Innate Lymphocytes in Inflammatory Arthritis

Xunyao Wu*

The Ministry of Education Key Laboratory, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Clinical Immunology Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Inflammatory arthritis (IA) refers to a group of chronic diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and other spondyloarthritis (SpA). IA is characterized by autoimmune-mediated joint inflammation and is associated with inflammatory cytokine networks. Innate lymphocytes, including innate-like lymphocytes (ILLs) expressing T or B cell receptors and innate lymphoid cells (ILCs), play important roles in the initiation of host immune responses against self-antigens and rapidly produce large amounts of cytokines upon stimulation. TNF (Tumor Necrosis Factor)-α, IFN (Interferon)-γ, Th2-related cytokines (IL-4, IL-9, IL-10, and IL-13), IL-17A, IL-22, and GM-CSF are involved in IA and are secreted by ILLs and ILCs. In this review, we focus on the current knowledge of ILL and ILC phenotypes, cytokine production and functions in IA. A better understanding of the roles of ILLs and ILCs in IA initiation and development will ultimately provide insights into developing effective strategies for the clinical treatment of IA patients.

Keywords: Inflammatory arthritis, innate-like lymphocytes, innate lymphoid cells, inflammatory cytokine, NK cells

INTRODUCTION

Inflammatory arthritis (IA) describes a group of autoimmune-associated diseases with sustained chronic inflammation that eventually result in disability and decreased quality of life. IA includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and other spondyloarthritis (SpA), which have similar and different clinical features (1). RA is characterized by joint inflammation, osteoclast-mediated cartilage, local bone destruction and usually affects the limbs first. Autoantibodies against citrullinated peptide (ACPA) and rheumatoid factor (RF) can be detected in the serum and inflamed synovial membrane of nearly two-thirds of RA patients (2). PsA is a seronegative, systematic inflammatory joint disease, and up to 30% of PsA patients have psoriasis. PsA displays heterogeneous musculoskeletal characteristics, including peripheral arthritis, entheses, dactylitis, and axial skeleton and dermal manifestations (3). AS is considered a genetic immune-mediated arthritis that has a strong correlation with HLA-B27. In AS patients, the joints of the spine are the most affected (4). AS also displays a number of other clinical characteristics, including peripheral arthritis, ligament, enthesis attachment and inflammatory bowel disease (IBD). Other SpA includes a subgroup of juvenile idiopathic arthritis, reactive arthritis and IBD-associated arthritis (5). It is widely accepted that IA is strongly associated with
immune disorders, but the current understanding of the immune pathogenesis of IA is still limited. Uncovering how inflammation is resolved could help the development of innovative strategies for clinical IA therapy.

Innate lymphocytes, including innate-like lymphocytes (ILLs) and innate lymphoid cells (ILCs), play important roles in the initiation of host immune responses against intracellular and extracellular pathogens or self-antigens. ILLs such as natural killer T (NKT) cells, mucosal-associated invariant T (MAIT) cells, γδ T cells, B-1 cells and marginal zone B (MZB) cells preferentially utilize specific TCR or BCR genes and respond immediately upon antigen exposure (6). ILCs are particularly abundant at barrier surfaces. These cells lack T cell or B cell receptors and do not undergo clonal selection. The ILC family consists of three major groups: Group 1 ILCs include conventional natural killer (NK) and Interferon (IFN)-γ-secreting ILC1s; Group 2 ILCs (ILC2s) mainly produce interleukin (IL)-4, IL-5, IL-9, and IL-13; and Group 3 ILCs (ILC3s), including lymphoid tissue inducer (LTI) cells, predominantly secrete IL-17 and IL-22 (7). In addition to their roles in orchestrating inflammatory responses to pathogens, innate lymphocytes also directly contribute to inflammation resolution and tissue homeostasis maintenance (8–10). In this review, we discuss the role of innate lymphocytes in IA and how current or potential new clinical approaches could be applied to modulate persistent inflammatory responses in IA patients.

INNATE LYMPHOCYTES-ASSOCIATED CYTOKINES IN IA

Cytokines have been demonstrated to play critical roles in IA, and anti-inflammatory cytokine therapies are therefore attractive therapeutic strategies. One of the key features of innate lymphocytes is their ability to produce large amounts of cytokines rapidly upon stimulation. Cytokine production mediates subsequent adaptive immune cell activation and raises the possibility of continuous cytokine production in self-reinforcing stimulatory loops during chronic inflammation (11). Moreover, proinflammatory cytokines can amplify local inflammation and further promote the generation of matrix-degrading proteolytic enzymes or reactive oxygen species, which result in organ damage and clinical symptoms of autoimmune diseases (12). Therefore, proper understanding of innate lymphocyte-associated cytokines in IA would help us gain a better understanding of innate lymphocytes in IA. The roles of innate lymphocytes-associated cytokines are summarized in Table 1.

TH1-RELATED CYTOKINES: TNF-α AND IFN-γ

It is widely accepted that uncontrolled TNF production is associated with IA development. The TNF inhibitors infliximab, etanercept, and adalimumab are current standard clinical treatments for IA (13). TNF-α is a key driver of sustained synovial inflammation by inducing prolonged IL-6 production and NF-κB activation in FLSs (14). Moreover, TNF-α is also a well-known inhibitor of osteoblast differentiation and is associated with bone destruction in IA (15).

Interferon-γ is a classic Th1-related proinflammatory cytokine and has been identified as the most important agent for the regulation of inflammation (16). IL-12 enhances the production of IFN-γ or other important IFN-γ inducers, such as IL-23, IL-18, and IL-27 (17). IFN-γ plays dual roles in IA. IFN-γ exhibits a protective effect in IA by the following mechanisms: (1) reducing inflammatory cell death by targeting necroptosis (18); (2) inhibiting IL-β1-induced matrix metalloproteinase (MMP) synthesis by RA FLSs, thereby limiting cartilage degradation (19); and (3) and inhibiting Th17 cell development and suppressing Th17 cell effector functions (20). On the other hand, in PsA, IFN-γ promotes the development of PsA either by activating antigen-presenting cells (APC) to further contribute to IL-17 induced pathology or directly effects skin and bone cells (21).

Moreover, in another study performed by Karonitsch et al., they revealed unique effects of IFN-γ in driving tissue remodeling in arthritis (22).

TH2-RELATED CYTOKINES: IL-4, IL-9, IL-10 AND IL-13

IL-4, IL-9, IL-10, and IL-13 are Th2-related cytokines that are associated with anti-inflammatory and antiosteoclastogenesis effector functions in IA. IL-4 and IL-13 share common IL-4Rα and STAT6 signaling pathways (23). IL-4/IL-13 secretion and STAT6 signaling activation play crucial roles in inhibiting IA development (24). IL-4 and IL-13 are also known to induce osteoblasts to produce osteoprotegerin (OPG), an inhibitor that prevents osteoclast formation. IL-4 induces a stronger effect on OPG production than IL-13 (25). IL-4 also suppresses TNF-α-mediated osteoclastogenesis by inhibiting stromal cell RANKL expression and directly affects stromal cells and osteoclast precursors (26).

IL-9 concentrations are higher in the synovial fluid (SF) of RA and PsA patients than in that of osteoarthritis (OA) patients. IL-9 could promote pathological T cell proliferation through the PI3K/Akt/mTOR signaling pathway in the synovium in IA (27). Synovial IL-9 could also prolong the survival of neutrophils, increase their MMP9 expression, and promote Th17 cell differentiation by inducing RORγt and STAT3 phosphorylation (28). The IL-9/IL-9R axis drives γδ T cell expansion and activation in PsA (29). However, the role of IL-9 in IA has been a subject of controversy, and recent research has demonstrated that ILC2-derived IL-9 mediates chronic inflammation resolution and protects against bone loss (30).

IL-10, a well-known immunosuppressive cytokine, can be produced by all leukocyte subsets and restrains IA development (31). IL-10-deficient mice display more severe arthritis than wild-type (WT) mice, demonstrating that IL-10 is able to ameliorate IA disease severity (32). In collagen-induced arthritis (CIA), macrophages from IL-10−/− mice show enhanced IL-17 and RORγt expression compared with those of WT mice (33). IL-10
exhibits a suppressive effect on Th17 cell activation and induces the generation of Foxp3\(^+\) Tregs in RA patients (34).

**TH17-RELATED CYTOKINES: IL-17A AND IL-22**

IL-17A is clearly critical in IA development and plays a role in many stages of IA. It is well established that IL-23 is a major inducer of IL-17A secretion and that the IL-23-IL-17A axis plays a key role in IA (35). IL-17A promotes IA in many respects. In the pathogenesis of RA, IL-17A promotes angiogenesis and induces human lung microvascular endothelial cell (HMVEC) migration through the PI3K/AKT1 pathway (36). IL-17 induces monocyte migration into the joints by binding to IL-17RA, and this migration is mediated through p38 MAPK signaling (37). Moreover, IL-17A induces inflammatory cytokines (including IL-6, TNF, IL-1, and RANKL) (38, 39), chemokines and MMP secretion in FLS (40). Furthermore, IL-17A synergizes with cobalt chloride (CoCl\(_2\)), a hypoxia mimetic, to exacerbate osteoclast-mediated bone erosion through the activation of the RANKL/NF\(\kappa\)B/NF\(\kappa\)Bc1 signaling pathway (41). Additionally, IL-17A promotes neutrophil migration through a CXC chemokine-dependent pathway (42).

IL-22, a Th17 cytokine, belongs to the IL-10 family. The pathogenic functions of IL-22 in the joints have been described. IL-22 enhances FLS expansion and RA FLS-derived MMP1 and S100A8/A9 production (43, 44). IL-22 has osteoclastogenic effects (including IL-6, TNF, IL-1, and RANKL) (38, 39), chemokines and MMP secretion in FLS (40). IL-22 also stimulates IL-1\(\beta\) production and promotes neutrophil infiltration in joints (46). In murine CIA, IL-22 is required for germinal center (GC) maintenance and might promote the generation of autoantibody-secreting plasma cells (47).

**OTHER CYTOKINES: GM-CSF**

Granulocyte-macrophage colony stimulating factor (GM-CSF) was first identified as a growth factor that induces hematopoietic progenitor cell differentiation into granulocytes and macrophages (48). GM-CSF has been shown to exacerbate IA disease and is absolutely required for pain development (45, 49). In RA, GM-CSFR blockade results in myeloid cell-derived proinflammatory mediator suppression and suppression of T cell activation (50). GM-CSF supports the differentiation of a subpopulation of monocytes into CD1c\(^+\) synovial inflammatory dendritic cells and is involved in FLS proliferation (51, 52). Moreover, GM-CSF activates and triggers proinflammatory responses in CCR2\(^+\)Ly6C\(^hi\) monocytes that mediate autoimmune-associated tissue damage (53).

**THE ROLE OF ILLs IN IA**

Innate-like lymphocytes include NKT cells, MAIT cells, γδ T cells, and innate-like B cells. Unlike conventional adaptive T and B cells, ILLs preferentially utilize specific TCR or BCR genes and rapidly respond to antigen stimulation. Below, we summarize the roles of ILLs in IA (Table 2).

**NKT CELLS**

Natural killer T cells, which co-express T cell and NK cell receptors, are able to rapidly secrete large amounts of cytokines, including GM-CSF, IFN\(\gamma\), IL-2, IL-4, IL-10, IL-13, IL-17A, and TNF, upon stimulation. NKT cell responses are modulated by glycolipid antigens such as α-Galcer, which is presented by CD1d, a non-classical MHC class I-like molecule. TCR\(\alpha\) rearrangement in CD1d-dependent NKT cells includes V\(\alpha_{14}\)-J\(\alpha_1\) in mice and V\(\alpha_{24}\)-J\(\alpha_1\) in humans (54).

Previous studies have shown that the percentage of NKT cells is decreased in PBMCs of RA patients compared with healthy controls, and IFN-\(\gamma\)-producing NKT cells were present in the SF of RA patients (55, 56). In previous studies, NKT cells have been demonstrated to have dual functions in different stages of murine arthritis. Anti-CD1d mAb administration in DBA/1J mice or knockout of V\(\alpha_{14}\) expressing NKT cells in B6 background mice resulted in the development of arthritis with reduced severity after CIA induction, suggesting that V\(\alpha_{14}\)-expressing NKT cells were effector cells in IA (57). In another antibody-induced murine arthritis model, Hye Young Kim et al. showed that IL-4- and IFN-\(\gamma\)-secreting NKT cells played an indispensable role at the end-stage of joint inflammation by suppressing TGF-\(\beta\) production (58). IL-17-producing NKT cells were increased with disease progression and involved in disease promotion in DBA/1 mice (59). However, in another antigen-induced C\(D1d\) KO/B6 mouse arthritis model, the lack of C\(D1d\)-dependent NKT cells resulted in the development of arthritis with reduced severity after CIA induction, suggesting that V\(\alpha_{14}\)-expressing NKT cells in the peripheral blood are CCR7\(^-\) (60). In the acute phase of arthritis accompanied by an enhanced arthritogenic Th1 response. These studies suggest a protective role of C\(D1d\)-dependent NKT cells during the priming phase of the disease (60). IL-17-secreting iNKT cells in the SpA joint displayed a ROR\(\gamma_t\)-T-bet\(^{low}\)PLZF\(^-\) phenotype (61, 62). A markedly increased NKT cell ratio was observed and found to predict radiographic changes in AS (63). iNKT cells play a regulatory role in dampening combined gut and arthritis inflammation in SpA (64).

**MAIT CELLS**

Mucosal-associated invariant T cells are innate T cells harboring a conserved T cell repertoire: V\(\alpha_{7.2}\)-J\(\alpha_{33}\) in humans and V\(\alpha_{19}\)-J\(\alpha_{33}\) in mice. MAIT cells are distributed in peripheral blood and tissues, including the liver, intestine, lung, kidney, prostate, and ovary (65). In humans, MAIT cells are universally defined as C\(D16_{1hi}\)C\(D26_{hi}\) and express transcription factors, including T-bet (TBX21), eomesodermin (EOMES), Blimp-1 (PRDM1), PLZF (ZBTB16), type 17 transcription factors ROR\(\gamma_t\) (RORC), and STAT3 (STAT3). MAIT cells in the peripheral blood are CCR7\(^-\) and exhibit an effector memory phenotype (C\(D62_{1low}\)C\(D45_{RO7}\)C\(D27_{hi}\)), which reflects their poor ability...
TABLE 1 | A Summary of innate lymphocytes-associated cytokines in inflammatory arthritis.

| Cytokines  | Role          | Mechanisms                                                                 | References |
|------------|---------------|-----------------------------------------------------------------------------|------------|
| TNF-α      | Pathogenic    | Induce prolonged IL-6 production and NF-κB activation in FLSs; Inhibit osteoblast differentiation and associated with bone destruction. | (14, 15)  |
| IFN-γ      | Dual roles    | (1) Protective: reduce cell death; inhibiting IL-1β-induced MMP synthesis by RA FLS; inhibit Th17 cell development and function. (2) Pathogenic: activate IL-17 induced pathology or directly effects skin and bone cells in PsA; | (16–22)   |
|            |               | drive tissue remodeling in RA.                                               |            |
| IL-4/IL-13 | Protective    | Prevent osteoclast formation; IL-4 also suppresses TNF-α-mediated osteoclastogenesis | (23–26)   |
| IL-9       | Dual roles    | (1) Pathogenic: promote pathological T cell proliferation; prolong the survival of neutrophils and increase their MMP9 expression; promote Th17 cell differentiation; drive γδ T cell expansion and activation. (2) Protective: ILC2-derived IL-9 mediates chronic inflammation resolution and protects against bone loss. | (27–30)   |
| IL-10      | Protective    | Exhibit a suppressive effect on Th17 cell activation; induce the generation of Foxp3+ Tregs in RA. | (31–34)   |
| IL-17      | Pathogenic    | Promote angiogenesis; Induce monocyte migration; Induce inflammatory cytokines, chemokines and MMP secretion in FLSs; Promotes neutrophil migration. | (36–42)   |
| IL-22      | Pathogenic    | Enhance FLS expansion and MMP production; Exhibit osteoclastogenic effects; Stimulate IL-1β production and promotes neutrophils infiltration in joints; Maintain GC and promote autoantibody secretion. | (43–47)   |
| GM-CSF     | Pathogenic    | Support monocytes differentiate into CD1c+ DCs and involve in FLS proliferation; Activates and triggers proinflammatory responses in CCR2+Ly6C+ monocytes. | (50–53)   |

TABLE 2 | Functions of ILLs in inflammatory arthritis.

| Subtypes | Subsets and distribution (Human) | Functions and mechanism (Mice) | References |
|----------|---------------------------------|--------------------------------|------------|
| NKT      | (1) IFN-γ+ NKI in SF of RA; (2) RORγt+ T-bet+PLZF- iNKT with Th17-like response in joints of PsA and other SpA. | (1) IL-17+ NKT promote murine arthritis; (2) CD1d-dependent NKl protect murine arthritis by dampening Th1 cell responses; (1) Dampening combined gut and joint inflammation in SpA. | (55–64) |
| MAIT     | (1) MAIT with IL-17 phenotype in SF of RA; (2) CD8+ IL-17+IL-23R+ MAIT in SF of PsA; (3) CD8+ IL-17+IL-23R+IL-7R+ MAIT in SF of SpA. | (1) MAIT exacerbate in murine CIA model; (2) IL-23/IL-17 axis in MAIT contribute to PsA; (3) IL-7/IL-17 axis in MAIT contribute to AS and other SpA. | (66–71) |
| γδ17 T   | (1) CCR5+CXCR3+ IL-17-producing Vδ2 T in RA; (2) TEM Vyγδ+Vα2+ IL-17-producing T cells with HLA-DR and CD86 expression in SF of RA; (3) TEM γδ17 T cells in peripheral and synovium of PsA; (4) IL-23R+RORγt+ γδ17 T cells in active AS and other SpA. | (1) In CIA murine arthritis, IL-17 producing Vyγδ+ γδ T promoted disease development; (2) In Il1rn–/– spontaneously developed arthritis, CCR2+Vγ6+ γδ17 T cells participate in disease progression. | (29, 62, 78–84) |
| Innate-like B | (1) Reduced B10 cells in PBMC of RA; (2) Impaired B10 cells in PBMC and SF of PsA; (3) CD19+CD24+CD38+ B10 cells decreased in PBMC and SF of SpA. | (1) CII-reactive MZB cells exhibit spontaneous IgM and significant APC capacity for murine arthritis development; (2) B10 is crucial for suppression of Th1/Th17 response and induction of T regulatory type 1 cells; (3) B10 directly inhibit Th17 cells generation via reduction of STAT3 phosphorylation and RORγt expression; (1) B10 present CD1d-lipid and induced NKl cells to secrete IFN-γ to ameliorate arthritis. | (59–99) |

... to migrate into secondary lymphoid organs (65). However, these cells express high levels of the chemokine receptors CCR2, CCR5, CCR9, and CXCR6, suggesting their ability to migrate into inflamed tissues. Upon stimulation, human peripheral blood-derived MAIT cells produce IFNγ, TNFα, IL-17A, and granzyme. The cytokine profile of MAIT cells differs among different tissues in mice, with high levels of IL-17A production in the spleen and intestine but preferential expression of GM-CSF, IL-4, and IL-13 in the thymus (65). An enrichment in IL-17-expressing MAIT cells was observed in the SF in IA and appeared to contribute to the inflammatory status in arthritis (66–68). In RA patients, elevated TNFα and IL-1β in SF stimulated the expression of CCL20, ICAM-1, and VCAM-1 on human blood vessel endothelial cells (HUVECs) to facilitate MAIT cell migration (69). The severity of CIA was ameliorated in MAIT cell-deficient mice, and reconstituting MAIT cells induced severe joint inflammation, demonstrating that MAIT cells could exacerbate arthritis. Moreover, in vitro...
stimulation of MAIT cells with IL-1β induced MAIT cell proliferation, and IL-23 promoted MAIT cell production of IL-17A (70). The majority of MAIT cells in the SF in PsA but not RA were CD8+ cells. CD8+ MAIT cells produce IL-17A, which is central to the pathogenesis of PsA. Moreover, the MAIT cells in the SF in PsA were enriched in IL-23R and proliferated upon IL-23 stimulation (71). IL-17+ MAIT cells in AS expressed high levels of both IL-7R and IL-23R, however, these cells only responded to FLS-derived IL-7. Activation of MAIT cells with IL-23 had almost no effect on IL-17 production (68). Taken together, these studies suggest that MAIT cells are critical in the aberrant IL-17 signaling pathway and contribute to the pathogenesis of IA.

γδ17 T CELLS

γδ T cell subsets contribute to tissue damage in various autoimmune diseases, including psoriasis-like disease, IA, colitis, and experimental autoimmune encephalomyelitis (EAE). IL-17+ γδ T cell subtypes are common in IA pathogenesis (72). γδ17 T cells are an innate source of IL-17A and share most phenotypic markers with Th17 cells. These cells express IL-23R, IL-17A, IL-22, and RORyt, as well as the chemokine receptors CCR6 and CCR2. These chemokine receptors are also expressed by Th17 cells and are reported to direct γδ17 T cells trafficking to the dermis (73). CCR2 promotes γδ17 T cell migration to the arthritic synovium during autoimmunity (74). Although γδ17 T cell development in the thymus requires a TCR signal, the peripheral activity of these cells could be directly activated by non-TCR signals, such as IL-23 and IL-1β (75). In mice, TCR-γ consists of six Vγ subsets, of which Vγ4+ and Vγ6+ γδ T cells are the main IL-17 producers (76). In some contexts, Vγ1+ γδ T cells could also secrete IL-17A. In humans, the majority of γδ T cells in peripheral blood are Vγ9+Vδ2+ T cells with distinct Th1 signatures. However, upon binding with IL-1β, IL-6, TGF-β, and IL-23 and AHR ligand polarization, Vγ9+Vδ2+ T cells differentiate into IL-17-producing γδ T cells (77).

IL-17-producing Vγ4+ γδ T cell numbers were significantly increased in CIA-induced murine arthritis, and the depletion of Vγ4+ γδ T cells obviously attenuated disease occurrence and severity (78). CCR2+Vγ6+ γδ17 T cells played a pathogenic role in IL-1Ra-deficient (Il1rn−/−) mice, an IL-17-dependent spontaneous arthritis murine model. Notably, γδ T cells but not Th17 cells were the primary source of IL-17A in joints (79). Yoshinago Ito et al. demonstrated that CCR6+ γδ T cells were the dominant producers of IL-17 in CIA-induced murine arthritis and that these cells were induced by IL-1β plus IL-23 independent of the T cell receptor. However, these cells can hardly be detected in the joints of RA patients (80). Other studies demonstrated the presence of γδ17 T cells in the synovium of RA patients. Mo et al. showed high levels of CCR5 and CXCR3 in IL-17-producing Vδ2+ cells driven by the TNF-α-induced NF-κB signaling pathway in the serum of RA patients (81). Recently, TEM Vγ9+Vδ2+ T cells stimulated by isopentenyl pyrophosphate could differentiate into CD45RA−CD27− effector memory cells (TEM) and exhibit an APC phenotype with HLA-DR and CD86 expression. These cells can recognize and present autoantigen peptides to cause excessive autoreactive CD4+ T cell immune responses (82). TEM Vγ9+Vδ2+ T cells had a stronger ability to secrete IL-17 than non-TEM Vγ9+Vδ2+ T cells. Subsequent findings indicated that TEM Vγ9+Vδ2+ T cells are the predominant γδ T subpopulation in the SF of RA patients (82). Expansion and activation of TEM Vγ9+Vδ2+ T cells driven by the IL-9/IL-23 axis were observed in the peripheral blood and synovium of untreated PsA patients (29). An enrichment in circulating IL-17A+IL-23+ γδ T cells was detected in patients with active AS and sJIA (83, 84). γδ17 T cells were enriched in PsA and AS patients, and their functions promoting disease progression were modulated by the key Th17 cell transcriptional regulator RORyt t (62).

INNATE-LIKE B CELLS

Rheumatoid arthritis is also characterized by autoantibody production. Innate-like B cells can be directly stimulated by Toll-like receptors rather than through BCR and TCR signaling. These cells quickly differentiate into antibody-secreting cells that produce T cell-independent "natural", polyreactive antibodies, as well as IL-10. Innate-like B cell subsets consist of MZB cells, B1 cells, and IL-10-producing regulatory B cells (Bregs) (85, 86). Recently, a novel B cell subset, natural killer-like B (NKB) cells, which have a CD19+NK1.1+ phenotype, was identified. These cells are present in mouse spleens and mesenteric lymph nodes and express IgM and NKP46. NKB cells secrete large amounts of IL-12 and IL-18 to subsequently activate ILC1s and NK cells (87). However, by using an array of mouse genetic models, Eric Vivier et al. demonstrated that NKB cells were not distinct populations and displayed the phenotypic and functional characteristics of conventional B cells (88). Since the existence and function of NKB cells remain controversial, whether they are involved in IA pathogenesis is inclusive.

CD23lowIgMhighCD21high MZB cells mainly reside on the border of the white pulp in the spleen and display reduced recirculatory potential. Autoantibodies against type II collagen (CII) play essential roles in murine arthritis development. Sandra Kleinu et al. showed that after CII immunization in DBA/1 mice, CII-autoreactive MZB cells expanded, were activated at the early stage and secreted large amounts of IgM that was reactive to autologous CII (89). Moreover, collagen-primed MZB cells displayed significant antigen-presenting capacities by inducing cognate T cell proliferation in vitro and IgG anti-collagen antibodies in vivo. The study highlighted autoreactive MZB cells as initiators that promote self-reactive responses in CIA (90).

B1 cells are the main producers of the T cell-independent antibodies IgM and IgA and are mainly located in the coelomic cavity (91). IL-10-producing CD1dhiCD5+ B cells, also defined as B10 cells, play an inhibitory role in arthritis development. Reduced B10 numbers were observed in PBMCs in RA and correlated with exacerbated disease activity (92, 93). Further in vitro studies of human B10 differentiation showed that STAT3 phosphorylation was indispensable for IL-10 production (94). B10 cells maintained immune tolerance by suppressing Th1/Th17 responses and inducing type 1 Treg cells in murine arthritis (95).
Further mechanistic studies showed that B10 cells could directly inhibit Th17 cell generation by reducing STAT3 phosphorylation and RORyt expression (96). A recent study demonstrated a novel mechanism by which Bregs present CD1d-lipid and induced iNKT cells to secrete IFN-γ, which in turn contributed to the down regulation of Th1 and Th17-adaptive immune responses and murine arthritis amelioration (97). In PBMCs and SF in PsA, B10 cells were decreased and inversely correlated with IL-17- and IFNγ-producing T cells (98). The percentage of CD24hiCD38hi B10 cells was lower in the SF than in PBMCs of JIA patients (99). Collectively, these studies suggested a regulatory role of B10 cells through dampening adaptive Th1 and Th17 responses in IA.

THE ROLE OF ILCs IN IA

As described above, the three major groups in the ILC family mirror the canonical T helper subsets Th1, Th2, and Th17. The ILC family is involved in chronic inflammation. Conventional NK (cNK) cells are classified as ILC1s because they share the common transcription factor T-bet and produce a large amount of IFN-γ upon stimulation. ILC1s/NK cells are involved in the pathogenesis of chronic hepatitis B, tissue fibrosis and chronic viral diseases (100–102). ILC2s are associated with chronic human diseases, such as allergy and asthma, skin inflammation, and pulmonary fibrosis, which correlate with IL-33, IL-25, and type 2 cytokines (103–105). ILC3s are the dominant producers of IL-17 and IL-22 in the skin and intestine and are associated with chronic inflammation. The frequencies and cytokine production of ILC3s are increased in the skin of patients with psoriasis, Crohn’s disease and graft-versus-host disease (GVHD) (106–109). As IFN-γ, type 2 cytokines, IL-17A and IL-22 are all implicated in IA pathogenesis, a summary of the diversity and functions of ILCs in IA might help offer new strategies for targeting IA in the clinic.

Recently, a new member of the ILC family was introduced by Wang et al., regulatory ILCs (ILCregs), which have the CD45+Lin−CD127hiIL-10+ phenotype (110). ILCregs reside in murine and human intestines and specifically produce IL-10 and transforming growth factor-β (TGF-β). Autocrine TGF-β is required for the expansion but not development of these cells. Although ILCregs produce similar cytokines to regulatory T cells (Tregs), they are defined by the distinct transcription factors Id3 and Sox4 but not Foxp3. As ILCregs are newly discovered and their roles in inflammation resolution in allergic airway inflammation or renal ischemia/reperfusion injury are limited (111, 112), whether these cells are involved in IA remains to be studied.

NK CELLS

Natural killer cells are essential components of the innate immune system and were originally characterized by their ability to kill tumor or virus-infected cells by directly releasing perforin- and granzyme-containing cytotoxic granules (113). Type I IFN, IL-2, IL-12, IL-15, and IL-18 are important cytokines for NK cell activation. Upon stimulation, NK cells can secrete cytokines such as IFN-γ, TNF-α, IL-5, IL-10, IL-13, and GM-CSF and the chemokines CCL3, CCL4, CCL5, and CXCL8 (114). In humans, NK cells can be classified into two major subtypes: CD56bright and CD56dim NK cells. CD56dim NK cells exhibit relatively reduced cytotoxicity with increased production of cytokines that are predominately found in the peripheral blood. CD56bright NK cells highly express CCR7 and CD62L to promote homing to secondary lymphoid organs. CD56bright NK cells are tissue-resident and mainly reside in different tissues (e.g., lymph nodes, tonsils, liver, and uterus) (115).

Infiltrating tissue-resident NK cells have been detected in IA patients. Both seropositive RA and PsA patients showed decreased NK cell counts, while AS patients had higher percentages of NK cells in the peripheral blood than healthy controls (116–119). Infiltrating CD56bright NK cells were observed in inflamed joints with high expression of activation markers (CD69 and NKP44) and enhanced TNF-α production regulated by CD94/NKG2A compared to those of PBMC subsets (120). IL-17-producing NK cells preferentially proliferate in the SF of active arthritis and undifferentiated SpA (121). An increased number of NKP44+ NK cells was detected in the inflamed gut of AS patients (122).

Natural killer cells were suggested to be potential promoters of bone destruction, T cell responses and FLS proliferation in RA. Kalle et al. discovered that NK cell depletion before murine CIA induction reduced the severity of arthritis and almost completely prevented the destruction of bone (123). Murine synovial NK cells express M-CSF and RANKL, which trigger monocyte differentiation into osteoclasts when NK cells are co-cultured with monocytes in vitro (123). SF from RA or PsA but not OA patients induced monocytes to differentiate into DCs in presence of NK cell-derived GM-CSF and CD154 (124). IL-22-secreting NK cell (NK-22) proportions were increased in SF compared with PBMCs from the same RA patient. Increased NK-22 cells can secrete IL-22 and TNF-α to promote RA FLS proliferation in vitro (125). However, in study performed by Jianmei W. et al. showed a regulatory role of NK cells in a murine CIA model. The researchers observed delayed arthritis progression with enhanced elimination of pathogenic Th1 and Th17 cells after activation of NK cells through blocking the inhibitory NKG2A/CD94 receptor (126). We reasoned that the contribution of NK cells to RA may differ from that of other NK subsets.

In PsA, NK cells contribute to disease amplification and persistence. Chiara et al. showed that NK cells infiltrated the psoriatic skin and exhibited the CD56brightCD16− phenotype (115). IL-2-primed NK cells released a large amount of IFN-γ, which can induce psoriatic keratinocyte activation and promote keratinocyte secretion of CXCL10 and CCL5 in vitro (127). The role of NK cells in the pathogenesis of SpA remains controversial. A previous study demonstrated a tissue-protective role of NKP44+IL-2-producing cells in the gut tissue of AS patients (122). However, another study showed that circulating CD56bright NK cells in AS patients promoted TNF-α secretion by autologous monocytes, which contributed to a worsened disease status (128). NK cells were thought to play a regulatory role
in sJIA, and the dysfunction of these cells in sJIA was strongly associated with macrophage activation syndrome (MAS) (129). In a mouse model of sJIA, NK cell depletion or blockade of the NK cell activating receptor NKG2D increased the severity of sJIA-like symptoms, as well as increased the number of activated inflammatory monocytes, further indicating a regulatory role for NK cells in sJIA (130).

**ILC1s**

Although they share the common feature of Tbet+IFNγ+ expression with NK cells, ILC1s express IL-7R and do not express cytotoxicity-related molecules, including perforin and granzyme B (131). A recent study showed that ILC1s played a critical role in viral infection through the rapid production of interferon (IFN)-γ, which occurs even earlier than in NK cells (132, 133). Moreover, unlike the capacity of NK cells to recirculate throughout the body, ILC1s appear to be tissue-resident. ILC1 populations were present in the SF and synovial tissue in inflamed RA, PsA and SpA patients (134). The frequency of ILC1s in the SF and synovial tissue was significantly increased compared with that of PBMCs from SpA patients (135). ILC1 frequency was significantly increased in RA or in individuals at risk of RA compared with that of controls, indicating a potential role of ILC1s in RA pathogenesis (136).

**ILC2s**

Innate lymphoid cells express the type 2 T helper (TH2) cell-associated transcription factor GATA-binding factor 3 (GATA3) and cytokines, including IL-4, IL-5, and IL-13 (137). The role of ILC2s in IA might differ from different cytokine-secreting ILC2 subsets. ILC2 numbers were significantly higher in the peripheral blood of RA patients than in HCs but were inversely correlated with disease activity. Adoptive transfer of ILC2s attenuated murine arthritis severity, and ILC2-derived IL-4/13 inhibited IL-1β and TNFα secretion by macrophages, which indicated the immunoregulatory function of the IL-4/13-producing ILC2 subset in RA (138). However, in another study using the SKG
model of autoimmune arthritis, Keiji Hirota et al. demonstrated that IL-2, IL33, or TLR9 ligands released from damaged tissue-resident cells in inflamed synovia could stimulate ILC2s to produce GM-CSF. Furthermore, the researchers found that ILC2-secreted GM-CSF was crucial in initiating autoimmune murine arthritis (139).

ILC3s AND LTI CELLS

ILC3s provide an innate source of IL-17A and IL-22 and depend on RORγt and AHR for development. ILC3s consist of two major subsets: NKp46+ ILC3s and LTi-like CCR6+NKp46− ILC3s. A previous study showed that ILC3 populations were present in the SF and inflamed joints of IA patients (134). A pathogenic role of ILC3s in IA has been suggested in previous studies. The proportions of CCR6+ ILC3s in arthritic mice were significantly higher than those in non-arthritic mice after CIA induction. Moreover, CCR6+ ILC3s in arthritic mice produced higher levels of IL-17A and IL-22 than those from control mice. In RA patients, the CCR6+ ILC percentage in SF was positively correlated with the number of tender and swollen joints (140). NKp44+ ILCs were hardly detected in PBMCs and SF in RA patients but were abundant in SF in PsA patients. Moreover, CCR6 and NKp44 were co-expressed on IL-17A-producing ILCs in SF, and the number of circulating NKp44+CCR6+ ILCs among PBMCs was negatively correlated with the disease activity of PsA patients (141). ILC3s characterized as Lyn−Tbet−RORc−NKp44+IL-23R+ that produced high levels of IL-17A and IL-22 were significantly expanded in the gut, SF and bone marrow of AS patients (142). Notably, epithelial cell-derived IL-7 but not IL-23-induced LTI cells to differentiate into ILC3s in AS patients (142). Proinflammatory CX3CR1+CD59+TL1A+ IL-23+ mononuclear phagocytes (MNP) were present in the synovial and bone marrow samples of PsA patients and exhibited the ability to induce ILC3 expansion and activation (143). However, understanding of ILC3s in IA is still limited and requires further investigation.

THERAPEUTIC IMPLICATIONS

Research on innate lymphocytes in IA has advanced our understanding of their roles in IA. Drugs that not only inhibit adaptive Th17 cells but also IL-17A-producing innate lymphocytes might be a useful therapeutic strategy in IA. For example, a recent study detected the expression and activation of the PI3Kδ-Akt-mTOR pathway in inflamed SpA synovial tissue. The authors identified a promising target by selectively inhibiting PI3Kδ (with a compound named seletalisib). Seletalisib suppressed IL-17A and IL-17F production by innate-like MAIT cells, γδ T cells and adaptive Th17 cells, thereby inhibiting downstream inflammation and tissue remodeling responses (144). Moreover, IL-17-producing innate-like T cells responded to IL-23 and IL-1β activation; therefore, targeting IL-23 might be a promising strategy for IA treatment. Recent studies using the IL-23 blocking reagent ustekinumab showed good responses in clinical AS and PsA treatment (145, 146). Finally, blocking ILC2-derived GM-CSF through anti-IL-33 mAbs might also be a promising strategy for clinical IA treatment.

CONCLUSION

A brief summary of ILLs and ILCs in IA is shown in Figure 1. The experimental evidence presented in this review indicated that both ILLs and ILCs might be important contributing sources of inflammatory cytokines in IA. Innate lymphocytes also affect adaptive immune responses and directly influence FLS and osteoclast proliferation, activation and function. Knowledge of the phenotype and detailed mechanisms of ILLs and ILCs in joints in IA is still limited. Deciphering the roles of ILLs and ILCs in IA initiation and development will ultimately provide insights into the mechanisms of IA and help design effective strategies for clinical treatments. Future work should focus on more in-depth studies about the functions of ILLs and ILCs in IA through genetically engineered mice and transcriptomic sequencing of patient samples.

AUTHOR CONTRIBUTIONS

XW conceived and wrote the manuscript.

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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