sensing that regulates tolerance. Mucosal tissue sites[23] and neutrophil extracellular traps[24,25] may provide relevant contextual signals through which citrullinated antigens gain immunogenicity, supporting that early steps of tolerance loss may occur in the lung and the gut. Nevertheless, how tolerance to the modified peptides is broken remains unclear, and a common denominator between citrullination, carbamylation and glycation that distinguishes them from other post-translational modifications has not emerged.

Mechanisms that control the stability and progression of the autoimmune stage are dependent on T cells. Healthy HLA-DR4$^+$ individuals and asymptomatic first-degree relatives of patients with RA have typical telomere damage and abnormal T cell differentiation[26,27], indicative of predisease immune system remodeling. Individuals who lose their autoantibodies and do not develop synovitis lack RA-associated HLA-DRB1 alleles. B cell depletion in individuals with arthralgias delayed the onset but did not prevent the development of synovitis[28]. T cell–dependent antibody isotype switching occurs early in the autoimmune process, since different autoantibody isotypes are generally present[15]. Also, somatic hypermutation appears important in disease progression, as it generates uncommon *N*-glycosylation sites in the V region of ACPAs[29]. More than 90% of ACPAs carry *N*-linked glycans in their V region, exemplifying the dependence of autoimmunity on T cell help.

Checkpoint 2—transition from asymptomatic autoimmunity to tissue inflammation

After a prolonged period of asymptomatic autoimmunity, patients with RA experience a second fundamental tolerance defect (Fig. 1). The initial breakdown of self-tolerance triggering autoantibody production occurs outside of the joint. Eventually, the disease process shifts localization and innate and adaptive immune cells enter the synovial membrane. Environmental exposures, such as exposure to the host's gut microbiota, may function as decisive risk elements[30]. CD3$^+$ T cells are present in most early synovitis cases[31,32], and the histologic phenotype of synovial biopsy samples predicts disease persistence and severity. A decreased frequency of naive CD4$^+$ T cells is the strongest predictor for the progression from ACPA positivity to synovitis[33]. Unbiased multiparametric studies in patients with early and untreated disease have confirmed that

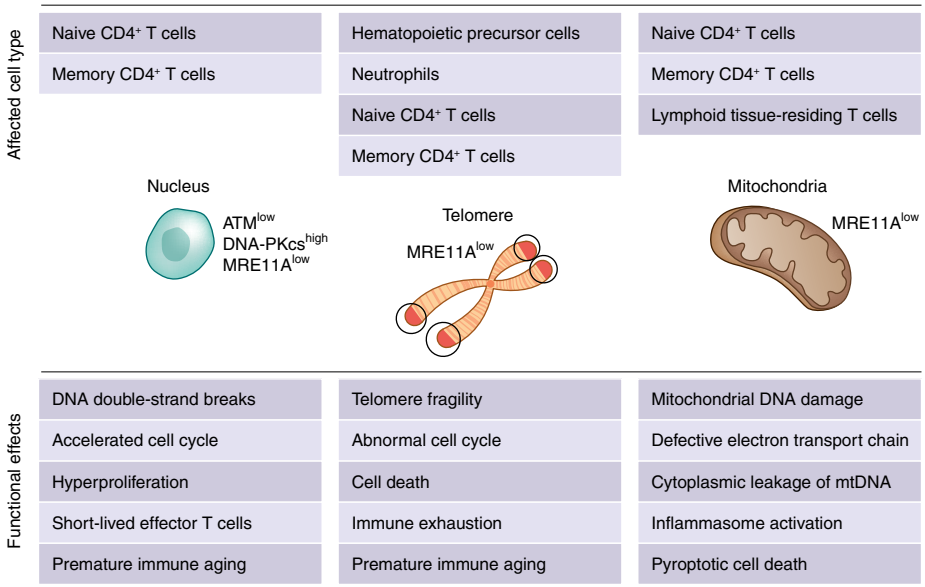

Fig. 2 | DNA repair deficits in rheumatoid arthritis. In patients with RA, molecular defects have been localized to the machinery that senses and repairs DNA double-strand breaks. Insufficient DNA repair occurs in hematopoietic stem cells, neutrophils and naive and memory CD4+ T cells. Age-inappropriate decline of the repair molecules ATM and MRE11A leads to the accumulation of damaged DNA in the nucleus, at the telomeric ends and in mitochondria. Downstream consequences include deviations in cell cycle passage, premature telomeric loss and cytoplasmic leakage of mtDNA, which triggers inflammasome activation. Ultimately, insufficient DNA repair gives rise to a T cell differentiation defect favoring the induction of short-lived effector T cells at the expense of long-lived memory precursor cells. Also, unrepaired DNA damage promotes T cell pyroptosis, immune exhaustion and premature immune aging. Breakage of mtDNA affects the electron transport chain, impairs the production of ATP and metabolic intermediates and reprograms the cell's energy production and biosynthetic program.

circulating CD4+ T cells with phosphorylated p38, cJun and NF-κB serve as the best classification parameter to distinguish patients with RA from healthy individuals[34]. Epigenetic studies at the earliest stages of joint inflammation and in patients who were drug naive have identified differential methylation patterns specifically in naive CD4+ T cells[35]. Lymphopenia-induced T cell expansion functions as a strong inducer and amplifier of chronic synovitis[36].

Checkpoint 2, marked clinically by the onset of synovial inflammation, is closely linked to cell-intrinsic defects in CD4+ T cells and is functionally caused by a misdifferentiation step during the conversion of naive resting CD4+ T cells into memory and effector T cells[37–39]. Naive CD4+ T cells from patients with RA transition into highly proliferative, tissue-invasive and proinflammatory effector cells, rather than into relatively quiescent memory T cells. Equipped with tissue-invasive features, RA CD4+ T cells rapidly induce synovitis in a human synovium mouse chimera model. This differentiation abnormality is mechanistically linked to defects in the DNA repair machinery and in the reprogramming of cellular bioenergetics, with the two deficiencies connected by the insufficient repair of mitochondrial DNA (mtDNA)[37,38,40] (Fig. 2). The presence of these defects in the naive CD4+ T cell population and in lymph-node-residing T cells[40] places the pathology outside of the joint. The major offspring of naive RA CD4+ T cells, short-lived effector T cells (SLECs), swiftly enter the synovial tissue environment, where they undergo pyroptotic cell death[40], sparking intense inflammation. Therefore, they may function as inducers of leukocyte-rich as well as leukocyte-poor synovitis.

Early studies revealed that naive RA CD4+ T cells have shortened telomeric sequences[41,42] and have shifted their cell surface phenotype[33,43,44]. When compared to patients with chronic hepatitis C infection or age-matched healthy individuals, patients with RA have a contracted diversity in the CD4+ T cell receptor repertoire[41]. These findings gave rise to the 'premature immune aging' hypothesis[45,46], which proposes that a diagnosis of RA is associated with accelerated immune aging, accumulation of expanded clonotypes and depletion of the proliferative reserve inherent in a healthy naive T cell population[47,48].

Telomeric erosion could be a consequence of high proliferative pressure. Recent studies, however, have linked telomeric shortening to the fragility of the terminal sequences, showing that the loss of telomeric sequences is a consequence of a defect in DNA repair[49]. The underlying molecular processes are now beginning to be understood (Fig. 2).

Mechanistic studies relevant for understanding the breakdown of tissue tolerance (checkpoint 2) need to capture the RA disease process before the establishment of synovitis. One approach is to examine naive T and B cell populations, which reside outside of the synovial lesions, and study their transition from the naive to the effector and memory states, which is required for tissue entry. This approach has yielded evidence for several defects in the DNA repair machinery (Fig. 2). RA T cells are low expressers of the serine/threonine kinase ataxia telangiectasis mutated (ATM)[50], which senses DNA double-strand breaks and activates the DNA damage checkpoint, controlling cell cycle progression and susceptibility to cell death[51]. Upon activation, ATM-deficient RA T cells accumulate unrepaired DNA[50] and bypass the G2–M cell cycle checkpoint, promoting a hyperproliferative phenotype[52]. While healthy naive T cells activate distinct signaling and transcription factor networks that guide their differentiation into SLECs or memory precursor cells (MPECs)[53], ATM-deficient T cells are strongly biased to develop into SLECs capable of infiltrating into the synovial membrane, wherein they function as effective drivers of tissue inflammation. Accumulation of DNA double-strand breaks induces upregulation of the damage sensor DNA-PKcs and activation of the stress kinase pathway, culminating in cell death[54]. As part of what appears to be a coordinated program of dampened DNA repair, RA T cells are also low expressers of the DNA repair nuclease MRE11A[49,55], a component of a multifunctional DNA damage repair machine that

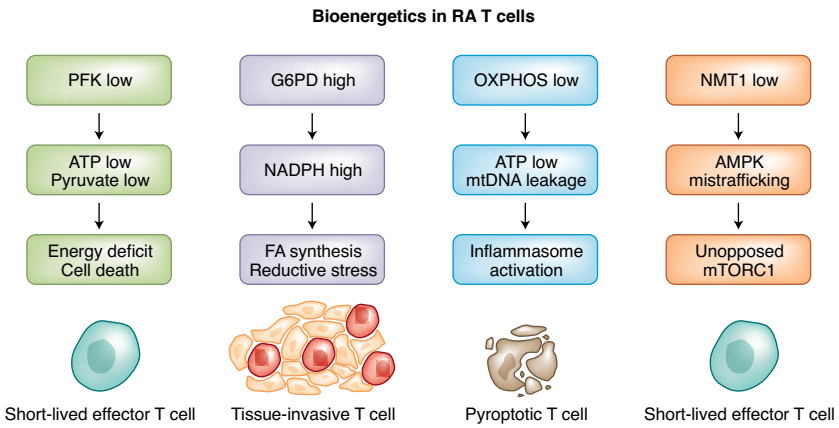

Fig. 3 | Metabolic reprogramming and proinflammatory effector functions in RA T cells. Several molecular defects that shift the metabolic and bioenergetic conditions in RA T cells have been identified, and they ultimately shift the cell's differentiation program and shorten survival. Transcriptional repression of the glycolytic enzyme phosphofructokinase (PFK) impairs pyruvate production and thus mitochondrial function, favoring SLECs over long-lived memory T cells. Increased activity of glucose-6-phosphate dehydrogenase (G6DH) shunts glucose into the pentose phosphate pathway, supporting biosynthetic activity and daughter cell generation. Oversupply of NADPH supports the lipogenic program and formation of tissue-invasive membrane structures. Damage to mtDNA weakens mitochondrial fitness and energy production and triggers inflammasome activation and, ultimately, immunogenic T cell death. Misrouting of the energy sensor AMPK away from the lysosomal surface, caused by *N*-myristoyltransferase 1 deficiency, enables unopposed mTORC1 activation and SLEC generation.

coordinates genomic stability programs at DNA replication forks and at double-strand break sites[56]. In naive and memory RA T cells, MRE11A is depleted from two critical territories: the telomeric ends and the mitochondrial genome. A functional consequence is that chromosomal ends become unstable, leading to damage patterns that are highly infrequent in healthy CD4$^+$ T cells but enriched in RA CD4$^+$ T cells[49]. MRE11A deficiency manifests as telomere fragility, accelerated aging exemplified by CD57 induction and a high propensity to invade synovial tissue and promote synovitis. Failure of MRE11A to protect genome stability has equally devastating consequences for mtDNA. MRE11A^{lo} RA T cells are compromised in operating the mitochondrial electron transport chain, expend low amounts of oxygen and produce low concentrations of ATP[55]. The bioenergetic failure is coupled with the accumulation and leakage of damaged mtDNA, leading to inflammasome assembly, caspase-1 activation and immunogenic cell death[55,57].

In essence, defective DNA repair responses commit RA T cells to abnormalities in cell differentiation. Functional outcomes include a bias toward SLECs instead of memory cell generation, a reduction in T cell longevity and the accumulation of effector cells inclined to leave lymphoid storage sites and settle in peripheral tissue environments (Fig. 3). The skewing toward SLECs and away from protective memory T cells may also compromise host immunity, which is typical for RA.

Implicating biased effector cell differentiation in RA gives rise to several predictions, many of which are fulfilled in the patients. (1) T cell memory responses in patients with RA would be predicted to be weakened. Supporting data come from studies of antibody responses against biopharmaceutical proteins, so-called anti-drug antibodies elicited by therapeutic biologics[58]. Patients with RA are significantly less efficient at producing anti-drug antibodies than patients with spondylarthritis[59]. (2) The longevity of RA T cells should be compromised[43,60]. In support of this, T cell populations in the lymph nodes of patients with RA are less dense and have activated caspase-1[55], resulting in cell death. The global T cell repertoire is contracted, with expanded clonotypes filling the space[41,61]. (3) The preferential differentiation of naive CD4$^+$ T cells into SLECs at the expense of MPECs imposes proliferative pressure to compensate for T cell loss. Surviving memory T cell populations, including central and effector memory T cells, are under constant demand to repopulate. First described in the RA synovium and in peripheral blood[61], CD4$^+$CD28$^-$ T cells have features of premature aging[62–64], are clonally expanded and autoreactive. The expansion of CD4$^+$CD28$^-$ T cells is a feature shared by patients with RA and patients with coronary artery disease (CAD)[65–67], providing a common pathomechanism for these two chronic inflammatory and age-associated disease states. In support of this, CAD risk in patients with RA is related to telomeric length, which is a marker of accelerated immune aging[68]. Typifying features of aged T cells are the high production of IFN-γ[69] and the acquisition of natural killer cell receptors and cytolytic activities[69–71], classifying them as 'innate-like' cells[72,73]. In a recent study, CD27$^-$CD28$^-$ T cells were found to mediate cytotoxicity through a sestrin–NKG2D–DAP12 complex, reminiscent of killing by NK cells[74]. In contrast to young and less differentiated T cells, such aged T cells are less dependent on antigen and on classical costimulatory signaling networks, rendering them highly competent in promoting chronic tissue inflammation. The enrichment of highly differentiated CD27$^-$ cytotoxic effector memory T cells in the synovial lesions of patients with RA has been confirmed by recent single-cell transcriptomic and mass cytometry approaches[75,76].

The exact timing of when end-differentiated and clonally expanded effector CD4$^+$ T cells appear in at-risk individuals is undetermined, but studies of unaffected siblings of patients with RA have demonstrated CD4$^+$ T cell oligoclonality[27], consistent with inheritance of the differentiation defect and excluding synovial inflammation as the causative driver. Similarly, telomeric erosion has been described in healthy individuals carrying the HLA-DRB1*04 disease risk haplotype[26], indicating that the premature immune aging phenotype in the adaptive immune system is part of the risk profile of individuals predisposed to RA but not a consequence of rheumatoid synovitis. Telomere fragility with age-inappropriate telomeric loss affects the neutrophil lineage of healthy individuals with HLA-DRB1*04 (ref. [26]) and the hematopoietic stem cell compartment in patients[77], impairing the capacity to replenish innate as well as adaptive immune cells.

Immunometabolic signatures of proinflammatory effector T cells

Insufficient DNA repair not only disrupts cell cycle passage, cell differentiation and cell fate, it also reprograms the cellular

bioenergetics of T cells. Rewiring of metabolic networks in RA T cells supports the cells' diversion toward SLEC generation (Fig. 3), linking metabolic programs to the breakdown of tissue tolerance[78]. Besides fostering the emergence of short-lived effectors, metabolic activity in RA T cells directly supports proinflammatory behaviors, for example, the T cell motility program[38,79] and immunogenic cell death[55].

Four key metabolic abnormalities have been identified in patient-derived naive CD4$^+$ T cells undergoing activation (Fig. 3)[37]. (1) RA T cells transcriptionally repress the key glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (ref. [80]), resulting in reduced pyruvate and lactate production. (2) RA T cells upregulate glucose-6-phosphate dehydrogenase, shunting glucose to the pentose phosphate pathway, away from glycolysis. With higher concentrations of NADPH[52,81], cellular redox signaling is impaired, the redox sensor ATM is insufficiently dimerized, the G2–M cell cycle checkpoint fails and cells hyperproliferate. A surplus of NADPH facilitates the lipogenic program, promotes the formation of invasive membrane structures and accelerates tissue invasion[79,82]. (3) RA T cells lose mitochondrial MRE11A, which damages mtDNA, impairs the electron transport chain and suppresses ATP production. mtDNA fragments leak into the cytoplasm, are recognized by the inflammasome, activate caspase-1 and trigger lytic cell death (T cell pyroptosis). Caspase-1 activation is a feature of RA lymph node T cells. Pyroptotic T cells are strongly proinflammatory but remain invisible in the tissue and escape detection by transcriptomic approaches[55,83]. Mitochondrial failure reduces the production of reactive oxygen species (ROS), aggravating the failure of redox signaling. T cell mitochondrial failure has been identified as the mechanism driving autoimmunity in C1q deficiency[84]. (4) Energy sensing is defective in RA T cells. Due to an insufficiency in *N*-myristoyltransferase 1, RA T cells fail to post-translationally modify the energy sensor 5′ AMP-activated protein kinase (AMPK)[85]. Non-myristoylated AMPK cannot be recruited to the lysosomal surface, remains inactivated and fails to prevent mTORC1 activation. Persistent mTORC1 activation is a hallmark of SLECs.

The metabolic program of RA T cells is disease-specific and distinct from that of other autoimmune diseases, specifically SLE. SLE T cells rely on high mitochondrial ROS production[86–89]. SLE type 17 helper T cells depend on metabolic signaling[90,91], which is consistent with metabolic conditioning diverting T cell differentiation from protective to pathogenic immunity.

Checkpoint 3—transformation of acute synovitis into chronic relentless synovitis

Many but not all patients who present at an early synovitis clinic progress to chronic synovitis and irreversible restructuring of the synovial environment[92]. Chronic synovitis, imposing further proliferative stress on innate and adaptive immune cells, may thus function as a disease amplifier[93]. The synovitic component of RA can be successfully targeted by a multitude of highly sophisticated antirheumatic drugs, and drug-induced remission is now accepted as the treatment goal. Nevertheless, withdrawal of anti-inflammatory medication for the most part prompts recurrence of joint inflammation[94], indicating that checkpoint 3 appears to have no regulatory control over the immune system's basic defects. Critical determinants in the transition from acute to chronic synovitis must derive from the local tissue environment, and detailed studies have demonstrated the active pathogenic role of dedifferentiated synoviocytes[95]. How such synovial fibroblasts are activated is insufficiently understood, but tissue-invasive T cells that undergo pyroptosis are potent inducers of inflammation and remodeling[55]. Another avenue through which pathogenic T cells drive chronicity relates to the formation of organized lymphoid structures[96] that lend intensity and durability to inflammatory immunity.

The application of high resolution techniques has provided unprecedented insight into the cellular composition of the synovial lesion[75]. In 51 synovial tissue samples (n =36 RA, n =15 osteoarthritis), four cell populations were separated (T cells, B cells, monocytes and stromal fibroblasts) and subjected to bulk RNA sequencing analysis. Twenty-six samples were analyzed with cytometry and 21 for single-cell RNA expression. To account for lesional variability, RA tissues were split into leukocyte-rich (n =19) and leukocyte-poor (n =17) samples. By integrating multiple data modalities, the study defined 18 cell subpopulations (Table 1), including four fibroblast subsets, four monocyte subsets, six T cell subsets and four B cell subsets. Mechanistic studies will need to explore how each of these 18 cell populations contributes to the lasting structural damage in the joint.

The healthy synovium is a thin mesenchymal membrane that, upon inflammatory attack, expands through fibroblast growth and extracellular matrix deposition. The inflamed synovial membrane is thickened and extensively vascularized, and the subintima is occupied by inflammatory cells (macrophages, T cells and B cells). Fibroblast growth, transformation and matrix production are part of a generalized wound response, exemplified by intimal hyperplasia in inflamed blood vessels[97–99]. Fibrotic responses to chronic tissue inflammation are maladaptive; proper tissue repair fails and stromal cells adopt tissue-destructive and proinflammatory features.

Elegant studies in RA synovial samples and in experimental murine arthritides have identified 4–5 synovial fibroblast (SF) types, all expressing the 'lineage marker' podoplanin (PDPN)[75,100–102]. One SF subset, characterized by the absence of the fibroblast marker CD90/Thy-1, has been located in the lining layer. Sublining SFs, all positive for CD90, have been classified into 3–4 subsets and have been functionally characterized as proinflammatory effector cells. In adoptive transfer experiments in a murine arthritis model, CD90/Thy-1$^+$FAPa$^+$ sublining fibroblasts function as amplifiers of inflammation, driving more severe and more persistent inflammation[102]. Transcriptomic analysis suggests that the SF subset with high HLA-DRA expression is a cellular source of interleukin (IL)-6[75]. Notably, all SF subsets express TNF receptor 1, but none of the stromal subpopulations were identified as TNF producers[75]. Considering the ability of SFs to sustain and exacerbate synovial inflammation, therapeutic modalities have been developed to block SF growth and function. A phase 2 clinical trial testing an anti-cadherin-11 antibody in RA has failed to demonstrate benefit[103].

Synovitic tissues of patients with RA are a macrophage-rich tissue niche[104]. Over the last 20 years, remarkable progress has been made in understanding mononuclear phagocytes. In particular, the recognition that tissues contain tissue-resident macrophages that are seeded during embryogenesis and fetal development have prompted studies to examine the cellular identity and the origin of synovial macrophages. Tissue-resident macrophages adapt to the specialized tissue compartment and contribute to the formation of tissue niches in which cell–cell interactions are optimized and tailored to local requirements. Notable examples include the microglia of the brain, alveolar macrophages and epidermal Langerhans cells. It appears that tissue-resident macrophages possess self-renewal capacities, possibly into adulthood[105]. During adulthood, fetal-derived resident macrophages can be gradually replaced by bone-marrow-derived macrophages, which then adapt to niche-specific phenotypes[106]. In the case of an increased demand for tissue-residing macrophages, such as during inflammatory conditions, bone-marrow-derived monocytes can compensate[107]. Thus, organ sites contain different macrophage subsets with distinct origins and longevity. Superimposed on the cellular heterogeneity of tissue-resident macrophages is their functional heterogeneity, ranging from the well-established pro-defense and proinflammatory functions to the reparative and inflammation-resolving capabilities associated with scavenger receptor expression, high phagocytic

Table 1 | Heterogeneity of cell populations in synovial tissue from patients with osteoarthritis and patients with rheumatoid arthritis

Cell type	OA	Leukocyte-poor RA	Leukocyte-rich RA	Number	Marker	Highly expressed genes	Feature	TNF producer	TNF R1
Fibroblasts	~60%	~50%	~25%	SC-F1	CD90$^+$CD34$^+$	*C3, FOS, PTGFR*	Sublining		*TNFRSF1A*
				SC-F2	CD90$^+$HLA-DRA^{hi}	*HLA-DRB1, HLA-DPA1, IL-6, IFI30*	Sublining Enriched in RA IL-6 producer		*TNFRSF1A*
				SC-F3	CD90$^+$DKK3$^+$	*CADM1, AKR1C2, CAPG, COL8A2*	Sublining		*TNFRSF1A*
				SC-F4	CD90$^-$CD55$^+$	*ITGA6, HBEGF, CLIC5, HTRA4, DNASE1L3*	Lining Enriched in OA		*TNFRSF1A*
Macrophages	~20%	~20%	~20%	SC-M1	IL-1B$^+$	*RGS2, NR4A2, PLAUR, HBEGF, IL1B, ATF3*	Proinflammatory IL-1 producer Enriched in RA	*TNFA*	*TNFRSF1A*
				SC-M2	NUPR1$^+$	*VSIG4, GPNMB, MERTK, NUPR1, CTSK, HTRA1*	IL-1 producer Lost in RA	*TNFA*	*TNFRSF1A*
				SC-M3	C1QA$^+$	*CD14, MARCO*		*TNFA*	*TNFRSF1A*
				SC-M4	SPP1$^+$	*LY6E, IFITM3, IFI6, SPP1*	IFN-activated Enriched in RA	*TNFA*	*TNFRSF1A*
T cells	~8%	~8%	~35%	SC-T1	CD4$^+$CCR7$^+$	*SELL, NFKBIZ, LEF1, IL7R*		*TNFA*	
				SC-T2	CD4$^+$FOXP3$^+$	*CTLA4, TIGIT, DUSP4, FOXP3*	Regulatory T cells	*TNFA*	
				SC-T3	CD4$^+$PDCD1$^+$CXCL13$^+$	*CD200*	T_{PH} and T_{FH} cells IFN-γ producer Enriched in RA	*TNFA*	
				SC-T4	CD8$^+$GZMK$^+$	*NKG7, GZMA*	IFN-γ producer	*TNFA*	
				SC-T5	CD8$^+$GNLY$^+$GZMB$^+$	*ZNF683, PRF1*	Cytotoxic lymphocytes (CTLs) IFN-γ producer	*TNFA*	
				SC-T6	CD8$^+$GZMK$^+$ GZMB$^+$HLA-DPA1$^+$ HLA-DRB1$^+$	*IFN-γ, HLA-DPA1, HLA-DRB1*	IFN-γ producer	*TNFA*	
B cells	~2%	~1%	~8%	SC-B1	IGHD$^+$CD27$^-$	*IL6, IGHM, CD83, BACH2, CXCR4*	Naive IL-6 producer	*TNFA*	
				SC-B2	IGHG3$^+$CD27$^+$	*HLA-DPB1, MS4A1, HLA-DRA*	Memory	*TNFA*	
				SC-B3	CD11c$^+$ITGAX$^+$ TBX21$^+$(T-bet) ACTB$^+$	*GBP1, ISG15, ITGAX, IFI44L, AICDA, ZEB2*	Autoimmune-associated B cell	*TNFA*	
				SC-B4	Immunoglobulin genes and XBP1	*SSR4, MZB1, XBP1, DERL3, CD27*	Plasmablasts		

RA samples were subdivided according to the leukocyte content into leukocyte-poor and leukocyte-rich samples. Cell subsets were assigned on the basis of clustering of transcriptomic single-cell RNA sequences. Highly expressed genes for each subset are given. Topographic assignments were made on the basis of immunostaining of tissue sections. TNF producer status and expression of tumor necrosis factor receptor 1 (TNFR1) are inferred from transcriptomic analysis. Modified from Zhang et al.[75]. OA, osteoarthritis.

capacities and contributions to wound healing[108,109]. In response to inflammatory stimuli, bone-marrow-derived monocytes rapidly travel to injured tissues sites and join the resident macrophage population. Here, a clear distinction between the proinflammatory M1 and the proresolving M2 phenotypes may not always be possible, particularly during chronic inflammation, when there are overlapping waves of proinflammatory and anti-inflammatory signals and cells[110].

CD45$^+$CD14$^+$ synovial cells fall into four subpopulations. In labeling studies, the pool of synovial macrophages was predominantly dependent on the influx of CD14$^+$ blood monocytes[111]. Studies utilizing fate mapping and reporter mice as well as light sheet microscopy have established a specific protective role for lining macrophages in the synovium. CX_3CR1^+ lining macrophages express the receptors VSIG4 and TREM2[112], indicative of anti-inflammatory and phagocytic capacities. VSIG4 inhibits proinflammatory macrophages by driving metabolic adaptations[25]. A remarkable feature of such synovial lining macrophages is the expression of a gene program enriched for genes related to tight junctions, desmosomes and cell polarity, compatible with a barrier function separating the tissue lining and the non-tissue space. In mice, CX_3CR1^+ lining macrophages are constantly replenished by MHC-II$^+$ interstitial

macrophages seated in the synovial sublining. Interestingly, MHC-II$^+$ macrophages supply a third population of RELMA$^+$ interstitial macrophages, with features of anti-inflammatory CD206$^+$ macrophages. The integrity of the shield formed by synovial lining macrophages proved highly protective against inflammation, and elegant studies in murine models demonstrated the disintegration of the macrophage barrier upon synovitis induction. Protective functions of this specialized macrophage subset may be related to the expression of a gene program implicated in the uptake of dying cells and lipid debris (*MERTK*, *AXL* and *TREM2*).

In contrast to the protective VISG4$^+$MERTK$^+$TREM2$^+$ lining macrophages (SC-M2, Table 1), IL-1B$^+$HBEGF$^+$ macrophages (SC-M1, Table 1) have all of the characteristics of proinflammatory tissue-damaging effector cells. Enriched in the RA synovium, HBEGF$^+$ macrophages promote fibroblast invasiveness in an epidermal growth factor receptor–dependent manner[113].

Synovial T cells are dominated by CD4$^+$ T cells, but CD8$^+$ T cells are functionally relevant as well[114]. Consistent with a persistent immune response, tissue-residing T cells have transitioned from naive to memory status. Single-cell transcriptomic analysis combined with cytometry has distinguished three CD4$^+$ and three CD8$^+$ subsets[75]. CD8$^+$ T cell clusters have distinct granzyme expression patterns. In leukocyte-rich RA samples, the CD4$^+$ T cell population includes CD4$^+$PD-1$^+$ICOS$^+$ T cells able to produce the chemokine CXCL13. Unlike circulating follicular helper T (T_{FH}) cells, these CD4$^+$ T cells lack expression of CXCR5; they have been named peripheral helper T (T_{PH}) cells and have been implicated in stimulating B cell responses in both RA and SLE[115–117]. Circulating clonally expanded, immunosenescent CD4$^+$CD28$^-$ end-differentiated effector T cells, equipped with cytotoxic functions and high IFN-γ release, home to the synovial tissue niche[61,62].

Unexpectedly, it was found that synovial T cells, together with synovial macrophages, are the cellular origin of TNF[75], and TNF receptor 1 is expressed on SFs and macrophages. TNF's role in RA synovitis is undebated, raising the possibility that the cytokine is a critical connector between abnormal adaptive immune responses and the adverse tissue remodeling process.

B cells are distinctly infrequent in osteoarthritis and leukocyte-poor RA synovial tissue and account for only 8% of synovial cells in leukocyte-rich RA samples. Nevertheless, they may be functionally important, as suggested by B cell depletion studies in engrafted synovial tissues[96] and by the clinical benefit of B cell depletion in both autoantibody-positive and autoantibody-negative patients with RA. High dimensional phenotyping revealed multiple activated B cell subsets as well as CD38$^+$CD20$^-$IgM$^-$IgD$^-$ plasmablasts, consistent with the notion that the inflamed synovium can serve as a site for tertiary lymphoid structures. The most interesting B cell subpopulation was CD11c^{hi}ITGAX$^+$TBX21$^+$ACTB$^+$ B cells, reminiscent of the autoimmune B cells described in the blood of patients with SLE[118]. Such autoimmune B cells were encountered in a small number of patients with RA, commensurate with the cellular heterogeneity of the chronic synovial lesion.

Conclusions and future perspectives

RA is now understood as a decades-long, if not life-long, process with phases distinct in time, space and pathogenesis. A central defect, or a causative antigen, giving rise to the series of pathogenic steps culminating in joint inflammation has not been identified. Genome-wide association studies have confirmed the MHC region as the strongest genetic risk factor and have identified >100 non-MHC RA risk loci. RA risk loci overlap with human primary immunodeficiency genes and genes mutated in hematological cancer, but the causal variants and the resulting pathogenic mechanisms remain largely unresolved. The systemic breakdown of peripheral self-tolerance, as evidenced by autoantibodies, occurs many years before detectable clinical manifestations and involves a set of antigens that are not synovium specific. Typically, it takes until the sixth decade of life before a second tolerance defect, the breakdown of tissue tolerance, allows the entrance of innate and adaptive immune cells into the synovial tissue space. This transition point is probably reached because of lifelong immune system remodeling, as well as enabling structural deficiencies in the synovial environment. Elegant studies applying fate mapping and single-cell sequencing have identified tissue-resident self-renewing synovial macrophages that build a joint protective barrier. The loss of these endogenous synovial macrophages is a critical element in exposing the synovial membrane to pathogenic immunity. The failure in T cell tolerance has been attributed to cell-endogenous abnormalities that are already present in naive T cells and, together, divert the differentiation program to favor the generation of SLECs instead of long-lived memory T cells. These defects include impaired DNA repair, which compromises telomeric function and mitochondrial fitness and drives a distinctly different metabolic program, characterized by slowed glycolytic breakdown, the preponderance of catabolic pathways to build biosynthetic precursors and the mistrafficking of AMPK away from the lysosome. This metabolic signature enables T cells to function as tissue-invasive proinflammatory effector cells. A recently described effector function of tissue-invading T cells, namely pyroptotic death triggered by the leakage of mtDNA, broadens the array of tissue-injurious pathways operational in synovitis.

What follows is the transition from acute tissue inflammation to chronic tissue inflammation and a maladaptive tissue remodeling process driven to a large extent by the stromal cells of the synovial tissue environment. Single-cell transcriptomic analyses combined with cytometry have highlighted the heterogeneity among immune and stromal cells in the inflamed synovium (Table 1). Functional studies have shown that select subsets of highly activated synovial fibroblasts adopt proinflammatory and tissue-invasive functionalities and join tissue-infiltrating macrophages and T cells as mediators of tissue damage.

Current treatment strategies target the end stage of disease and are broadly anti-inflammatory. The recognition that RA runs through relatively stable stages and the molecular characterization of the relevant transition points has the potential to identify upstream targets that could re-engineer the immune system to halt the disease process prior to irreversible tissue damage. The emerging array of pathogenic pathways in RA reveals entirely new territories for combatting autoimmunity, for example, by targeting genome stability, mitochondrial biology, organelle biogenesis, cytoskeletal dynamics and the cellular endomembrane system[49,55,79,85,119].

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Competing interests

The authors declare no competing interests.

Additional information

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