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The Immunology of Rheumatoid Arthritis

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Abstract

The immunopathogenesis of rheumatoid arthritis (RA) spans multiple decades and begins with production of autoantibodies against posttranslationally modified proteins (Checkpoint 1). After years of asymptomatic autoimmunity and progressive immune system remodeling, tissue tolerance erodes, and joint inflammation ensures as tissue-invasive T effector cells emerge, and protective joint-resident macrophages fail (Checkpoint 2). The transition of synovial stromal cells into auto-aggressive effector cells converts acute synovitis into chronic-destructive synovitis, which is often irreversible (Checkpoint 3). Mechanisms of immune tolerance breakdown are now much better understood. The loss of T cell tolerance is linked to cell-intrinsic defects in the DNA repair machinery, resulting in abnormal cell cycle dynamics, telomere fragility and instability of mitochondrial DNA. Mitochondrial and lysosomal anomalies culminate in a T cell differentiation defect favoring differentiation into short-lived effector T cells with high proliferative activity and tissue invasive potential. This differentiation defect builds on a metabolic platform that shunts glucose away from energy generation towards the cell building and motility program. The next frontier in RA will utilize the prolonged period of asymptomatic autoimmunity to attempt the development of curative interventions by reprogramming T cells back to a tolerant state.

Introduction

Initial evidence for an autoimmune pathogenesis of 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 Dr 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 misfunction 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 >100 genetic 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 through modifying protein antigens.

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Two developments have dovetailed to give rise to new concepts in the understanding of human autoimmune disease and both have spearheaded new perspectives in the conception 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 technology have added granularity to the analysis of immune responses. Equally impactful 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 life-long 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, documented by prototypic autoantibodies that are reactive against posttranslationally modified proteins, often citrullinated antigens. Individuals carrying such antibodies to modified protein antigens (AMPA) are asymptomatic for years to decades. Eventually, some enter a new phase and becomes 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 lifetime includes distinct transition points, at which the disease process takes a dimensional 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 Pre-clinical RA

As a clinical entity, RA is a disease of the 6th decade of life[1]. As an immunological entity, RA begins years to decades earlier (Fig.1)[2]. Genetic polymorphisms contribute 30–60% of risk[3,4]. HLA-class II alleles confer the strongest risk; specifically, *HLA-DRB1* alleles containing a sequence stretch from position 71–74 of the β-chain[5,6]. This sequence stretch (“shared epitope”), together with amino acid residue 11 and 13, forms an antigen-binding pocket, pocket 4, implicating the HLA-antigen-T-cell-receptor complex in disease risk. Amongst 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. 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 during 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]. Time dependence identifies immune system and tissue aging as critical in all stages of RA. The concept of a temporal separation of tolerance breakdown and immune-mediated tissue destruction and the recognition that autoantibodies precede clinical disease by years to decades is a generalized rule in human autoimmune disease. Prospective studies of children at-risk for type 1 diabetes mellitus (T1DM) revealed antibodies reactive against pancreatic β-cells antigens long before target tissue destruction. Autoantibodies against nuclear antigens are present years before the diagnosis of SLE and the spectrum and number of autoantibody specificities progressively increases up to the time of clinical disease[11,12].

Checkpoint 1 – Systemic Breakdown of self-tolerance

Moving the initial tolerance breakdown outside of the joint has opened opportunities to define causally relevant upstream events. Epidemiologic studies in the early 90's revealed the presence of RFs long before synovitis[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 fragment[16]. Thus, RA autoimmunity is not directed against native peptide sequences but, as a rule, against post-translationally modified proteins, introducing a high degree of multi-reactivity. Since thymic selection does not purge T cells recognizing protein modifications, a peripheral tolerance defect is believed 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 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 genetic risk factors, peripheral tolerance is maintained by the context in which post-translational modifications occur. Citrullination and carbamylation are quite 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. In contrast, citrullination is an enzyme-mediated deimination of an arginine residue. Tissue inflammation and smoking upregulate peptidyl arginine deiminase (PAD) expression[22]. Although intuitive, self-antigen abundance appears not to be important in the process of quorum sensing that regulates tolerance. Mucosal tissue sites[23] and neutrophil nets[24,25] may provide relevant context signals through which citrullinated antigens gain immunogenicity, supporting the concept that early steps of tolerance loss may occur in the lung and in the gut. However, how tolerance to the modified peptides is broken remains unclear and a common denominator between citrullination, carbamylation and glycation as opposed to other post-translational modifications has not emerged.

Mechanisms that control the stability/progression of the autoimmune stage are dependent on T cells. Healthy HLA-DR4$^+$ individuals and asymptomatic first-degree relatives of RA patients have typical telomere damage and abnormal T cell differentiation[2627], indicative of pre-disease immune system remodeling. Individuals who lose their autoantibodies and do not develop synovitis lack RA-associated HLA-DRB1 alleles. B cell depletion in subjects with arthralgias delayed the onset but did not prevent development of synovitis[28]. T cell-dependent antibody isotype switching occurs early in the autoimmune process since autoantibodies are generally present in different isotypes[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 at 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, RA patients 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 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. Decreased frequencies of naïve CD4$^+$ T cells are the strongest predictor for progression from ACPA positivity to synovitis[33]. Unbiased multiparametric studies in early and untreated patients have confirmed that circulating p-p38$^+$p-cJun$^+$p-NFkB$^+$CD4$^+$ T cells serve as the best classification parameter to distinguish RA patients from healthy individuals[34]. Epigenetic studies at the earliest stages of joint inflammation and in drug-naïve patients have identified differential methylation pattern specifically in naïve 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 defined by a misdifferentiation step as naïve resting CD4$^+$ T cells convert into memory and effector T cells[37–39]. Naive CD4$^+$ T cells from RA patients transition into highly proliferative, tissue-invasive, and pro-inflammatory effector cells, instead of giving rise to 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 reprogramming of cellular bioenergetics, with both deficiencies connected through insufficient repair of mitochondrial DNA[37,38,40] (Fig.2). Presence of these defects in the naïve CD4$^+$ T cell population and in lymph node-residing T cells[40] places the pathology outside of the joint. The major offspring of naïve RA CD4$^+$ T cells, short-lived effector T cells, 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 naïve RA CD4 T cells have shortening of telomeric sequences[41,42] and have shifted their cell surface phenotype[33,43,44]. Compared to patients with chronic hepatitis C infection or age-matched healthy individuals, RA patients contract the diversity of the CD4 T cell receptor repertoire[41]. These findings gave rise to the "premature immune aging" hypothesis[45,46] proposing 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 naïve T cell population[47,48].

Telomeric erosion could be a consequence of high proliferative pressure. Recent studies, however, have introduced a new concept, linking telomeric shortening to fragility of the terminal sequences, thus recognizing the loss of telomeric sequences as a defect in DNA repair[49]. Underlying molecular processes are beginning to be understood (Fig.2).

Mechanistic studies relevant for the breakdown of tissue tolerance (Checkpoint 2) need to capture the RA disease process before the establishment of synovitis. One approach is to examine naïve T and B cell populations, which reside outside of the synovial lesions, and study their transition from the naïve to the effector/memory state, a transition 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 naïve T cells activate distinct signaling and transcription factor networks that guide their differentiation into short-lived effector (SLEC) or memory precursor cells (MPEC)[53], ATM-deficient T cells are strongly biased to develop into SLECs, capable of infiltrating into the synovial membrane, where 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 meiotic recombination 11 homolog 1 (MRE11A)[49,55], a component of a multifunctional DNA damage repair machine that co-ordinates genomic stability programs at DNA replication forks and at double-strand break sites[56]. In naïve and memory RA T cells, MRE11A is depleted from two critical territories; the telomeric ends and the mitochondrial genome. Functional consequences include instability of chromosomal ends, leading to damage patterns that are highly infrequent in healthy CD4 T cells, but enriched in RA CD4 T cells[49]. MRE11A deficiency manifests with telomere fragility, accelerated aging exemplified by CD57 induction and high propensity to invade synovial tissue and promote synovitis. Failure of MRE11A to protect genome stability has equally devastating consequences for mitochondrial DNA (mtDNA). MRE11A^{low} 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 accumulation and leakage of damaged mtDNA, leading to inflammasome assembly, caspase1 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 towards SLEC instead of memory generation, a reduction in T cell longevity and accumulation of effector cells inclined to leave lymphoid storage sites and settle in peripheral tissue environments (Fig.3). The skewing towards SLECs away from protective memory T cells may also compromise host immunity that is so typical for RA.

The disease concept gives rise to several predictions, many of which are fulfilled in RA patients. (1) T cell memory responses in RA patients 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]. RA patients are significantly less efficient in producing anti-drug antibodies than patients with spondylarthritis[59]. (2) Longevity of RA T cells should be compromised[43,60]. In support, T cell populations in lymph nodes of RA patients are less dense and activated caspase1[55]. The global T cell repertoire is contracted with expanded clonotypes filling the space[41,61]. (3) The preferential differentiation of naïve $CD4^+$ 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 RA synovium and 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 shared feature of patients with RA and patients with coronary artery disease(CAD)[65–67] providing a common pathomechanisms for these two chronic inflammatory and age-associated disease states. In support, CAD risk in RA patients is related to telomeric lengths as 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 most recent work, $CD27^-CD28^-$ T cells were found to mediate cytotoxicity through a sestrin-NKG2D-DAP12 complex, reminiscent of the 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 co-stimulatory signaling networks, rendering them highly competent in promoting chronic tissue inflammation. The enrichment of highly differentiated $CD27^-$ cytotoxic effector memory T cells in synovial lesion of RA patients has been confirmed by recent single cell transcriptomic and mass cytometry approaches[75,76].

The exact timing of when at-risk individuals develop expansion of end-differentiated and clonally expanded effector $CD4^+$ T cells is undetermined, but studies of unaffected siblings of RA patients have described $CD4^+$ 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 HLA-DRB1*04^+ individuals[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 pro-inflammatory effector T cells

Insufficient DNA repair not only deviates cell cycle passage, cell differentiation and cell fate, it also reprograms cellular bioenergetics of T cells. Rewiring of metabolic networks in RA T cells supports the cells' divergence towards SLEC generation (Fig. 3), linking metabolic programs to breakdown of tissue tolerance[78]. Besides fostering the emergence of short-lived effectors, metabolic activity in RA T cells directly supports pro-inflammatory behaviors, e.g. the T cell motility program[38,79] and immunogenic cell death[55].

Four key metabolic abnormalities have been identified in the patient-derived naïve 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 (PFKFB3)[80], resulting in reduced pyruvate and lactate production.

2. RA T cells upregulate Glucose-6-phosphate dehydrogenase (G6PD), shunting glucose away from glycolysis to the pentose phosphate pathway (PPP). With increased concentration 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. 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, damaging mtDNA, impairing the electron transport chain and suppressing ATP production. mtDNA fragments leak into the cytoplasm, are recognized by the inflammasome, activate caspase1 and trigger lytic cell death (T cell pyroptosis). Caspase1 activation is a feature of RA lymph node T cells. Pyroptotic T cells are strongly pro-inflammatory, but remain invisible in the tissue, and escape detection by transcriptomic approaches[55,83]. Mitochondrial failure reduces 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 insufficiency of N-myristoyltransferase 1 (NMT-1), RA T cells fail to posttranslationally 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 in other autoimmune disease, specifically SLE. SLE T cells rely on high mitochondrial ROS production[86–89]. SLE Th17 cells depend on metabolic signaling[90,91] consistent with the concept that metabolic conditioning diverges 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 to an early synovitis clinic, progress to chronic synovitis and irreversible restructuring of the synovial environment[92]. Chronic synovitis, imposing further proliferative stress upon innate and adaptive immune cells, may per se function as a disease amplifier[93]. The synovitic component of RA can be successfully targeted by a multitude of highly sophisticated anti-rheumatic drugs and drug-induced remission is now accepted as the treatment goal. Nevertheless, withdrawal of anti-inflammatory medication mostly 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 of acute to chronic synovitis must derive from the local tissue environment and detailed studies have demonstrated the active pathogenic role of de-differentiated 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.

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 (OA)), four cell populations were separated (T cells, B cells, monocytes, stromal fibroblast) and subjected to bulk RNA seq analysis. Twenty-six samples were analyzed by cytometry and 21 by 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 cellular subpopulations (Table1), including 4 fibroblast subsets, 4 monocyte subsets, 6 T cell subsets and 4 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.

(1) Synovial fibroblasts

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, extensively vascularized and the subintima is occupied by inflammatory cells, (macrophages, T cells, B cells). Fibroblast growth, transformation and matrix production are a generalized wound response, exemplified by intimal hyperplasia in inflamed blood vessels[97–99]. Fibrotic responses in response to chronic tissue inflammation are maladaptive; proper tissue repair fails, and stromal cells adopt tissue-destructive and pro-inflammatory 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 to the lining layer. Sublining SFs, all positive for CD90, have been subsetted into 3–4 subsets and have been functionally characterized as pro-

inflammatory 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 for IL-6[75]. Notably, all SF subsets express TNF receptor 1, but none of the stromal subpopulations was identified as a TNF-α producer[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-cadherin11 antibody in RA has failed to demonstrate benefit[103].

(2) Synovial macrophages

Synovitic tissues of RA patients are a macrophage-rich tissue niche[104]. Over the last 20 years, remarkable progress has been made in understanding mononuclear phagocytes. Especially, 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 tissues niches in which cell-cell interactions are optimized and tailored to local requirements. Notable examples are 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 that then adapt to niche-specific phenotypes[106]. In case of increased demand for tissue-residing macrophages, such as under inflammatory conditions, bone-marrow derived monocytes can compensate[107]. Thus, organ sites contain different macrophage subsets, with distinct origin and distinct longevity. Superimposed on this cellular heterogeneity of tissue-resident macrophages is their functional heterogeneity, ranging from the well-established pro-defense and pro-inflammatory functions to the reparative and inflammation-resolving capabilities associated with scavenger receptor expression, high phagocytic capacities and contributions to wound healing[108,109]. Upon inflammatory stimuli, bone-marrow derived monocytes rapidly travel to injured tissues sites and add to the resident macrophage population. Here, a clear distinction between the pro-inflammatory M1 and the pro-resolving M2 phenotypes may not always be possible, particularly not during chronic inflammation, when overlapping waves of pro-inflammatory and anti-inflammatory signals and cells are co-existing[110].

CD45^{+}CD14^{+} synovial cells fall into 4 subpopulations. In labeling studies, the pool of synovial macrophages was majorly dependent on the influx of CD14^{+} blood monocytes[111]. Studies applying fate mapping and reporter mice as well as light sheet microscopy have established a specific protective role of lining macrophages in the synovium. CX_3CR1^{+} lining macrophages expressed VSIG4 and TREM2[112], indicative of anti-inflammatory and phagocytic capacities. VSIG4 inhibits pro-inflammatory macrophages by driving metabolic adaptations[25]. A remarkable feature of such synovial lining macrophages is the expression of a gene program suggestive for 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 from $MHCII^+$ interstitial macrophages seated in the synovial sublining. Interestingly, $MHCII^+$ macrophages supply a third population of $RELMA^+$ interstitial macrophages with features of anti-inflammatory $CD206^+$ macrophages. Integrity of the shield formed by synovial lining macrophages proofed 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, TREM2).

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

(3) Synovial T cells

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 the naïve to the 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 $CD4^+PD\text{-}1^+ICOS^+$ T cells able to produce the chemokine CXCL13. Unlike circulating Tfh cells, these CD4 T cells lack expression of CXCR5; they have been named T peripheral helper (Tph) 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].

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

(4) Synovial B cells

B cells are distinctly infrequent in OA 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 RA patients. 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 of tertiary lymphoid structures. The most interesting B cell subpopulation were $CD11c^{hi}ITGAX^+TBX21^+ACTB^+$ B cells reminiscent of the autoimmune B cells described in the blood of SLE patients[118]. Such

autoimmune B cells were encountered in a distinctly small number of RA patients, commensurate with the cellular heterogeneity of the chronic synovial lesion.

Conclusions and future perspectives

RA is now understood as a decade-long, if not life-long process that falls into phases distinct in time, space, and pathogenesis. A pinnacle 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 till 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 likely reached because of lifelong immune system remodeling combined with 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 naïve T cells and together diverge the differentiation program to favor the generation of SLECs instead of long-lived memory T cells. These defects include impaired DNA repair compromising telomeric function and mitochondrial fitness and a distinctly different metabolic program, characterized by the slowdown of 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, pro-inflammatory effector cells. A more recently described effector function of tissue-invading T cells, namely pyroptotic death triggered by the leakage of mitochondrial DNA, broadens the array of tissue-injurious pathways operational in synovitis.

What follows is the transition of acute tissue inflammation into 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 (Table1). Functional studies have shown that select subsets of highly activated synovial fibroblasts adopt pro-inflammatory 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 and re-engineer the immune system to halt the disease process prior to irreversible tissue damage. The emerging array of pathogenic pathways in RA inspires

entirely new territories for combatting autoimmunity, e.g. by targeting genome stability, mitochondrial biology, organelle biogenesis and the cellular endomembrane system.

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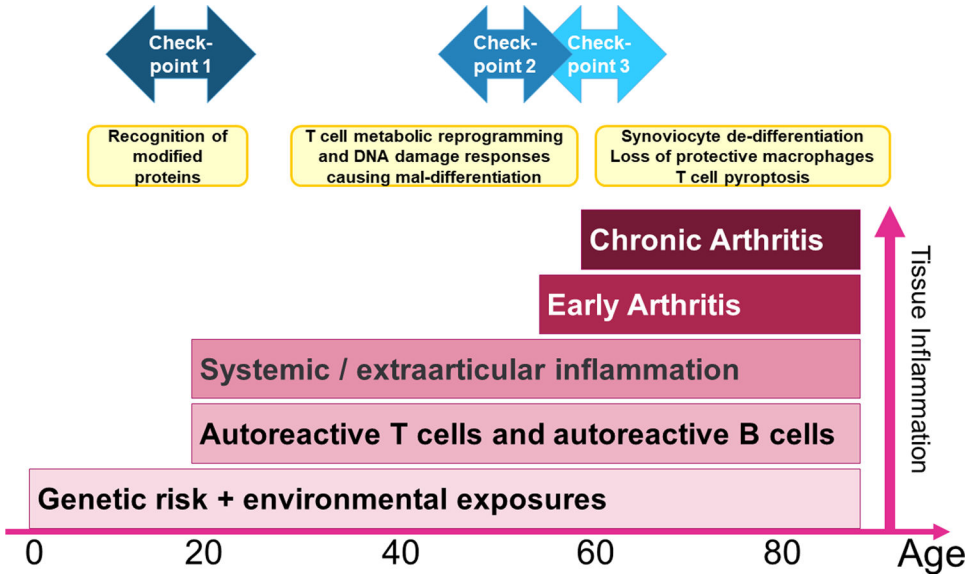

Figure 1. Evolution of Rheumatoid Arthritis over Lifetime.

The disease process of RA begins with transition of an at-risk host to a host with overt autoimmunity. Recognition of modified protein antigens and emergence of autoantibodies mark the loss of self-tolerance (Checkpoint 1). Timing and space of this tolerance defect are not precisely identified, but autoantibodies appear years to decades prior to frank joint disease. The host with overt autoimmunity is clinically asymptomatic. A cell-intrinsic shift in metabolic networks and DNA instability drive T cell mal-differentiation towards tissue-invasive short-lived effector T cells. Failure of tissue tolerance manifests as early synovitis during the sixth decade of life (Checkpoint 2) and transitions relatively fast into chronic synovitis (Checkpoint 3). Auto-aggressive de-differentiated 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.

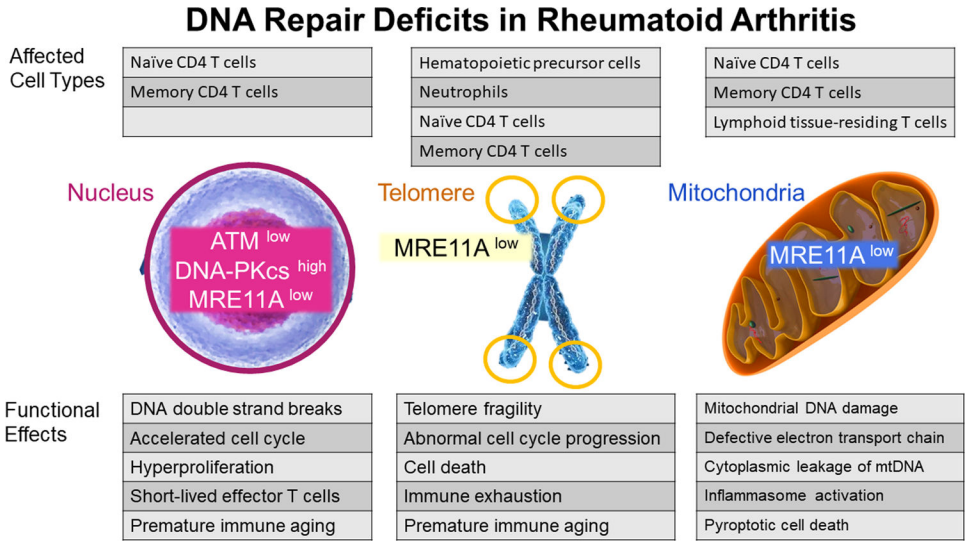

Figure 2. DNA Repair Deficits in Rheumatoid Arthritis.

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 naïve and memory CD4+ T cells. Age-inappropriate decline of the repair molecules ATM and MRE11A leads to accumulation of damaged DNA in the nucleus, at the telomeric ends and in the mitochondria. Downstream consequences include deviations in cell cycle passage, premature telomeric loss and cytoplasmic leakage of mitochondrial DNA triggering 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 mitochondrial DNA affects the electron transport chain, impairs production of ATP and metabolic intermediates, and reprograms the cell's energy production and biosynthetic program.

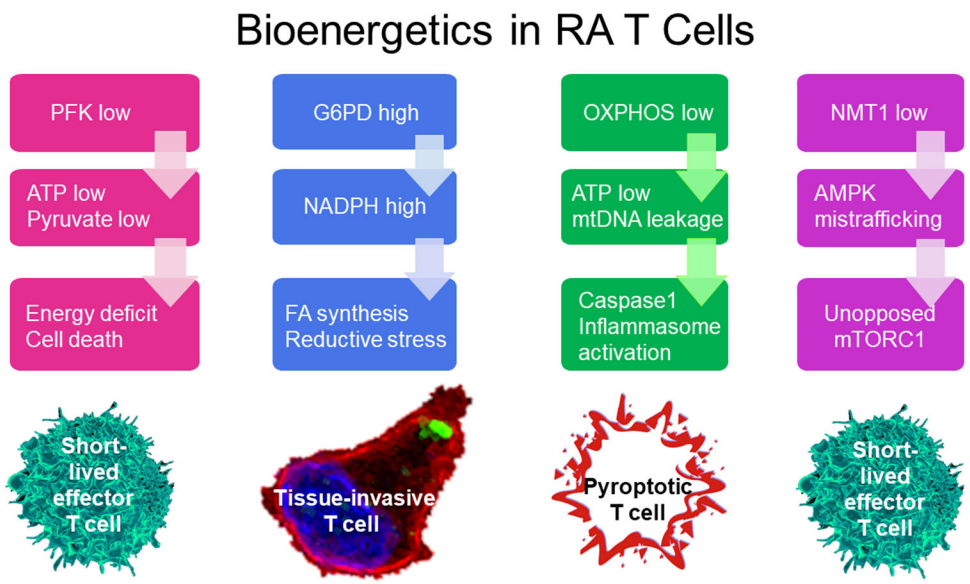

Figure 3. Metabolic reprogramming and pro-inflammatory effector functions in RA T cells.

Several molecular defects have been identified which shift the metabolic and bioenergetic conditions in RA T cells, ultimately deviating the cell's differentiation program and shortening survival. Transcriptional repression of the glycolytic enzyme phosphofructokinase (PFKFB3) impairs pyruvate production and thus mitochondrial function, favoring induction of short-lived effector T cells (SLEC) 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 of mitochondrial DNA 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 deficiency of N-myristoyltransferase 1, enables unopposed mTORC1 activation and SLEC generation.

Table 1

Heterogeneity of cell populations in synovial tissue from patients with osteoarthritis (OA) and patients with rheumatoid arthritis (RA).

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

Cell type	OA	Leukocyte poor RA	Leukocyte rich RA	#	Marker	Highly expressed genes	Feature	TNF-α producer	TNF R1
Fibroblasts	~60%	~50%	~25%	SC-F1	$CD90^+$ $CD34^+$	*C3, FOS, PTGFR*	sublining		*TNFRSF1A*
				SC-F2	$CD90^+$ HLA-DRAh	*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	$IL\text{-}1B^+$	*RGS2, NR4A2, PLAUR, HBEGF, IL1B, ATF3*	pro-inflammatory 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} 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	$CD8^+$ $GZMK^+$ $GZMB^+$ $HLA\text{-}DPA1^+$ $HLA\text{-}DRB1^+$	*IFN-γ, HLA-DPA1, HLA-DRB1*	IFN-γ producer	*TNFA*	

Cell type	OA	Leukocyte poor RA	Leukocyte rich RA	#	Marker	Highly expressed genes	Feature	TNF-α producer	TNF R1
B cells	~2%	~1%	~8%	SC-B1	IGHD^{+}CD27^{-}	*IL6, IGHM, CD83, BACH2, CXCR4*	naïve 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 (ABC)	*TNFA*	
				SC-B4	immunoglobulin genes and XBP1	*SSR4, MZB1, XBP1, DERL3, CD27*	plasmablasts		