Commentary

Rheumatoid arthritis viewed using a headache paradigm

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Abstract

Results and new hypotheses in animal models often stimulate development of new paradigms in how we view rheumatoid arthritis (RA). The complexity of RA does, however, eventually lead to the rejection of these hypotheses. Here, it is argued that the large number of so-far described animal models, when taken together, also reveals a complex disease. Fortunately, detailed study of each of the animal models will reveal this complexity, and may also be helpful in elucidating the complexity of the human disease. Benoist and Mathis [1] recently contributed a new animal model in which an autoimmune response to a ubiquitous antigen leads to an antibody-mediated inflammatory attack in the joints. It is argued that this new model, as with other animal models, is unlikely to explain RA, but it will add to the tools available to reveal the complexity of RA.

Keywords: animal models, genetics, pathogenic antibodies, rheumatoid arthritis

Introduction

RA as diagnosed by the American Rheumatism College (ARC) criteria is a common disease, estimated to affect 0.5 to 1% of the world's population. Its relatively high frequency is evidence of a complex etiology and pathogenesis. RA is probably not one disease but, rather, a syndrome caused by several widely different pathologic processes. In this respect, RA could be likened to headache. No one would seriously think of trying to find a single explanation for headache. Rather, widely divergent causes, such as stress, migraine, or brain tumors, would quite rapidly be seen to be associated with quite different diseases. Similarly, it may be time to start thinking of a variety of different pathways leading to RA rather than searching for one single explanation.

Need for variety of animal models

Likewise, more than one animal model for RA is needed. More and more kinds of manipulation, genetic or environmental, lead to arthritis in experimental animals. Thus, arthritis can be induced by the injection of live bacteria, such as *Staphylococcus aureus* [2] or *Borrelia burgdorferi* [3]; of bacterial cell-wall fragments, such as in streptococcal-induced arthritis [4] and in mycobacterium adjuvant-induced arthritis [5], or of purified bacterial products such as lipopolysaccharide [6] or muramyl dipeptide [7]. Arthritis can also be induced by the injection of various exogenous or endogenous oils permeable in cell membranes, such as mineral oil, pristane, squalen, or C16-C17 fatty acids [8–12], or by immunization with ubiquitous antigens such as C1q [13] or gp39 [14], or with cartilage proteins

ARC = American Rheumatism College; GPI = glucose-6-phosphate isomerase; RA = rheumatoid arthritis.

such as type II collagen [15], type XI collagen [16], cartilage oligomeric matrix protein [17], aggrecan [18], or aggrecan link protein [19]. Arthritis can also develop after induction of immune complexes in the joint [20], after transfer of cartilage-specific antibodies [21], or after transfer of activated T cells [22]. Moreover, it may develop during the induction of a graft-versus-host disease. Arthritis also develops spontaneously in normal inbred strains [23–25] or in genetically manipulated strains that overexpress foreign proteins, such as the human T cell leukemia virus-I glycoprotein [26,27], molecules of the human major histocompatibility complex [28], or inflammatory cytokines such as tumor necrosis factor alpha [29]. Adding to this list, it has now been reported that expression of a T-cell receptor encoding for glucose-6-phosphate isomerase (GPI) will lead to arthritis through the production of antibodies specific for the same antigen [30].

All these models constitute an extremely valuable asset for the analysis of different pathways leading to arthritis. Most of these models use different arthritogenic pathways, and there are arguments in support of the existence of each of them for studies of RA.

Uses and limitations of the new GPI model

The newly described model in which antibodies specific for GPI induce acute arthritis adds to our arsenal and will be very useful for analyzing downstream mechanisms leading to arthritis. Although there is no evidence that GPI antibodies are found in humans, the availability of antibodies that readily induce arthritis is useful for understanding effector mechanisms. Furthermore, the main component of acute arthritis in the widely used collagen-induced arthritis model most likely mimics the same pathway [21,31–33]. An essential part is mediated by antibodies binding to the cartilage surface and through complement and macrophage IgGFc-receptor-dependent pathways initiating arthritis in the joints.

The descriptions of the arthritides induced in the GPI-antibody model and in the type II collagen-antibody model do not seem to differ in any essential point, although further study will probably reveal some differences. One difference is certainly the target epitope. The epitopes in the type II collagen-antibody model are definitely type II collagen in the cartilage [34,35], though the precise epitopes and mechanisms are not fully clarified, whereas in the GPI model the target epitope *in situ* has not yet been demonstrated. GPI may be exposed extracellularly in the joints, or there may be a joint cross-reactive neo-epitope that attracts the binding of the antibodies.

It is less likely that the GPI model will provide information on the upstream initiation of arthritis. By chance, researchers have found many starting points for the triggering of arthritis in animal models, as mentioned above. The upstream events, or etiology, of arthritis are likely to be more divergent than the downstream effects that are defined by the ARC criteria. It seems more fruitful to find the most important springs by starting downstream and following the river upstream.

Need for a new paradigm

It is time to change the paradigm for our thinking about the causes of RA. I certainly agree that pathways involving pathogenic antibodies have more recently been lost sight of in RA research and that lessons from the collagen-induced arthritis model, as well as from the more recently described GPI model, should be taken into account, particularly as corresponding anti-type II collagen antibody reactivities in humans have been identified [36,37]. However, there have been some disappointments when premature or misinterpreted findings from animal models have been seen as offering an explanation for RA: the induction of arthritis with T cells reactive to mycobacterium heat-shock proteins, a pathogenic oligoclonal T-cell repertoire induced by superantigens, regulatory effects by class II molecules, oral bystander vaccination, and cartilage-specific T cells primed in the joints, just to mention some examples.

Conclusion

It is time to accept that RA is a complex disease with multiple causes and pathways. Recent advances will now enable us to address these complexities and put forward new hypotheses. Particularly exciting is the possibility of understanding complex diseases through their genetic susceptibility [38–40] – why certain subtypes of RA develop in some but not other individuals due to their genetic makeup and their environmental exposure. Different diseases, with different pathways, will eventually be identified in what we today call 'RA'. There are strong reasons to believe that the genetic makeup and the selective forces leading to arthritis are conserved between rodents and humans. Furthermore, rodents can be used to express the relevant human genes and test their importance [41–43]. Animal models such as this with well-characterized, testable pathways are excellent tools in this endeavor, and the GPI model is an important addition to the arsenal.

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