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Molecular and cellular heterogeneity in the Rheumatoid Arthritis synovium: Clinical correlates of synovitis

Michael J. Townsend, Ph.D.

Immunology Tissue Growth and Repair Diagnostic Discovery, Genentech Research and Early Development, 1 DNA Way, South San Francisco, CA 94080, USA

A B S T R A C T

Rheumatoid Arthritis is characterized by autoimmune-mediated attack of the joint synovial lining resulting in destruction of bone and cartilage, and is a clinically and biologically heterogenous disease with respect to both course of disease and outcome to therapy. The current armamentarium of approved therapies does not result in complete clinical response in all patients. Improved techniques for imaging and performing biopsies on the rheumatoid synovium have facilitated multiple studies of the dysregulated cellular and molecular pathways in disease, and have provided evidence for a spectrum of pathogenic phenotypes across RA patients. These phenotypes are differentially affected by targeted therapies such as anti-TNFα and anti-CD20, and their presence prior to treatment impacts upon subsequent clinical outcomes. Ongoing histologic and molecular assessment of these synovial phenotypes through the implementation of routine synovial biopsy or using systemic biomarkers will improve targeting of therapies to specific patient subsets in both clinical trials and practice.

Introduction

Rheumatoid Arthritis (RA) is a chronic and systemic inflammatory disease characterized by autoimmune-mediated attack of the joints [1]. A hallmark of this disease is inflammation of the

E-mail address: townsend.michael@gene.com.

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synovial membrane (synovitis) characterized by infiltration of multiple immune lineages, concomitant joint swelling and tenderness, systemic inflammation with elevation of acute phase reactants, and production of autoantibodies such as Rheumatoid Factor (RF) directed against the Fc component of IgG, and anti-citrullinated protein antibodies (ACPAs). These processes lead ultimately to destruction of joint tissues with erosion of bone by osteoclasts and degradation of cartilage by proteases.

Treatment of RA patients with Disease Modifying Anti-Rheumatic Drugs (DMARDs), comprising both targeted therapies such as anti-TNFα, as well as therapies with broader anti-inflammatory mechanisms of action such as methotrexate, have demonstrated significant clinical benefit in reducing signs and symptoms as well as decreasing joint destruction. However, these therapies are not effective in all patients, and not all patients demonstrate a satisfactory clinical outcome. Indeed, both randomized placebo-controlled clinical trials as well as open label studies of multiple distinct therapies show a proportion of patients are resistant to therapy and continue to present with synovitis and ongoing joint destruction [2]. It is likely that underlying disease heterogeneity contributes to incomplete drug response, and underscores the importance of a deeper understanding of disease pathogenesis to better treat patients by matching them to specific therapies as well as identifying new therapeutic drug targets. Such approaches could indicate approaches to identify biomarker-defined RA patient subpopulations that could be used for clinical decision-making in terms of disease prognosis and choice of appropriate therapy. In this review, we discuss current knowledge around synovial cellular and molecular heterogeneity, clinical correlations with these disease processes, and their impact on and response to drug treatment.

Cellular and molecular subsets of synovitis

The primary manifestation of RA is autoimmune-mediated synovitis involving the large-scale infiltration of leukocytes into the synovial tissues. Importantly, however, is the emerging understanding that multiple processes precede the onset of synovitis by quite a considerable time period. It has been recognized for many years that the strongest genetic association lies within the *HLA-DRB1* locus, and that alleles containing a 'shared epitope' within this region are strongly associated with antibody reactivity to anti-citrullinated proteins [3], likely through preferential binding of post translationally-modified peptides for the binding groove of this HLA. Other risk alleles lie within regions associated with T cell receptor signaling such as *PTPN22*, the NF-κB pathway such as *TRAF1-C5*, and regulation of TNFα and IL-12 signaling such as *TNFAIP3* and *STAT4* [4–7]. A recent large meta-analysis of ~30,000 RA cases and >70,000 control subjects confirmed prior identified risk loci [8] and identified a further 42 novel loci to bring the total number of RA risk alleles with genome wide significance to over 100 [9]. Strikingly many of these loci lie within or adjacent to immune system associated genes, indicating that genetic risk is tied to immunological perturbation. Furthermore, assessment of the joints by magnetic resonance imaging and biopsy of individuals who are seropositive for prototypical autoantibodies such as RF and ACPAs but who have not yet developed fulminant disease indicate that the synovial lining is relatively normal, with only minor infiltration of T cells being associated with subsequent development of disease [10]. Such data suggests that a break in immune tolerance and development of auto-reactive lymphocytes has its genesis in other anatomic sites. Attention has focused on the presence of infectious agents such as *Escherichia coli* that may trigger the immune system and result in autoimmunity through molecular mimicry of self-antigens [11]. In particular the presence of the micro-organism *Porphyromonas gingivalis*, present in periodontal disease, has been associated with RA through its production of Peptidyl Arginine Deiminase (PADI) 4, an enzyme that catalyzes citrullination of native arginine residues in host proteins [12]. Thus, a systemic break in tolerance occurs prior to onset of pathophysiology in the joints, and magnification of this response through epitope spreading to additional self-antigens present in joints can lead to onset of synovitis [13].

Synovitis itself is characterized by several closely interlinked processes, and is characterized by the invasion of the synovial lining by leukocytes including B cells, T cells, macrophages and mast cells with concomitant expression of a multitude of inflammatory cytokines and chemokines. Auto reactive T cells have long been appreciated as contributors to synovitis, and are supported by abundant levels of myeloid cells and dendritic cells in the synovium that produce T cell stimulating cytokines such as IL-