Viewpoint

Direct interaction of immunoglobulins with synovial fibroblasts: a missing link in the pathogenesis of rheumatoid arthritis?

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It has been well established that the pathogenesis of rheumatoid arthritis (RA) comprises three distinct but interdependent phenomena: the hyperplasia of synovial tissue, chronic inflammation (both local and systemic), and alterations in the immune response, including changes in the T-cell repertoire and the production of autoantibodies [1]. The precise nature of these interactions, however, particularly the role of autoantibodies in RA pathogenesis, is not yet fully understood. Whilst the occurrence of autoantibodies has been recognised as a characteristic feature of disease, and certain autoantibodies have become valuable tools for diagnosis, their contribution to the initiation and perpetuation of disease has remained largely elusive.

A recent article by Terry Smith and William Cruikshank in the *Journal of Immunology* provides fascinating yet unexpected insights into how autoantibodies contribute to the maintenance of inflammatory disease processes in RA [2]. The authors report that IgG antibodies from the sera of patients with RA (RA-IgG) can stimulate RA synovial fibroblasts (RASFs) through interaction with insulin-like growth factor receptor 1 (IGF-R1). This interaction of RA-IgG with IGF-R1 increases the production of IL-16 and RANTES in RASFs provoking chemoattraction of T cells. The data demonstrate, for the first time, a bridging link between B-cell activity and T-cell trafficking. In addition, they are of potential importance for the development of innovative therapeutic strategies, in which interrupting the IGF-1/IGF-1R axis could result in sustained disease modification by affecting both the growth-factor triggered activation of fibroblasts and the accumulation of T lymphocytes.

The significance of this research for understanding the pathogenesis of RA (and potentially other autoimmune disorders) goes beyond these two obvious aspects for several reasons. Although there have been reports that IgG may interact with mesenchymal cells [3-5], the present data establish a new role for (B-cell derived) autoantibodies in the pathogenesis of autoimmune disease. The hypothesis that autoantibodies not only constitute an epiphenomenon but also contribute directly to the pathogenesis of synovial inflammation and joint destruction has seen a 'revival' over the last couple of years [6,7]. This is mainly due to the observation that passive transfer of serum or immunoglobulins from arthritic K/BxN mice to healthy animals can cause arthritis [8, 9]. However, these effects have been attributed mainly to the activation of complement and Fc-γ receptor pathways [6], and it has been suggested that, at a cellular level, mast cells link the autoantibodies to soluble mediators as well as to other effectors in arthritis [10].

The present data shed new light on the interaction of B-cells (more precisely B-cell derived immunoglobulins) and resident fibroblast-like cells of mesenchymal origin in the perpetuation of RA. They demonstrate clearly that antibodies may interact directly with fibroblast-like cells and through this interaction form part of a signalling loop that ultimately results in the maintenance of local inflammation. Consequently, the findings add to the growing body of evidence suggesting that resident stromal cells are a key element of the local immune response [11] and contribute significantly to the switch from acute to chronic inflammation in RA [12].

In this context, the observation that the effects of RA-IgG are seen with RASFs but not osteoarthritis synovial fibroblasts (OASFs) is of particular importance. Several lines of evidence suggest that, unlike normal synovial fibroblasts or OASFs, RASFs exhibit features of stable

IGF-R1 = insulin growth factor receptor 1; IL = interleukin; OASF = osteoarthritis synovial fibroblast; RA = rheumatoid arthritis; RASF = rheumatoid arthritis synovial fibroblast.

cellular activation (also known as transformation), that leads to alteration in their apoptotic response, the attachment of these cells to articular cartilage and subsequently to the degradation of the cartilage matrix [11, 13]. This notion has been derived from *in vitro* studies as well as the SCID-mouse *in vivo* model of cartilage destruction. Although a number of molecular pathways have been identified that contribute to the stable activation of RASFs, the precise cause and nature of this activation, as well as its relevance and consequences, are matters of debate. The present data indicate very clearly that stable alterations in the fibroblasts themselves are indispensable for (auto)antibodies to exert their effects on IL-16 (and RANTES) mediated chemoattraction. It has to be emphasised that the experiments were done with fibroblasts that had been cultured for 3–10 passages *in vitro* before being exposed to the immunoglobulins. Consequently, the data suggest that the local stromal environment in the joint (and based on previous data from the group other organs as well [14]) to a large extent determines the disease specific immune response. Given the variety of signaling pathways initiated by IGF-1 in fibroblasts, it may be speculated, as the authors mention briefly, that binding of antibodies to IGF-1R exerts a number of other, potentially disease relevant effects in autoimmune diseases such as RA.

Finally, the paper draws our attention back to IL-16, a cytokine that has been demonstrated at elevated levels in the sera [15,16] and synovial fluids [17] of patients with RA, but that has not been studied extensively in RA due to controversial data on its role in the pathogenesis of disease [18]. The present research on the interaction of RA-IgG and RASFs as well as other recent data, however, may change the picture. It has been reported by Huizinga and colleagues that in a cohort of patients with recent onset arthritis, patients who later developed RA showed significantly higher serum levels of IL-16 than patients with undifferentiated arthritis and that high IL-16 levels correlated positively with the degree of joint destruction over a 2-year period [16]. These data extend the aforementioned observations and link IL-16 to the disease process of RA. In this context it is of interest, that CD4 expression per se is not sufficient to mediate IL-16 effects [19]. Rather, IL-16 mediated T cell migration appears to be linked to CCR5, a receptor that is expressed predominantly in Th1 cells and is physically associated with CD4 [20]. RASFs have been identified as major producers of IL-16 in the rheumatoid joint, and it has been demonstrated that inflammatory cytokines present in the RA synovium such as TNFα and IL-1β can upregulate IL-16 in fibroblasts [21]. By demonstrating that in addition to these cytokines, growth factor signals trigger the release of IL-16 in RASFs, the present research from Smith and Cruikshank extends the panel of signals involved in the regulation of IL-16 at least under pathologic conditions. Although the study does not explain why RASFs and OASFs react differently to stimulation with RA-IgG, other data suggest that the expression of IL-16 may be regulated by different pathways in RASFs and OASFs [22].

Taken together, the data alter current concepts of how the immune system interacts with resident fibroblast-like cells and, even more intriguingly, add to the notion that alterations in the local fibroblast environment determine the specific immune response.

Competing interests

The author(s) declare that they have no competing interests.

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