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Autoimmune or Autoiflammatory? Bad to the Bone

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Inflammatory arthritis is a joint disease characterized by leukocyte invasion and synoviocyte activation followed by cartilage and bone destruction. There are multiple types of inflammatory arthritis including the most common, juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Variable etiologies contribute to the pathogenesis of these diseases, and at large, remain poorly understood.

Autoimmune or Autoinflammatory?

JIA, also known as juvenile rheumatoid arthritis (JRA)**,** is the most common form of arthritis in children and adolescents. The word idiopathic, which is derived from the Greek word idio, (ἴδιο = self) denotes spontaneous pathogenicity. Similarly the related rheumatic diseases RA, PsA and AS are refereed as autoimmune diseases where the prefix auto (αὐτό = itself) again denotes spontaneous pathogenicity through the immune system. Despite the variable etiologies contributing to the progression of these diseases early hypotheses concerning the spontaneous pathogenicity and self-inflicting properties of such rheumatic diseases were attributed to the presence of autoantibodies [1]. Initial evidence came from *in vivo* murine models such as the KRNxNOD murine model where pathological features that emulated human disease (rheumatoid arthritis) where completely rescued in KRNxNOD mice devoid of B cells [2]. The role of B cells took a prominent role in inflammatory arthritides as these data suggested that a joint-specific disease need not arise from response to a joint-specific antigen but can be precipitated by a breakdown in general mechanisms of self-tolerance resulting in systemic self-reactivity.

Interestingly, systemic juvenile idiopathic arthritis (sJIA), a subset of juvenile idiopathic arthritis (JIA) is set apart from all the other forms of JIA due to the markedly distinct

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pathogenesis, which does not show any association with HLA genes or with autoantibodies. Instead, it is characterized by an uncontrolled activation of phagocytes and aberrant IL-1 and IL-6 secretion. In fact, sJIA shows common features with macrophage activation syndrome (MAS), which involves activation of macrophages and the release a high amount of pro-inflammatory cytokines. Therefore sJIA is appropriately classified as an autoinflammatory disease related to abnormality of the innate immune system.

Osteoclasts at the intersection of innate and adaptive immunity

Despite the variation in the clinical features within rheumatic diseases bone erosion is a prominent common feature in RA, JIA, PsA and AS, and this is specifically important as bone resorption is only carried out by specialized bone resorbing cell the osteoclast. Osteoclasts are derived from hematopoietic precursors through the regulation of receptor activator for nuclear factor κ B ligand (RANKL) and macrophage colony stimulating factor (MCSF). RANKL is a trans-membrane protein expressed by activated osteoblasts, and activated T cells and synoviocytes and its actions are inhibited by its soluble receptor osteoprotegerin (OPG), which is also produced by a variety of cells [3]. It is generally appreciated that during inflammation the RANKL/RANK/OPG axis that tightly regulates osteoclast formation and bone resorption is shifted towards bone resorption [4]. However, the presence of excess RANKL has not been observed in animal models with prominent bone loss phenotype that emulate inflammatory arthritis, suggesting that other events may be equally important in bone destruction but more importantly provide new links between the innate immune system and the pathogenesis of inflammatory arthritides [5].

Although the presence of autoantibodies is not required for sJIA it is evident that aberrant cytokine expression and activation of the innate immune system suffices to induce pathology. In agreement with the observations made in sJIA, where aberrant cytokine expression and innate immunity has a protagonist role, overexpression of pro-inflammatory cytokines such as TNF, IL-1, IL-6, and IL-17 in TNFtg IL-1tg and various gene transfer models recapitulate the arthritic phenotype in vivo [6]. The role of cytokines in the pathogenesis of autoimmune arthritis is linked with generalized inflammation as it can affect diverse cellular subtypes including T and B cells, neutrophils, and dendritic cells [7]. However, recent evidence suggests that in vivo gene transfer of IL-17 and/or IL-23 is sufficient to induce the activation and differentiation of osteoclasts from their myeloid precursors and therefore implicates pro-inflammatory cytokines in more elaborate roles in inflammatory arthritis [5, 8]. The activation of myeloid cells in rheumatic diseases has been challenging to study due to the enormous heterogeneity of macrophages and their ability to respond to a variety of complex stimulus [9].

Macrophages get activated during infection and tissue injury to perform their routine innate immune functions through Toll-like receptors (TLRs), NOD-like receptors, RIG-I like receptors, C-type lectin receptors, leukotriene receptors and immunoreceptor tyrosine-based activation motif (ITAM)-associated receptors. In inflammatory arthritis, crosstalk among these pathways result in osteoclast differentiation with catastrophic consequences for bone and joint function [10, 11]. New and old evidence also point to the fact that these alternative pathways may also utilize a different subset of osteoclast precursors [10],[12]. Taken

together, the specific erosive phenotype of the various inflammatory arthritides may simply be a reflection of the differences in the availability of osteoclast precursors within the inflammatory infiltrate and the nature of the activation signal.

In keeping with these observations, in other inflammatory arthritides such as RA the association of several autoantibodies such as anti-tissue transglutaminase (AGTAs), and anti-thyroid peroxidase (anti-TPO) autoantibodies has been challenged [13]. As less and less autoantibodies seem to contribute to pathogenicity in arthritis the role of the innate immune system becomes more prevalent. Recent analysis revealed that monoclonal IgG antibodies generated from joint derived B cells of RA patients exhibited a strong bias toward citrullinated autoantigen recognition [14]. Antibodies targeting citrullinated proteins (ACPAs [anticitrullinated protein antibodies]) have recently been linked with cells of the mononuclear phagocyte system and their activation and differentiation to osteoclasts [15]. It is therefore possible that B cells and autoantibodies present in the inflammatory infiltrate of rheumatic diseases provide RANKL-co-stimulatory or RANKL-independent signals to facilitate and/or induce osteoclast differentiation.

Concluding remarks

Bone erosion, as observed in RA, JIA, PsA and AS is solely dependent on osteoclast activation as to date no other cell type possesses the cellular and molecular machinery required to perform the bone resorbing function. In these inflammatory arthritides the extent of bone resorption correlates with an increase of synovial fluid mononuclear cells and synovial macrophage in the synovial inflammatory infiltrate. Therefore as the search for the precise pathogenic signals in these inflammatory arthritides continues, it is becoming clearer that one common denominator, at least the bone resorbing phenotype, depends on the osteoclast precursor infiltration into the joint and their activation and differentiation to osteoclasts.

So, as the debate of whether some inflammatory arthritides are autoimmune or autoinflammatory continues, it would be prudent to study and intervene at a common intersection which is the activation of innate immune cells and osteoclast differentiation.

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