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Review article

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Innate immune memory in inflammatory arthritis

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Abstract

The concept of immunological memory was demonstrated in antiquity when protection against re-exposure to pathogens was observed during the plague of Athens. Immunological memory has been linked with the adaptive features of T and B cells; however, in the past decade, evidence has demonstrated that innate immune cells can exhibit memory, a phenomenon called 'innate immune memory' or 'trained immunity'. Innate immune memory is currently being defined and is transforming our understanding of chronic inflammation and autoimmunity. In this Review, we provide an up-to-date overview of the memory-like features of innate immune cells in inflammatory arthritis and the crosstalk between chronic inflammatory milieu and cell reprogramming. Aberrant pro-inflammatory signalling, including cytokines, regulates the metabolic and epigenetic reprogramming of haematopoietic progenitors, leading to exacerbated inflammatory responses and osteoclast differentiation, in turn leading to bone destruction. Moreover, imprinted memory on mature cells including terminally differentiated osteoclasts alters responsiveness to therapies and modifies disease outcomes, commonly manifested by persistent inflammatory flares and relapse following medication withdrawal.

Sections

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Key points

- The failure of adaptive immune suppression to achieve sustained remission in inflammatory arthritis highlights the existence of an innate memory phenotype within the immune joint cellular infiltrate.
- Pro-inflammatory cytokines can induce innate memory on haematopoietic and progenitor stem cells that exhibit either an increased or an immunosuppressive inflammatory response, resulting in perpetuation or resolution of inflammatory arthritis, respectively.
- This acquired memory is demonstrated in osteoclast precursors and potentially terminally differentiated osteoclasts that have the capacity to recycle to osteomorphs and produce stronger secondary responses and increased bone resorption under chronic arthritic conditions.
- Innate immune memory serves as an immunomodulatory factor that contributes to various clinical patterns in inflammatory arthritis such as remission, flares and treatment response rate.

Introduction

The concept of immune memory is increasingly gaining worldwide attention owing to its importance in the protection conferred by vaccines. Immune memory was initially considered a privilege of adaptive immune memory T and B cells[1]. However, substantial amounts of data have accumulated demonstrating that innate cells display adaptive-like features following exposure to exogenous or endogenous triggers, reflected by an altered secondary response to subsequent triggers, a phenomenon termed 'trained immunity'[2] (Box 1). This concept described the intriguing ability of natural killer cells and macrophages, as prototypical innate immune cells, to mount a hyper-inflammatory response to a secondary challenge[3,4]. This memory phenotype of innate immune cells constitutes an interesting therapeutic tool to confer protection against viral infections[5,6] and control of cancer progression[7,8]. However, a sustained capacity of innate immune cells to respond positively to inflammatory triggers leads to systemic autoinflammatory disorders[9]. This phenomenon is particularly relevant in inflammatory arthritis, wherein inappropriate activation of the immune system leads to chronic systemic inflammation and tissue destruction.

Inflammatory arthritis describes a group of diseases that includes rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA), which clinically involve joint and skin damage, and systemically extend to vital organs such as the lungs, heart, kidneys and nervous system[10]. T and B cells have long been implicated as the principal mediators of autoimmunity; these cells contribute to inflammation persistence via the expression of highly specific antigen receptors, which enable them to rapidly express effector molecules and mature isotype-switched antibodies upon re-challenge by the same antigen[11]. The resulting memory T and B cells persist in the circulation, lymphoid organs and inflamed tissue, where they can sense their specific antigen. In rheumatic diseases, chronic antigen persistence constitutes a continuous challenge to T and B cells; accordingly, memory T cells adapt to this chronic inflammatory milieu and display an impaired phenotype with an incapacity to activate regulatory T cells, which, when activated, suppress immune responses and achieve self-tolerance[12]. Similarly, memory B cells differentiate into memory plasma cells that localize in the bone marrow where the cytokine milieu promotes their sustained production of pathogenic antibodies[13]. The immunological memory of rheumatic inflammation as it relates to T and B cells is well appreciated and has been reviewed elsewhere[14]. However, a large proportion of patients with inflammatory arthritis are either resistant to conventional immunosuppressive therapies targeting T and B cells[15,16] or experience a relapse after immunosuppression is discontinued[17,18]. Moreover, the reset of pathogenic adaptive immunological memory through an intense myeloablation followed by autologous stem cell transplantation fails to achieve long-term, sustained remission in all patients, suggesting that other immune memory pathways contribute to disease chronicity independently of T and B cells[19–21]. The observation of this phenomenon initiated a number of studies around the effect of joint inflammation on the epigenetic imprinting and residual memory of synovial fibroblasts (Box 2, Fig. 1).

More recent mechanistic evidence of this phenomenon comes from a number of observations that involve innate immune training. In one study, β-glucan innate immune training was associated with enhanced recovery of myelopoiesis following chemotherapy-induced myeloablation[22]. This myeloid 'skewing' is dependent on IL-1β and granulocyte–macrophage colony-stimulating factor (GM–CSF) signalling, and results in specific metabolomic and transcriptomic alterations of the medullar haematopoietic progenitors[22]. Similar observations were noted with bacillus Calmette–Guérin vaccine[23,24] and/or with metabolic changes induced by intake of a Western diet[25]; in all cases, haematopoietic progenitors evolved to a 'trained state' of myeloid cells with heightened immune responsiveness (Box 1). Such training adaptations of myeloid progenitors might increase their susceptibility to inflammatory signals in inflammatory arthritis, thus generating a vicious circle that perpetuates the disease and creates a barrier against effective therapy[26]. Understanding the mechanisms that drive the induction of immunological memory in innate immune cells and their consequences for the pathogenesis of rheumatic diseases is fundamental for the development of effective therapeutic strategies. Herein we discuss the latest findings related to the adaptive-like features of innate immune cells that support their role in the persistence of joint inflammation and bone loss, and provide an up-to-date overview of the potential involvement of innate immune memory in the variability of clinical outcomes and treatment response in patients with inflammatory arthritis.

Innate immune memory in inflammatory arthritis

Innate immune cells play a crucial role in the pathogenesis of inflammatory arthritis by orchestrating at different levels the inflammation cascade and its resolution. Circulating monocytes and tissue macrophages are on the front line in danger signal sensing, antigen presentation and cytokine production, thus modulating the activity of a large array of cellular subtypes including T and B cells as well as fibroblasts, which have also been shown to display phenotypic characteristics reminiscent of immunological memory[27] (Box 2). A finely tuned balance between the pro-inflammatory and regulatory functions of macrophages is required for tissue homeostasis. This dual activity is possible because of the high level of heterogeneity in macrophage origin and function, and is achieved via continuous specialization and differentiation driven by the integration of multiple signals from the surrounding microenvironment[28]. The bone marrow milieu is critical for myeloid progenitors, which express a wide array of cytokine and growth factor receptors to sense peripheral inflammation and adapt via active proliferation[22].

Maladaptive myelopoiesis in inflammatory arthritis

The adaptation of bone marrow myelopoiesis to an inflammatory microenvironment is complex and involves multiple signals, including

Box 1

Innate immune memory or 'trained immunity'

The past decade has challenged the classical immune response dogma, highlighting the capacity of innate immune cells to build an immunological memory, a phenomenon called 'trained immunity' or 'innate memory'[58]. Originally, evidence for the existence of innate memory was derived from clinical and experimental studies showing the non-specific, T and B cell-independent protection conferred by bacillus Calmette-Guerin vaccine and by β-glucan challenge to secondary infections[130–132]. Depending on the type of activating ligand (pathogen-associated molecular patterns, damage-associated molecular patterns or cytokines) and the signalling pathway engaged by the first antigenic exposure, innate immune cells display characteristics of trained immunity as evidenced by substantial phenotypic and functional modifications. These alterations include an altered expression of membrane markers, such as pattern-recognition receptors (Toll-like receptor 2 (TLR2), TLR4, the β-glucan receptor dectin-1)[131,133,134], co-stimulatory molecules (CD40, CD80, CD86, CD83)[132,133], C-type lectin receptors (CD206, CD209)[132,133] and chemokine receptors (CCR1, CCR2, CXCR4)[126,132], which modulates the cellular interaction with the extracellular milieu. Long-lasting heightened capacity to produce pro-inflammatory cytokines (IL-1β, IL-6, TNF) and chemokines (CCL2, CCL5) usually accompanies the phenotypic modifications[126,131,133]. Conversely, innate immune cells can also retain a hypo-responsive memory as a long-term adaptation to chronic inflammatory conditions[135], a phenotype initially called innate immune tolerance. Thus, macrophages exposed to persistent or high-dose lipopolysaccharide or some helminth products display a blunted immune reaction with a shift towards an anti-inflammatory cytokine balance[133,136]. Adaptive-like behaviour has since been evidenced in a broader population of immune cells (group 2 and group 3 innate lymphoid cells[137,138]), and non-immune cells (including haematopoietic stem cells[22,23] and skin epithelial cells[139]) that contribute to tissue homeostasis[140]. Intertwined metabolic and epigenetic reprogramming underlie the phenomenon of innate memory induction[4]. Among several metabolic pathways, the modulation of glycolysis and oxidative phosphorylation seems to be the main regulator of the epigenetic rewiring in innate memory induction[60]. Metabolites generated from the altered metabolic process modulate the activity of histone-modifying enzymes that either repress or enhance chromatin accessibility[135,141]. Importantly, such alterations can occur at the level of haematopoietic stem and progenitor cells. The release of inflammatory cytokines (IL-1β, IFN-γ, IFN-α and IFN-β), pathogen-associated molecular patterns and damage-associated molecular patterns during chronic inflammation and infection shapes the epigenetic landscape of haematopoietic stem and progenitor cells, which are responsible for the induction of long-lasting specific memory phenotypes in myeloid cells[22,23,25,142].

cytokines, growth factors and pattern-recognition receptor (PRR) signalling[26]. Data from animal models showed that gene transfer of the pro-inflammatory cytokines IL-23 and IL-17 expands myeloid populations in the bone marrow[29,30]. Disease severity in those animal models of inflammatory arthritis was directly related to the expansion of multiple myeloid progenitors, including $CD11b^+ Gr1^{low}$ monocytes and $CD11b^+ Gr1^{high}$ neutrophils. Within the expanded monocyte population, there was a significant increase in osteoclast precursors expressing both receptor activator of nuclear factor-κB (RANK) and macrophage colony-stimulating factor 1 (M-CSF) receptor, which renders them hyper-resorptive. Notably, these cells retained their hyper-responsiveness to RANK ligand (RANKL) signalling in ex vivo cultures even after removal from the bone marrow[29]. Similar to pre-osteoclasts, adoptive transfer of bone marrow neutrophils from IL-17A-overexpressing mice to naive mice was sufficient to induce skin inflammation, suggesting that neutrophils isolated from diseased mice retain pathogenic characteristics[31]. Inflammatory arthritis has also been linked to increased myelopoiesis and innate immune training of myeloid cells within the bone marrow. Specifically, experimental periodontitis induced an expansion of myeloid cells and the epigenetic reprogramming of haematopoietic stem and progenitor cells (HSPCs) through the overactivation of IL-1β signalling, leading to increased susceptibility to inflammatory stimuli[32]. Similar to the IL-23 and IL-17 gene transfer models, the expansion of monocytes and neutrophils exacerbated inflammatory arthritis; more importantly, the study elegantly demonstrated that this maladaptive innate training of myelopoiesis is transmissible by bone marrow transplantation[32].

In experimental inflammatory arthritis, γδ T cells, which regulate the activation of polymorphonuclear neutrophils through granulocyte colony-stimulating factor, GM–CSF and M-CSF[33,34], orchestrate skin and joint pathology[35]. The contribution of these pathways in the pathogenesis of SpA is of paramount importance as $IL\text{-}17A^+$ γδ T cells and $IL\text{-}17A^+$ $GM\text{–}CSF^+$ γδ T cells have been identified in patients with SpA[36,37]. Similarly, natural killer cell-derived GM–CSF was shown to potentiate inflammatory arthritis, providing yet another mechanism of maladaptive myelopoiesis[38]. Moreover, maladaptive myelopoiesis is not an autonomous event but is rather shaped by the dysregulation of the cytokine milieu and the impairment of lymphoid cell function under arthritic conditions, which often results in excessive osteolytic activity[39,40]. Collectively, these data illustrate the link between trained myelopoiesis in the bone marrow and its effects on monocytes and neutrophils that egress to the circulation and subsequently to the joint and other tissues, where they exacerbate inflammatory arthritis and perpetuate chronic inflammatory disorders (Fig. 2).

Macrophage memory in inflammatory arthritis

During the onset of inflammatory arthritis, synovial macrophages are not only dramatically increased in number[41] but also adopt a potent pro-inflammatory profile[42]. This pro-inflammatory profile includes the upregulation of TLRs (TLR2, TLR4 and TLR9), co-stimulatory molecules (CD80 and CD276) and chemokine receptors (CCR3 and CCR5), which results in increased production of IL-1β, TNF and monocyte chemoattractant protein 1 (MCP-1)[43,44]. Despite the observed differences in the

Box 2

Immunological memory in synovial fibroblasts

Synovial fibroblasts are important contributors to the pathogenesis of inflammatory arthritis, and their phenotypic and functional modifications are extensively studied in this setting. Despite their non-immune origin, synovial fibroblasts express a large array of pattern-recognition receptors (PRRs) including the Toll-like receptors TLR2, TLR3 and TLR4, and are able to respond to stimuli by producing various cytokines and chemokines[143]. Synovial fibroblasts exhibit an aggressive phenotype in inflammatory arthritis characterized by the expression of cadherin 11 and podoplanin[144,145]. These fibroblasts are pivotal in the maintenance of inflammation chronicity and the promotion of osteoclastogenesis owing to their increased proliferation and invasiveness and an enhanced production of pro-inflammatory cytokines, receptor activator of nuclear factor-κB ligand (RANKL), chemokines and matrix metalloproteinases (MMPs)[144,146–148]. Early observations demonstrated that rheumatoid arthritis (RA) synovial fibroblasts exhibit altered chromatin organization with a prolonged mRNA transcription of pro-inflammatory mediators following stimulation by TNF[149]. Chronic exposure to TNF consolidates these histone modifications and enhances the capacity of these cells to produce pro-inflammatory chemokines following stimulation by interferons[150]. Consistently, extensive genomics studies of synovial fibroblasts from patients with RA showed substantial alterations in the epigenetic landscape, including DNA methylation, histone modifications and microRNA expression[151,152].

Analysis of the transcriptional network and chromatin accessibility of synovial fibroblasts showed an enrichment of enhancer marker H3K27ac upstream of the *TNFSF11* locus (encoding receptor activator of nuclear factor-κB ligand) and identified the transcription factor ETS1 as responsible for the pathogenic polarization of tissue-destructive fibroblasts in chronic arthritis[153]. In addition, in experimental arthritis, repeated injection of monosodium urate crystals and/or zymosan aggravates arthritis outcomes through the inflammatory sensitization of synovial fibroblasts, which acquire an enhanced capacity for migration, invasiveness and osteoclastogenesis[154]. This inflammatory 'imprinting' is dependent on sustained activity of the serine/threonine-protein kinase mTOR–hypoxia-inducible factor-1α (HIF-1α) pathway and the NLRP3 inflammasome, and a shift towards enhanced glycolysis, which is reminiscent of the metabolic basis of trained macrophages upon β-glucan stimulation[65]. Similar studies have demonstrated that chronic exposure to TNF in vitro increases glycolysis in synovial fibroblasts, in a GLUT1–HIF-1α-dependent manner, which confirms the metabolic shift that occurs in chronically inflamed synovial fibroblasts in RA[155]. This inflammatory imprinting can be abrogated by the inhibition of bromodomain proteins, which translate epigenetic changes into transcription[156]. Collectively, these findings support the concept that under chronic inflammatory conditions, synovial fibroblasts acquire a memory-like phenotype that closely resembles adaptive immunity (Fig. 1).

activation states of inflammatory macrophages in RA and PsA[45], the innate immune activation or 'trained immunity' mechanisms might be shared across a number of rheumatic diseases. Indeed, monocytes from patients with systemic lupus erythematosus also show an upregulation of CD80, CD86, HLA-DR, CX3CR1 (ref. 46), the activating Fcγ receptor FcγRI (CD64)[47] and CD40 ligand[48], along with a heightened production of IL-6 and IL-23 (ref. 49) and of TNF[50] upon ex vivo stimulation. Patients with systemic lupus erythematosus have elevated levels of oxidized LDL[51], which activates NLRP3 in macrophages and induces a long-lasting memory phenotype through IL-1β production[25]. In addition, circulating monocytes from patients with RA display a phenotype of metabolic and inflammatory dysfunction that precedes their accumulation in the joints and clinical manifestation of the disease[52].

The increased frequency of trained monocytes in the synovium of individuals with arthralgia and positive autoantibodies but no clinical signs of inflammation reflects the deleterious impact of macrophage reprogramming, and can be used to identify individuals at risk of developing arthritis and predict the severity of erosive inflammatory arthritis[52]. Early observations have shown that chronic exposure of macrophages to low doses of IFN-γ and TNF induces a shift towards pro-inflammatory signal transducer and activator of transcription 1 (STAT1)-dominated responses[53,54]. In a series of elegant experiments, it was demonstrated that lipopolysaccharide (LPS) challenge of macrophages pre-treated with IFN-γ resulted in profound chromatin remodelling, characterized by histone acetylation of promoters at the *TNF*, *IL6* and *IL12B* loci and a prolonged binding of the transcription factors STAT1 and interferon regulatory factor 1 (IRF-1). This epigenetic modification, originally described as 'priming', did not result in the transcription of these factors but rather enabled a stronger immune response upon secondary activation[55]. These experiments clearly indicated how the altered cytokine milieu in inflammatory disorders might promote a 'priming' or 'training' of macrophages, and implicate the existence of residual innate transcriptional memory. Although IFN-γ priming induces the formation of de novo latent enhancers via the activation of STAT1 and IRF elements to activate gene transcription and recruit chromatin-remodelling enzymes[56], immune training is characterized by the acquisition of persistent histone modifications, such as H3K27 acetylation at distal enhancers and H3K4 trimethylation at the promoters of stimulated genes[57], suggesting that the mechanisms of priming and training might be partially distinct.

Mechanistically, the induction of trained immunity has been closely associated with an active interplay between epigenetic and metabolic reprogramming[58]. Indeed, macrophages exposed to pro-inflammatory stimuli are characterized by an enhanced glycolytic influx and a fragmented tricarboxylic acid cycle, leading to the accumulation of intermediate metabolites such as succinate and acetyl coenzyme A[59] that serve as cofactors for epigenetic remodelling enzymes[60]. The analysis of circulating monocytes and synovial macrophages in patients with inflammatory arthritis has demonstrated increased glycolysis and an altered fatty acid metabolism, which could explain

the accumulation of intermediate metabolites such as succinate and glutamate in the synovial fluid of inflamed joints[61,62]. Importantly, these metabolic abnormalities correlate with an enhanced capacity of arthritic monocytes to release pro-inflammatory factors upon ex vivo stimulation[52,63].

Besides the role of the hypoxic microenvironment, the increased level of syntenin-1 in inflamed joints was also shown to amplify the inflammatory and glycolytic networks of synovial macrophages through serine/threonine-protein kinase mTOR signalling[64], in line with the training effects of β-glucan[65].

Following these observations, several epigenome-wide association studies have provided strong evidence for the involvement of epigenetic mechanisms in the aetiology of rheumatic diseases[66]. Among the multiple epigenetic signatures described in patients with inflammatory arthritis, the acetylation of histone H3 as well as the trimethylation of H3K4 (refs. 67,68) and H3K27 (ref. 69) at the promoter site of genes encoding pro-inflammatory cytokines (IL-6)[70,71] and chemokines (CCL2)[72] are amongst the mechanisms involved in innate memory induction. Modifications of the microRNA signature of macrophages, which interfere with TNF, mitogen-activated protein kinase and Wnt signalling cascades[73], participate in innate immune memory via the modulation of chromatin remodelling factors[74–76]. Moreover, the altered expression of ten-eleven translocation (TET) and DNA methyltransferase (DNMT) enzymes, which regulate DNA methylation, has been reported in the monocytes of patients with RA, and the subsequent methylome change correlated with disease activity and therapeutic intervention[77,78]. Importantly, the observed transcriptomic heterogeneity and DNA methylome alteration amongst rheumatic monocytes is attributed to cytokine priming or training, modulated partly by IL-1β, TNF and interferon signalling[77,79], demonstrating the critical role of the inflammatory synovial milieu in genetic imprinting (Fig. 3).

Macrophage memory and resolution of inflammatory arthritis

Although the effects of macrophage training in driving inflammatory arthritis are now well appreciated, emerging data point towards a protective role of certain macrophage phenotypes, associated with resolution of inflammatory arthritis. In 2020, a study in a large cohort of patients with RA showed that the expression of tyrosine protein kinase Mer (MerTK) by a specific subtype of tissue macrophages was predominant in the synovium of patients who maintained remission after drug withdrawal. Synovial MerTK$^+$ macrophages from patients with RA showed an immunoregulatory transcriptomic signature and a heightened capacity for IL-10 production upon ex vivo stimulation[80]. MerTK belongs to the TAM receptor family, associated with inhibiting innate immune response through the upregulation of suppressor of cytokine signalling 1 (SOCS1) and SCOS3 (refs. 81,82) (Fig. 3). Nonetheless, it remains unclear whether the expression of MerTK by synovial macrophages during drug-free remission is merely a marker of re-established tissue homeostasis or MerTK effectively governs

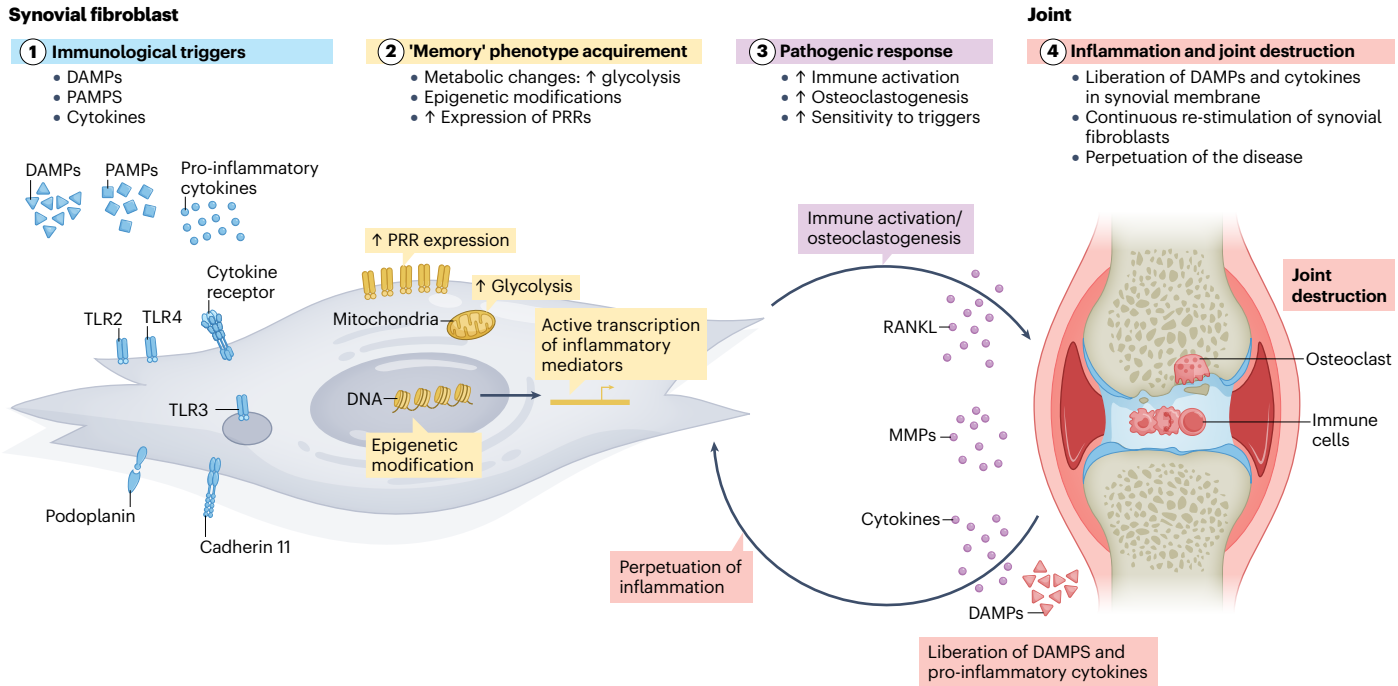

Fig. 1 | Inflammatory imprinting of synovial fibroblasts in arthritis. In inflammatory arthritis, several stages of inflammatory imprinting contribute to the synovial fibroblast phenotype. 1) A subset of synovial fibroblasts express cadherin 11, podoplanin and a wide array of pattern-recognition receptors (PRRs), which are activated by pathogen-associated molecular patterns (PAMPS) from infiltrating pathogens, damage-associated molecular patterns (DAMPS) released during tissue damage-induced inflammation, and pro-inflammatory cytokines. 2) Activation of signalling pathways downstream of PRRs and cytokine receptors reprogrammes the cellular metabolic machinery towards increased glycolysis and induces epigenetic modifications. 3) These epigenetic modifications augment the sensitivity of synovial fibroblasts to inflammatory stimuli and enhance their capacity to produce inflammatory mediators and to activate osteoclastogenesis. 4) The liberation of DAMPS and pro-inflammatory cytokines in the synovial milieu upon tissue degradation and bone loss acts as an antigenic challenge to synovial fibroblasts, triggering an enhanced secondary inflammatory response and thus perpetuating the disease. MMPs, matrix metalloproteinases; RANKL, receptor activator of nuclear factor-κB ligand; TLR, Toll-like receptor.

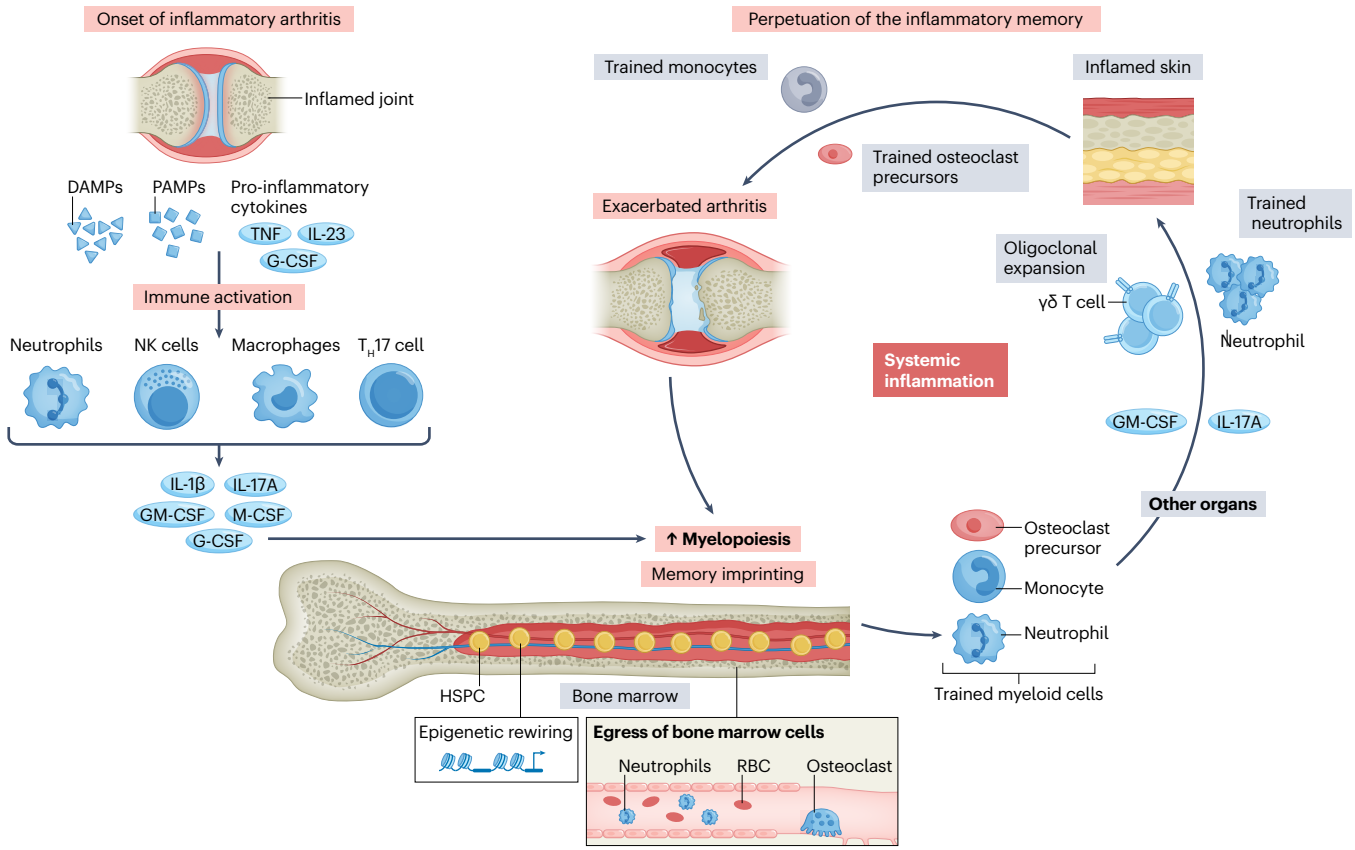

Fig. 2 | Peripheral inflammation and maladaptive bone marrow myelopoiesis. Early inflammatory events in inflammatory arthritis are shaped by various stimuli, including infection, damage-associated molecular patterns (DAMPS) and the local cytokine milieu, which induce the activation of local and peripheral immune cells. These activated cells release pro-inflammatory cytokines and factors that support the expansion of myeloid cells, which induce metabolic and epigenetic modifications in haematopoietic stem and progenitor cells (HSPCs). These modifications result in increased osteoclast formation in the bone marrow, which enhances the egress of bone-marrow cells, including neutrophils, and memory imprinting of bone marrow myeloid cells with a skewing towards enhanced myelopoiesis and inflammatory hyper-responsiveness. The trained myeloid cells generated are recruited to different organs and inflamed tissues, where they mount a heightened secondary response, thereby supporting the proliferation of activated neutrophils and the oligoclonal expansion of γδ T cells. The enhanced production of pro-inflammatory cytokines promotes the recruitment of the trained monocytes and osteoclast precursors to the inflamed joint, resulting in exacerbated tissue destruction and inflammation that perpetuates the maladaptive inflammatory memory cycle. GM–CSF, granulocyte–macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; M-CSF, macrophage colony-stimulating factor 1; NK, natural killer; PAMPs, pathogen-associated molecular patterns; RBC, red blood cell; T_H17, T helper 17.

the restoration of immune homeostasis in the joint. Further studies are necessary to formally establish a causal link between MerTK expression and the induction of an immunoregulatory memory-like macrophage phenotype and, more importantly, to identify the immunological mechanisms that lead to its emergence in the context of inflammatory arthritis.

More evidence of the potential involvement of macrophage innate memory in the resolution of inflammatory arthritis comes from studies deciphering the favourable response of patients with RA to early treatment with DMARDs[83]. For instance, it has been shown that the incubation of RA macrophages with TNF-blocking agents results in the downregulation of the co-stimulatory molecules CD40 and CD80 and a heightened capacity for IL-10 production[84]. Furthermore, methotrexate-exposed human macrophages fail to produce IL-6 and IL-1β following exposure to inflammatory stimuli, through the upregulation of the NF-κB suppressor protein A20, which controls excessive macrophage-mediated inflammation by inhibiting NF-kB signalling[85]. Importantly, A20 expression is induced through epigenetic modification at its promoter via increased H3K4 methyltransferase activity[86]. Other studies have shown that methotrexate therapy is able to reverse aberrant epigenetic modifications in immune cells from patients with RA by targeting DNA methylation[78], but data on its effects on histone methylation are still lacking.

Innate memory in erosive arthritis

Our current understanding clearly supports the presence of adaptive-like features amongst circulating monocytes and synovial macrophages in inflammatory arthritis. These features negatively and positively regulate the extent of bone resorption in erosive arthritis. Bone resorption in inflammatory arthritis is largely controlled by osteoclasts, which are specialized cells found on trabecular and endosteal cortical bone surfaces. Multinucleated osteoclasts derive from the

fusion of haematopoietic myeloid progenitors following RANKL and M-CSF signalling, which induces the transcription of genes involved in bone resorption function (*NFATC1*, *TNFRSF11A*, *FMS*, *ACP5*, *CTSK*, *MMP9* and *ATP6V0D2*)[87,88]. The exact osteoclast precursor is yet to be defined but derives from HSPCs, which differentiate into various cells including synovial macrophages and immature dendritic cells[89]. Synovial macrophages are capable of osteoclast differentiation and therefore any aforementioned 'priming' or 'training' of these cell populations is likely to affect the extent of bone destruction and erosive severity of inflammatory arthritis[90]. Therefore, the expansion of myeloid cells in inflammatory arthritis is directly linked to trained immunity of HSPCs and synovial osteoclast precursors.

In inflammatory arthritis, multiple pathways contribute to the terminal differentiation and maturation of osteoclasts[91]. For instance, IL-17A promotes the expansion of IL-17RA$^+$ CD11b$^+$ Gr1^{low} osteoclast precursors in the bone marrow and induces the expression of RANK and M-CSF receptor, rendering these cells hyper-responsive to osteoclast differentiation signalling[30,92]. Other pro-inflammatory cytokines,

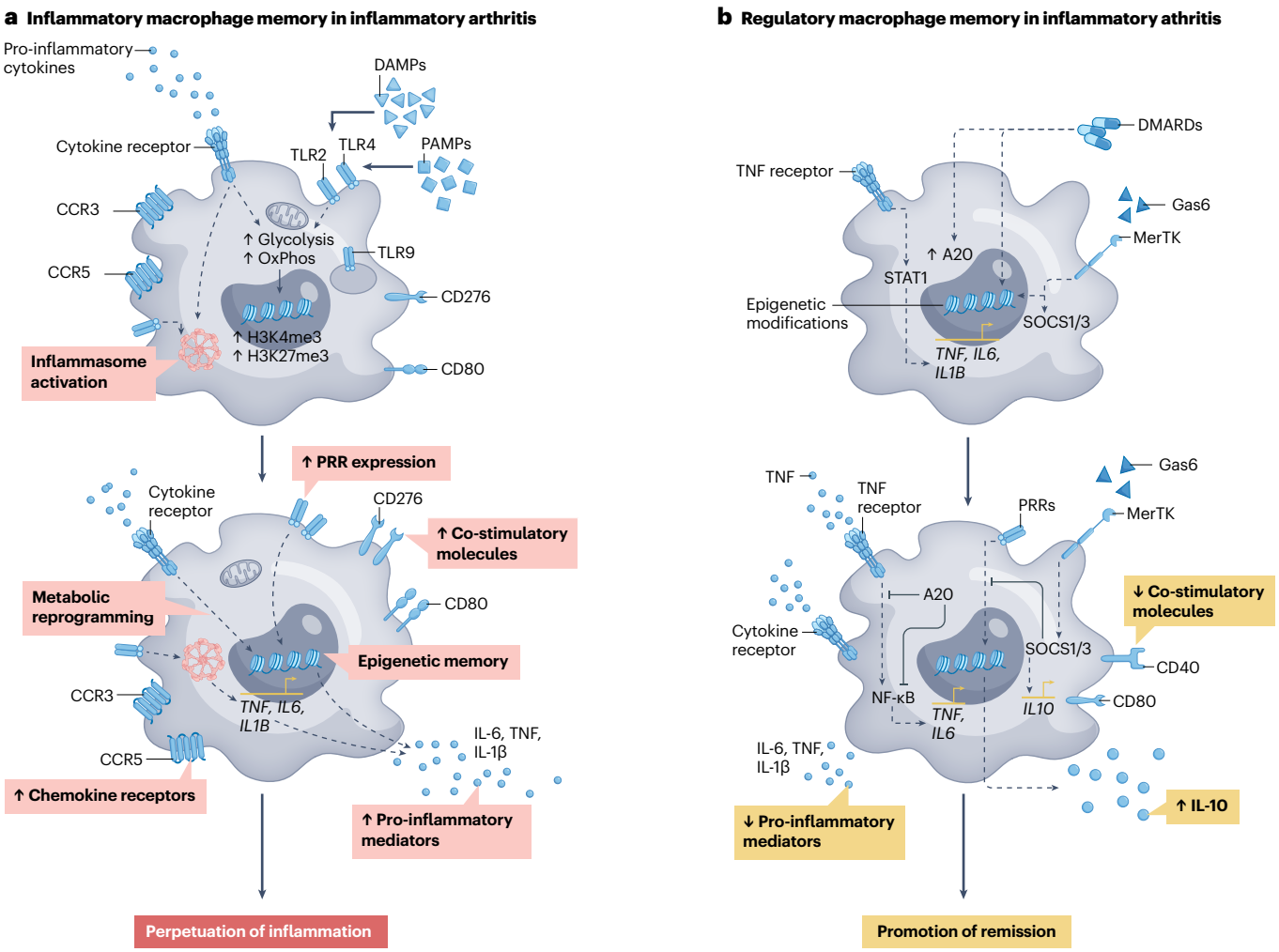

Fig. 3 | Macrophage immune memory in inflammatory arthritis. a, Pro-inflammatory cytokines, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPS) constitute immunological triggers that induce metabolic and epigenetic reprogramming, leading to macrophage memory in inflammatory arthritis. Downstream signalling via pattern-recognition receptors (PRRs) and cytokine receptors promotes NLRP3 inflammasome activation, metabolic reprogramming (increased glycolysis and/or oxidative phosphorylation) and epigenetic rewiring (increased H3K4 and H3K27 trimethylation), modulating gene transcription leading to increased expression of co-stimulatory molecules CD80 and CD276, PRRs and chemokine receptors CCR3 and CCR5. These alterations are imprinted in macrophages and persist after the initial triggers are removed. The re-exposure of the reprogrammed macrophages to inflammatory stimuli induces a heightened secondary response, characterized by increased production of TNF, IL-1β and IL-6, that perpetuates joint inflammation. **b**, Conversely, exposure to DMARDs (such as methotrexate and TNF-blocking agents) upregulates the NF-κB suppressor protein A20, and hampers the signal transducer and activator of transcription 1 (STAT1) signalling pathway, which dampens the immune responsiveness of macrophages, prevents hyperinflammatory epigenetic imprinting and induces long-lasting immunoregulatory properties characterized by a shift towards augmented secretion of the anti-inflammatory cytokine IL-10, a reduced transcription of pro-inflammatory *TNF* and *IL6* and a downregulation of co-stimulatory molecules and PRRs. Additional receptors including the tyrosine protein kinase (MerTK) receptor are associated with a regulatory macrophage phenotype via the upregulation of suppressor of cytokine signalling 1 (SOCS1) and SOCS3 but its role in inflammatory arthritis is uncertain (depicted by the dashed arrows). NF-κB, nuclear factor κB.

such as IL-23 and TNF, can affect intracellular calcium signalling, which affects the differentiation of osteoclast precursors via the activation of the transcription factor nuclear factor of activated T cells, cytoplasmic 1 (NFATc1)[93,94]. IL-23 also activates innate immunoreceptors such as myeloid DAP12-associating lectin 1 (MDL-1), a C-type lectin that pairs with DAP12 (TYRO protein tyrosine kinase-binding protein) receptor and activates the transcription factors PU.1 and NFATc1, which are essential in osteoclast differentiation[93,95]. Activation of these immunoreceptors is critical in inflammatory arthritis as it not only induces myelopoiesis, but also affects osteoclast differentiation via co-stimulatory pathways. The immunoreceptor macrophage-inducible C-type lectin (Mincle) also shifts osteoclast metabolism towards oxidative phosphorylation, associated with an enhanced migration and bone-resorption capacity[96]. These activation pathways mimic the RANK signalling pathway, which reprogrammes the metabolic machinery of osteoclast precursors and mature osteoclasts towards enhanced glycolysis and oxidative phosphorylation[97,98]. Under arthritic conditions, this metabolic reprogramming is synergized by the highly hypoxic synovial milieu that suppresses the expression of the negative regulator COMM domain-containing protein 1, resulting in enhanced osteoclastogenesis[99].

Epigenetic modifications have not only been documented to lead to the activation of pro-osteoclastogenic genes such as *MMP9* but are also responsible for the repression of negative regulators of osteoclastogenesis such as IRF8 (ref. 100). A 2022 study demonstrated that exposure of macrophages to TGFβ increases the chromatin accessibility at osteoclastic gene loci and induces IRF8 degradation in response to TNF stimulation[101]. Epigenetic changes, including DNA methylation and histone modifications, influence the transcription factors PU.1, NFATc1 and IRF8 and control osteoclast differentiation and function[97,98,102]. It is evident that immunoreceptors such as MDL-1 and Siglec-15 are modulating DAP12 co-stimulatory pathways[93,103]. However, it is not clear whether immunoreceptors that are associated with trained immunity and epigenetic modifications in osteoclast precursors continue to affect terminally differentiated osteoclasts[104].

The notion that innate immune memory occurs not only in HSPCs, synovial macrophages and other osteoclast precursors, but also in terminally differentiated osteoclasts, which are thought to be incapable of conferring memory, was implied by a 2021 study. Advanced imaging analysis revealed that terminally differentiated osteoclasts divide into smaller cells called osteomorphs, a phenomenon distinct from apoptosis[105]. Restimulation of the osteomorphs with RANKL re-induces their fusion into mature bone-resorbing osteoclasts with a heightened capacity to respond to RANKL differentiation signals. Interestingly, osteomorphs exhibit an altered transcriptomic signature compared with osteoclasts and/or macrophage precursors, with an upregulation of several novel genes (including *Ccr3*, *Axl*, *Vcam1*, *Cal1* and *Cd74*) involved in both bone tissue homeostasis and immune regulation[105]. This novel concept is supported by clinical studies reporting the rebound phenomenon of accelerated bone loss and increased vertebral fracture in patients several months after discontinuation of anti-RANKL treatment[106]. Indeed, this newly described recycling mechanism of osteoclasts that leads to the production of primed osteomorphs that fuse and respond rapidly to changing conditions closely resembles the phenomenon of trained immunity[58]. Although the factors involved in the regulation of osteoclast recycling, as well as the epigenetic changes associated with the cell priming, trained immunity and differentiation, still need to be defined, these findings substantially enhance our understanding of bone erosion in inflammatory arthritis and introduce innate immune memory as a plausible target to control aberrant osteoclastogenesis and bone resorption[91].

In addition to innate immune memory and osteoclast bone-resorbing function, the shared myeloid origin of the monocytes/macrophage lineage and dendritic cells supports the idea that osteoclasts might exhibit potent immune properties, thereby regulating the inflammatory process in pathological conditions. Indeed, upon treatment with RANKL, osteoclasts secrete CCL3, CCL4, CCL5 and CXCL10 chemokines, thus affecting T cell migration[107]. In addition, stimulation of osteoclasts with LPS upregulates the expression of MHC II and the co-stimulatory molecules CD80, CD86 and CD40, along with notable production of the cytokines IL-6, TNF, IL-1β and IL-10 (ref. 108). Interestingly, in a mouse model of colitis with severe bone destruction, osteoclasts exhibited an upregulation of the chemokine receptor CX3CR1, which promoted TNF-producing $CD4^+$ T cells in an IL-17A-dependent manner, whereas osteoclasts deriving from the bone marrow of control mice (without colitis) induced the immunosuppressive $FOXP3^+CD4^+$ T cell subset[109]. More recently, a transcriptomic analysis performed in ovariectomized mice, a model in which osteoclastogenesis is driven by TNF and RANKL-producing $CD4^+$ T cells, identified $CX3CR1^+$ and $CX3CR1^-$ osteoclasts subsets that contrasted considerably in transcriptional and functional aspects, thus supporting the heterogeneity of osteoclasts in the context of chronic inflammation[110].

Collectively, this evidence indicates that innate immune memory could regulate multiple functions of terminally differentiated osteoclasts, including recycling in the form of osteomorphs, increased bone resorption and/or modulating immune responses in the bone microenvironment (Fig. 4), which need to be further investigated in future studies.

Clinical relevance of innate memory in inflammatory arthritis

Despite major advances in the clinical diagnosis and therapeutic management of inflammatory arthritis, several clinical aspects and unexpected events remain enigmatic, including the frequency of comorbidities and the variability of treatment response, sustained remission and episodes of disease flare.

The response rate to an effective treatment is extremely variable among patients with RA, and sustained drug-free remission is an unusual event, occurring in <15% of treated patients[111]. Accumulating evidence indicates that clinical remission involves active immunological processes that dampen the chronic inflammation but that fail to achieve a total recovery of joint homeostasis. Residual subclinical synovitis is likely to persist in patients with RA and PsA in remission[112,113]. More importantly, gene transcriptional profiling of peripheral blood mononuclear cells of children with polyarticular juvenile idiopathic arthritis in remission showed a balance between pro-inflammatory and anti-inflammatory genes, rather than a return to a normal state[114]. A study demonstrated that synovial macrophages acquire a pro-inflammatory phenotype under arthritic conditions that persists even after a primary immune stimulus resolves, suggesting that these cells contribute to the maintenance of joint-specific memory in quiescent joints[115]. A systematic literature review also highlighted the beneficial long-term effects of the 'window of opportunity' paradigm, wherein early and aggressive treatment with DMARDs is disproportionally associated with sustained drug-free remission[116]. Accordingly, in a multicentre, randomized, placebo-controlled trial, it was concluded that the early initiation of TNF inhibition (with golimumab) accelerates remission of PsA[117]. Similarly, in patients with RA who have subclinical joint inflammation

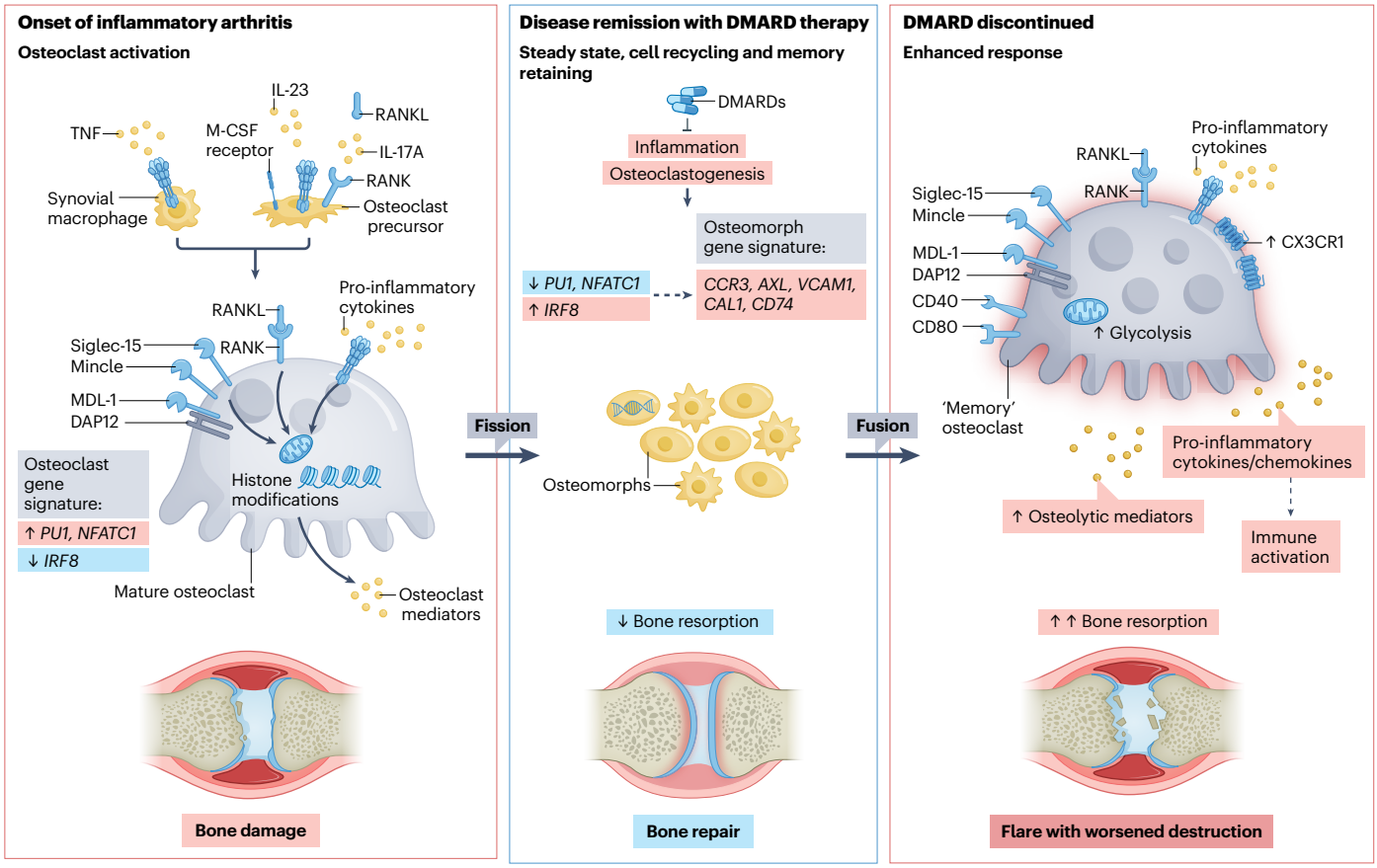

Fig. 4 | Memory imprinting of osteoclasts during chronic inflammation. Under arthritic conditions, the release of IL-23, IL-17, TNF and receptor activator of nuclear factor-κB ligand (RANKL) by activated immune cells promotes the differentiation of osteoclast progenitors and synovial macrophages into mature osteoclasts. Inflammatory osteoclasts have increased expression of immunoreceptors MDL-1, Mincle, Siglec-15 and DAP-12, which act as co-stimulators of osteoclast differentiation in addition to receptor activator of nuclear factor-κB (RANK), and display a metabolic shift towards increased glycolysis. The activation process is also accompanied by epigenetic changes that enhance accessibility to osteoclastic genes by modulating the transcriptional regulation of transcription factor PU1, nuclear factor of activated T cells (NFATc1) and interferon regulatory factor 8 (IRF8). Once the stimulatory signal is removed, the mature osteoclasts undergoes a fission that results in the formation of smaller, more motile daughter cells described as osteomorphs. The osteomorphs undergo substantial transcriptomic changes but retain the ability to fuse, upon stimulation with RANKL, into mature osteoclasts with an enhanced osteolytic activity. Furthermore, chronic inflammatory conditions confer to the osteoclasts the ability to produce pro-inflammatory cytokines and the upregulation of activating membrane markers such as co-stimulatory molecules (CD40 and CD80) and the chemokine receptor CX3CR1, resulting in the activation of immune cells, which aggravates the inflammatory process within the joint. M-CSF, macrophage colony-stimulating factor 1; VCAM1, vascular cell adhesion protein 1.

(detected by MRI), early treatment with methotrexate failed to prevent the establishment of clinical arthritis, but had a sustained positive impact on the disease severity and chronicity of inflammation[118]. Although the exact disease-specific mechanisms of these DMARDs are inconclusive, several observations suggest they have immunomodulatory effects on innate immune cells. Indeed, circulating monocytes from patients with RA treated with the TNF inhibitor infliximab show a downregulation of the chemokine receptors CCR2 and CXCR4 and an increased expression of the immunoregulatory marker CD163 (ref. 119). Previous data demonstrated that the pre-treatment of macrophages with infliximab in vitro enhances their capacity to produce anti-inflammatory IL-10 following LPS challenge[120]. These findings, combined with the aforementioned immunoregulatory reprogramming effect of methotrexate and TNF inhibitors on macrophages, suggest that the early initiation of anti-inflammatory treatment could prevent an intense 'memory' imprinting of the innate immune response, by modulating the immune cells at a less-activated and more-reversible stage.

Hence, the modulation of innate immune memory is directly relevant to disease severity, treatment response rate and sustained remission. Moreover, it could provide an explanation for disease flare events, which are associated with accelerated joint damage and aggravation of co-morbidities[121].

The role of infectious episodes in the onset or the flare of underlying chronic inflammatory disorders has been suggested, and associations between infections and the risk of RA onset are widely described[122,123]. Conversely, a large population-based case–control study showed that a history of gastrointestinal and urogenital Gram-negative bacterial infections is associated with a decreased risk of RA[124]. Gram-negative bacterial infection is known to be associated with macrophage tolerance[125] and with alleviated symptomatology in other

Table 1 | Immunological mechanisms linking innate immune memory and clinical features of inflammatory arthritis

Related disease	Immune trigger	Impact on innate memory	Functional consequences	Mechanism(s)	Clinical effect	Refs.
RA	Methotrexate	Macrophage tolerance	↓ IL-1β and IL-6 ↓ MAPK, NF-κB and TRIF1 signalling ↑ DNA methylation	↑ NF-κB suppressor protein A20 ↓ DNA demethylation enzymes (TET1, TET2,TET3)	Positive effect on disease severity	78,85
RA	Pemetrexed	Macrophage tolerance	↓ TNF and IL-6 production capacity ↓ TLR4 signalling	↓ Expression of soluble and macrophage membrane-bound CD14	Increased treatment response rate	129
RA AS PsA	TNF blocking agents	Macrophage tolerance	↓ CCR2 and CXCR4 expression ↓ CD40 and CD80 expression ↑ MerTK and CD163 expression ↑ IL-10 secretion capacity	↑ Activation of IL-10–STAT3 axis	Improved remission rate and bone-preserving effect	84,119
RA	Oxidized LDL	Innate immune training	↑ IL-6, TNF, MCP-1 ↑ Ly6C, CCR5 ↓ SR-B1	↑miR-24 ↓ IRAK-M expression ↑ NLRP3 activation ↑ H3K4me3 pro-inflammatory mediators	Increased atherosclerosis and cardiovascular comorbidities	127,128
RA	Periodontitis	Innate immune training	↑ Pro-inflammatory mediators	↑ IL-1 signalling in HSPCs ↑ Chromatin access to pro-inflammatory genes	Disease flare and perpetuation of inflammation	32,122,123

AS, ankylosing spondylitis; CCR, C-C chemokine receptor; CXCR, C-X-C chemokine receptor; H3K4me3, trimethylated histone H3 lysine 4; HSPC, haematopoietic stem and progenitor cell; IRAK-M, IL-1 receptor-associated kinase M; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; MerTK, tyrosine protein kinase MER; miR, microRNA; NF-κB, nuclear factor-κB; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SR-B1, scavenger receptor class B type 1; STAT3, signal transducer and activator of transcription 3; TET, ten-eleven translocation; TLR4, Toll-like receptor 4; TRIF1, Toll/IL-1 receptor domain-containing adaptor inducing IFN-β.

chronic inflammatory conditions[126]. Other reports link innate immune memory and the high prevalence of cardiovascular comorbidities in rheumatic diseases[127,128].

Collectively, these data support the involvement of innate memory in the modulation of the clinical presentation of inflammatory arthritis (Table 1). Further investigations are required to provide novel biomarkers as promising tools for clinicians to better diagnose and monitor those chronic disorders.

Conclusions

Over the past decade, trained immunity has emerged as one of the most dynamic fields of study in contemporary immunology. The awareness of its immunomodulatory effects on anti-infectious immune responses has grown in parallel with a general recognition of its involvement in the pathogenesis of several immune-mediated chronic inflammatory disorders. In inflammatory arthritis, a complex interaction occurs between the chronic release of pro-inflammatory mediators, the endogenous danger signals from damaged tissues and exogenous factors such as infectious triggers and therapeutic intervention. This interaction confers to the cells of the innate system, as well as to some non-immune cells, a pathogenic memory that perpetuates the inflammation and tissue damage. Nonetheless, beneficial effects of innate immune memory in chronic inflammatory diseases can be achieved with certain stimuli. Remarkably, it is currently challenging to predict the amplitude and longevity of this innate memory, given the multiple variable factors it comprises. Hence, clarifying how the innate immune cells integrate the complex array of surrounding signals in the inflamed joint and process it into long-lasting memory will provide new insights into the pathogenesis of inflammatory arthritis. Additionally, the identification of the different damage-associated molecular patterns released from damaged synovial tissue and the study of their potential immune-training effect might enable the development of more-effective targeted treatments. Accordingly, the use of large-scale transcriptomic and sequencing techniques along with advanced bioinformatics analysis would help to dissect the signalling pathways and the epigenetic and metabolic modifications that characterize the innate immune and non-immune cells involved in inflammatory arthritis. The goal is to design new personalized molecular tools that specifically target the aberrant accumulation of epigenome-modifying metabolites while preserving the general metabolic machinery responsible for cellular survival and function.

In addition, the expansion of genome-wide experimental and computational techniques could provide important insights into the role of post-transcriptional gene regulation by mRNA modification, a field under-explored so far in innate immune memory. These insights could provide a molecular basis for the development of new therapeutic strategies and would help to facilitate individualized approaches to treating chronic inflammatory disorders.

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