Pre-arthritis: a concept whose time has come

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'The time has come to make the topic of pre-arthritis a major item on the research agenda of the current decade.'

Rheumatoid arthritis (RA) is characterized by synovial inflammation and the destruction of bone and cartilage. Joint destruction is brought about primarily by the differentiation and increased activation of osteoclasts [1–4], which is dependent on the presence of various cytokines [5]. Among these cytokines tumor necrosis factor (TNF)-α, a pivotal mediator of RA [6,7], plays an important role in the generation of osteoclasts [8], and, in fact, expression of TNF-α in the joint is much higher in RA, when compared with other forms of arthritis [9–11].

With the advent of novel treatment strategies and therapies [12,13], RA has lost a great deal of its adverse effects, such as the relentless progression of disability and premature death. Similarly, extra-articular diseases, such as vasculitis or amyloidosis, have become rare within the last decade. Major progress has occurred with the insight that diagnosis and specific therapy have to be effected in the early stages of disease [14–16] and modified consequently by setting low disease activity as the therapeutic goal [13,17].

Current trends, which are governed by the success of such treatment strategies, have meanwhile moved towards even more ambitious end points: remission is the current ultimate therapeutic aim, although this has not been seen in more than 10–15% of patients in recent clinical trials, if stringent rather than soft end points are used [18–21]. Such stringent criteria are, however, needed if we ever want to achieve a state of minimal or no disease activity. Such criteria will also be needed to monitor the absence of disease activity in patients off treatment, a common situation in other diseases. Although the ultimate goal of a cure is not yet in sight for most patients with RA, it appears to be getting nearer, for some of them at least.

Currently, predictive indicators for general therapeutic response, remission in particular, are missing. It has been widely established, however, that patients bearing certain markers fare worse than those without these characteristics, also indicating greater resistance to achieving reversal of synovitis. These markers comprise autoantibodies such as rheumatoid factor (RF) [22,23] and the recently described antibodies to citrullinated peptides (anti-CCP) [23,24], high acute-phase reactant levels [18,25,26] and genetic factors [27,28]. Van der Helm-van Mil and Huizinga have summarized some facets of the association of RA and RA severity with genetic background and autoimmune response [29].

A hallmark of RA is symmetric joint swelling due to the underlying synovitis. The synovial cellular infiltrate, which comprises an accumulation of macrophage-like cells and fibroblasts, as well as activated T cells and autoantibody-producing B-lineage cells, is not pathognomonic for RA. Interestingly, cellular infiltration of the synovial membrane may be found in RA in the absence of any joint pain or swelling [30]. However, it is not known how long such inflammatory changes antedate the evolution of RA symptoms. Importantly, even the development of bone erosion might precede the manifestation of signs and symptoms, as indicated by the presence of radiographic changes in patients with very short duration of arthritis [31]. In fact, in experimental arthritis, activated osteoclasts are found in the joints, even at a time when clinical signs are still absent [Unpublished Data]. All these data, in conjunction with the high propensity and rapidity of erosive disease and the potential to reverse RA from destructive to nondestructive arthritis by TNF blockade [32], presumably by reducing TNF levels below a threshold concentration promoting osteoclastogenesis [8], support the concept of an 'osteoclastocentric' nature of RA.

Synovial inflammation is not the only abnormality preceding the clinical commencement of RA; autoantibodies frequently antedate the appearance of first symptoms. This has long been established for RF [33] and also recently shown for anti-CCP [34,35]; likewise it may be true for other autoantibodies, such as anti-RA33 [36]. Moreover, elevations of acute-phase reactant levels have also been found to foreshadow RA [37]. However,

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previous studies have analyzed RA patients retrospectively, and the incidence of RA in healthy individuals who carry one or more of the mentioned autoantibodies is unknown. Prospective epidemiological studies will be needed to better understand the consequences of their occurrence. To this end, autoantibody-positive healthy persons will have to be studied for the frequency of subsequent development of RA, as well as the potential return to an autoantibody-negative state. After all, autoimmunity does not necessarily translate into autoimmune disease [38]; autoantibodies may occur transiently in apparently healthy individuals and often in the context of transitory infections [39–41]. In such a context, one has to bear in mind that RA has been linked to certain pathogens [42], although a causative role has so far not been unambiguously assigned to any single infectious agent. Nevertheless, the long period of clinical silence associated with the persistence of autoantibodies before the occurrence of clinical symptoms of arthritis might be related to a slow infection – or a combination of etiological agents. In any case, the current evidence for autoimmunity, local inflammatory changes and increases in acute phase reactants (signifying systemic inflammation) at a preclinical stage suggests that these changes constitute harbingers of RA, implying a state of 'pre-arthritis'. This state is apparently frequent in individuals who will develop RA, although variable in length.

The existence of a pre-arthritic, clinically quiescent stage of RA has several implications. First, it is the point in time that should be used to search for the cause of RA; the start of the autoimmune and/or inflammatory response might be associated with potential etiological agents. Second, once prospective epidemiological data confirm a high risk for patients with certain characteristic features to develop RA, 'latent RA' could become a standard diagnosis. Third, such diagnosis will demand the design of therapeutic strategies to interfere with and reverse the incipient immunoinflammatory cascade, in order to treat the disease before it occurs – to prevent its clinical appearance and consequences. Therapy at that point in time could span a wide range of theoretical interventions, from disease-modifying antirheumatic drugs or glucocorticoids, to vaccination strategies. Clearly, ethical considerations (such as treating someone who is still healthy) will have to be weighed against the potential benefit.

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The era of treating pre-arthritis is still distant (and may never occur). Nevertheless, we need to face the concept of the prevention of arthritis. It is satisfying that rheumatologists have realized the importance of early therapeutic intervention to, at the very least, prevent the establishment of chronic, persistent and destructive arthritis [43–48]. Such interventions will have to include treating arthritis intensively, even if a clear diagnosis has not yet been made [49–51]. Importantly however, despite a high success rate, even very early disease-modifying antirheumatic drug therapy does not prevent the evolution of persistent disease in a significant proportion of patients [16,52]. These insights, in conjunction with our current inability to cure RA once it is established, necessitate the need to progress from trying to prevent disease sequalae to trying to prevent disease occurrence. Inherent to this conceptual change of approaching RA is the shift from the diagnosis of arthritis to screening for harbingers of arthritis. This will bring the concept of pre-arthritis to life and allow the development of strategies to prevent disease.

The time has come to make the topic of pre-arthritis a major item on the research agenda of the current decade. The insights obtained from clinical and basic sciences have been so rapid over the last few years that the issue can be easily addressed.

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