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Of mice and men: how animal models advance our understanding of T-cell function in RA

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Abstract

The involvement of autoreactive T cells in the pathogenesis of rheumatoid arthritis (RA) as well as in autoimmune animal models of arthritis has been well established; however, unanswered questions, such as the role of joint-homing T cells, remain. Animal models of arthritis are superb experimental tools in demonstrating how T cells trigger joint inflammation, and thus can help to further our knowledge of disease mechanisms and potential therapies. In this Review, we discuss the similarities and differences in T-cell subsets and functions between RA and mouse arthritis models. For example, various T-cell subsets are involved in both human and mouse arthritis, but differences might exist in the cytokine regulation and plasticity of these cells. With regard to joint-homing T cells, an abundance of synovial T cells is present in humans compared with mice. On the other hand, local expansion of type 17 T helper (T_H17) cells is observed in some animal models, but not in RA. Finally, whereas T-cell depletion essentially failed in RA, antibody targeting of T cells can work, at least preventatively, in most arthritis models. Clearly, additional human and animal studies are needed to fill the gap in our understanding of the specific contribution of T-cell subsets to arthritis in mice and men.

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Introduction

"Arthritis: where are the T cells?" This question was raised by Kamradt and Frey in an editorial in a 2010 issue of *Arthritis Research & Therapy*.[1] In their commentary, Kamradt and Frey referred to our study in which only a minuscule population of T cells was found in the joints of mice with proteoglycan-induced arthritis (PGIA).[2] In the same study, depletion of T cells from the peripheral blood of mice, which led to a reduction of T-cell numbers in the synovial fluid, failed to diminish joint inflammation.[2] This observation raises a more general question: how closely do animal models resemble human rheumatoid arthritis (RA)? Certainly a major, and clinically relevant, question is why T-cell depletion strategies failed in RA when, mostly preventatively but in some models also therapeutically, they worked in mouse arthritis.

RA is an autoimmune–inflammatory rheumatic disease characterized by synovitis of multiple joints eventually leading to cartilage and bone destruction.[3] Although RA is a T-cell-dependent disease, no definitive 'arthritogenic' T-cell populations have yet been characterized. It is very likely that impaired immune regulation, resulting from deficiencies in the number and/or function of regulatory T (T_{REG}) cells and the resistance of effector T cells to T_{REG}-cell-mediated suppression, is involved in the development of synovial inflammation.[4] Furthermore, in addition to the 'loss of control' within the inflammatory environment, autoreactive T cells outside the joints and autoantibodies generated via T-cell-dependent processes are key players in the pathogenesis of RA.

Animal models are needed for in-depth investigation of pathogenic pathways that are involved in RA but are not accessible in humans.[5] For example, animals can be subjected to experimental procedures such as arthritis-inducing immunizations, cell depletion or transfer, selective cross-breeding, genetic manipulations, *in vivo* cell-homing studies and, most importantly, numerous preventative and therapeutic targeting strategies, most of which cannot be carried out in humans. Numerous arthritis models have been well characterized.[5–7] In past decades, we have obtained considerable amounts of information about the function of T-cell subsets that drive the pathogenic processes in the mouse PGIA model.[7–9]

Here, we provide a review of our current understanding of autoreactive T cells, various T-cell subsets, joint-homing T cells and T-cell-dependent autoantibodies in arthritis. We briefly present data obtained in human RA and compare these findings with those obtained from studies on animal models of arthritis. As our greatest expertise is in PGIA, we focus primarily on this model. However, some studies performed in other inducible models, such as type II collagen (CII)-induced arthritis (CIA) and glucose-6-phosphate isomerase (G6PI)-induced arthritis, as well as in spontaneous arthritis in K/BxN or SKG mice, are also discussed. Finally, we touch on the question as to why most T-cell-targeting strategies failed in patients with RA and how suitable animal models are in predicting the clinical efficacy of T-cell-directed biologic agents in RA.

Rise and persistence of autoreactive T cells

The importance of T cells in arthritis

T cells have various roles in RA and in mouse models of the disease; the major similarities and differences between human and mouse disease with respect to T cells are summarized in Table 1. Several lines of evidence suggest that, similarly to in human RA, T cells have a critical role in inducible animal models of arthritis, including PGIA and CIA, as well as in spontaneous arthritis in K/BxN and SKG mice. T cells are also involved in the generation of 'arthritogenic' antibodies that can passively transfer arthritis following injection into naive

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mice. In PGIA, T-cell depletion using anti-CD4 antibodies led to complete inhibition of arthritis development, whereas treatment with anti-CD8 antibodies resulted in increased disease severity.[10] As $CD8^+$ T_{REG} cells exist in human RA, depletion of these cells by anti-CD8 antibodies could indeed result in aggravation of the disease. CD4-depleting antibodies also suppressed CIA when administered before, but not after, arthritis development, suggesting a greater role of T helper (T_H) cells in the initiation phase of the disease than in the effector phase.[11] In the same study, *in vivo* activated $CD4^+$ T cells specific for CII were found to be quite resistant to antibody-mediated depletion.[11] This study could, at least in part, explain why most anti-CD4 antibody studies in human RA have failed. In adoptively transferred PGIA and CIA, which are induced in naive mice by the transfer of immune cells from mice with PGIA or CIA, removal of $CD3^+$ T cells (that is, all T cells) or $CD4^+$ T cells from the donor population inhibited the transfer of arthritis to severe combined immunodeficient (SCID) mice (which lack functional B and T cells).[2, 12] Therapeutic depletion of $CD4^+$ cells—after onset of arthritis—abrogated G6PI-induced arthritis.[13] In conclusion, $CD4^+$ T cells possibly have an important role in the development of arthritis in various mouse models. Their involvement might be crucial in the early phase of the disease, suggesting that anti-CD4 antibody therapy could be effective early in the disease course.

Abnormal T-cell selection

Abnormal T-cell selection and low T-cell signalling capacity might have a role in the development of autoimmune arthritis. Normally, most self-reactive T cells are deleted in the thymus during their development or are deleted or suppressed in the periphery. In SKG mice, however, a point mutation in the gene encoding ZAP70, a tyrosine kinase involved in T-cell receptor signal transduction, results in aberrant TCR signalling, which might enable self-reactive T cells to escape thymic deletion.[14] Such self-reactive T cells (of as-yet-unknown antigen specificity) are thus thought to drive the development of spontaneous autoimmune arthritis in SKG mice, which have an arthritis-prone BALB/c background.[15] Similarly, in humans, RA and other autoimmune diseases such as SLE and scleroderma have also been associated with low signalling capacity of self-reactive T cells, which might protect these cells against negative selection.[14, 16]

Autoreactive T-cell activation

MHC restriction of antigen recognition—Antigen presentation to $CD4^+$ T cells is MHC class II restricted. Thus, in both RA and its rodent models (Table 1), the recognition of particular autoantigens can depend on the MHC class II genotype of the individual. For example, the major T-cell epitope (amino acids 259–273) in CII—an autoantigen that might contribute to autoimmunity in a proportion of patients with RA—is preferentially presented by antigen-presenting cells (APCs) that express HLA-DRB1*04 (HLA-DR4) molecules in RA.[17] Similarly, T-cell responses to citrullinated (deiminated) self proteins are detected more frequently in patients with RA who express the HLA-DRB1 'shared epitope' (a five-amino-acid sequence present in some HLA-DRB1 alleles) than in those negative for shared-epitope-containing HLA class II molecules.[18] In line with these findings, genetic studies have established that certain *HLA-DRB1*01* and *HLA-DRB1*04* alleles containing sequences encoding the shared epitope are associated with RA.[19,20]

As in patients with RA, the MHC haplotype (referred to as H2 in mice) is a major determinant of arthritis susceptibility in mouse models. For example, only a few mouse strains are susceptible to PGIA or CIA.[8, 21] Moreover, PGIA-susceptible BALB/c mice (which have the $H2^d$ haplotype) are resistant to CIA, and conversely CIA-susceptible DBA/1 mice (which have the $H2^q$ haplotype) are resistant to PGIA.[8] An interesting dichotomy of MHC class II-dependent T-cell antigen recognition was described in mice carrying a KRN TCR transgene. In the wild-type strains, T cells expressing the transgenic KRN TCR

recognize bovine ribonuclease in the context of A^k MHC class II molecules. However, when crossed with nonobese diabetic (NOD) mice to generate K/BxN hybrids, KRN TCR-transgenic T cells recognize the ubiquitous self-antigen G6PI in the context of the MHC class II molecule A^{g7}, which is derived from the NOD background.[22, 23] These G6PI-specific T cells then provide help to B cells, leading to overproduction of anti-G6PI antibodies and spontaneous arthritis development in K/BxN mice.[22] Not surprisingly, treatment with anti-CD4 antibodies prevented the development of arthritis in this model.[23] Furthermore, transfer of T-cell-depleted K/BxN splenocytes to immunodeficient mice was unable to induce arthritis, also indicating the critical role of autoreactive T cells in the disease process.[22]

A number of non-HLA genes related to T cells have also been associated with RA and with mouse models of the disease. These genetic associations are discussed briefly in Box 1.

Box 1

Associations of T-cell-related genes with RA

SNPs within numerous chromosome regions (loci) have been reported in GWAS of patients with RA. Among the >30 confirmed non-HLA loci contributing to RA risk, probably the strongest associations have been found with loci containing the *PTPN22* (protein tyrosine phosphatase, non-receptor type 22) and *IL23R* (IL-23 receptor) genes. In brief, these genes, as well as the *CTLA4* (cytotoxic T-lymphocyte antigen 4), *CCR6* (CC-chemokine receptor 6) and *CD40* alleles that have also been associated with RA, are highly likely to be involved in T-cell function underlying the pathogenesis of RA.[20,113] SNPs in *PADI4* have also been identified in patients with RA. The PADI4 enzyme can catalyse the citrullination of proteins, which then can trigger the production of autoantibodies to citrullinated epitopes in patients with RA. [20,113] Autoantibody production is highly linked to pathogenic T cell involvement.

Arthritis-associated MHC and non-MHC loci have also been identified in GWAS carried out in CIA and proteoglycan-induced arthritis mouse models.[20,114] Some of these mouse loci overlap between the two models as well as with RA susceptibility alleles.[20,114]

Abbreviations: CIA, collagen-induced arthritis; GWAS, genome-wide association studies; RA, rheumatoid arthritis; SNP, single nucleotide polymorphism.

Autoantigen specificities—Autoreactive T cells can recognize a number of autoantigens in patients with RA, such as various epitopes in CII[17, 24] or the citrullinated form of the 5/4E8 epitope (amino acids 84–103) of the human cartilage proteoglycan aggrecan (citPG).[18,25] Multifunctional T-cell responses directed towards both native and glycosylated variants of the $CII_{259–273}$ epitope are sustained during the RA disease course.[17] Similarly, citPG induces T-cell responses in patients with RA but not in healthy controls, whereas the non-citrullinated aggrecan epitope does not stimulate such responses.[25] In addition, citrullinated proteins have been detected in fibrin deposits within RA synovial tissue, and citrullinated fibrin could be the major target of anti-filaggrin antibodies in the synovium *in vivo*.[31] In a comparative study on T-cell responses towards various citrullinated peptides, citPG was the most immunogenic, especially in patients with RA carrying the HLA-DRB1 shared epitope.[18] Interestingly, a T-cell response to the citPG epitope (or no response) was detected in early RA, whereas longstanding disease was associated with T-cell responses to citrullinated epitopes of multiple proteins.[18] This varied responsiveness is a good example of epitope spreading, a process involved in the progression of autoimmunity. Such epitope spreading also occurred during sustained T-cell responses to CII.[17]

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With regard to animal models, mouse $CD4^+$ T-cell lines specific for citrullinated fibrinogen have been found to enhance arthritis severity when transferred to mice with CIA.[27] Furthermore, T-cell responses to the mouse analogue of the citPG epitope after priming of BALB/c mice with the mouse citPG peptide were shown to be stronger than responses to the native (noncitrullinated) self epitope after priming with that peptide.[9] Thus, T-cell responses against citrullinated protein antigens have been identified in both humans and mice.

T-cell clonal expansion

Clonal expansion of $CD4^+$ T cells has been described in patients with RA.[28,29] Indeed, in one early study of 15 patients with this disease, oligoclonally expanded T cells were identified in the peripheral blood of all the patients, whereas such T-cell subpopulations were found in few healthy controls or patients with other types of arthritis. These 'RA-specific' expanded T-cell subpopulations persisted for years and infiltrated the synovial tissue.[28] Oligoclonal expansion of a unique $CD4^+$ T-cell subset lacking the co-stimulatory molecule CD28 on their surface has also been described in RA. These $CD4^+CD28^-$ T cells have been found to be resistant to apoptosis, which might explain the chronic persistence of the expanded populations in patients with RA.[29]

T-cell subsets in arthritis

Function and plasticity of T_H1 and T_H17 cells

A large body of literature suggests that the type 1 T helper (T_H1)-cell and T_H17-cell subsets have important pathogenic roles in RA. For many years, T_H1 cells, which produce interferon γ (IFN-γ), and a disturbed T_H1–T_H2 balance have been thought to drive organ pathology in RA as well as in other autoimmune diseases.[4, 30–32] However, the T_H1-cell concept has significantly changed since the discovery of IL-17-producing T_H17 cells. These cells, and IL-17, are major contributors to synovial inflammation, as well as to cartilage and bone damage.[32,33] T-cell responses to CII and citPG in RA have been associated with increased production of IFN-γ and IL-17, respectively.[17,18,24,25] Indeed, *ex vivo* stimulation of RA synovial fluid mononuclear cell populations (containing CII-reactive T cells) with CII resulted in increased production of the T_H1-type cytokines IL-12 and IFN-γ but not of the T_H2-type cytokine IL-4.[17,24] Moreover, T_H1-cell-associated epigenetic changes, such as demethylation of the *IFNG* locus, have been detected in $CD4^+$ T-cells from RA synovial fluid.[34] With regard to citPG, *ex vivo* stimulation of peripheral blood mononuclear cells with this epitope induced proliferative responses of T_H17 cells and prominent IL-17 production in patients with RA.[25] Similarly, another study showed that the proliferative T-cell response to citPG was associated with the release of the T_H17-type cytokines IL-6, IL-17 and TNF.[18]

Among animal models of inflammatory arthritis, PGIA has been shown to be a T_H1-cell-driven disease.[35] IFN-γ is necessary for the onset and progression of the disease, and the absence of this cytokine leads to reduced incidence and severity of arthritis and weaker proteoglycan-specific IgG2a antibody responses.[36] Increased IFN-γ levels decrease the number and percentage of activated T_{REG} cells in PGIA.[37] Moreover, compared with the standard protocol for induction of PGIA (in which BALB/c mice are injected with proteoglycan in complete Freund's adjuvant [CFA]), immunization of BALB/c mice with proteoglycan in the synthetic adjuvant dimethyl-dioctadecyl ammonium bromide (DDA) induced a strong T_H1 shift, and this effect led to a somewhat more severe manifestation of PGIA.[38] Conversely, a shift towards a T_H2-type response suppresses PGIA; for example, administration of T_H2-type cytokines, such as IL-4 and IL-10, before the onset of arthritis prevented the development of histopathological changes in the joints and clinical arthritis. IL-4 also inhibited proteoglycan-specific IFN-γ responses and reduced pro-inflammatory

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cytokine expression at target sites in PGIA.[35] Furthermore, arthritis was markedly more severe in IL-4-deficient BALB/c mice than in their wild-type counterparts.[36]

Substantial T_H17-cell responses have been detected in both human and mouse arthritic joints.[32,39,40] T_H17 cells have a crucial role in CIA, as CIA was markedly suppressed in IL-17-deficient mice.[41] Arthritis suppression in these mice was associated with reduced cellular and humoral responses to CII. By contrast, in PGIA, ablation of IL-17 had no effect on inflammatory cell recruitment or bone erosion in the arthritic joints, nor did it affect the generation of proteoglycan-specific T cells and IgG2a antibodies.[42] In a comparative study, immunization of BALB/c mice with proteoglycan in CFA was associated with the dominance of T_H17 over T_H1 cells, whereas the same immunization protocol using DDA adjuvant had the opposite effect.[43] Nonetheless, although T_H1–T_H17 polarization was clearly influenced by the adjuvant used, subset dominance had no significant impact on disease onset or severity.[38,43] The cytokine regulation of T_H17-cell regulation and function in human RA and its mouse models are illustrated in Figure 1 and discussed in Box 2.

Box 2

Cytokine regulation of T_H17-cell differentiation and function

The STAT3-activating cytokine IL-6, in combination with other cytokines described below, is a major inducer of T_H17-cell responses in both mice and humans.[32] It was first shown in mice that TGF-β and IL-6 are the main cytokines involved in the induction of the key T_H17-cell transcription factor RORγt and thus in T_H17-cell development.[32] Although early reports suggested that in RA, unlike in mouse models, TGF-β might not be needed for the development of T_H17 cells, subsequent studies have confirmed that TGF-β is also required for human T_H17-cell differentiation.[66,67,115,116] In RA, TGF-β induces the expression of both RORγt and the key T_{REG}-cell transcription factor FOXP3 in naive T cells and thus stimulates their differentiation into either T_H17 or induced T_{REG} cells, depending on the inflammatory environment.[66,67,115,116] IL-1, which only transiently induces RORγt, also induces T_H17-cell development in humans.[66,67,115,116] Thus, in RA, IL-6 and IL-1, rather than TGF-β, might be the main inducers of T_H17-cell development. However, IL-1 might not be as important in the induction of T_H17 cells in mice, although this cytokine, especially in combination with IL-23, promoted T_H17-cell proliferation in mice deficient of IL-1 receptor antagonist (Figure 1, Table 1).[110] An IL-21 and STAT3-dependent positive feedback loop exists in mice, in which IL-21 produced by naive T cells promotes T_H17-cell development, and these cells also produce IL-21.[32] This positive IL-21-dependent feedback loop might also be present in RA;[111] indeed, IL-21 is also required for human T_H17-cell differentiation.[115] IL-23, another STAT3-activating cytokine, also supports T_H17-cell polarization in both species.[32] Lastly, IL-2 stimulates the sustained production of the T_H17-cell cytokines IL-17 and IL-22 in RA, and might induce T_{REG} cells at the expense of T_H17 cells in mice (Figure 1).[4,32]

Abbreviations: RA, rheumatoid arthritis; TGF-β, transforming growth factor β; T_H17 cell, type 17 helper T cell; T_{REG}, regulatory T cell.

In RA, the inflamed synovium contains an abundance of T_H1 over T_H17 cells, suggesting that the local expansion of T_H17-cell populations within the arthritic joint is limited.[4,44] The lower proportion of T_H17 cells might be a result of the epigenetic instability of T_H17-cell chromatin structure, which leads to phenotypic plasticity of this subset.[45] Bifunctional T_H1–T_H17 cells producing both IFN-γ and IL-17 have been identified in RA synovial fluid, but not in peripheral blood.[40,46] Moreover, in *ex vivo* cultures, synovial fluid, but not peripheral blood, T_H17 cells produced both IL-17 and IFN-γ.[4,40] On the other hand, addition of IL-12,

a T_H1-cell-promoting cytokine found in RA synovial fluid, enhanced the conversion of peripheral blood T_H17 cells to the T_H1 phenotype.[40] Therefore, T_H17 cells, under the influence of locally produced cytokines such as IL-12, might transform into T_H1-like cells, leading to an increased ratio of T_H1:T_H17 cell numbers at inflammatory sites such as arthritic joints.[4,40]

The developmental plasticity of mouse T_H17 cells, by means of their conversion to the T_H1 phenotype, has been described in *in vitro* studies and in an animal model of colitis.[47] Whether the inflammatory microenvironment in arthritic mouse joints facilitates the T_H17 to T_H1 cell conversion, as it does in RA,[4,40] remains to be determined. In addition, mouse T_{REG} cells can be converted into IL-17-secreting cells, indicating plasticity between T_H17 and T_{REG} cells in the mouse system.[32] By contrast, mouse T_H1 and T_H2 cells seem to be phenotypically stable, terminally differentiated subsets.[32]

Follicular helper T cells

B-cell maturation in germinal centres (GCs) and autoantibody production are regulated by T cells.[48–50] GC-like structures, which are signs of lymphoid neogenesis, have been described in the severely inflamed RA synovium,[49] and these ectopic GCs have been shown to contain $CD4^+$ T cells.[49] However, unlike in severe RA, ectopic lymphoid structures have never been reported in the arthritic mouse synovium.

Within GCs, the fate of B cells is highly dependent on their ability to present antigens to a specialized subset of T cells known as follicular helper T (T_{FH}) cells. T_{FH} cells uniquely co-express CXC-chemokine receptor 5 (CXCR5; required for their homing to B-cell follicles) and the inhibitory receptor programmed cell death protein 1 (PD1).[50,51] They also express the transcription factor BCL6, a master regulator of T_{FH}-cell function.[50,51] Through downregulation of IL-2 production, PD1 is thought to help maintain high levels of BCL6 in T_{FH} cells.[51] Within GCs, T_{FH} cells promote the development of high-affinity memory B cells and long-lived plasma cells. Elevated numbers of T_{FH} cells have been associated with RA,[48] and given the critical role of these cells in B-cell activation and antibody production, the failure of T_{FH} cells to maintain self-tolerance and their potential contribution to autoimmunity have drawn much attention.[48,52,53] PD1 is abundantly expressed by RA synovial T_{FH} cells, yet these cells are fairly resistant to PD1–PD1 ligand 1 (PDL1)-mediated inhibition of proliferation (Table 1).,55 The decreased response of synovial T cells to PD1 ligation might be attributable in part to the presence of a soluble isoform of PD1 in RA synovial fluid, which can interfere with, although not completely block, PDL1 binding to these cells.[55]

In mice, expansion of T_{FH} cells might occur in the spleen, as observed in Pdl1-deficient BALB/c mice following induction of PGIA.[56] PDL1 regulates autoimmunity by suppressing autoreactive $CD4^+$ T-cell responses. In addition, expression of PDL1 on a non-B and non-T cell type promotes B-cell survival by restraining the expansion and activation of T_{FH} cells through interaction with PD1. In the PGIA model, Pdl1-deficient mice exhibited increased autoreactive T_H1-cell responses, as well as an elevated frequency and activation status of T_{FH} cells, which were associated with death of GC B cells in the spleen and worsening of arthritis symptoms.[56]

Developmental plasticity of mouse T_{FH} cells has also been described. Early T_H1-cell differentiation was associated with transient appearance of T cells with T_{FH} or dual T_H1–T_{FH} phenotypes. At a later phase of T-cell development, there was a repression of T_{FH}-cell function that permitted full T_H1-cell differentiation.[57] Such plasticity has not yet been described in RA (Table 1).

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Regulatory T cells

The role of T_{REG} cells and the loss of regulatory control of effector T cells in the pathogenesis of RA has been reviewed in this journal by Wehrens *et al.*,[4] so this issue is only briefly discussed here. Crucially, the resistance of effector T cells to T_{REG}-cell suppression might be a key explanation for the loss of control and the perpetuation of autoimmune inflammation in RA. The two main populations of T_{REG} cells—thymus-derived 'natural' T_{REG} cells and peripherally induced T_{REG} cells—have both shared and distinct properties, but they both can suppress effector T cells. In addition to emerging markers distinguishing between them, the signature T_{REG}-cell transcription factor FOXP3 has been shown to be constitutively expressed in thymus-derived T_{REG} cells, whereas its expression requires the presence of TGF-β in induced T_{REG} cells.[58] In RA, diminished function of thymus-derived T_{REG} cells has been associated with defects in CTLA4-mediated signalling, and disease control via anti-TNF therapy cannot overcome this defect.[59] By contrast, anti-TNF therapy in RA increases the number and function of induced T_{REG} cells, in a TGF-β-dependent manner, and these cells seem to be able to suppress pathogenic T cells.[60–62]

T_{REG} cells also have an important role in regulating arthritis in animal models. Transfer of $CD4^{+}CD25^{+}$ T_{REG} cells into mice with CIA slowed disease progression and reduced acute-phase protein production, although CII-specific T-cell and antibody responses were not affected.[63] In mice with PGIA that underwent a therapeutic bone marrow transplantation (BMT), $CD25^{+}FOXP3^{-}$ memory T_{REG} cells contributed to rapid improvement of arthritis 1 week after BMT, and 3 weeks after BMT $FOXP3^{+}$ T_{REG} cells emerged that stabilized the disease at a lower severity level than before BMT.[64] Conversely, depletion of the T_{REG}-cell subset by administration of an anti-CD25 antibody led to severe arthritis in asymptomatic proteoglycan-immunized mice.[64] Moreover, reduced disease severity in PGIA following administration of a B-cell-depleting anti-CD20 antibody, rituximab, was associated with increased numbers of $FOXP3^{+}$ T_{REG} cells as well as diminished B-cell numbers.[37] Indeed, depletion of these treatment-induced T_{REG} cells using an anti-CD25 antibody restored the severity of PGIA to a level equal to that observed in untreated mice.[37]

Although T cells constitute a minor population of cells in the synovial fluid of arthritic K/BxN mice, 45–70% of these T cells belong to the $CD25^{+}FOXP3^{+}$ T_{REG}-cell subset.[65] In the absence of T_{REG} cells, for example in K/BxN mice harbouring a loss-of-function mutation in the *Foxp3* gene, a higher degree of local destruction in the joints was observed and otherwise unaffected joints also became inflamed.[65] T_{REG} cells seemingly accumulated in the arthritic joints regardless of antigen specificity, as T_{REG} cells were also found in elevated numbers in non-K/BxN animals following passive transfer of arthritis with serum from K/BxN mice.[65] Thus, T_{REG} cells accumulate in arthritic joints through either recruitment or conversion from another phenotype. Such cells might locally suppress effector T cells; however, as shown in RA, their potency might be reduced in the inflammatory environment.

In both mice and humans, a reciprocal relationship exists in the development of $T_{H}17$ and T_{REG} cells, with a high degree of plasticity between these T-cell subsets.[4,66,67,68] Under pro-inflammatory conditions, such as in the inflamed joint, $T_{H}17$-cell development is enhanced by various cytokines, including IL-6, TGF-β and IL-1β, and also potentially through IL-2 consumption by T_{REG} cells. Furthermore, in the inflammatory milieu, a small proportion of unstable induced T_{REG} cells might be converted into effector $T_{H}17$ cells that produce IL-17 (Figure 1).[4,67,68] In patients with RA treated with TNF antagonists, T_{REG} cells can gain control over $T_{H}17$ cells, at least in part, by inhibiting IL-6 production.[62] Thus, mouse models of arthritis have helped us to understand the role of T_{REG} cells in RA. Passive transfer experiments and assessment of T_{REG} plasticity are more accessible in the animal models.

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Of note, some differences exist between mouse and human T_{REG} cells. For example, IL-2 promotes T_{REG}-cell development at the expense of T_H17 cells in mice, but not in humans (Figure 1).[32] With regard to TNF, both human and mouse T_{REG} cells express TNF receptor 2 (TNFR2).[4,69] In humans, TNF inhibits T_{REG}-cell expansion[4,69] and, correspondingly, neutralization of this cytokine by anti-TNF biologic agents promotes T_{REG}-cell expansion in patients with RA.[60,61] Furthermore, in RA, inhibition of TNF by various anti-TNF biologic agents or defective TNFR2 signalling improves the suppressive function of T_{REG} cells. It has been suggested that human T_{REG}-cell function is dependent on the phosphorylation status of FOXP3. In accordance with this hypothesis, TNF-induced FOXP3 dephosphorylation is associated with impaired T_{REG}-cell function,[70] and anti-TNF treatment improves defective T_{REG}-cell function in RA by restoring FOXP3 serine phosphorylation.[70] By contrast, in mice, TNF promotes the expansion of T_{REG} cells[4,71] and, at least in some studies, TNF neutralization was shown to suppress the function of this subset.[72] Thus, TNF or anti-TNF treatment might have opposite effects on T_{REG} cells in mice and humans.[4]

Joint-homing T cells in arthritis

Phenotype and function

As described above, the local inflammatory milieu within the RA joint highly influences the proportion and function of T_H1, T_H17 and T_{REG}-cell subsets.[4] Local enrichment and differentiation of T_H1 and T_{REG}-cell subpopulations is accompanied by a relatively limited local expansion of T_H17 cells within the inflamed synovium, possibly triggered by cells with APC function.[4,73] Pro-inflammatory cytokines downregulate FOXP3 expression and stimulate IL-17 production by $CD25^+FOXP3^+$ synovial T_{REG} cells, leading to their differentiation towards the T_H17-cell phenotype.[4,74] Yet, T_H17 cells are present in relatively low quantities in the synovial fluid of patients with RA, which might be a consequence of T_H17-cell conversion to the T_H1 phenotype.[39,40] The inflammatory environment also influences the suppressive function of T_{REG} cells in the RA joint. A substantial population of T_{REG} cells is present in RA synovial fluid, and these cells have the capacity to suppress effector T cells. However, the presence of pro-inflammatory mediators in this environment abrogates such suppressor activity.[4,75]

Unlike in RA, T cells constitute a very minor population of joint-homing cells in mouse models including PGIA,[2,76] CIA[77] and K/BxN arthritis.[65] In adoptively transferred PGIA, serial *in vivo* visualization of fluorochrome-labelled donor T cells failed to identify T cells entering the joints of recipient mice, whereas accumulation of donor T cells was readily detectable in the lymph nodes of the host following transfer and during arthritis development.[2] In CIA, introduction of a human RA-susceptibility *HLA-DR4* transgene into MHC class II-deficient DBA/1 mice made it possible to identify T cells specific for HLA-DR4-restricted $CII_{261–273}$ peptide in the joints *ex vivo*.[77] These CII-specific $CD44^+$ (activated) T cells were detectable in acutely arthritic joints, but they disappeared from the synovial fluid by 2 weeks after the onset of CIA. Although the phenotype of joint-homing T cells was not investigated in this study, given the preferential attraction of the $CD25^+FOXP3^+$ subset to sites of inflammation[63,65] it is possible that the majority of these cells were T_{REG} cells.

Recruitment to the joint

Chemokines and their receptors provide directional cues for T-cell migration to lymphoid organs and inflammatory sites. In RA and animal models of arthritis, mostly CC-type chemokines, together with their receptors, are involved in T-cell homing to the joints.[78] Among the CC-type chemokines, CCL2 (also known as MCP1), CCL3 (also known as MIP1α), CCL5 (also known as RANTES), CCL7 (also known as MCP3), CCL8 (also

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known as MCP2), CCL13 (also known as MCP4), CCL17 (also known as TARC), CCL18 (also known as PARC), CCL19 (also known as ELC), CCL20 (also known as MIP3α) and CCL21 (also known as SLC) have all been detected in the sera and joints of patients with RA.[78,79] CCL20 preferentially recruits T_H17 cells via CCR6.[80] CCR1, CCR2, CCR5 and CCR7 are abundantly expressed in the RA synovium and on various cells in the synovial tissue.[79] CCR5 is the most prominent CC-chemokine receptor in T_H1-cell-dominated inflammatory infiltrates.[81,82] Moreover, increased homing of $CCR5^+$ and $CXCR3^+$ T cells was observed in patients with seronegative arthritis, underscoring the significance of these T cell subsets in the development of the disease.[83] Expression of CCR6 on T_H17 cells, which supports the ingress of these cells into the RA joint, is attenuated by anti-TNF therapy.[80,84,85] CCR4 and CCR6 are expressed by both T_H17 and T_{REG} cells, as well as on T cells with a dual T_H17/T_{REG} cell phenotype (Figure 1).[66] Thus, CCR1, CCR4, CCR5, CCR6 and their ligands, CCL3, CCL5, CCL7, CCL8 and CCL20, seem to be the most relevant chemokine receptor–ligand pairs involved in T-cell recruitment to the RA joint.[78,79]

Animal models lend themselves to real-time *in vivo* analyses of T-cell recruitment and behaviour in lymphoid organs that are not accessible for *in vivo* studies in humans. For example, T-cell motility changes associated with antigen presentation, T-cell–APC interactions, and competition between antigen-experienced and naive T cells for access to antigen-bearing APCs can be visualized in real time in the joint-draining lymph nodes of mice with PGIA.[2,76,86] However, as described above, monitoring of T-cell influx into distal joints *in vivo* revealed poor T-cell recruitment in these sites.[2] This limited recruitment might be a drawback of all popular mouse arthritis models when it comes to studying T cells within the joints. In addition, the small volume of synovial fluid in rodent joints and the paucity of joint-homing T cells make it difficult to isolate such T cells and study their function *ex vivo*.[5,8]

T-cell-dependent autoantibody production

RF and ACPA

Probably the best-characterized autoimmune feature of RA is the presence of antibodies against self IgG (rheumatoid factor [RF]) and against citrullinated proteins (anti-citrullinated protein antibodies [ACPA]) in the sera of patients, with ACPA being more disease-specific than RF.[87,88] Most of these autoantibodies have undergone isotype switching, suggesting that their production by B cells requires T-cell help.[87,89,90] Numerous citrullinated proteins have been identified in RA synovial tissue and fluid.[87,91–93] However, the broad epitope repertoire and the apparent lack of joint (that is, cartilage matrix protein) specificity of ACPA make it difficult to identify an ‘arthritogenic’ population of ACPA. Several ACPA specificities target serum proteins, such as citrullinated fibrinogen, or intracellular proteins including vimentin and α-enolase.[94–96] Although antibodies reacting with filaggrin, mutated citrullinated vimentin, and citrullinated cyclic peptides (CCP) have been used for diagnostic purposes by several laboratories, to date fibrinogen, fibrin and vimentin have been the main citrullinated proteins identified in the RA synovium. In fact, citrullinated fibrin chains are a major target of anti-filaggrin antibodies.[26]

It has been demonstrated that epitope spreading of ACPA starts in the preclinical phase of RA, and is, at least in part, responsible for the perpetuation of the disease.[94] Moreover, ACPA fine-specificities have been associated with clinical responses to biologic agents in patients with RA.[95] However, as mentioned above, arthritogenic ACPA specificities have not yet been elucidated, although the synovial T-cell repertoire is quite different in ACPA-positive and ACPA-negative subsets of patients with RA. For example, an altered distribution of TCR complementarity-determining region 3 (CDR3) lengths, which is associated with monoclonal or oligoclonal T-cell expansion, was detected more frequently

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in ACPA-positive than ACPA-negative RA, suggesting the preferential involvement of clonally expanded T cells in seropositive disease.[97]

In animal models, ACPA responses to intracellular proteins develop during the early stages of CIA, and mice with chronic CIA exhibit expansion of antibody reactivity against citrullinated peptides.[98] Both ACPA and RF are produced in PGIA, which makes this model, as well as human PG G1 domain-induced arthritis,[99] more relevant to seropositive RA than other mouse models, and also a suitable model for investigating the potential pathogenic role of ACPA in RA development.

Other autoantibodies

T-cell–B-cell crosstalk is clearly involved in autoantibody production in various mouse models of RA. In CIA, autoantibodies of the IgG2 isotype that crossreact with mouse CII have been shown to cause chondrocyte death in the presence of complement;[21] thus, T-cell help in switching to the IgG2 isotype is crucial for producing pathogenic antibodies that can mediate cell death. As mentioned above, citrullinated-fibrinogen-specific T cells transferred to mice with CIA enhanced the production of anti-CII autoantibodies, providing further evidence of T-cell–B-cell crosstalk.[27] These findings might also be of relevance to human disease, as anti-CII antibodies have been detected in patients with early RA.[100] In PGIA, antibodies against mouse proteoglycan are generated after the second immunization with human proteoglycan, and the progression from anti-human to self-reactive anti-mouse proteoglycan antibodies correlates with the development of arthritis.[8] IgG-containing deposits are detected in the joints before arthritis onset, indicating that the formation of complement-fixing immune complexes containing proteoglycan and anti-proteoglycan antibodies might be the primary event that initiates the local activation of synovial macrophages and fibroblasts and the recruitment of leukocytes, which collectively drive inflammation and tissue destruction.[7,8] T cells are involved in the initiation of B cell activation and autoantibody production, as well as the maintenance of autoimmunity throughout the disease course.

In K/BxN arthritis, linked T-cell and B-cell recognition of G6PI leads to overproduction of self-reactive anti-G6PI antibodies.[22] It has been suggested that immune complexes formed inside the joints of K/BxN mice can fix complement and activate Fc receptors, thereby initiating leukocyte recruitment as well as local inflammatory mediator production.[22] However, although treatment of K/BxN mice expressing human CD20 with the anti-human-CD20 antibody rituximab markedly reduced serum levels of anti-G6PI antibodies, it failed to suppress arthritis, suggesting that the level of circulating autoantibodies does not necessarily correlate with disease severity. On the other hand, transfer of arthritic K/BxN serum to naive mice can induce disease in a wide range of mouse strains, including B-cell-deficient or lymphocyte-deficient hosts, via G6PI-specific autoantibodies.[22,101] However, passive induction of arthritis is not a universal phenomenon, as serum from mice rendered arthritic by immunization with G6PI,[13] or from other models including PGIA,[102] cannot transfer disease. This finding indicates that a certain threshold level of autoantibodies, perhaps of a particular antigen specificity and isotype, in the circulation might be required for arthritis induction. Although inflammation induced by arthritic K/BxN serum transfer recapitulates the major histopathological features of disease seen in the donor mice, arthritis is transient. Inflammation declines 2 weeks after serum transfer, and previously swollen joints show little or no evidence of inflammation or cartilage destruction. Arthritis transience can be overcome by repeated injections of serum from arthritic K/BxN mice, suggesting that a continuous supply of even the most potent autoantibodies is necessary for sustained inflammation.[22] Although arthritis cannot be transferred via serum injection in the PGIA model, administration of immune sera accelerates the development of arthritis induced by lymphocyte transfer.[102]

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In conclusion, the production of autoantibodies, including ACPA and RF, is characteristic of both RA and mouse arthritis, but among the mouse models ACPA and RF are produced concurrently only in PGIA. ACPA specificities may differ substantially between RA and animal models. Antibodies to citrullinated fibrinogen (and perhaps other, unknown antigens) might have a central role in humans and mice. Transferability of arthritis by autoantibody-containing sera to naive mice (which certainly cannot be tested in humans) might challenge the current paradigm regarding a direct contribution of joint-homing T cells to arthritis initiation.

Therapeutic targeting of T cells

Therapies targeting T cells in RA have held great promise since the 1990s. Several anti-CD4, anti-CD5, anti-CD7 and anti-CD52 antibodies have been developed and tested, but no clear-cut clinical efficacy could be demonstrated in clinical trials, and no correlation has been found between antibody-induced T-cell depletion and disease status in RA.[103] To date, only one strategy of T-cell inhibition—blockade of signalling through the co-stimulatory molecule CD28 using a CTLA4-Ig fusion protein known as abatacept—has shown efficacy in clinical trials, leading to the registration of abatacept for the treatment of RA.[104]

With regard to indirect T-cell blockade, B-cell inhibition by the anti-CD20 antibody rituximab also affects T cells. Rituximab administration might decrease the activated phenotype of peripheral and tissue-resident T cells by abolishing antigen presentation by B cells.[105] Much controversy has surrounded the effect of B-cell blockade on T_{REG} cells. Rituximab treatment might enhance the numbers and function of these cells;[105] however, in another study, anti-CD20 therapy did not influence the frequency of T_{REG} cells in RA.[106] Finally, a $CD20^{+}$ T-cell subset has been characterized and shown to comprise terminally differentiated T cells with immunoregulatory and pro-inflammatory properties. Rituximab also depleted this T-cell population, an effect that might have a role in the beneficial effects of B-cell targeting in RA (Table 1).[107]

As CC chemokines and their receptors have been implicated in T-cell homing to the joint, we briefly touch on the efficacy of chemokine receptor blockade. To date, antibody-mediated blockade of CCR2 and CCR5 has yielded disappointing results in RA, and variable outcomes have been reported for CCR1 blockade. However, the fact that CC-chemokine receptor blockade failed in most clinical trials does not necessarily mean that chemokine receptors are not legitimate targets in RA. Rather, it seems to be critical to achieve very high levels of receptor occupancy in order to continuously inhibit leukocyte migration into the synovial compartment.[79,108] Of note, patients with RA treated with TNF antagonists exhibit low expression levels of CCR6 in T_H17 cells and reduced proportions of these cells in the joints.[85]

In contrast to RA, numerous T-cell-targeting therapies using anti-CD4 antibodies or genetic manipulations have shown great efficacy in preventing arthritis in animals, including in the PGIA,[10] CIA[11] and K/BxN[22] models. There might be important reasons for this discrepancy. RA is characterized by a ‘waxing and waning’ of disease symptoms, and a persistence of polyclonally or oligoclonally expanded T cells including self-reactive populations. By contrast, arthritis is ‘monophasic’ in most rodent models, and joint inflammation is preceded by a robust and single-antigen-focused T-cell response, only a part of which is directed against self. It is relatively easy, therefore, to prevent arthritis in animal models by deleting T cells or knocking out molecules essential for the effector function of T cells. The early involvement of T cells in arthritis also means that anti-CD4 treatment works best when applied preventatively, before the appearance of clinical symptoms.[11] In the CIA model, anti-CD4 treatment administered after arthritis onset failed to suppress disease or

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eliminate the CII-reactive pathogenic population of T cells,[11] which might, in part, explain the inefficacy of a similar treatment in established RA. In addition, in the majority of animal models, counter-regulatory mechanisms mainly involving innate immune cells such as joint-infiltrating myeloid-derived suppressor cells[109] kick in early during the course of inflammation. These innate immune cells can effectively reduce T-cell responses and inflammation in a reasonably short period of time, thereby masking the potentially beneficial effects of T-cell-targeting therapeutics administered after disease onset (Table 1).

As indicated by the clinical success of abatacept-mediated blockade of T-cell co-stimulation,[104] treatment strategies that indirectly influence T cells may be more effective in RA than antibody-induced depletion or neutralization of these cells. For example, as mentioned above, adoptive transfer of $CD25^+$ T_{REG} cells and T_{REG}-cell-inducing BMT suppressed ongoing CIA[63] and PGIA,[64] respectively, suggesting that *in vivo* induction or transfer of *ex vivo*-induced autologous T_{REG} cells could be an effective therapy in RA. B-cell depletion via anti-CD20 antibody administration, which is also highly effective in RA, not only reduced T-cell-dependent autoantibody production in PGIA and the K/BxN model,[37, 68] but also diminished proteoglycan-specific T-cell responses and increased T_{REG}-cell activity in PGIA.[37] These animal studies suggest that B-cell depletion via rituximab in RA probably has an indirect effect on T cells by shifting the balance between pathogenic and suppressive subsets in favour of suppressive T_{REG} cells.

In summary, the inefficacy of T-cell depletion in RA may be explained by differences between RA and mouse arthritis in disease course as well as in the potency or persistence of autoreactive T cells. Even in mouse models, anti-CD4 treatment works only when initiated before the onset of arthritis, and not in established disease. Animal studies suggest that therapies that restore or stabilize the number and suppressive function of T_{REG} cells are the key to further success in the treatment of RA.

Conclusions

It is widely accepted that autoreactive T cells have a major role in the pathogenesis of RA as well as in a number of animal models of the human disease. MHC-restricted autoreactive T-cell responses and T-cell-dependent autoantibody production have been extensively characterized in both species. However, the specific contribution of T cells to joint inflammation is not clear in either RA or mouse models of arthritis. Despite similarities in T-cell subset composition, there are differences between humans and mice in the cytokine regulation of T_H-cell polarization, the developmental plasticity of T cells, and the T_H17 cell–T_{REG} cell axis. Finally, whereas most T-cell depletion strategies have failed in RA, elimination of T cells has prevented or suppressed arthritis in numerous animal models. In conclusion, although animal models such as PGIA or CIA bear significant resemblance to the human disease, additional studies are needed to refine our understanding of T-cell pathology in autoimmune arthritis and to further enhance the value of preclinical animal studies in predicting the outcome of T-cell-focused therapeutic interventions in RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Autoreactive T cells have an important role in the pathogenesis of both rheumatoid arthritis (RA) and mouse models of the disease
- In addition to similarities, some differences exist in the regulation of the development and plasticity of T_H1, T_H17 and T_{REG} cell subsets in humans and mice
- The contribution of joint-homing T cells to local inflammation is not clear in either species
- Unlike in mouse arthritis, most T-cell-targeting strategies failed in RA; only a few of them (such as abatacept) succeeded
- Anti-cytokine and anti-B-cell targeting strategies might indirectly suppress pathogenic T cells in human and mouse arthritis

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Review criteria

Relevant full-text English-language papers published between 1980 and 2013 were collected from PubMed. The search terms used were: “rheumatoid arthritis”, “arthritis models”, “proteoglycan-induced arthritis”, “collagen-induced arthritis”, “G6PI-induced arthritis”, “SKG arthritis”, “K/BxN arthritis”, “autoreactive T cell”, “T_H1”, “T_H17”, “T_{FH}”, “T_{REG}”, “joint homing T cells”, “RF”, “ACPA”, “autoantibodies”, “TNF-α”, “cytokines”, “chemokines”, “MHC” and “genetics of RA”.

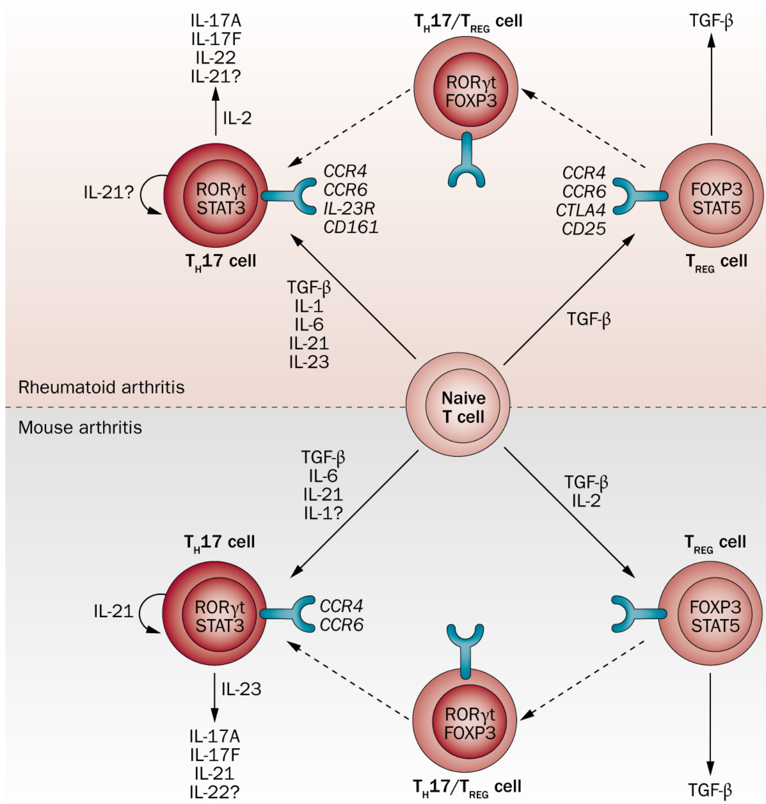

Figure 1.

Cytokine regulation of the T_H17–T_{REG} cell axis in human RA and its mouse models. Naive T cells can differentiate into either T_H17 or T_{REG} cells and there is high plasticity between these T cell subsets. This figure summarizes inflammatory mediators enabling the differentiation of these T-cell subsets, and those mediators produced by these cells in humans and mice. Similarities and differences between human and mouse arthritis with respect to T-cell subsets are further explained in the main text and in Table 1. Abbreviations: CCR, CC-chemokine receptor; FOXP3, forkhead box P3; RA, rheumatoid arthritis; ROR, retinoic acid receptor-related orphan receptor; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor β; T_{REG}, regulatory T; T_H, T helper.

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Table 1

Similarities and differences between mouse arthritis models and human RA with respect to T cells

Category	Feature	Mouse models(reference)	Human RA(reference)
Autoreactive T-cell development and function			
	MHC restriction	Yes[8,21]	Yes[17,18]
	T-cell responses to CII	Yes[11]	Yes[17,24]
	T-cell responses to citrullinated proteins	To citPG[9] and citFib[27]	To multiple citrullinated epitopes[18,25]
T-cell subsets			
	T_H17–T_{REG} cell plasticity	Yes[4,32]	Yes[4]
	$T_H17 \rightarrow T_H1$ cell conversion	Yes[38,43]	Yes[40,46]
	$T_H2 \rightarrow T_H17$ cell conversion	No[32]	No[32]
	TGF-β-dependent T_H17 cell induction	No[32]	Yes[32]
	IL-6–STAT3- dependent T_H17 cell development	Yes[32]	Yes[32]
	IL-1-dependent T_H17 cell induction	In some studies[110]	Yes[32]
	IL-2-dependent stimulation	T_{REG} cells[4,32]	T_H17 cells, IL-17[32]
	IL-21-dependent positive feedback loop	Yes[32]	In some studies[111]
	IL-22 production by T_H17 cells	In some studies[110]	Yes[32]
	IL-23-dependent maintenance of T_H17 cell responses	Yes[32]	Yes[32]
	TGF-β-dependent T_{REG} cell growth	Yes[4,32]	Yes[4, 32]
	TNF effects on T_{REG} cells	Promote expansion[4,71]	Inhibit expansion[4,69]
	Ectopic lymphoid structures in synovium	NR	Yes[49]
	Role of PD1 in T_{FH} cells	Yes[56]	Yes[54]
	T_H1–T_{FH} cell plasticity	Yes[57]	NR
Joint-homing T cells			
	Level of T-cell recruitment to synovium	Low, majority T_{REG} cells[65,76,77]	High, majority T_H1 cells[30,32]
	Synovial T_H17 cells	Locally expanded[4]	Limited local expansion[4]
	Diminished T_{REG} cell suppressor capacity in arthritic joints	NR	Yes[4]
T-cell-dependent autoantibodies			
	ACPA, RF	Yes[98]	Yes[87,91]
	Anti-CII antibodies	Yes[21]	Yes[100]
Therapeutic interventions			
	Efficacy of T-cell- depleting therapies	Yes (mostly preventatively)[11,22]	No[112]
	Rituximab effects on effector T cells	Yes[37]	Yes[105,107]

Category	Feature	Mouse models(reference)	Human RA(reference)
	Rituximab effects on T_{REG} cells	Increased T_{REG} cell numbers[37]	Controversial[105,106]

Abbreviations: ACPA, anticitrullinated protein antibodies; citFib, citrullinated fibrinogen; citPG, citrullinated proteoglycan; NR, not reported; PD1, programmed cell death protein 1; RA, rheumatoid arthritis; RF, rheumatoid factor; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor β; T_{FH} cell, follicular helper T cell; T_H cell, helper T cell; T_{REG}, regulatory T cell.

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