
The central role of T cells in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory syndromes. As such, RA is often considered the prototype disease for defining both the molecular and pathological basis of immune-mediated chronic inflammatory disease, and for validating targeted therapies.

The immunogenetics of RA suggest a key role for aberrant pathways of T-cell activation in the initiation and/or perpetuation of disease. In the T-cell activation process, CD4⁺ T-cells are engaged by antigenic peptide fragments in a complex with HLA class II molecules, in addition to co-stimulatory molecules, such as CD80/CD86, expressed on the surface of professional antigen presenting cells. The strongest evidence supporting a role for CD4⁺ T cells in disease pathogenesis is the association between RA and HLA-DRB1; however, the functional role of this association has yet to be defined. Susceptibility to RA may also be linked with several RA-associated allelic variants of genes, especially PTPN22, but also CTLA4, IL2RA, IL-2RB, STAT4, PTPN2 and PADI4, many of which encode molecules directly implicated in pathways of T-cell activation.

The presence of inflammatory infiltrates, such as follicular structures, in the synovial membrane provides compelling evidence of ongoing immune reactions in moderate to severe RA. These structures likely play a key role in T cell – B cell cooperation and the local generation of specific autoantibodies; as such, chronically activated synovial T cells represent key cellular targets for therapy. Evidence also supports a role for T-helper (Th) cells, Th17 cells, and impaired CD4⁺CD25^{hi} regulatory T cell (Treg) function in the pathogenesis of RA.

In addition to discussing a range of issues regarding T-cell activation in RA, this review describes how therapeutic modulation of T-cell function, as op-

posed to profound immunosuppression or immunodepletion, has been associated with better disease outcomes in clinical trials. Ultimately, elucidation of the distinct effects of co-stimulation modulation with abatacept on T cells should provide key insights into understanding how to restore immune homeostasis in patients with RA.

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory syndromes, and has become the prototype disease for defining the molecular and pathological basis of immune-mediated chronic inflammatory disease, as well as for validating targeted therapies. Rheumatoid arthritis targets the synovial lining of joints, bursae and tendon sheaths. At least in the early phase, RA is distinct from other organ-specific autoimmune diseases in that, rather than causing cell death and tissue destruction at the outset, the disease is characterized by the activation and proliferation of stromal tissues in the target organ. Furthermore, no antigen or antigens have been defined in RA that reflect the specific target organ. Given the strong genetic associations between RA and genes encoded within the major histocompatibility complex (MHC), a major challenge over many decades has been to understand how aberrant MHC class II restricted T-cell responses might provoke persistent immuno-inflammatory responses that target the synovial joint. Recent advances in genetics, together with data acquired from animal models of autoimmune arthritis, have provided important new clues.

The immunogenetics of rheumatoid arthritis

In spite of heritability estimates of up to 60% (1), the identification of allelic variants that underpin RA disease pathogenesis has been hindered by the fact that RA susceptibility genes

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confer low to moderate risk and have low penetrance (2). The only exception to this is the MHC, for which five genome-wide linkage scans of multiplex families have unambiguously established an important contribution, and allelic variation at the HLA-DRB1 locus remains the dominant, although not exclusive, MHC locus contributing to disease susceptibility (2). Nevertheless, a contemporary approach to understanding the biology of complex polygenic traits proposes that disease-associated gene polymorphism is pathway specific rather than disease specific. This notion is supported by the fact that susceptibility genes impose subtle phenotypic variation in the function of biologic pathways shared between autoimmune syndromes (3).

The most comprehensively studied pathway is undoubtedly T-cell activation. In this activation process CD4⁺ T-cell clones, expressing rearranged antigen T-cell receptor (TCR) α and β chains, recognize and are engaged by antigenic peptide fragments in a complex with HLA class II molecules and co-stimulatory molecules, such as CD80/CD86, expressed on the surface of professional antigen-presenting cells (APCs). The association between RA and HLA-DRB1, which encodes the polymorphic HLA class II DR β chain where the greatest variation is confined to a stretch of the DR β chain alpha helix (residues 67–74) known as the shared epitope (SE) (4), remains perhaps the strongest evidence for a role of CD4⁺ T cells in disease pathogenesis. However, the functional basis for this association remains the subject of some debate. The most obvious functional impact of HLA-DRB1 polymorphism would be to influence TCR recognition, either through the selection of distinct peptide epitopes for presentation to T cells or through direct effects on MHC/TCR contact residues, altering MHC/TCR avidity during thymic development and the activation of T cells in the periphery (5, 6). Other studies have proposed a link between particular subtypes of HLA-DR4 and the replicative history, based on the erosion of telomeres in the hematopoietic compartment (7, 8). It is thought that this might arise from the

expansion of self-reactive T-cell clones through homeostatic proliferation in both naïve and memory T-cell compartments and subsequent contraction of the T-cell repertoire documented in patients with RA (9). Why this should be associated with HLA-DR4 and not other HLA-DR molecules is unclear.

More recent studies propose that RA-associated HLA-DR $\alpha\beta$ molecules may promote immune responses to modified self, including citrullinated proteins (10), that appear to be influenced by environmental factors such as chronic exposure to tobacco smoke (11). According to this model, different subsets of RA-associated HLA-DR molecules might present a distinct profile of citrullinated autoantigens to T cells. The finding of an association between gain-of-expression variants of *PADI4*, which encodes one of several peptidylarginine deiminase (PAD) enzymes that citrullinates proteins, and disease in Japanese, US and European RA populations is, therefore, of particular interest (12, 13). Emerging data further support the notion that RA-associated allelic variants may impose subtle phenotypic effects on pathways of T-cell activation and the resolution of immune responses. For example, the hematopoietic tyrosine phosphatase Lyp, encoded by *PTPN22*, has recently been identified as a major risk factor for several autoimmune diseases, including type I diabetes, autoimmune thyroiditis, systemic lupus erythematosus, myasthenia gravis and RA, with odds ratios in the range of 1.5–2.0 (2, 3). Although expressed in many cell types within the hematopoietic compartment, the best understood function of this phosphatase is to switch off TCR signaling (14–16). Intriguingly, the disease-associated allelic variant, R620W, has been reported to be a gain-of-function mutant paradoxically impairing the association between Lyp and C-terminal Src kinase (CSK), a negative regulator of TCR signals, while at the same time enhancing intrinsic phosphatase activity (17); the sum effect is to increase thresholds of TCR signaling. Whether this impacts on thymic selection or the propagation and/or function of regulatory T cells (Tregs) remains to be determined. However, there does appear

to be an association between carriers of the *PTPN22* minor allele and autoantibody production (18, 19).

Finally, there exist associations between RA and polymorphism in genes encoding proteins that serve to regulate immune responses. One of these associations, albeit weak, is with polymorphism at the *CTLA-4* locus, another general susceptibility locus for autoimmunity (3, 13). Surface cytotoxic T-lymphocyte-associated antigen (CTLA)-4 functions as a negative regulator of T-cell activation, binding to CD80/CD86 on APCs, although it can promote the function of Tregs, both features making it a good candidate gene. However, studies suggest that the human risk haplotype may be associated with lower levels of a splice variant encoding a soluble form of CTLA-4, which would serve to block the interaction between the activating co-stimulatory molecule CD28 and its ligands CD80 and CD86 (20). The recently published genome-wide association study suggests that there may be additional RA candidate susceptibility genes likely to influence T-cell function and immune homeostasis, with allelic variation in the regions of the interleukin (IL)-2 receptor alpha (*IL2RA*) and beta (*IL2RB*) chains, as well as the protein tyrosine phosphatase, non-receptor type 2 (*PTPN2*) (3). The fact that these associations have also been documented in other autoimmune diseases, such as type I diabetes, makes them all the more intriguing (3). Together, these data provide compelling evidence to support a role for perturbations in T-cell function in the initiation of RA, and identify potential targets for therapeutic intervention.

Pathways of T-cell activation and differentiation in RA

Over recent years, it has become clear that autoimmune inflammatory arthritis cannot be explained simply in terms of a classical antigen-driven expansion of effector T-cell clones that target synovial joints. Furthermore, pathways of differentiation do not appear to conform to the traditional polarized pathways of T-cell differentiation, as early studies of rodent arthritis models

have implied, although T helper (Th)1 cells expressing interferon (IFN)- γ and tumor necrosis factor (TNF)- α are detected in RA synovial joints in established disease (21, 22). This anomaly may have as much to do with the inflammatory, hypoxic environment in the inflamed synovium, which is known to impair TCR responsiveness (23), as has the accelerated immune senescence that may accompany the 'pre-arthritis' phase of disease (24). Moreover, the precise anatomical site of the early phase of T-cell differentiation may also influence this pathway. A recent analysis of cytokine profiles determined in synovial fluid from patients with very early inflammatory synovitis documented an unexpected Th2 profile, characterized by expression of IL-4, IL-5 and IL-13, while expression profiles in synovial fluid from those patients who subsequently fulfilled the classification criteria for RA lacked these cytokines at detectable levels (25). In established disease, it is generally accepted that synovial T cells express low amounts of IFN- γ and IL-10, as well as TNF- α , while expression of IL-2 and IL-4 is virtually absent (26). The recent finding of an association between RA severity and an IL-4R allelic variant that impairs IL-4R signaling and Th2 differentiation is of particular interest in this regard (27). New data from animal models of autoimmunity have placed increasing importance on IL-17 expressing CD4⁺ T cells, known as Th17 cells, and how they might contribute to disease pathogenesis (28). Thus, collagen-induced arthritis is markedly attenuated in IL-17 deficient mice (29), and spontaneous arthritis in IL-1Ra deficient mice can be completely prevented in the absence of IL-17 (30). More recently, the spontaneous arthritis developing in Balb/c mice carrying a point mutation in ZAP-70 has been shown to be completely dependent on the expansion of differentiating Th17 T cells (31). These observations may go some way to explain the disease-exacerbating effects of IFN- γ R deficiency in arthritis models on the one hand (32, 33), and the protective effects of IL-6 deficiency or inhibition on the other hand (34), given

the reciprocal roles of these cytokines in Th17 differentiation in mice. IL-17 is produced spontaneously in RA synovial cell cultures, and by immunohistochemistry identified in perivascular T-cell rich zones (35). IL-23, which may promote the survival and expansion of Th17 cells, is also detectable in RA synovial joints. The IL-17 receptor is ubiquitously expressed and so may be expected to have pleiotropic effects. Thus, T-cell derived IL-17 (likely to include IL-17A and IL-17F family members) promotes monocyte-dependent IL-1 and TNF- α production (36), induces expression of the osteoclast differentiating factor RANKL (37), and stimulates synovial fibroblasts to express IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), prostaglandin E2 (PGE₂) and matrix metalloproteinases (MMPs) (38). Further studies in RA patients are required to confirm whether T cells expressing IL-17 are crucial effectors of the chronic, persistent phase of synovial inflammatory responses.

Pathways of T-cell effector function

One of the striking characteristics of patients with moderate to severe RA is the presence in the synovial membrane of inflammatory infiltrates that resemble tertiary lymphoid structures, including follicular or germinal center-like reactions (39). These structures likely play a key role in T-B cell cooperation and the local generation of specific autoantibodies. While this pattern of lymphocytic infiltration is found in a subset of patients, it provides robust evidence for ongoing immune reactions at the site of joint inflammation. It is likely that these structures harbor the core cell-to-cell interactions between T cells and B cells essential for immunoglobulin synthesis, as well as those between T cells and macrophages and resident stromal fibroblasts.

There are also a growing number of reports pointing to the importance of T-cell contact-dependent pathways of inflammatory cytokine production by both monocytes and synovial fibroblasts. For example, synovial T cells promote IL-1, TNF, IL-6 and chemokine expression by macrophages in a

cell-contact dependent manner that may involve LFA-1-ICAM-1, CD2-LFA-3, CD40L-CD40 and CD69 engagement (40-42). This effect can be reproduced by stimulating T cells from healthy donors with a cocktail of cytokines including IL-2, IL-6, TNF or IL-15. T cells, through direct cell contact, can also stimulate fibroblasts to produce PGE₂, MMPs and IL-6 (43, 44), an environment that, at least in mice, would favor the reciprocal activation and differentiation of IL-17 producing T cells. Finally, data support a model where, through expression of TNF- α , IL-17 and RANKL, chronically activated T cells promote bone resorption by augmenting pathways of osteoclast differentiation through their direct action on myeloid precursors (45, 46). Chronically activated synovial T cells, therefore, are key initiators and orchestrators of inflammatory pathways in RA joints, and as such remain valid cellular targets for therapy.

This discussion, above all, highlights the persistence and survival advantage of effector T-cell clones, among other activated cell types. Why chronic immune responses fail to resolve in the susceptible host is not understood. One possible explanation is that effector T cells persist through the failure of immunoregulatory pathways.

Are pathways of immune regulation abnormal in RA?

The primary mechanism that leads to tolerance to self-antigens is thymic deletion of self-reactive T cells. However, since some self-reactive T cells physiologically escape this process (and autoreactive CD4⁺ T cells are, therefore, present in the peripheral circulation of healthy individuals where they retain their capacity to initiate autoimmune inflammation), negative selection in the thymus is not enough to prevent sustained activation of self-reactive T cells in the periphery. Thus, regulatory mechanisms in the peripheral immune system are required to protect against both the generation of self-directed immune responses and the consequence thereof – the initiation of autoimmune-mediated pathology (47). One such mechanism of peripheral tolerance involves the

active suppression of T-cell responses by CD4⁺ T cells with potent regulatory capacity. A major subset of these T cells is the CD4⁺CD25⁺ regulatory T cell (Treg) subset (48). Tregs are characterized by low proliferative capacity upon triggering of the TCR with polyclonal or allogeneic stimulation *in vitro*, and by their ability to suppress CD4⁺ and CD8⁺ T-cell immune responses via cell-contact dependent mechanisms.

In recent years, several studies have proposed that the function of Tregs is severely impaired in autoimmune rheumatic disease, suggesting that in fact a breakdown of Treg-mediated peripheral tolerance may have occurred (49). This would contribute directly to the development of disease by allowing the initial autoimmune response to evolve into a sustained inflammatory response. However, despite this being an attractive hypothesis, these data have to be interpreted with some caution. First, in the absence of a specific surface marker, the identification of Tregs currently still relies on the detection of T cells expressing the transcription factor forkhead box p3 (Foxp3) that in mice has been shown to be highly specific for Tregs (50). However, recent evidence has clearly established that human effector T cells transiently upregulate Foxp3 without imposing regulatory functions (51). Thus, functional studies of Foxp3-expressing T cells in patients with a disease characterized by immunological activity, such as inflammatory rheumatic disease, may in fact include a mixture of Tregs and variable frequencies of contaminating, recently activated effector T cells. Second, it also has been established that *in vitro* assays conventionally employed to assess the regulatory capacity of Tregs do not necessarily reflect their *in vivo* function. For example, whereas Tregs are anergic in these *in vitro* assays, they proliferate vigorously *in vivo* (52). Future studies are clearly required to determine the role of Tregs in human rheumatic diseases more precisely, to analyze their contribution to initiation, perpetuation and regulation of the autoimmune inflammation and also to define their potential role as a therapeutic option to downregulate ongoing inflammation by means of cellular therapy.

A second CD4⁺ T-cell population with the potential to counteract T-cell driven inflammation in the periphery is the Th2 cell population. Th2 cells, by means of their signature cytokine IL-4, prevent the generation of both Th1 and Th17 cells, and are able to down-modulate their effector functions (53). As outlined above, Th2 cells and their cytokines are virtually absent in established RA, potentially hinting at a pathogenetically important imbalance of T-cell differentiation associated with disease. In fact, it has been shown that T-cell differentiation is severely altered in patients with early RA (54). Whereas an increased generation of IFN- γ producing Th1 cells from uncommitted CD4⁺ precursor T cells can be detected in *in vitro* assays at the time of disease onset, Th2-cell differentiation is impaired in the majority of patients already at these very early stages of the disease, suggesting that there may exist a profound defect in Th2-cell differentiation in early RA. The data imply that an alteration in the functional ability of T cells to generate immunomodulatory Th2 effectors with the potential to downregulate ongoing Th1-driven inflammation may reflect a breakdown of peripheral tolerance and, thus, may be critically involved in the evolution of sustained rheumatoid inflammation from the outset of the disease-provoking autoimmune response.

Recent data, however, suggest that impaired Th2-cell differentiation is not only critical for the initiation of sustained rheumatoid inflammation, but also impacts on long-term clinical outcome. When patients from the initial T-cell differentiation studies were followed for up to 5 years by repeatedly assessing their disease activity and progression of joint destruction, it became clear that treatment that was conducted at the discretion of an independent rheumatologist induced a meaningful reduction of clinical disease activity in 92% of the patients in whom Th2-cell differentiation could be induced at their first visit, but failed to do so in 64% of the patients with impaired Th2-cell differentiation at disease onset ($\chi^2 = 8.92$, $p < 0.003$). Even more striking was the observation that bone erosions occurred

in 36% of the patients who were able to produce Th2 cells, but in as many as 81% of the patients who were unable to generate Th2 effectors ($\chi^2 = 9.01$, $p < 0.003$) despite aggressive drug treatment (Mueller, Skapenko and Schulze-Koops, unpublished observations). These data demonstrate that reduced Th2-cell generation is associated with persistently aggressive and erosive disease, and may, in fact, suggest that a lack of regulatory immune mechanisms, such as the absence of IL-4 producing Th2 cells, contribute to sustained inflammatory activity, which eventually results in severe tissue pathology.

Has T-cell targeted therapy provided evidence for a role of T cells in disease pathogenesis?

If the major role of T cells in RA suggested from the discussion above is of relevance to established clinical disease, we would predict that T-cell directed therapies should be effective. Is this indeed the case? After all, most successful approaches to RA therapy target the effector phase of the disease – either at or downstream of – the monocyte/macrophage level (methotrexate and TNF blockade being good examples).

While the recent introduction of co-stimulatory blockade with abatacept has re-established the modulation of T-cell co-stimulation as a valid therapeutic approach in RA, this is a particularly relevant question because anti-T cell therapy has not been one of the major success stories of rheumatology until now. Several different antibodies against CD4 have been investigated in the treatment of RA. Direct comparison of the results has been difficult as study design and definitions of clinical response varied greatly. What is evident is that depleting CD4⁺ T cells with antibodies to CD4 does not result in the sustained reduction of systemic disease activity, or in sustained clinical efficacy. For example, keliximab, a chimeric cynomolgus monkey/human chimeric antibody that depletes CD4⁺ T lymphocytes, has been evaluated in clinical trials. American College of Rheumatology (ACR) 20 response rates of 47% and 69% were achieved only at the highest dosages, with placebo

response rates of 30% and 19%, respectively (55). Interestingly, the coating rather than the depletion of CD4⁺ T cells with the antibody to CD4 was found to correlate best with therapeutic responses (55). This prompted attempts to switch from the use of a depleting immunoglobulin (Ig)G1 therapeutic monoclonal antibody (mAb) to the less-depleting IgG4 antibody isotype. One such reagent, clenoliximab was shown to be non-depleting, but to strip CD4 off the surface of T lymphocytes (56). Theoretically, these data suggest modulation of T-lymphocyte function rather than T-cell depletion as the major mode of action. Efficacy results of clenoliximab, however, have not been reported.

A different mAb from CD4, OKTcdr4a, was derived from the murine mAb to CD4, OKT4a, by engrafting its CDR regions onto a human IgG4/k immunoglobulin (57). A multicenter, placebo-controlled, randomized, double-blind study was initiated in patients with RA refractory to standard therapy with disease-modifying antirheumatic drugs (DMARDs) (58). Clinical response, as assessed by modified Paulus criteria, was achieved after the first treatment week in 67% of the patients who received the anti-CD4 mAb, compared with 25% of the placebo-treated group. Six weeks after treatment, the clinical effect had waned. However, 1 week after the second treatment cycle (*e.g.* after 6 weeks), all patients who had received the mAb had a clinical response, compared with 25% of the patients in the placebo group. There was a significant decrease in C-reactive protein (CRP) levels in all patients 1 week after mAb administration. By contrast, no significant changes were observed after placebo treatment. Remarkably, the administration of OKTcdr4a was not associated with a drop in the numbers of total white blood cells, lymphocytes, neutrophils, monocytes or CD4⁺ T cells.

Together, the results of these studies support the notion that coating rather than depletion of CD4⁺ T cells might be effective in ameliorating immunological activity in RA. It is tempting to speculate that the failure of antibodies that deplete CD4⁺ T cells to show clinical

efficacy might relate to the depletion of regulatory CD4⁺ T cells. Of course an alternative approach to blocking T-cell activation is to prevent the interaction between T cells and accessory cells at the outset of TCR engagement. Such a strategy, which would include co-stimulatory blockade, will be discussed in more detail in subsequent contributions to this review series.

In the context of T-cell targeted therapy, consideration must also be given to conventional DMARDs that have long been believed to act through their effects on T-cell function. Cyclosporin A, a calcineurin inhibitor, mainly targets the Ca²⁺/nuclear factor of the activated T cell (NFAT) pathway, an essential component for activating the IL-2 promoter. Full activation and survival of activated T cells are, therefore, attenuated by cyclosporin A therapy, which most likely constitutes a therapeutic approach targeting T lymphocytes.

For RA, there is sufficient evidence to suggest that cyclosporin A is effective. In fact, many of the concerns about the drug have had more to do with its toxicity profile rather than its lack of efficacy. In clinical studies, cyclosporine A was superior to placebo at 10 mg/kg, 5 mg/kg and as low as 2.5 mg/kg (59-61). Cyclosporin A also inhibited radiographic progression (60). Patients with inadequate responses to methotrexate benefited from additional cyclosporin A compared with prolonging methotrexate monotherapy (62). In early RA, cyclosporin A in combination with low-dose methotrexate (7.5 mg/week) demonstrated improved ACR20 responses compared with methotrexate (63). Finally, the combination of cyclosporin A and methotrexate was also superior to methotrexate alone with regard to radiographic progression (64). Although cyclosporine A is likely to modify Ca²⁺/NFAT signaling responses in cell subsets besides T cells, these data have provided a cogent argument for a role of T cells in RA. They do, however, lend further support to the idea that combination therapies that target both lymphocyte and macrophage function may be more effective.

The other DMARD that acts by specifically targeting T cells is leflunomide.

By inhibiting the enzyme dihydro-orotate dehydrogenase, the active metabolite of the drug blocks *de novo* pyrimidine synthesis, which is most prominently involved in the proliferation of activated T lymphocytes. While leflunomide may also have effects on other cells, and monocytes/macrophages in particular (65), its major effect is T-cell related. In this regard, it is of interest that leflunomide preferentially inhibits the activation of pro-inflammatory Th1 cells while promoting the differentiation of potentially anti-inflammatory Th2 cells (66).

Leflunomide has been shown to be superior to placebo in large, randomized clinical trials, and as effective as methotrexate or sulfasalazine both in controlling inflammatory disease activity and in retarding radiographic progression (67-69). When added to methotrexate, leflunomide shows additional benefit compared with placebo (70), but it is not clear whether the addition of leflunomide is indeed more efficacious than switching to leflunomide would be (71).

Several trials have proven leflunomide and cyclosporin A to be effective DMARDs for RA, including efficacy with regard to reducing joint erosions. Their mechanisms of action are likely to be distinct; indeed the combination of the two proved to be more effective than either one alone (72). While CD4-directed therapy has not led to a clinical breakthrough to the same extent as the more recent biologic agents, there appears to be evidence of therapeutic efficacy. For none of these three approaches is it presently clear how they might affect the function and/or number of Tregs. Thus, their apparent efficacy could either be explained by differential modulation of effector versus Treg responses, or by a suppression of Treg function in RA, which, as a consequence of the pronounced inflammatory activity, would render Tregs ineffective and attribute lesser importance to their downmodulation in active disease.

This brief review has sought to crystallize a range of issues regarding T-cell activation in RA; these are summarized in the **Key points box**. It also serves to highlight the need to better understand

the phenomenon of immune homeostasis *in vivo* both at the molecular and cellular levels, and to devise assays to evaluate the dynamics of immune function in patients in response to therapeutic intervention. If this can be achieved in the near future, we should be better placed to examine how new generation T-cell targeted therapies, such as co-stimulatory blockade, exert their beneficial therapeutic effects in the clinic.

Key points box

- The immunogenetics of RA point to a key role for aberrant pathways of T-cell activation in the initiation and/or perpetuation of disease. Besides *HLA-DRB1* and *PTPN22*, susceptibility to disease may be associated with *CTLA-4*, *IL-2RA*, *IL-2RB*, *STAT4*, *PTPN2* and *PADI4*
- Patterns of lymphoid infiltrates, especially follicular structures with or without germinal centers, provide strong evidence of ongoing immune reactions in established RA
- Spontaneous arthritis in rodents (*e.g.*, K/BxN, *IL-1Ra*^{-/-}, gp130 mutant and SKG mice) have been shown to be T-cell dependent models of disease
- Activation and differentiation of T-helper (Th) cells in RA over time may lead to the accumulation of Th1 as well as IL-17 producing T cells, in association with the impaired differentiation of Th2 cells (at least in established disease)
- More robust markers for CD4⁺ CD25^{hi} regulatory T cells (Tregs) are required before it can be conclusively established whether or not Tregs are, in relative terms, impaired in number and/or function in RA
- Therapeutic modulation of T-cell function, as opposed to profound immunosuppression or immunodepletion, has been associated with better disease outcomes in clinical trials. Co-stimulatory blockade

provides one such strategy for modifying T-cell function

- Defining the distinct effects of co-stimulatory blockade with abatacept on T-cell subsets should provide key insights into understanding how to restore immune homeostasis in patients with RA

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