Review
T cells in rheumatoid arthritis

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Abstract

Over the past decade and a half, advances in our understanding of the pathogenesis of immune-mediated diseases such as rheumatoid arthritis (RA) have translated directly into benefit for patients. Much of this benefit has arisen through the introduction of targeted biological therapies. At the same time, technological advances have made it possible to define, at the cellular and molecular levels, the key pathways that influence the initiation and persistence of chronic inflammatory autoimmune reactions. As our understanding grows, it is likely that this knowledge will be translated into a second generation of biological therapies that are tailor-made for the patient. This review summarizes current perspectives on RA disease pathogenesis, with particular emphasis on what RA T cells look like, what they are likely to see, and how they contribute to persistence of the chronic inflammatory response.

Introduction

What is rheumatoid arthritis (RA)? Traditional teaching would have us believe that RA is one of a cluster of autoimmune diseases, to be included in the same category as type I diabetes, autoimmune thyroiditis, and celiac disease. There are some important distinctions, however. The term 'RA', when used in the clinical context, probably represents a spectrum of distinct clinical entities (for review [1]). This spectrum manifests not only at the clinical level - presenting as a range of specific clinical phenotypes - but also at the cellular, molecular, and genetic levels. This is best illustrated by the variations observed in patterns of inflammatory infiltrates in histological sections of RA synovial tissue, the patterns of disease expression defined by serological profiles, and the emerging subsets of patients stratified according to genotype [1]. Such an approach to disease stratification means that we are now in a position to redefine subtypes of disease based on objective laboratory parameters, independent of clinical manifestations. By defining disease according to perturbations in cellular and molecular phenotypes and genotypes, we should be better placed to predict disease

outcome and to select the most appropriate therapy for our patients.

Diseases such as RA, but also inflammatory bowel disease and psoriasis, are better characterized as a group of prototypic chronic inflammatory diseases. The most convincing evidence for such a notion comes directly from the clinic, in particular the striking clinical responses to anticytokine biological therapy [2]. Finally, RA is somewhat distinct from other organ-specific autoimmune diseases in the sense that, rather than destroying the target tissue, the inflammatory process stimulates and induces proliferation of synovial stromal tissues, especially in the early phase of disease [3]. Thus, RA is perhaps better described as the prototype chronic inflammatory disease, with features of autoimmunity.

These distinctions should be taken into account when considering pathways of disease pathogenesis, especially immune-mediated pathways. This review highlights current concepts of RA pathogenesis, with a specific focus on the immunobiology of the RA T cell.

What should an RA T cell look like?

If the immunobiology of RA plays by the rules governed by traditional paradigms of autoimmunity, then we would predict that RA synovial T cells infiltrating affected synovial joints would express a cell surface phenotype that is compatible with prior antigen experience, is indicative of extensive proliferative activity, is suggestive of clonal expansions of subsets of antigen-specific T cells, is consistent with enhanced migratory competence, and favors survival *in situ*. Current paradigms of adaptive immunity would also predict differentiation of T-helper cell subsets along a distinct effector T-cell lineage, whereas histological analysis of synovial tissue explants might reveal the presence of T cells as components of diffuse inflammatory infiltrates, with a

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APC = antigen-presenting cell; CCL = CC chemokine ligand; CCP = cyclic citrullinated peptide; CCR = CC chemokine receptor; CXCL = CXC chemokine ligand; CXCR = CXC chemokine receptor; GC = germinal center; HLA = human leukocyte antigen; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; MIC = MHC class I chain related; NK = natural killer; PAD = peptidyl-arginyl deiminase; RA = rheumatoid arthritis; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; Th = T-helper; TNF = tumor necrosis factor; Treg = regulatory T cell.

prevalence of CD4^{+} over CD8^{+} T cells, in close association with antigen-presenting cells (APCs). If RA were to fulfil the criteria for a *bona fide* organ-specific autoimmune disease, then elaboration of T cells derived from synovial tissue explants should identify T cells that are activated and maintained *in vivo* by tissue-specific autoantigens derived from synovium, matrix, bone, or a combination of the three. Finally, the persistence of the chronic inflammatory process should predict that there might exist a relative paucity of regulatory T-cell subsets in terms of either cell number or function. How do these predictions match up with what we have learnt from laboratory studies?

What do RA T cells really look like?

The most convincing evidence for the involvement of T cells in chronic immune activation comes from the analysis of RA synovial biopsies [4]. In keeping with the spectrum of clinical entities that we classify as RA, distinct patterns of synovitis have been identified, suggesting topographical organization of lymphoid microarchitecture at a cellular level [4-6]. We now know that this process is directed by expression of cytokines and chemokines, such as lymphotoxin-$\alpha1\beta2$ and B-lymphocyte chemokine/CXC chemokine ligand (CXCL)13 [7]. Patterns of synovitis include diffuse inflammatory infiltrates of T cells, B cells, macrophages, and dendritic cells (about 50%); clusters of lymphoid follicular aggregates comprising T cells, B cells, and dendritic cells (about 20%); structures with germinal center (GC)-like reactions (about 25%); and, rarely, granulomatous lesions (<5%; which have features similar to those of rheumatoid nodules). Of most interest are those tissues comprising secondary follicles and GCs, because these are characterized by the presence of follicular dendritic cells, which are critical components in follicle formation in the synovium and for perpetuation of adaptive immunity and autoimmunity [6,7]. Thus, the synovial microenvironment and spatial relationships between cell subsets appear optimal for supporting antigen requisition, storage, processing, and presentation by APCs to T cells.

Data suggest that patterns of inflammatory infiltrate are relatively stable over time and common to tissues from different joints from the same patient, including unaffected joints, suggesting that they may reflect true disease variants [6,7]. Furthermore, recent support for this notion comes from a comparison of RA knee joint synovial tissue from anti-cyclic citrullinated peptide (CCP) positive and negative patients [8]. That study demonstrated higher numbers of infiltrating lymphocytes (CD3^{+}, CD8^{+}, CD45RO^{+}, and CXCL12^{+}) associated with ectopic GC reactions, less extensive fibrosis, and a thinner synovial lining layer in the anti-CCP^{+} subset [8]. It is noteworthy that the direct contribution of CD8^{+} T cells to GC^{+} follicular dendritic cell networks has previously been demonstrated [9,10]. The anti-CCP^{+} associated synovial phenotype is also associated with more radiographic damage [8]. Emerging data have uncovered a gene expression profile for GC^{+} synovial tissue (CD21L^{+}), which complements

immunohistochemical analysis, characterized by elevated expression of CXCL13, CXCL12, CC chemokine ligand (CCL)19, CCL21, CXC chemokine receptor (CXCR)4, CXCR5 and CC chemokine receptor (CCR)7 [11]. In this study, Gene Ontology pathway analysis suggested that many pathways active in T cells, including JAK/STAT (Janus kinase/signal transducer and activator of transcription), T-cell receptor (TCR), IL-2R, IL-7R, and co-stimulatory signalling pathways are important features that may promote the cellular interactions that are required to support the organization of these tertiary lymphoid structures.

What is the phenotype of RA T cells at the cellular level? There are a number of distinguishing features. First, synovial T cells express an extensive array of cell surface antigens that reflect prior antigen experience (Figure 1). Principle among these are markers of effector memory cells, including the expression of specific chemokine receptors and integrins. The profile of chemokine receptors suggests that there is an element of selective trafficking of T-cell subsets in response to local production of chemoattractants by synovial stroma.

Aging is an important risk factor for RA. How does aging manifest itself at the cellular level? The immune system of patients with RA, including those developing the disease at a relatively early age, exhibit features of premature aging, as determined by accelerated erosion of telomeres, which are repetitive DNA sequences that cap the ends of chromosomes that are lost with cell replication [12]; loss of telomere length provides an estimate of the number of completed cell cycles. In RA this process of telomere erosion is found in both the naïve and memory T-cell compartments, which cannot therefore be accounted for exclusively by a specific antigen-driven response. The data suggest an ongoing process of replicative stress that occurs very early or that may even predate disease onset. It could arise in part through reduced generation of new thymic emigrants and/or homeostatic expansion of the peripheral naïve T-cell repertoire to environmental stimuli (cytokines or cognate antigen), based on enumeration of TCR excision circles [12,13]. Nonetheless, the aging phenotype is not confined to the T-cell compartment, because telomere shortening has been documented in hematopoietic stem cells, which may explain the features of senescence in both granulocyte and B-cell compartments. Of particular interest was the finding of an association between human leukocyte antigen (HLA)-DR4 status and premature telomere erosion in healthy donors as well as in patients with RA, in spite of high telomerase repair activity [14]. These data provide interesting, if still poorly understood, insights into the genetic determinants of immune senescence in RA. They also define a molecular basis for impaired T-cell responsiveness characteristic of RA, given the close relationship between telomere erosion and growth arrest.

As mentioned above, the synovial microenvironment provides an ideal setting in which to support adaptive immune

Figure 1
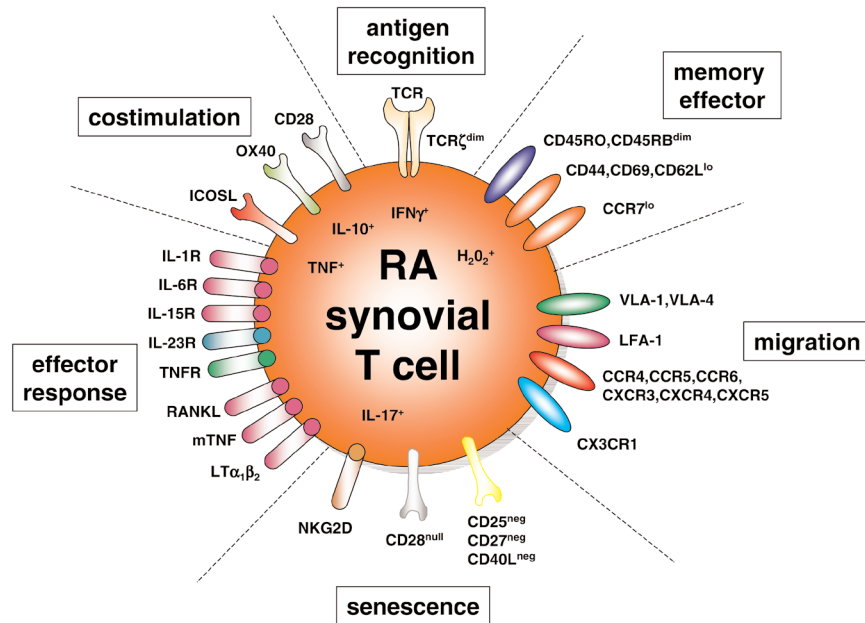
The phenotype of RA synovial T cells. The schematic depicts examples of cell surface antigens and receptors that confer distinct phenotypes according to antigen experience, differentiation, and acquisition of memory, migratory competence, terminal differentiation and immune senescence, and effector function. CCR, CC chemokine receptor; CX3CR, CX3C chemokine receptor; CXCR, CXC chemokine receptor; LFA, lymphocyte function-associated antigen; LT, lymphotoxin; mTNF, membrane-associated tumor necrosis factor; NK, natural killer; RA, rheumatoid arthritis; RANKL, receptor activator for nuclear factor-κB ligand; TCR, T-cell receptor; TNFR, tumor necrosis factor receptor; VLA, very late antigen.

responses. These cellular interactions, combined with an abundance of inflammatory cytokines and reactive oxygen intermediates in a hypoxic setting, are probably responsible for imposing distinct characteristics on synovial T cells. Specific characteristics of such cells include an intrinsic resistance to apoptosis *in vivo* [15]; loss of expression of CD25, CD28, CD27, CD40L, and the invariant TCR subunit TCR-ζ [16-18]; enhanced expression of inflammatory cytokines such as IFN-γ and tumor necrosis factor (TNF)-α [19]; and expression of CCR4, CCR5, CXCR3, and CXCR5 [20]. Expansion of CD4+CD28^{null} T cells is of interest because it has been found to correlate with systemic co-morbidities associated with severe RA, such as vasculitis and acute coronary syndrome [21,22]. Although this terminally differentiated CD28^{null} subset may become relatively independent of co-stimulation through CD80/CD86 engagement, co-stimulation through other pathways such as OX40 may compensate [23]. Indeed, the acquisition of a distinct gene expression program resembling that of natural killer (NK) cells, including expression of the activating NK cell receptors NKG2D and KIR2DS2, and acquisition of DAP10 and DAP12 adaptor proteins for signalling, may explain how these cells are such potent producers of IFN-γ [24,25]. Synovial T cells can receive signals *in situ*, because the counter-ligands for NKG2D, major histocompatibility complex (MHC) class I chain related (MIC)A and MICB, are expressed on synovial fibroblasts [26].

In summary, an RA synovial T cell is ideally equipped to survive *in situ* through interactions with APCs, macrophages, B cells, and stromal elements. However, RA T cells are likely to depend for their effector function on a more promiscuous range of stimuli, besides cognate antigen presented by MHC class II molecules. Indeed, aberrant or excessive pathways of costimulation may permit the T cell to respond to low-affinity self peptides in the periphery, in spite of both inherited and acquired defects in TCR signaling.

What do RA T cells see?

Classical paradigms of autoimmunity state that tissue specificity is determined largely by recognition of tissue-specific self antigens by autoreactive T and B cells. In the past there was much enthusiasm for the idea that RA was driven by joint-specific antigens, for instance type II collagen, the cartilage protein HCgp-39, and proteoglycans such as aggrecan, especially because these antigens were inducers of autoimmune arthritis in appropriate strains of rodent [27-29]. At the same time, antigens such as heat shock proteins and BiP (immunoglobulin binding protein) have also been suggested to be autoantigenic targets [30,31]. These are ubiquitous proteins expressed at high levels, which are certainly not tissue specific. It should follow from this paradigm that in RA it should be possible to detect expansions of specific clones that express distinct *TCRB* gene recombinations that are indicative of antigen drive.

The aberrations in the TCR repertoire are perhaps best understood within the context of aging. Thus, as thymic function declines with age, homeostatic proliferation of naïve peripheral T cells is required to 'fill the space' - that is, to undertake the task of T-cell generation. As a consequence of aging, which is accelerated in RA [12], large clonal expansions of T cells are observed [32]. These expansions are global, affecting both CD4+ and CD8+ subsets, as well as naïve and memory T-cell populations. Because the process of homeostatic proliferation is dependent on the recognition by TCRs of complexes of MHC and self peptide, it will inevitably lead to the selection of higher affinity autoreactive TCRs with the capacity to compensate for the functional, proliferative defects of senescent T cells [33]. Accordingly, there is profound repertoire contraction associated with a lack of diversity. Indeed, by the age of 40 to 50 years, patients with RA have already lost 90% of their available TCR repertoires, whereas the naïve repertoire has expanded 10-fold to fill the space [16,34-36].

Whereas the expression of distinct HLA-DR molecules can play an important role in repertoire development through loss of diversity and contraction of T-cell repertoires in both CD4+ and CD8+ T-cell compartments, as discussed above, there are also data pointing to antigen-independent pathways of activation. Thus, both naïve and memory T cells may proliferate and differentiate in response to the inflammatory milieu into effector T-cell populations with specific cell surface phenotypes and functional properties, including cytokine expression, cell contact dependent activation of monocytes, and B-cell help [37]. This pathway can be reproduced in vitro using IL-2, IL-6, and TNF-α, and would account for the dilution of TCR excision circles in the CD45RA+ naïve compartment in patients with RA [13].

What MHC/peptide complexes might these T cells see? In RA we know that T cells see the 'shared epitope', a stretch of DRβ chain α-helix sequence exposed to the TCR encoded by RA disease associated HLA-DRB1 alleles [38]. We also know from recent genetic and epidemiological studies that carrying shared epitope positive alleles is a risk factor not so much for RA but for immunity to citrullinated proteins [39], arising through post-translational conversion of arginine residues to citrulline, which is catalyzed by a family of enzymes known as peptidyl-arginyl deiminases (PADs) [40]. This manifests as the presence of autoantibodies to citrullinated protein antigens [41]. Because these are IgG autoantibodies, it can be inferred that these responses come about as a consequence of T-cell recognition of related T-cell epitopes and T-cell help for B-cell antibody production. The precise T-cell determinants are still being defined, but there are studies that suggest that T cells may recognize citrullinated peptide epitopes. For example, studies in HLA-DR4 transgenic mice demonstrate a requirement for deimination to generate immunogenic peptides from a range of candidate antigens, through the conversion of an epitope with arginine at P4 that binds poorly to HLA-DR4, to an epitope with citrulline with more favorable binding kinetics [42]. These important observations provide a molecular basis for the association between HLA-DRB1 and anti-citrulline immunity.

The anti-CCP2 test is a robust diagnostic screening tool for anti-citrulline immunity that is now established in clinical practice, but the CCP2 antigen is not an autoantigen per se. Emerging data have defined reproducible autoantibody responses to citrullinated fibrin, vimentin, α-enolase, histones, and collagen II [43]. We can speculate that T cells from patients with RA might therefore see at least a subset of these antigens. Consistent with this notion is the observation that autoantibody responses to these specific antigens are also found in patients who carry 'at risk' HLA-DRB1 alleles [39]. For example, anti-calpastatin immunity is associated with HLA-DRB1*0404 [44], whereas anti-citrullinated α-enolase antibody responses are associated with HLA-DRB1*0401 and *0404 (Venables P, Lundberg K, personal communication). Finally, the generation of a specific monoclonal antibody that recognizes the immunodominant epitope of HCgp-39 in a complex bound to HLA-DR4 has made it possible to demonstrate in situ the presence of MHC II-peptide complexes in the inflamed RA synovial joint [45]. This observation would be entirely in keeping with previous studies demonstrating through autologous mixed lymphocyte reactions the capacity for synovial APCs to present endogenous antigenic peptides to T cells [46].

Multiple T-cell effector pathways contribute to the chronic inflammatory process

By convention, it is acknowledged that cytokines secreted by lineage specific T-helper (Th) cells provide the 'flavor' of the effector phase of cell-mediated immunity. In RA many studies have provided evidence for a Th1 bias, with the cytokine profile expressed by synovial Th effector cells derived from patients with established disease dominated by expression of IFN-γ and TNF, but also IL-10 (for review [47]). Expression of IL-2, IL-4, IL-5, and IL-13 is low or absent. This contrasts with the profile of cytokines expressed by synovial T cells and stromal cells very early in disease, which is dominated by IL-2, IL-4, IL-13, IL-17, IL-15, basic fibroblast growth factor, and epidermal growth factor [48]. The mechanisms underlying this transition are unclear, although reported data have led to the proposal that there is an intrinsic defect in Th2 differentiation that is explained in part by allelic variants of the IL-4R, which attenuate activation of STAT6 and induction of GATA-binding protein 3 [49], both of which are requisites for commitment to Th2 cell lineage differentiation.

The recent excitement following the identification of a third Th cell subset, characterized by the expression of IL-17A and IL-17F (hence termed Th17), as well as IL-22, IL-21 and TNF, has raised the possibility that Th17 cells may be an important effector T-cell subset in diseases such as RA, multiple sclerosis, and inflammatory bowel disease [50]. Much of the

evidence is derived from rodent models. Certainly, expression of IL-17, IL-17RA, and IL-17RC has been described in RA synovial tissue and juxta-articular bone by immunohisto-chemistry [51,52], and IL-17 protein production has been detected in synovial fluid and culture supernatants of synovial mononuclear cell explants [48,53]. Indeed, the cytokine milieu in the joint, with IL-1β, IL-6, and IL-23 in particular, would certainly support Th17 differentiation. What is unclear is the precise phenotype of fully differentiated Th17 cells, because - unlike murine Th17 cells - IL-17+IFN-γ+ cells occur in humans. Nonetheless, IL-17 is a strong candidate effector cytokine that probably contributes to the pathogenic features of established disease, such as the following [54]: induction of TNF, IL-1, IL-6, and CCL20; synergistic actions with TNF and IL-1; and - through stimulation of stromal cells, macrophages, osteoblasts and chondrocytes - promotion of cartilage and bone destruction. Recent studies have demonstrated low frequencies of CD4+CD45RO+ T cells expressing IL-17 and TNF-α, when compared with corresponding peripheral blood T cells, with their Th1 counterparts being more abundant [55]. More data are therefore required to establish the contribution that this subset makes to early and established phases of the disease.

The spatial context of chronically activated T cells within the inflamed synovium is important. This has led investigators to explore the consequences of cell-to-cell interactions, and to uncover robust induction of monocyte-derived inflammatory cytokines, chemokines, and matrix metalloproteinases upon contact with activated T cells [56-58]. The receptor-ligand pairs involved in these interactions are likely to be numerous, but integrin and membrane TNF-dependent signaling appear to have been demonstrated consistently [59], and the reciprocal interactions between NKG2D and its ligands MICA and MICB may well contribute to the persistence of autoreactive T cells within the joint [26], as suggested above. Whereas the survival of T cells may also be supported through stromal cell derived type I IFNs [15], reciprocal inter-actions are also important because T cells downregulate collagen synthesis by fibroblasts, and are potent inducers of fibroblast-derived IL-6, prostaglandin E_2, chemokines such as CXCL12, CXCL16 and CCL20, and matrix metalloproteinases [60-62]. Joint and bone matrix destruction is also induced in part through RANKL (receptor activator for nuclear factor-κB ligand)-positive T cells that promote bone erosion through activation and differentiation of osteoclast precursors [63]. Examples of these cellular interactions are shown in Figure 2.

Why do effector T-cell responses persist?

A major challenge to our understanding of the pathogenesis of immune-mediated diseases is to elucidate why pathways of peripheral tolerance might fail. To this end, efforts have been invested in evaluating the number and function of regulatory cell subsets, in order to test the hypothesis that at sites of synovial inflammation there may be defects in path-ways of peripheral tolerance. Studies have been thwarted to

Figure 2
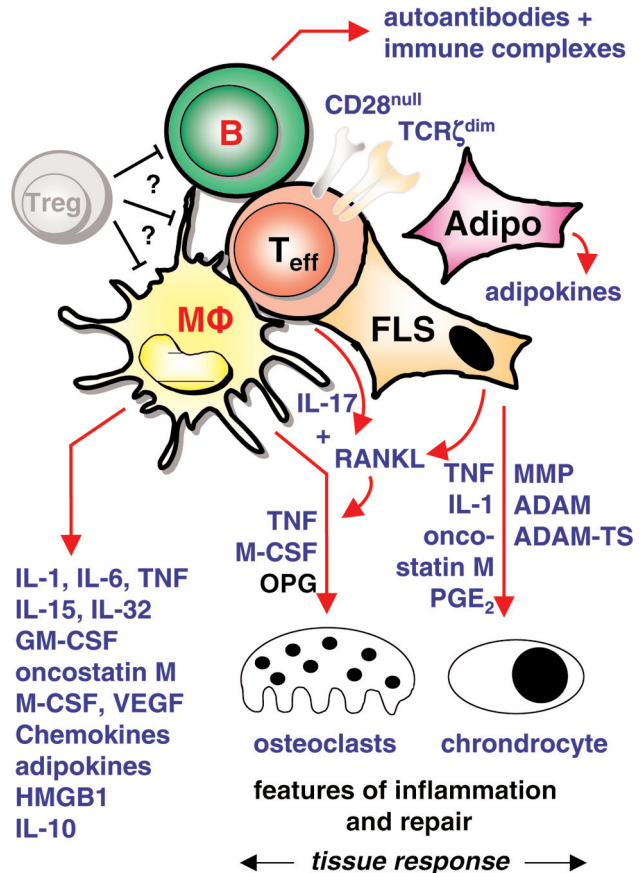
Cell contact-dependent effector function. Spatial and temporal organization of synovial inflammatory infiltrates favor cell contact-dependent effector responses between T cells, B cells, macrophages, and resident stromal cells and adipocytes. The extent to which Tregs influence these effector pathways is presently unclear. ADAM, a disintegrin and metalloprotease; ADAM TS, ADAM with ThromboSpondin-like motifs; FLS, fibroblast-like synoviocytes; GM-CSF, granulocyte macrophage colony-stimulating factor; HMGB1, high-mobility group box-1 proteins; IL, interleukin; M-CSF, macrophage colony-stimulating factor; MΦ, macrophage; MMP, matrix metalloproteinase; PG, prostaglandin; RANKL, receptor activator for nuclear factor-κB ligand; TCR, T-cell receptor; T_{eff}, effector T cell; TNF, tumor necrosis factor; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

an extent because until recently the enumeration of subsets of naturally occurring regulatory T cells was based purely on CD4 and nonselective high level expression of the T-cell activation antigen CD25 (hereafter referred to as regulatory T cells [Tregs]). Even the inclusion of Foxp3 into the phenotyping armamentarium has not solved the problem, because this master transcription factor, which plays a central role in the function of Tregs [64], is also induced upon TCR engagement of CD4+CD25- T cells [65]. Furthermore, there remains controversy as to whether there are genuine defects in the numbers of circulating Tregs in RA. This may

Figure 3
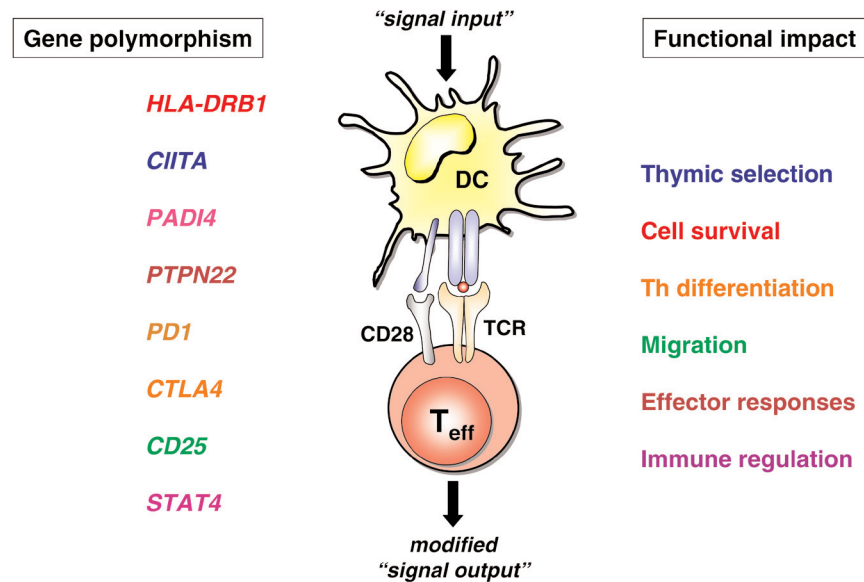
Pathway biology: the impact of RA-associated allelic variants. Multiple single nucleotide polymorphisms may contribute to the disease-prone state through subtle modifications in antigen presentation ('single input') and T-cell antigen receptor responsiveness ('signal output'). It is proposed that these variants may influence multiple pathways of T-cell activation, differentiation, and effector function. DC, dendritic cell; RA, rheumatoid arthritis; TCR, T-cell receptor; T_{eff}, effector T cell; Th, T-helper cell.

have as much to do with their selective migration and accumulation in synovial joints compared with peripheral blood [66], given that Tregs are known to express CXCR4, CCR4 and CCR8, and a phenotype commensurate with fully differentiated CD45RO+HLA-DR+CD69+CD62L- T cells, besides the Treg markers CTLA4 (cytotoxic T-lymphocyte antigen 4) and GITR (glucocorticoid-induced TNF receptor) [67]. Whether the inflammatory milieu influences their survival and function remains a topic of great debate. This is because, despite expression of transforming growth factor-β, which might promote the expression and function of Treg subsets, inflammatory cytokines such as IL-7, IL-15, and TNF have been shown to suppress Treg activity [68]. One study reported that high levels of TNF downregulate Foxp3 expression [69], whereas a second proposed that TNF may attenuate the generation of adaptive or inducible Tregs *in vitro* and *in vivo* [70]. A third study proposed that, cell for cell, there did not appear to be a consistent intrinsic defect of RA synovial Treg suppressor function, but rather synovial effector T cells might acquire resistance to regulation by Tregs [71]. This concept is in keeping with recent reports of synovial T cells being resistant to the immunosuppressive effects of indoleamine 2,3-dioxygenase [72]. How this state of refractoriness comes about is a key question and requires further investigation.

A recent study of Tregs in the KRN serum transfer model of autoimmune arthritis demonstrated that more than 40% of CD4+ T cells were CD25+Foxp3+ in the synovial fluid of either arthritic KRN mice or of C57BL/6 mice 14 days after injection

with arthritogenic serum, indicating preferential recruitment of Tregs to inflamed joints, rather than local expansion [73]. When the scurfy loss-of-function Foxp3 mutant was crossed onto the KRN background, onset of arthritis was faster and more aggressive. Unexpectedly, the spectrum of affected joints changed to include joints that were normally clinically unaffected, including the hip, shoulder, and temporo-mandibular joint. The authors of this study raise the intriguing possibility that Tregs actively suppress lymphoid and nonlymphoid effector cells, actively protecting larger, proximal joints and rendering them refractory to arthritis. Thus, pathways of peripheral tolerance appear to be operational in chronic inflammatory disease, but are clearly insufficient for resolution of the autoimmune response.

Inherited factors and T-cell-mediated immunity in RA

What has the immunogenetics of RA taught us about disease pathogenesis? We have acknowledged the contribution of the HLA-DRB1 locus for decades, but we have only relatively recently learnt to appreciate that RA-associated HLA-DR molecules are not disease susceptibility alleles, but rather are risk factors for immunity to citrullinated antigens and for accelerated telomere erosion [14,39]. Using a candidate gene approach, investigators have identified other disease-associated single nucleotide polymorphisms that would be expected to influence T-cell activation, either by modifying expression of HLA-DR (*MHC2TA*) [74], predisposing the host to increased levels of the citrullinating PAD enzymes

(*PADI4*) [75], or by perturbing intracellular signals, which serve to regulate TCR signal transduction (*CTLA4* and *PD1*) or its downstream consequences (*STAT4*) [76-78]. RA-associated allelic variants that would have an impact on pathways of T-cell activation are shown in Figure 3.

Perhaps the allelic variant that has received the most attention is the 1858T mutation of the *PTPN22* gene [79], which encodes a hematopoietic protein tyrosine phosphatase called Lyp, whose homolog in the mouse (called PEP) is a potent negative regulator of TCR signaling. Lyp is thought to switch off TCR signaling by dephosphorylating tyrosine residues in a range of substrates, including ZAP-70, CD3ε, TCR-ζ, Vav, and src kinases [80]. Targeting of the src kinase Lck arises through direct protein-protein associations between a complex of Lyp and the tyrosine kinase Csk (through the P1 domain of Lyp and the SH3 domain of the tyrosine kinase Csk) and Lck. Although the Lyp R620W mutation is thought to reduce this association [79], the disease-associated variant is in fact a gain-of-function phosphatase mutant that further attenuates TCR signaling [81]. Defining how this contributes to autoimmunity is crucial because this same mutant has been found to be associated with a wide range of autoimmune syndromes, including systemic lupus erythematosus, autoimmune thyroiditis, Grave's disease, and type I diabetes, suggesting that it imparts a fundamental autoimmune diathesis [82].

One possibility is that the attenuation of TCR signaling by the Lyp R620W mutant may lead to a selection shift in thymic development, favoring the generation in the periphery of a repertoire of high-avidity autoreactive T cells. This hypothesis would certainly be in keeping with observations made in the SKG mouse, a model of spontaneous autoimmune inflammatory arthritis that arises through a point mutation in the protein tyrosine kinase ZAP-70 [83]. In this model there is clear evidence of a thymic selection shift in favor of autoreactive T cells, which - in spite of impaired TCR signals - proliferate vigorously *in vivo* in response to self antigen/MHC complexes and differentiate into Th17 effector T cells [84]. Impaired function of both human Lyp R620W and mouse SKG regulatory T cells has also been proposed to contribute to the autoimmune diathesis, through similar mechanisms relating to TCR signaling defects. Data to date are sparse, but one recent study [85] confirmed that *PTPN22* 1858T carriers make less IL-2 and IL-10 in response to TCR stimulation, whereas TNF-α and IFN-γ are spared. Interestingly, the number of memory CD4$^+$ T cells is also expanded, which might arise as a direct consequence of enhanced self reactivity. It remains to be determined whether this mutation imposes a distinct T-cell phenotype, or whether the function of B cells, NK cells, and/or dendritic cells is also affected.

Conclusion

RA is perhaps best described as a prototype chronic inflammatory disease with features of autoimmunity. The target of autoreactivity remains unclear, but emerging data suggest that in RA there are immune reactions to inflammation arising as a consequence of tissue damage and cell death, a process that is clearly dependent on aging and immune senescence. There exist both acquired and inherited defects in antigen receptor signaling that probably have impacts on both central thymic and peripheral pathways of tolerance. In the inflamed synovial joint, persistence is probably mediated more through over-exuberant co-stimulatory pathways in T cells than through conventional pathways of antigen-specific activation. Clearly, this has implications for therapy, and may explain why the more selective approaches for targeting adaptive immunity have been more successful than those based on more conventional immunosuppression. Because we now have the tools to define disease subtypes at the tissue, cellular, and molecular levels, patient-tailored therapy could soon be a reality.

Key messages

- Our understanding of the phenotype and function of RA peripheral blood and synovial T cells points to a key role for inflammation and aging in the pathogenic process.

- Extensive phenotypic analysis has defined a number of cell surface molecules that can be exploited for therapeutic purposes, including co-stimulatory molecules.

- The antigenic determinants recognized by autoreactive T cells remain poorly defined in RA. However, a growing appreciation of the specificity of serum autoantibodies is likely to underpin attempts to define the relevant pathogenic antigen reactive T cell clones in the near future.

- T-cell effector pathways in RA are complex. The precise role and contribution of Th1 and Th17 T cells, and how they contribute to the chronicity of the inflammatory process, remain to be determined.

- More detailed phenotypic analysis and characterisation of regulatory T cell subsets are required in RA to determine whether any functional deficiencies reside in the Treg or responding T effector cell populations (or both).

- Advances in defining genetic susceptibility to RA suggest that aberrant pathways of T-cell activation, differentiation, and persistence are key. Apart from *HLA-DRB1*, disease-associated variants include *PTPN22*, *CTLA4*, *IL2RA*, *IL2RB*, and *STAT4*.

Competing interests

Acknowledgements

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