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Targeting the programmed cell death-1 pathway in rheumatoid arthritis

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Abstract

Since the introduction of TNF- α inhibitors and other biologic agents, the clinical outcome for many treated rheumatoid arthritis patients has significantly improved. However, there are still a substantial proportion of patients that are intolerant, or have inadequate responses, with current agents that have become the standards of care. While the majority of these agents are designed to affect the inflammatory features of the disease, there are also agents in the clinic that instead target lymphocyte subsets (e.g., rituximab) or interfere with lymphocyte co-receptor signaling pathways (e.g., abatacept). Due in part to their ability to orchestrate downstream inflammatory responses that lead to joint damage and disease progression, pathogenic expansions of T and B lymphocytes are appreciated to play key roles in the pathogenesis of rheumatoid arthritis. New insights into immune regulation have suggested novel approaches for the pharmacotherapeutic targeting of lymphocytes. In this review, we discuss deepening insights into human genetics and our understanding of the interface with rheumatoid arthritis pathogenesis providing a strong rationale for exploiting the co-inhibitory receptor programmed cell death-1 signaling pathway as a better approach for the treatment of this chronic, often progressive destructive joint disease.

Keywords

rheumatoid arthritis; programmed cell death-1; lymphocytes; signaling; autoimmunity

Introduction

Rheumatoid arthritis (RA) is a chronic debilitating disease that is also associated with early mortality. As one of the most common autoimmune disorders, it is estimated to affect ~1% of adult populations in the developed world¹. Inflammation in the joints leads to synovocyte proliferation and hyperplasia, with infiltration by lymphoid and myeloid cells, which form a pannus responsible for erosion of the bone, cartilage and periarticular structures. Due to progressive joint injury, patients suffer pain, impaired mobility and disability, and if

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untreated the inflammatory process is linked to accelerated atherosclerosis and decreased life expectancy².

Current standard of care therapy includes small synthetic molecules termed disease modifying anti-rheumatic drugs (DMARDs) as well as the newer classes of drugs collectively termed 'biologic therapy', which target key soluble cytokines (TNF- α , IL-1, IL-6), immune cell receptors (CTLA-4, CD20), and more recently developed, inhibitors of downstream kinase isoforms of the Janus kinase (JAK) family. When treatment is effective, any of these agents with very different mechanisms of action can trigger a sequence of events that lead to the resolution of the cellular infiltrates that cause the synovitis in RA.

Since the advent of biologic therapy in the late 1990's, many RA patients have fared better. Clinical response rates have increased and clinical outcomes have improved. Clinical data³⁻⁷ suggest that approximately 60–70% of patients that receive anti-TNF- α (tumor necrosis factor) therapy achieve an ACR20 (American College of Rheumatology 20 score; more than or equal to 20% improvement from baseline) and up to 30% achieve ACR70 (more than or equal to 70% improvement) response compared to baseline. While these advances are encouraging, at best the disease is suppressed and not cured as flares are expected if therapy is withdrawn. Moreover, substantial proportions of treated patients have inadequate responses or develop unacceptable toxicities or immunosuppression leading to serious infections. The primary endpoints for pivotal trials generally focus on relieving the signs and symptoms of disease and reductions in the markers of innate immune activation. Recent results may also indicate that although ranges of mechanisms of action have been investigated, we nonetheless may have reached a ceiling with current modalities. To further improve research, we need to reconsider that seropositive RA is triggered and subsequently driven by the adaptive arm of the immune system, namely auto reactive B and T cells. Our research efforts should therefore have a renewed focus on attaining a better understanding of the underlying the biologic pathways and immunoregulatory events that control these cellular elements.

T cells play a central role in the pathogenesis of rheumatoid arthritis

While many aspects of the etiopathogenesis of RA remain poorly understood, it is likely that the earliest triggers involve a combination of specific inherited genetic variants (e.g., HLA-DR4), environmental factors (e.g., smoking) and perhaps transmissible agents (e.g., EBV infection and the intestinal microbiome). For more than 70 years our understanding of the layered mechanisms of disease have deepened, and it is now accepted that this disease reflects a loss of immune tolerance to a specific type of modified self-antigen, (e.g., citrullinated self-proteins), which become processed then presented in the context of MHC molecules to effector cells (e.g., CD4⁺) that further recruit other cells of the adaptive immune system (e.g. CD8⁺ cells and B cells) and are intertwined in a self-perpetuating activation process. While T cells clearly play major central roles, all earlier approaches to specifically target T cells proved inadequate or conveyed unacceptable risk of serious infection.

During the course of pathogenesis, the arthritis is a consequence of the infiltration of the hyperplastic synovial lining by a range of immune cells, which commonly develop into an invasive hyperplastic inflammatory tissue, with local release of angiogenic factors. These pathologic tissues take on many of the features of malignant transformation, with alterations in cell cycle, programmed cell death as well as apoptotic cell clearance. The affected joints of a RA patients also often contain oligoclonal expansions of CD4⁺ T cells⁸, which can also be detected amongst the recirculating lymphocytes in the bloodstream⁹ where they can potentially spread to other joints. In addition, these T cell expansions may also reflect abnormalities of the *p53* tumor suppressor gene that can become dysregulated in RA synovial tissue^{10–12}.

Familial aggregations of RA provided the first evidence of the role of genetics in susceptibility, and we now know that there are specific genetic variations that together account for about 60% of the heritability of RA^{13,14}. During the search for susceptibility genes, the “shared epitope hypothesis” emerged¹⁵. In their hypothesis, Gregersen and colleagues described a shared structure that is part of the MHC (major histocompatibility complex) class II that is presented to T cells composed of 7 amino acids at positions 67–74. Class II MHC and the HLA-DRB1 alleles confer the greatest risk for disease in humans. Other non-HLA genes have also been studied with single nucleotide polymorphism (SNP), copy number variable (CNV), or genome wide association studies (GWAS) analyses and have found over 100 susceptibility genes in different populations¹⁴. Importantly, many of these genes are implicated in T cell signaling pathways, such as *STAT3* and *Wnt* that are differentially expressed in CD4⁺ T cells¹⁶ (Table 1).

Animal models of inflammatory joint disease, including collagen-induced arthritis (CIA), adjuvant arthritis and bovine serum albumin induced arthritis¹⁷, have been extensively investigated as these conditions have features that in different ways emulate the pathogenesis of RA. In the widely investigated mouse model, MHC class II susceptible rodent animal hosts are immunized with either bovine or chicken type-II collagen, which causes a cross-reaction with self, type II collagen. Arthritis typically develops within 28 days after immunization. In this model, T cells play an important role in the initiation of disease, as treatment with anti-CD4 antibodies prevents disease progression¹⁸. These data support the importance of T cells in driving this disease.

Other T cell models, such as the SKG mouse model, develop spontaneous inflammatory arthritis. In mice with the BALB/c background, a single point mutation in the SH2 domain of the T cell kinase Zap70 leads to proliferative invasive and erosive pannus, as well as other features of extra-articular RA, such as rheumatoid nodules and interstitial lung disease¹⁹. In these mice the pannus is infiltrated with CD4⁺ T cells and adoptive transfer of thymocytes or peripheral CD4⁺ T cells can transfer disease from one animal to another, indicating strong pathogenic drive of these T cells. To summarize, the advantage of using murine models of arthritis is to further elucidate the contribution of T cells to the development of autoimmune arthritis and to test the therapeutic potential of T cell specific approaches.

Many human studies have also shown the prominence of infiltrating T cells in RA disease pathogenesis. In particular, RA synovial biopsy specimens often display a preponderance of

T cell infiltrates, that form into architectural organizations with features of ectopic germinal centers that may be sites of expansions of autoreactive lymphocytes^{20, 21}. Additionally, amongst the first evidence of pathogenetic roles of CD4⁺ cells were reports that patients infected with HIV/AIDS, which is associated with deletion of CD4⁺ T cells, have lower rates of concomitant RA and RA remissions have been reported in patients that have contracted HIV infections²². Cytostatic drugs (such as azathioprine and methotrexate) and immunophilin inhibitors (such as cyclosporine and tacrolimus), which preferentially target T cells, have been shown to provide benefits for some RA patients, although responses are not predictable and are often limited.

In what has become a proven approach to interfere with lymphocyte signaling, a therapeutic agent, abatacept (CTLA-4-Ig), was developed by generating recombinant proteins in which the extracellular domain of the inhibitory CTLA-4 ligand was fused to a IgG1 Fc to improve serum half-life. In vitro, abatacept prevents T cell activation via CD28 signaling by blocking access of B7 family members to CD80/86 molecules arrayed on the surface of antigen-presenting cells. While initially designed as means to interfere with co-stimulation via CD28 on T cells by macrophage and dendritic cells, new perspectives have suggested co-stimulation is bidirectional, and that in a self-perpetuating autoimmune response memory B cells likely represent the most important antigen-presenting cells. Abatacept has seen clinical success in the treatment of RA in patients who have failed anti-TNF- α therapy alone or in combination with methotrexate^{23- 26}. It has been argued that abatacept treatment may also be associated with lower rates of serious infections, when compared to TNF- α inhibitors²⁷.

In summary, mounting evidence supports that genetic variations found in T cells are associated with increase susceptibility to RA and have also highlighted previously unsuspected potential therapeutic targets. Indeed, experimental models have provided the rationale for developing agents that effectively deplete T cells from infiltrated hyperplastic synovium and are likely to provide alternative and potentially more effective agents to improve clinical outcomes in RA patients.

The role of B cells in rheumatoid arthritis

B lymphocytes share many features with T cells, which include antigen receptor mediated activation and clonal selection that is a consequence of the integration of both positive and negative co-receptor signaling, as well as signals from their B cell antigen receptors (BCR). Moreover, in addition to the high-level antibody responses provided by B cells, cross-linking of the membrane associated BCR also mediates antigen uptake and processing that is required for full T cell clonal activation. While immunoinhibitory programmed cell death-1 receptor, PD-1, has been shown to be expressed on activated T cells, our understanding of the involvement in the B cell compartment is much more limited. In mice, PD-1 expression is induced on splenic B cells by in vitro stimulation with anti-IgM antibody²⁸. By contrast, neither growth factor deprivation, dexamethasone nor lipopolysaccharide affect PD-1 levels on these lymphocytes. These results suggest that the expression of the PD-1 antigen on B cells is also tightly regulated.

In humans, PD-1 is also present on the major human B-cell subsets that populate the lymph nodes and peripheral blood²⁹. While PD-1 is detectable on naive B cells, it is differentially expressed on peripheral IgM memory B cells, with generally lower levels on other types of memory B cells, and its expression is low or absent on B cells recruited into germinal centers. Moreover, TLR9 activation induces increased expression of PD-1 ligands (PD-Ls). In addition, upon antigen encounter PD-1 has been shown to co-associate in the cell membrane with the BCR²⁹. In contrast, the blockade of PD-1/PD-L1 and PD-L2 pathways indeed increased B-cell activation, proliferation and the production of inflammatory cytokines. Altogether, akin to the effects on T cells, PD-1/PD-Ls signaling system can also act as inhibitors of the B-cell activation cascade. These findings highlight the potential importance of devising future therapies that can modulate lymphocyte activation through the targeting of the PD-1/PD-Ls pathways²⁹.

To study the molecular mechanisms responsible for the negative regulation of B-lymphocytes through the PD-1 receptor, a B lymphoma cell line that expresses membrane IgG as its BCR, was transfected with a chimeric construct for expression of an IgG Fc receptor type IIB extracellular region fused to the cytoplasmic region of PD-1³⁰. In these cells, treatment with an intact anti-IgG Ab, resulted in co-ligation of the BCR and chimeric PD-1 cytoplasmic domain, which was shown to inhibit BCR-mediated growth and Ca^{2+} mobilization. Recruitment of the PD-1 cytoplasmic domain also blocked tyrosine phosphorylation of select effector molecules, including the $Ig\beta$ cytoplasmic tail, Syk, phospholipase C- $\gamma 2$, and Erk1/2, whereas there was no effect on phosphorylation of Lyn and Dok. Mutagenesis studies of the PD-1 cytoplasmic domain further revealed that these inhibitory effects do not require the N-terminal tyrosine in the immunoreceptor tyrosine-based inhibitory motif-like sequence, but do involve a distinct tyrosine residue adjacent to the C-terminal tail. In fact, the phosphorylation of this tyrosine induced by co-ligation of PD-1 with BCR led to recruitment of the homology 2-domain-containing tyrosine phosphatase 2 (SHP-2). Taken together, these results show that PD-1 can inhibit BCR signaling by recruitment of the SHP-2 phosphatase to its phosphotyrosine. These data suggest that the dephosphorylation of key signal transducers of BCR signaling may have significant effects to limit disease-associated B cell activation in conditions such as RA.

While the above described studies have suggested a role for PD-1 in the regulation of antigen-specific B cell clonal responses, interactions of the ligand PD-L1 with PD-1 receptor have also been shown to contribute to immune surveillance of B cell lymphomas³¹. In patients with Hodgkin's lymphoma, there is amplification of the gene encoding PD-L1, and increased expression of this protein on Reed-Sternberg cells. Correspondingly, PD-1 blockade with the therapeutic anti-PD-1 antibody, nivolumab, is reported to have response rates of 87% in unselected patients with relapsed and/or refractory Hodgkin lymphoma³². As a consequence, in May 2016 the FDA approved nivolumab for this indication. Recent clinical experience with this agent has provided support the notion that the PD-1 axis is commonly responsible for immune evasion by these lymphomas, especially those arising in patients with evidence of viral etiologies such as HIV-1 and Epstein Barr-Virus (EBV)³¹.

During physiologic immune responses, B cells and T cells collaborate in Germinal Center (GC) reactions that arise in highly specialized architectural sites in peripheral lymphoid

tissue. Through a tightly coordinated process, the GC response also results in BCR hypermutation and successful antigen-mediated clonal selection. This process is mediated in the GC reactions, which facilitate the competition and selection of B cell clonal daughter cells with the highest affinity for antigen. The final products are high affinity memory B cells and high level antibody secreting plasma cells (PCs)³³. It is well known that in the GC specialized CD4⁺ T cells, T follicular helper (T_{FH}) cells have high expression of the immunoinhibitory receptor PD-1. The role of PD-1 signaling in humoral responses have therefore been investigated, and GC B cells were found to have high-level expression of the PD-1 ligands PD-L1 and PD-L2 during effective immune responses. In contrast, immunization of mice deficient in PD-L2, PD-L1 or PD-1 had fewer long-lived plasma cells (PCs). Furthermore, in the absence of PD-1, there was much greater GC B cell death and lower levels of cytokine production by T_{FH} cells. Antigenic selection also appeared to be affected as the remaining PCs had greater affinity for the experimental antigen used in these GC studies. Cumulatively, these studies suggested that PD-1 expression on T cells, and PD-L2 expression on B cells, controlled T_{FH} cell and PC numbers. Thus, PD-1 regulates selection and survival in the GC, affecting the quantity and quality of long-lived PCs²⁹.

In autoimmune disease, especially those in which autoantibodies are prominent, ectopic lymphoid structures often develop at sites of inflammation in target tissues (reviewed elsewhere³⁴). These infiltrates have been well documented in autoimmune diseases, such as Sjogren's syndrome, multiple sclerosis, myasthenia gravis, and systemic lupus erythematosus, and especially in seropositive RA. These tissue infiltrates are characterized by the formation of organized T/B cells aggregates, which in some cases can acquire follicular dendritic cell networks, which support the development of structures with the cellular organization of ectopic germinal centers. These ectopic GCs have been postulated to have abnormalities in the mechanisms that are otherwise responsible for maintaining immune tolerance, and as a consequence are believed to be sources of clonally expanded auto-reactive memory B cells and autoantibody-secreting cells (ASC). These findings may suggest that in these pathologic sites, there can be dysregulation of the PD-1 axis. We therefore wonder whether the therapeutic enhancement of the PD-1 expression or interactions with PD ligands could provide therapeutic opportunities in these autoimmune diseases³⁵.

Inhibitory receptors and the regulation of T cell function

When antigen is presented on an MHC molecule on antigen-presenting cell, interactions with cognate T cells lead to formation of a tri-molecular complex responsible for the propagation of downstream T cell signaling pathways, and this followed by secondary signals where co-stimulatory or co-inhibitory receptors bind to their ligands. These encounters are believed to provide the molecular rationalization for the two-signal model of T cell activation that was first proposed in the 1970's by Bretscher and Cohn³⁶ to explain how TCR interactions with antigen alone result in immune tolerance, whereas two signals that include T cell encounter with a loaded antigen-presenting cell and appropriate cytokine exposure or co-stimulation leads to activation. Hence, the cell fate or destiny of a T cell may be determined by an absence of effective second signal, such as the engagement of membrane-associated stimulatory or inhibitory co-receptor molecules.

The first identified co-stimulatory receptors belong to the B7 family, and these display the beta barrel structure of the Ig superfamily (IgSF). The prototype of this family is, CD28, which is a co-stimulatory receptor expressed on T cells that positively regulates T cell proliferation and activation. Its ligands are CD80 and CD86 found on antigen presenting cells. These same ligands, CD80/CD86, can bind a co-inhibitory receptor, cytotoxic T lymphocyte antigen 4 (CTLA-4) with greater affinity, which down regulates CD28 signaling and promotes an inhibitory signal³⁷. Interestingly, CD4⁺CD28⁻ T cells accumulate in the joints of RA patients and may be present for years³⁸ and display a functional inactivation (anergic) phenotype, likely due to the absence of an effective second co-stimulatory signal.

PD-1 (programmed cell death-1) is a co-inhibitory receptor found on the surface of T cells encoded by the *pdc1* gene. It is a member of the immunoglobulin superfamily and is expressed on T cells and B cells after activation. The PD-1 receptor has two ligands, PDL1 and PDL2. PDL1 is expressed ubiquitously on all cell types, while PDL2 expression is limited to antigen presenting cells. PD-1 transmits signals through intracellular signaling domains, an ITSM (immunoreceptor tyrosine-based switch motif) and an ITIM (immunoreceptor tyrosine-based inhibitory motif). When ligated, the function of the PD-1 pathway is to down regulate cytokine secretion, proliferation and cell adhesion. Its function in vivo is important for T cell homeostasis and the maintenance of peripheral tolerance.

In a setting of chronic antigen exposure (i.e., chronic viral infection such as HIV or HCV and malignancy) T cells may become inactive due to “exhaustion”. The exhaustion phenotype is reflected in a loss of effector functions, an increase in inhibitory receptor surface expression (e.g. PD-1, CTLA-4, TIM3 etc.) and failure to return to quiescent state after in vitro activation. In a seminal paper, Wherry and colleagues described the molecular signature of exhausted CD8⁺ T cells in mice induced by chronic infection³⁹. Subsequently, it has been shown that in malignant conditions T cell exhaustion also occurs in human T cells (reviewed elsewhere⁴⁰). To this end, based on the assumption that cancer can arise due to ineffective immunosurveillance by chronically stimulated T cells, PD-1 antagonists have been successfully targeted in the treatment of certain malignancies.

A new class of drugs called ‘immune checkpoint inhibitors’ is being used to treat advanced stage cancers harnessing the activation of T cells to combat carcinoma. These drugs antagonize the CTLA-4 pathway (e.g., ipilimumab) and the PD-1 pathway (nivolumab, pembrolizumab and atezolizumab). Currently, either drug or combinations of these drugs have been approved in the treatment of metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma and Hodgkin’s lymphoma as well as others. The introduction of these drugs has changed the landscape of medical oncology. One of the major adverse effects from this class of drugs is referred to as immune-related adverse events (irAE)⁴¹. These irAEs affect most organ systems and are manifest as dermatitis, colitis, pneumonitis as well as thyroiditis and hypophysitis. Case reports of new onset rheumatic diseases such as seronegative spondyloarthritis and RA have also emerged raising further questions about the link between inhibitory receptors and autoimmunity.

The role of inhibitory receptors in rheumatoid arthritis

PD-1 in murine models

The PD-1 pathway has been extensively studied in mice. Nishimura and others, first reported that C57/BL6 PD-1 null mice developed late onset inflammatory arthritis and mild glomerulonephritis, suggesting that PD-1 is important in *in vivo* peripheral tolerance to self and is involved in negative regulation of the immune response⁴². Interestingly, the autoimmune phenotype is different in a BALB/c background where these mice develop autoimmune dilated cardiomyopathy⁴³. Given this molecule's impact on the immune system, investigators were interested to learn what effect stimulation of the pathway would have on autoimmune disease, including forms of inflammatory arthritis.

Wang and colleagues used the CIA murine model to study the effect of the PD-1 pathway on arthritis. The authors reasoned that since the PD-1 gene is associated with RA, it would be important in disease pathogenesis. They evaluated the effect of PDL1-Ig on the development and progression of CIA and found that using soluble PDL1 as an agonist ameliorated disease activity and reduced inflammatory cytokine production (e.g., IL-17, IL-23)⁴⁴.

In another study, Raptopoulou and colleagues, investigated the effect of PD-1 deficiency on the development of CIA. They found that PD-1 knockout mice were more susceptible to CIA and developed more severe disease. In addition, they observed increased T cell proliferation in inguinal lymph nodes in the PD-1 knockout mice suggesting a more robust autoimmune response. Subsequently, they induced CIA in B6 mice and treated them with PDL1-Fc, which stimulates the PD-1 pathway. This treatment also suppressed disease activity, similar to the study described above. In humans, this group evaluated synovial tissue by histopathology with PD-1, PDL1 and PDL2, which RA patients had more of compared with osteoarthritis. Additionally, there were many more CD4⁺ T cells in the synovial tissue of RA patients with PD-1 up regulation⁴⁵. These data suggest that the PD-1/PDLs pathway is affected in patients with RA, as many patients have evidence of PD-1⁺ T cells in circulation as well as in target tissues. Also, in animals, treatment with PDL1-Ig can significantly improve disease activity. While its role in disease pathogenesis is unclear, PD-1, should be considered as a treatment target for patients with RA.

PD-1 polymorphisms predispose to rheumatoid arthritis

Autoimmune disorders are multifactorial diseases with genes predisposing to autoimmunity. In RA, after the early studies performed in the 1970's, genetic polymorphisms became a topic of interest as illustrated above. Increasingly, an expanding set of genetic polymorphisms were identified that are significantly associated with disease susceptibility in diverse autoimmune conditions, ranging from type 1 diabetes to systemic lupus erythematosus (SLE). For each disease, these genes generally clustered into a limited of pathways, which highlighted potential therapeutic targets. In a series of reports, polymorphisms within the PD-1 locus (*pdcd1*) have been linked to RA susceptibility⁴⁶⁻⁴⁹.

Prokunina et al.,⁵⁰ reported the evidence that genetic polymorphism in PD-1 gene complex were also involved in SLE predisposition⁵⁰. Subsequently, this group evaluated the same mutation in 1,175 patients with RA⁴⁶. The mutation, PD1.3A is an A/G single nucleotide

polymorphism (SNP) located in the enhancer region of the gene, the result of which inhibits Runx1 transcription factor from binding to that region. Interestingly, this SNP was associated with RA patients negative for rheumatoid factor and the shared epitope⁴⁶. The authors concluded that similar genetic allelic variations may at times predispose to different autoimmune diseases.

In 2004, Lin et al., RA published a study associating polymorphisms in PD-1 to RA in Chinese patients⁴⁷. In their study, the investigators conducted genotypes for a single nucleotide polymorphism (C+872T) within the cDNA of the human PD-1 gene in 84 patients with RA and 98 patients with SLE. Their conclusion was that this particular SNP was significantly associated with RA susceptibility. In their study of 320 Han Chinese patients with RA, Liu et al., described a polymorphism located in the promoter region that confers risk⁴⁸.

However, there is a discrepancy between differing ethnicities. In a study by Mori et al., they observed that a particular SNP associated with SLE (PD-1.3A) was only found in Caucasian and African American subjects, but not in Japanese subjects.⁵¹ Additionally, Tahoori et al.,⁴⁹ evaluated SNPs from 120 Iranian patients with RA at the PD-1 locus. Their findings suggest that PD-1.1 allele at position 538 in the promoter region is associated with an increased risk for RA versus the control population (OR 2.9 vs. 0.7).

Polymorphism in ligands for PD-1 became of interest as PDL2 may increase risk for SLE in Taiwanese patients as evaluated by Wang et al.,⁵² The same group evaluated 129 patients with RA for the PD-L1 and PD-L2 polymorphisms and found no association between the polymorphism and disease⁵³.

PD-1 in rheumatoid arthritis T cells

As T cells are major cellular players in the pathogenesis of RA, studying those T cells is of particular interest. The hypothesis is that since PD-1 is responsible for peripheral tolerance and polymorphisms may predispose patients to disease, there must be associations and observations from RA patients that one may draw conclusions from. Data from patients indicates that surface PD-1 expression levels are higher in RA patients compared to controls^{45,54–56}. In fact, this is more evident in the synovium with high levels of PD-1 staining from RA patients⁵⁴.

In the aforementioned study, Raptopoulou et al., evaluated synovial tissue from patients with RA by histopathology. They concluded that there was a significant amount of PD-1, PD-L1 and PD-L2 compared with synovial tissue from osteoarthritis patients. Additionally, on flow cytometry, they observed that there were many more CD4⁺ T cells in the synovial tissue of RA patients as well as PD-1 upregulation⁴⁵.

Highlighting the importance of the PD-1 system in immunoregulation, recent studies have identified a new PD-1^{hi}CXCR5⁺CD4⁺ T cell subset, which has been termed 'peripheral helper T cells' (T_{PH}), as these cells appear to be critical for promoting B survival as well as induction of plasma cell differentiation⁵⁷. In this important recent report, mass cytometry was used to characterize lymphoid cells found in RA synovium, which demonstrated the

prominence in RA synovium of cells bearing markers of T_{PH}⁵⁷. These findings highlight the overlap of PD-1^{hi} cell subsets such as T_{FH} cells that are required for physiologic GC reactions and a related T cell subset that is now implicated in aberrant autoimmunity-associated responses in rheumatoid synovium.

In related studies, Hatachi et al.,⁵⁴ examined PD-1 levels in cells recovered from synovial fluid and peripheral blood of RA patients. While they observed that T cells from peripheral blood expressed only low or absent levels of PD-1, large populations of cell with much higher levels of PD-1 were found among the synovial fluid T cell populations. Additionally, a larger proportion of PD-1 positive cells in the synovial fluid were CD4⁺ T as opposed to CD8⁺ T cells. With intracellular cytokine staining, they observed that CD4⁺PD1⁺ cells had only low levels of IL-2, suggesting that these cells were not functionally active.

In flow cytometric studies of peripheral CD4⁺ and CD8⁺ T cells from RA patients, Li et al.,⁵⁵ reported that RA patients have low levels of PD-1, as well as low soluble PD-1 in the blood by immunoassay. In addition, they found that in these cross-sectional studies of RA patients the mean cell surface levels PD-1 was inversely proportional to clinical disease activity, based on the DAS28 scale. However, the greater significance of these findings remain unclear, as they did not make comparisons with healthy control subjects or with subjects with other forms of arthritis.

Greisen et al.,⁵⁶ measured soluble PD-1 levels in RA patients at baseline and 9 months into their treatment. They found that patients with either early or chronic RA had higher soluble PD-1 levels compared with healthy volunteers. In addition, they showed that PD-1 levels in the synovial fluid were higher than in the plasma, and within an individual RA patient there was a significant direct correlation between these values at the two anatomic sites. Soluble PD-1 levels in the plasma were also found to have an inverse correlation with total Sharp score, a quantitative measure of RA disease-associated skeletal erosions, suggesting that sPD-1 may somehow provide a protective influence from erosive disease that otherwise may convey poor prognosis.

Other inhibitory receptors in rheumatoid arthritis

The importance of co-inhibitory receptors in autoimmunity cannot be overstated. Given the success of the decoy CTLA-4 ligand, other inhibitory receptor systems in rheumatoid arthritis are also being investigated. Many of these same co-inhibitory receptors are also being evaluated as targets for cancer therapy. Liu et al.,⁵⁸ investigated expression levels of T cell immunoglobulin-3 (TIM3), an inhibitory co-receptor originally discovered on the surface of IFN- γ producing cells. These authors observed that the peripheral blood cells from rheumatoid arthritis patients generally displayed only low levels of TIM3. Moreover, therapeutic treatments with methotrexate and tocilizumab led to both improvement in clinical disease activity and concurrent increases in TIM3 receptor levels. Li et al.,⁵⁵ studied levels of TIM3 on the surface of CD4⁺ and CD8⁺ T cells from the blood and the synovial fluid of RA patients. Similar to PD-1, they found that TIM3 was also elevated in both the peripheral blood, with even higher levels in the synovial fluid lymphocytes of RA patients. They also observed that levels of TIM3 in the peripheral blood and synovial fluid were inversely proportional to RA disease activity (by DAS28).

Summary

Recently, PD-1 antagonist drugs (such as pembrolizumab and nivolumab) have been found to be particularly effective in the treatment of previously untreatable advance stage cancers, which in many cases induced sustained remissions. Some of the adverse events have been autoimmune in nature with exacerbations of pre-existing autoimmune disease or new onset disease. These patients are often treated with immunosuppressant agents. While effective, they may impede with the intended anti-cancer effect of the PD-1 targeted treatment. Understating the mechanism of anti-PD-1 secondary autoimmunity may shed light on the pathogenesis of other primary autoimmune condition such as RA. Extrapolating from oncology in which a hyperactive PD-1 system is therapeutically targeted to enhance the efficiency of T cell mediated immunosurveillance of the tumor, investigators are beginning to consider that a therapeutic enhancement of the PD-1 axis may suppress auto-reactive inflammatory T cells and thereby provide substantial benefits for patients with autoimmune disease. Given animal data and other high quality evidence, it is conceivable that an agonist agent targeting PD-1 may prove to be an effective treatment for RA strongly suggesting a role for additional research support for investigating fundamental aspects of PD-1 biology and its mechanism of action.

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Take-home messages

- T cells are important cellular mediators driving the pathogenesis of rheumatoid arthritis.
- PD-1 positive T cells accumulate in RA patient synovial fluid.
- PD-1 knock out animals develop inflammatory arthritis.
- Inhibitory receptors can be effectively targeted for treatment, as evidenced by the CTLA-4-Ig agent that modulates the B7 co-stimulatory axis.
- The PD-1 system should be evaluated as a target for the treatment of rheumatoid arthritis.

Table 1

T cell genes involved in Rheumatoid Arthritis

Gene	Function	Reference
<i>PTPN22</i>	Phosphatase that regulates T and B cells function, affects binding to the kinase Csk while mutations are associated with gain of function phenotypes.	59, 60
<i>STAT4</i>	Transcription factor important in T _H 1 responses.	61
<i>TRAF1-C5</i>	Complement component 5.	62, 63
<i>CTLA-4</i>	Co-inhibitory receptor found on T cells.	64
<i>HLA-DRB1</i>	Shared epitope.	15, 65–67
<i>CCR-6</i>	Surface marker for T _H 17 cells.	68, 69
<i>PADI4</i>	Peptidylarginine deaminase enzyme catalyzing conversion of arginine residues to citrulline.	70, 71
<i>CCL21</i>	Chemokine important in trafficking of T cells to secondary lymphoid organs.	64, 72
<i>IL2RA, IL2RB</i>	The receptors of IL-2, T cell “growth factor”.	73
<i>CD2</i>	Co-stimulatory molecule on surface of NK cells and T cells.	64, 74