Adaptive immunity plays central roles in the pathogenesis of rheumatoid arthritis (RA), as it is regarded as an autoimmune disease. Clinical investigations revealed infiltrations of B cells in the synovium, especially those with ectopic lymphoid neogenesis, associate with disease severity. While some B cells in the synovium differentiate into plasma cells producing autoantibodies such as anti-citrullinated protein antibody, others differentiate into effector B cells producing proinflammatory cytokines and expressing RANKL. Synovial B cells might also be important as antigen-presenting cells. Synovial T cells are implicated in the induction of antibody production as well as local inflammation. In the former, a recently identified CD4 T cell subset, peripheral helper T (Tph), which is characterized by the expression of PD-1 and production of CXCL13 and IL-21, is implicated, while the latter might be mediated by Th1-like CD4 T cell subsets that can produce multiple proinflammatory cytokines, including IFN-γ, TNF-α, and GM-CSF, and express cytotoxic molecules, such as perforin, granzymes and granulysin. CD8 T cells in the synovium are able to produce large amount of IFN-γ. However, the involvement of those lymphocytes in the pathogenesis of RA still awaits verification. Their antigen-specificity also needs to be clarified.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects systemic synovial joints. Clinical application of reagents targeting inflammatory cytokines has greatly improved the prognosis of RA, verifying the importance of cells of innate immune system in the pathogenesis. However, the mechanism for the activation of innate immunity in RA is yet to be clarified. Autoimmunity, the adaptive immune response to self-antigens, is implicated here, and there are reasons supporting this hypothesis. The chronic synovitis in multiple joints without the evidence of persistent microbe infection can be simply explained by immune responses against synovial self-antigen(s). The presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), indicates the involvement of autoimmunity at least in the disease process. Furthermore, there are various animal models of arthritis induced by autoimmune responses. In fact, synovium of RA patients shows an infiltration of lymphocytes including both T cells and B cells, and significant progress has been made in understanding their functions over the past few years. This review will summarize current knowledge on the cells of adaptive immune system infiltrated in human RA joints.

2. B Cells in RA Joint

2.1. Clinical relevance of local B cell infiltration in the pathogenesis of RA

It has been known that the pattern of cellular infiltrate in the synovium varies among RA patients. Recent analysis of biopsy samples of synovial membrane (SM) from a cohort of treatment-naïve early RA patients classified the histological feature into three groups (pathotypes): lymph-myeloid, diffuse-myeloid and pauci-immune types. They found that B cell-rich, lymphoid-myeloid group showed the highest disease activity and seropositivity [1]. Response to disease-modifying anti-rheumatic drug (DMARD) therapy correlated with the expression levels of myeloid and lymphoid-associated genes [1], while the pauci-immune pathotype predicts poor response to a TNF-α inhibitor (TNFi) [2]. An analysis on two cohorts of early and established TNFi-inadequate response (IR) RA by semiquantitative B cell scoring revealed that the frequency of B cell-rich pathotype was higher in TNFi-IR established RA than early RA [3]. They also observed...
significantly higher disease activity in B cell-rich patients in the early RA cohort. Higher levels of cellular infiltrate with B cells were shown in ACPA-positive than negative RA, although another study detected no difference [4,5]. It was also demonstrated that the expression levels of CXCL13, a chemoattractant for B cells, correlated with local disease activity, ACPA level, and erosive disease [6]. Taken together, local infiltration of B cells generally associates with the severity and prognosis of RA.

2.2. Formation of ectopic lymphoid neogenesis in the synovium of RA

In about half cases of RA, T and B cells diffusely infiltrate in the synovium, while in others aggregates consisting of T and B cells are observed, a portion of which forms ectopic lymphoid neogenesis (ELN), an organized aggregation of T and B cells with networks of follicular dendritic cells (FDCs), resembling germinal center (GC) in secondary lymphoid organs [7,8]. ELN formation in RA synovium is associated with the expression of LTβ, CCL21, and CXCL13 [7,9,10]. Gene expression analysis revealed an involvement of IL-7 pathway [11]. The level of IL-23 but not IL-17A, IL-6 nor TNF-α in synovial fluid (SF) was also associated with the presence of ELN [12]. Importantly, Manzo et al. showed that small aggregates formed in perivascular area, while ELN was only detected within large aggregates in the same samples, suggesting sequential appearance of ELN. The expression of CXCL13 and CCL21 might precede ELN formation, as it was also detected in non-organized clusters and small aggregates [9].

It has been a matter of interest whether the presence of ELN discriminates clinical phenotypes of RA, including seropositivity. Thurlings et al. detected ELN in one-third of RA patients, who showed higher level of cellular infiltrate and had higher CRP and ESR, but the presence of ELN and RF or ACPA positivity had no association [13]. Cantaert et al. reported that ELN formation was associated with histological degree of inflammatory infiltrate but was not associated with local production of ACPA and RF [14]. Furthermore, ELN was also formed in the synovium of spondyloarthritis (SpA), including psoriatic arthritis (PsA), and ceased in treatment responders [14,15]. A longitudinal observational study reported that ELN can be detected in any forms of early arthritis and is neither diagnostic for RA nor predict development of persistent and erosive arthritis. The pattern of lymphocyte infiltration can be changed overtime [16]. These all indicate that local disease activity but not seropositivity predicts the presence of ELN.

There are somewhat conflicting data on the relationship between the presence of ELN and treatment response of RA patients. For instance, Canete et al. reported that the presence of ELN is a negative predictor of TNFα response, although reversal of ELN formation occurred in the TNFi responders [17]. On the other hand, Klaasen et al. observed better response to IFX in patients with lymphoid aggregates, although only quarter samples with lymphoid aggregates (one-third of all patients) had ELN formation. Nevertheless, they also found a decrease of lymphocyte aggregate after TNF-α blockade in both RA and PsA [8], again supporting the idea that ELN formation is a consequence of high disease activity.

2.3. Antibody production by joint-infiltrating B cells in RA

Although the presence of ELN does not directly relate with serum autoantibody status, it has been known that B cells in RA synovium produce autoantibodies, namely RF and ACPA. Expression of RF by plasma cells (PCs) in RA synovium was reported as early as in 1959 [18]. It was later demonstrated that CD20–CD38+ PCs in SF from seropositive RA patients actively produce RF [19], although the major cellular source of circulating RF might not be synovial cells but bone marrow cells [20]. This might also be the case of ACPA. Although ACPA is detected in SF of RA patients [21], it is detected in the serum before RA onset, when no histological evidence of synovitis is observed [22]. Nevertheless, it is worth noting that ACPA detection in SF is not simply due to passive diffusion from the serum. It was shown by using ELISPOT assay that up to quarter of SF B cells spontaneously produced IgM ACPA in vitro [23]. Intriguingly, they found B cells in peripheral blood (PB) from healthy donors as well as RA patients were able to produce IgM ACPA after stimulation. IgG ACPA production by B cells in PB and SF was reported later by Kerkham et al. [24]. They found that SF cells spontaneously produced higher amount of IgG ACPA and the frequency of IgG ACPA producing cells was higher in SF than PB, which is in line with a study showing relative enrichment of IgG ACPA in SF compared to the serum [25]. They argued that SF mononuclear cells provide an environment for long-term survival of ACPA-secreting cells, irrespective of where they had been generated.

It remains unclear whether the ACPA-producing cells home to the joint or are generated in the joint. In this regard, it is of interest to know whether there is any difference in the antigen-specificity between those in the joint and PB. Sohrabian et al. found somewhat different reactivity of ACPA in the
form of immune complex between serum and SF [26]. However, this could either result from local ACPA production by different B cell repertoire or accumulation of different ACPAs from serum according to the expression level of corresponding antigens. Doorenspleet et al. compared B cell receptor (BCR) of B cells from PB and synovium by next-generation sequencing. They found that B cells from synovium showed multiple dominant clones with autoreactive features including the usage of IGHV4-34 and longer CDR3 lengths. There was limited overlap between PB and synovial BCR clones, further suggesting their local expansion [27]. On the other hand, Elliot showed certain extent of clonal relationship in BCR between PB and synovial compartments, suggesting B cell trafficking between PB and synovium, although synovial samples showed greater extent of clonal expansion [28]. Some studies established ACPA-producing B cell clones from the joint, although it is difficult to draw conclusion on the difference from those in PB due to small number of samples. Steen et al. isolated four IgG ACPA-secreting B cell clones from the SF and generate recombinant mAbs. They found those antibodies highly mutated and recognizing diverse array of citrullinated peptides [29]. One of the four ACPA clones showed signs of local expansion. Germar et al. generated immortalized B cell clones by retroviral transduction of Bcl-6 and Bcl-x but were able to obtain only two ACPA-producing clones. They differed from non-ACPA clones in the expression of CD40 and C5a receptor 1 [30]. Lastly, Elliot et al. reported TNF-α production from macrophages stimulated with immune complex that contain recombinant ACPA cloned from RASF [28].

Some studies investigated antibody production from ELN in the synovium of RA. By analyzing locally expressed BCR by microdissection of tissue sections, a clonal relationship between B cells in the follicle and the surrounding plasma cells was demonstrated [31]. In line with this finding, a histological study showed activation-induced cytidine deaminase (AID) expression in ELNs, which is surrounded by ACPA-positive plasma cells. Furthermore, human ACPA was detected in the serum of SCID mice transplanted with the RA synovium expressing AID [32]. B cells within ELN frequently reacted with citrullinated histones in neutrophil extracellular trap (NET), which was shown to form in RA joint [33,34]. Somatic hypermutation and resulting Fab-glycosylation in BCR is important for the reactivity to NET, further suggesting the involvement of GC reaction [35]. Epstein–Barr virus has long been implicated in the pathogenesis of RA and, interestingly, a study showed Epstein–Barr virus infection of ACPA-producing plasma cells surrounding synovial GC [36]. Taken together, ELNs are likely involved in local differentiation of ACPA-producing B cells, even though they are not the primary sites of ACPA production.

2.4. Effector functions of joint infiltrating B cells in RA

So far, the best proof for the importance of B cells in the pathogenesis of RA is the therapeutic effect of B cell-depletion by the anti-CD20 mAb, rituximab. Interestingly, although rituximab induces better response in ACPA-positive RA [37], its efficiency does not necessarily correlate with the decrease of antibody levels [38]. Furthermore, the reduction of ACPA production follows the appearance of clinical effect of rituximab as well as depletion of synovial B cells [39]. In fact, there are lines of evidence that B cells are involved in the pathogenesis of RA other than by autoantibody production.

First, synovial B cells potentially produce proinflammatory cytokines. Yao showed mRNA expression of various cytokines, including IL-1, IL-6, IL-12, and TNF-α, by SF B cells [40]. A single-cell RNA sequence analysis also demonstrated expression of IL-6 and TNF-α in synovial B cells [41]. Regarding the phenotype of these cytokine-producing cells, Cowan et al. showed that IgG + CD27- B cells secreted TNF-α and were enriched in the synovium [42], while Floudas et al. reported PD-1-positive B cells, which express higher levels of TNF-α and IL-6 than PD-1-negative B cells, accumulated in the joint [43]. The relevance of B cell-derived TNF-α and IL-6 in the activation of synovial fibroblast was suggested by an in vitro culture system [44]. Proinflammatory functions of citrulline-specific B cells have been shown. The immortalized B cell clones established by Germar et al. secreted both pro- and anti-inflammatory cytokines, including TNF-α and IL-10, although there was no difference between citrulline-reactive and non-reactive clones [30]. Krystyanto et al. identified ACPA-specific SF B cells by flow cytometry and found them expressing IL-8 that induces neutrophil infiltration in the joint [45], which might explain the link between the clinical efficacy of rituximab and ACPA positivity [37].

Receptor activator of NF-κB ligand (RANKL) plays a critical role in the development of osteoclasts involved in the joint destruction in RA. Expression of RANKL on fibroblast, osteoblast, and T cells is well known, but a portion of B cells also express RANKL. Yeo et al. reported that the synovial B cells express RANKL in addition to IL-6 and TNF-α [40]. Such RANKL+B cells expressed FcRL4 [46] and,
notably, some FcRL4+ B cell clones showed reactivity toward citrullinated proteins [47]. RANKL+B cells localize with RANK+ osteoclast precursors and support their differentiation in vitro [48]. We have demonstrated IFN-γ plays an important role in the generation of CXCR3 + RANKL + B cells, which are increased in RA joint [49]. IFN-γ induced expression of T-bet and CXCL9/10, the ligands for CXCR3, in B cells, which might further recruit IFN-γ-producing Th1 cells as well as CXCR3 + RANKL + B cells in the joint [50].

Antigen presentation to T cells is another role of joint-infiltrating B cells, which is presumably involved in the pathogenesis of RA. Except for ELN lesion, B cells and activated T cells usually aggregate together in the synovium. Takemura et al. demonstrated by using SCID mice engrafted with the synovium from RA patients that activation of tissue infiltrating CD4 T cells is B cell-dependent [51]. This suggests a role for B cells as critical APC for CD4 T cells, which might also be the mechanism of action of rituximab in RA.

### 3. T Cells in RA joint

#### 3.1. Importance of CD4 T cells in the pathogenesis of RA

T cells, especially CD4 T cells, are the critical conductor of adaptive immune responses, and there are lines of evidence suggesting the involvement of CD4 T cells in the pathogenesis of RA. First, there is a massive infiltration of CD4 T cells in synovium of RA, which is not only found in joint synovium but also in tenosynovium [52]. Most CD4 T cells in the synovium show activation markers [53]. Second, RA has a strong genetic association with certain MHC class II alleles, the HLA-DR ‘shared epitope (SE)’, which is prominent in seropositive RA [54]. Again in most animal models, CD4 T cells play essential roles in the development of arthritis [55]. Finally, reagents that inhibit T cell activation, such as abatacept (CTLA4-Ig), exert clinical effect on RA. Although CD8 T cells might also be affected, the therapeutic effect of abatacept associates with ACPA-positivity and the presence of SE [56,57], suggesting that inhibition of CD4 T cells is its main mode of action. CD4 T cells can be involved in the pathogenesis of RA by inducing inflammation and by helping B cell antibody production, details of which will be introduced in the following sections.

#### 3.2. Pro-inflammatory CD4 helper T cell subsets in RA joint

Delayed type hypersensitivity (DTH) reaction is the typical T cell-mediated inflammatory response, which involves activation of macrophages and is a mechanism for host defense against intracellular pathogens. IFN-γ-producing T helper 1 (Th1) cells mediate DTH reaction. Because infiltration of activated macrophages and CD4 T cells is the typical histological feature of RA synovitis, RA was once believed as a Th1-mediated disease. However, in many cases, only low level of IFN-γ was detected in the SF or synovium of RA [58,59], casting a doubt on the importance of T cells in the pathogenesis [60].

On the other hand, a novel T cell-derived cytokine was discovered in 1993, IL17 (IL-17A) [61], which was later detected in the joint of RA [62,63]. IL-17 induces mobilization of neutrophils, activates fibroblasts and induces RANKL expression, all of which fit well with the pathological features of RA synovium [63,64]. In fact, animal models of RA demonstrated an importance of IL-17 in the development of arthritis [65,66]. Finally, a distinct CD4 T cell subset that produces IL-17, but neither IFN-γ nor IL4, was identified in mice in 2005 and was named Th17 [67], leading to an idea that RA is a Th17-mediated disease. The presence of Th17 cells in human was reported a couple of years later first in patients with Crohn’s disease [68]. At that time, we were examining the frequency of Th17 cells in peripheral blood and joint of RA patients, but we unexpectedly found that Th17 cells neither increased in PB of RA nor correlated with disease activity [69]. Furthermore, the frequency of Th17 cells was rather lower in the joint than peripheral blood, while the frequency of Th1 cells was clearly higher in the joint than PB. Similar observation was made by others [70]. In line with those findings, it was revealed later that targeting IL-17 is not beneficial for RA, although it was highly effective in the treatment of psoriasis [71]. This formally indicates that Th17 cells are not essential in the pathogenesis of RA, at least not through IL-17 production in the established stage.

GM-CSF is a proinflammatory cytokines that is produced by innate immune cells, and clinical trials have proved GM-CSF being a target of RA [72]. Recently, an importance of CD4 T cell-derived GM-CSF in the pathogenesis of RA was reported [73]. Among helper CD4 T cell subsets, Th17 was shown to be the main producer of GM-CSF in mice, but it had been unclear for human. In addition, a distinct subset of helper T cells producing GM-CSF was reported in human [74]. We, therefore, examined which CD4 T cell populations produce GM-CSF in RA and found that most GM-CSF-producing cells in the joint also produced IFN-γ, while those in PB produced GM-CSF alone [75]. Aside from GM-CSF production, a high-dimensional single-cell analysis...
identified a cluster of IFN-γ-producing CD4 T cells increased in RA PB and enriched in the joint, accounting for up to 10% of CD4 T cells. These are phenotypically CD27- HLA-DR+ effector memory CD4 T cells and express cytotoxic molecules, such as PRF1, GZMB, GZMA, and GLNLY (genes for Preforin-1, Granzyme B, Granzyme A, and Granulysin, respectively) [76]. Thus, Th1-like cells equipped with multiple pro-inflammatory and cytotoxic functions infiltrate in RA joint, although there has been no formal proof for their involvement in the pathogenesis.

### 3.3. Tph cell, a novel helper T cell subset first identified in RA joint

PD-1 is an inhibitory receptor expressed on T cells after activation as a negative feedback mechanism. Blocking PD-1 on T cells continuously expressing PD-1, which are seen during chronic infection or in tumor microenvironment, reverses their exhaustive state [77]. PD-1 might also be expressed on autoreactive T cells chronically stimulated with self-antigens. In fact, an increased expression of PD-1 on CD4 T cells in RA joint was reported in 2003 [78], but it attracted much attention after identification of a unique cluster of CD4 T cells expressing PD-1 in the joint of seropositive RA by a recent comprehensive single-cell analysis [79]. Similar to follicular helper T (Tfh) cells, which help GC B cells in secondary lymphoid organs and express PD-1, the PD-1-positive CD4 T cells in RA joint secrete IL-21 and induce antibody production from B cells in vitro. However, they express neither CXCR5 nor the transcription factor BCL6, unlike Tfh cells. Hence, the PD-1-positive CD4 T cells in RA joint secrete IL-21 and induce antibody production from B cells in vitro. Notably, Sox4 does not induce CXCL13 production from mouse CD4 T cells, again pointing a difficulty of studying human immune pathogenesis in mice. On the other hand, it was demonstrated that murine CD4 T cells undergone lymphopenia-induced proliferation resemble human Tph cells in that they exhibit PD-1+ CXCR5- phenotype and provide help for antibody production of B cells by producing IL-21 [88]. It is of interest to investigate its relevance to the mechanism of human Tph cell differentiation.

### 3.4. Functions of CD8 T cells in RA joint

There has been a little information on the role of CD8 T cells in the pathogenesis of RA. Little genetic association is detected between MHC class I and RA, in contrast to the case of MHC class II. However, it has been known that CD8 T cells in the joint express higher levels of activation markers than those in PB, similar to the case of CD4 T cells [53,89]. Moreover, recent comprehensive analysis on the cells in RA joint has attracted attention to CD8 T cells. A single-cell mRNA analysis revealed three CD8 T cell subsets present in RA joint defined by the expression pattern of cytotoxic molecules including GZMK, GZMB, and GLNLY, while mass cytometry divided CD8 T cells into four subsets by the
expression of HLA-DR and PD-1, among which PD-1-HLA-DR + cells include GZMK + GZMB + effector cells and GLNY + GZMB + cytotoxic T lymphocytes (CTL) [41]. Notably, CD8 T cells of any subsets express higher levels of IFN-γ than any CD4 T cells in RA joint. Regarding PD-1+ CD8 T cells in RA joint, we recently found them producing IL-21 and not expressing CXCR5, similar to Tph cells [90]. An association between ELN formation in the synovium and the presence of CD8 T cells expressing CD40L was also shown [91]. The requirement of CD8 T cells for the formation of ELN in the synovium was demonstrated by depleting CD8 T cells of RA synovial grafts in SCID mice [92]. Thus, CD8 T cells might be involved in the pathogenesis of RA more deeply than previously anticipated.

### 3.5. Autoreactivity of T cells in RA joint

Despite the longstanding belief that RA is a T cell-mediated autoimmune disease, demonstrating autoreactivity of joint-infiltrating T cells is still a challenging issue. An expansion of TCR clonotype in RA joint has long been observed and is thought to reflect their autoreactivity. Earlier studies examined TCRV/β usage but showed somewhat conflicting results on the clonality of synovial T cells [93,94]. Among those studies, similarly biased TCR V/β usage by synovial T cells in different joints was reported [95]. Yamamoto has developed an improved method for evaluating TCR clonality, single-strand conformation polymorphism (SSCP) analysis, and demonstrated clonal expansion of T cells, which is shared among different areas of the same joint [96]. Analysis of complementary determining region 3 (CDR3) sequence has later been used to demonstrate the presence of dominant clones in the joint [97]. Interestingly, a study showed higher extent of clonal expansion in ACPA-positive synovium [5]. This might be related with the presence of Tph cells in seropositive RA, as we observed a biased TCR usage by Tph cells (Sakuragi et al., in press). Recent studies utilized non-biased, next-generation sequencing of TCR to investigate T cell expansion in RA joint. Klarenbeek et al. showed highly expanded clones, which are shared between different joints of the same patients [98]. They later showed that the overlap between synovial tissue and SF was limited, indicating these are two separate compartments [99]. However, the phenotype, functions, as well as antigen specificity of the expanded T cell clones identified by these studies are unclear.

Another approach for addressing autoreactivity of joint-infiltrating T cells is examining their reactivity to candidate self-antigens. Most recent studies focused on citrullinated protein antigens, such as tenacullin-C [100], alpha-enolase [101], and type II collagen [102]. There have been many studies analyzing PB T cells [103–105]. However, it should be kept in mind that the T cells inducing local inflammation and those helping APCA production, presumably Tfh cells in lymph nodes, do not necessary have the same antigen specificity. Interestingly, in many cases, citrullinated peptide-specific CD4 T cells showed Th1 phenotype. Nevertheless, pathogenicity of these self-antigen specific T cells is unclear. Except for the case of Tph cells that spontaneously produce CXCR13, as described above, production of effector cytokines by any other synovial T cell subsets requires in vitro restimulation.

On the other hand, the antigen specificity of Tph cells is yet to be clarified. Although Tph cells have been detected in other inflammatory and tumor conditions [106], their antigen specificity has only been demonstrated in Celliac disease; that is gluten [107]. Identifying antigen(s) recognized by Tph cells in RA joint is an important issue.

There are other concerns on the autoreactivity of T cells in RA joint. Brennan et al. have argued that synovial T cells are more like T cells stimulated with a cocktail of cytokines, including IL-2, IL-6 and TNF-α, than TCR-activated T cells [108]. These cytokine-activated T cells (Tck) and synovial T cells induce contact-dependent TNF-α production from monocytes via the same signaling pathways. Tck cells are induced from memory CD4 T cells and express increased levels of CD25 CD69, and HLA-DR [109]. Tck cells showed chemotaxis toward synovial fibroblast from RA patients [110]. Thus, Tck cells can explain the massive infiltration of activated T cells with diverse TCR repertoire in RA joint. However, now that we know the variety of helper T cell subsets in RA joint, it needs to be addressed which one correspond to Tck. More detailed single-cell analysis on the similarity of Tck and synovial T cells will provide much information. For Tph cells, as far as we have tested, the cocktail of cytokines could not induce them (Sakuragi et al., in press), although it remains possible that a different combination of cytokines with longer culture period induces Tph development.

Antigen non-specific accumulation of memory/activated T cells is another confounder in analyzing specificity of T cells in the joint. There are actually several reports showing an expansion of pathogen-specific T cells, including viral, bacterial and protozoan antigen-specific T cells, in RA joint [111–113]. Interestingly, Fazou et al. showed an oligoclonality of viral antigen specific T cells, which is observed in separate joints of the same patient [114]. Accumulation of bystander T cells to an
inflammatory site is inevitable, because cell migration *per se* is regulated by antigen-nonspecific factors, such as chemokines and adhesion molecules. Although it is also possible that those pathogen-specific T cells actually proliferate locally by recognizing the corresponding antigens, this again indicates that oligoclonality of T cells does not necessarily mean autoreactivity. It is important to develop means to precisely identify synovial T cells that are receiving antigenic stimulation *in situ*.

4. Conclusions

This review summarized current knowledges on the cells of adaptive immunity in the joint of RA (Figure 1). The progress in human immunological research has shed light on novel functions of B and T cells infiltrated in the joint and identified previously unacknowledged cell subsets, which have not been found in animal models. These have greatly advanced our understanding on the molecular pathogenesis of RA, especially in the aspect of inflammatory cytokine networks. Nevertheless, the pathogenicity of these lymphocytes still remains elusive. An infiltration of lymphocyte is not necessarily be a cause but a consequence of inflammation. In the case of RA, the infiltrate is actually decreased by effective treatment such as TNFi. The presence of pauci-immune type early RA also needs attention. Identifying the true pathogenic lymphocytes and defining their antigen-specificity is the critical issue to be addressed in the future, provided that RA is an autoimmune disease.

**Disclosure statement**

The author reports that they have no conflict of interest.

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