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The role of ACPAs in at-risk individuals: Early targeting of the bone and joints

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A B S T R A C T

Autoimmunity precedes inflammation in patients with rheumatoid arthritis (RA), opening the possibility to search for early changes in the tissue preceding the onset of systemic inflammation. Autoantibodies are important and early drivers of bone damage in RA. This article summarizes current evidence for the role of RA-related autoantibodies in mediating bone loss. Rheumatoid factor (RF) and antibodies recognizing modified (citrullinated) proteins have been used as diagnostic markers for RA over many years. Their role as pathogenic players, however, has long been unrecognized. Recently, several pieces of evidence suggested that bone-resorbing osteoclasts are highly responsive to RA-related autoantibodies, providing a novel association between autoimmunity and bone. These developments have allowed the unraveling of the underlying mechanisms, which are responsible for the well-known clinical observation that anti-citrullinated protein antibodies and RF are associated with a more severe disease course. Furthermore, these mechanisms also explain the onset of inflammation in the joints of RA patients.

Introduction

Current concepts of rheumatoid arthritis (RA) suggest a step-wise disease process, which originates from the generation of autoimmunity against post-translationally modified proteins, followed by the augmentation, diversification, and maturation of the autoimmune response, and finally leads to the

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progression from autoimmunity to chronic inflammatory disease [1,2]. Presently, “RA” is classified on the basis of its clinical appearance as polyarthritis with or without autoantibodies [3]. Such a phenomenon-based description has its limitations as it describes more a syndrome than an individual disease. More mechanistically orientated disease concepts of RA can be envisioned in the future, which consider that the preclinical and clinical phases of the disease associated with the formation of anti-modified protein antibodies, in particular anti-citrullinated protein antibodies (ACPAs), are just different phases of a single disease.

The role of ACPAs in the onset of RA

ACPAs precede the onset of disease by many years [4–6]. Recent findings investigating patients with ACPA positivity but no signs of RA suggested that these very early stages of the disease are based on very similar autoantibody-induced tissue pathologies, such as lung and bone diseases, which are observed in established disease [7,8]. These data have revised our perception of ACPAs, emphasizing a direct pathogenic role in the disease process. The key role of ACPAs in the development of RA is particularly illustrated by an English study on patients with new-onset musculoskeletal symptoms, where the progression to inflammatory arthritis (defined by joint swelling) was as high as 47% over 1 year if ACPAs were present, while it below 2% if no autoantibodies were found [9]. It is remarkable that the relative risk for developing RA in ACPA-positive individuals with new-onset musculoskeletal symptoms is 66.8%. Similar findings were also reported in another cohort [10], although the effect of ACPAs on the development of RA was somewhat less pronounced. Importantly, RF only plays a role in increasing the risk in conjunction with ACPAs but not alone, and shared epitope positivity does not further contribute to risk prediction because of the high overlap with ACPAs [10].

Bone loss associated with ACPA

The particular effect of ACPAs on bone is reflected by three important clinical observations. First, RA patients typically have low bone mass at the start of their disease, indicating that bone damage already occurs before clinical inflammation starts [11,12]. This concept is based on the assumption that no bone damage, such as bone erosion or osteopenia, should be present if inflammation has just started because it takes time for the effect of inflammatory cytokines on the bone to become visible. Hence, recent-onset RA should not exhibit signs of bone damage if inflammation is the sole contributor to bone loss. However, as mentioned, antibodies precede the onset of disease by many years [4–6] and therefore represent an interesting alternative explanation for this finding.

The second observation supporting ACPAs' involvement in bone damage is the remarkable consistency of the finding that autoantibody ACPA-positive RA shows more severe bone lesions than that in ACPA-negative RA. This observation holds true for both local and systemic bone loss [6,13–15]. The finding that ACPA-positive RA represents a more severe form of RA largely goes back to the finding of a higher progression of bone erosion and joint destruction in this subset. More importantly, subjects with ACPAs but no clinical signs of arthritis show bone changes in high-resolution computed tomography scans in the absence of inflammation [7]. In particular, cortical bone changes such as a thinning of the cortex and cortical micro-breaks are found in this very early non-inflammatory stage of this disease, where ACPAs are the sole pathologic finding. These architectural changes of the joints in conjunction with ACPAs may “prime” joints for later sustained inflammation. Importantly, the porosity of cortical bone allows interactions between the synovial space and the bone marrow, which may be important for bringing immune cells to the joints [16]. Furthermore, bone metabolism was found to be perturbed already in these preclinical stages of RA [17]. These structural and biochemical findings in ACPA-positive individuals at risk to develop RA may later translate into intra-articular (formerly known as “periarticular”) bone loss [18], which is a typical radiographic finding in early RA patients [19] and precedes the development of bone erosions [20,21].

Finally, the third piece of evidence that supports a causal role of ACPAs in bone damage in RA is the observation that some RA patients progress in bone loss even when in clinical remission [22]. This at first sight paradoxical finding, however, may be explained by the sustained presence and bone-

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