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How undifferentiated arthritis evolves into chronic arthritis

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A B S T R A C T

Undifferentiated arthritis (UA) is a frequently occurring clinical presentation with a variable outcome. While some forms of UA will spontaneously remit, other forms will progress to chronic arthritis; an outcome that would preferably be prevented.

Which immunological factors are normally at the basis of resolution of inflammation, and what, on the other hand, causes inflammation to persist? This review provides an overview of the immunological mechanisms involved in these two scenarios, including specific examples of how these mechanisms apply, or can be influenced in rheumatic diseases.

Furthermore, what do we know about risk factors for chronic arthritis, such as the development of autoantibodies? The recent years have provided many insights concerning risk factors for autoantibody-positive versus autoantibody-negative rheumatoid arthritis, which are discussed along with a possible pathophysiological model incorporating autoantibodies into the larger process of disease development. Finally, the evolution of the autoantibody response over time is described.

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Introduction

In clinical practice, patients frequently present to the rheumatologist with recent-onset undifferentiated arthritis (UA). From a clinical point of view, UA defines clinical symptoms and analytical findings that do not allow a definite diagnosis based on current classification criteria [1]. Therefore, it is a term based on definitions developed to maximize the likelihood of a correct diagnosis, and it describes a common symptom of different potentially underlying inflammatory and immunological processes. As such, the term is variable and dependent on our knowledge of immunological mechanisms. This is exemplified by the recent revision of the 1987 American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis (RA). Integration of serological biomarkers in the criteria set strongly reduced the frequency of patients with UA in early arthritis cohorts, as more patients fulfilled the criteria of having RA [1,2]. Thus, UA does not exclude the presence of chronic disease and should not imply reversibility of inflammation even though, indeed, more patients will spontaneously achieve remission in groups with UA than in those with established RA. Thus, the concept of UA is difficult to place in a context of immunological mechanisms, but its definition is relevant for clinical use, as epidemiological studies apply it to calculate risk for progression or chance of remission, all of which help to counsel patients and guide treatments.

In this review, we provide an overview of the immunological mechanisms involved in the persistence versus the resolution of inflammation, followed by a discussion of the RA-specific (risk) factors such as autoantibodies which are thought to play a role in the development of chronic arthritis.

From an immunological point of view, recent-onset UA represents a state of (acute) inflammation for which the question arises as to which factors are involved in its initiation and cessation, and which factors determine its persistence. Chronicity, in this context, is not so much a matter of duration of the inflammatory response but rather related to the failure to achieve its spontaneous and complete resolution, and can thus be seen as a state of irreversibility. Whether irreversibility is intrinsic to the disease process of, for example, RA, or whether it is acquired during the immunological process of (synovial) inflammation is still an open issue of debate. Acquired irreversibility would suggest that timely intervention could resolve inflammation and, thus, prevent chronic disease, whereas “imprinted” chronicity would render success less likely. The following section outlines immunological mechanisms involved in the development of chronic inflammation that, in part, are also operational in RA.

Resolution of acute inflammation and the role of the antigen

Acute inflammation is the result of a physiological response to a signal of danger, which can be anything from tissue damage via chemical compounds and allergens to invading pathogens [3]. Numerous immune cells and soluble factors such as complement components, cytokines, chemokines, and coagulation factors effectuate this response. It is controlled and fine-tuned by tissue-specific factors such as endothelial cells or specialized tissue-resident immune and stromal cells. Its primary aim is removal of the danger signal, that is, the triggering agent, be it in the form of clearance of pathogens or wound repair. To keep collateral tissue damage to a minimum and to prevent persistent inflammation, effective shutdown mechanisms exist that limit the inflammatory response, clear effector cells and detritus, and resolve inflammation. Failure of these mechanisms can be fatal, as exemplified by the destructive power of uncontrolled inflammation observed in situations such as sepsis or severe inflammatory response syndromes (SIRS).

In the case of chronic, persisting inflammation, the question arises as to the role of the agent that initially triggers the inflammatory process. Examples from allergy suggest that the trigger is crucial to maintain the response as most allergic inflammatory reactions, whether antibody or T-cell mediated, resolve completely in the absence of allergen. In autoimmune inflammation as seen in RA, agents triggering the inflammatory response are frequently self-antigens. Most self-antigens, however, are cell-specific antigens such as platelet antigens in immune thrombocytopenic purpura, or are expressed in various tissues. This makes their removal difficult, if not impossible. Exceptions are tissue-specific antigens expressed in (nonvital) organs that can be cleared by therapeutic intervention. Indeed, Graves' disease ceases upon total thyroidectomy or radioactive ablation, or upon immune-mediated