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Review

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.

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1. 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 world [1]. Inflammation in the joints leads to synoviocyte 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 untreated the inflammatory process is linked to accelerated atherosclerosis and decreased life expectancy [2].

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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 data [3–7] 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.

2. 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 RA patients also often contain oligoclonal expansions of $CD4^+$ T cells [8], which can also be detected amongst the recirculating lymphocytes in the bloodstream [9] 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 inheritability of RA [13,14]. During the search for susceptibility genes, the "shared epitope hypothesis" emerged [15]. 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 populations [14]. Importantly, many of these genes are implicated in T cell signaling pathways, such as *STAT3* and *Wnt* that are differentially expressed in $CD4^+$ T cells [16] (Table 1).

Animal models of inflammatory joint disease, including collagen-induced arthritis (CIA), adjuvant arthritis and bovine serum albumin induced arthritis [17], 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 progression [18]. 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 disease [19]. 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 infections [22]. Cytostatic drugs (such as azathioprine and methotrexate) and immunophilin inhibitors (such as cyclosporine and tacrolimus), which preferentially target T cells, have been shown

Table 1
T cell genes involved in rheumatoid arthritis.

Gene	Function	Reference
PTPN22	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]
STAT4	Transcription factor important in T_H1 responses.	[61]
TRAF1-C5	Complement component 5.	[62,63]
CTLA-4	Co-inhibitory receptor found on T cells.	[64]
HLA-DRB1	Shared epitope.	[15,65–67]
CCR6	Surface marker for T_H17 cells.	[68,69]
PADI4	Peptidylarginine deaminase enzyme catalyzing conversion of arginine residues to citrulline.	[70,71]
CCL21	Chemokine important in trafficking of T cells to secondary lymphoid organs.	[64,72]
IL2RA, *IL2RB*	The receptors of IL-2, T cell "growth factor".	[73]
CD2	Co-stimulatory molecule on surface of NK cells and T cells.	[64,74]