Animal Models in Rheumatoid Arthritis

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Knowledge of the pathogenesis and treatment of rheumatoid arthritis (RA) has experimented great advances in the past 25 years. The development of molecular biology techniques has contributed, without a doubt, to this advance, but it is not a coincidence that the start of this period came hand in hand with the development of animal models, such as antigen-induced arthritis (AIA) or specially, the discovery of the model of type II collagen-induced arthritis (CIA).

The list of murine models used for the study of RA and for the experimentation of new treatments is extense.[1-3] The adjuvant induced arthritis model in rats, which depends on the stimulation of macrophages and the consequent appearance of autoimmune B and T cells was widely used in the sixties to evaluate non-steroidal anti-inflammatory drugs (NSAIDs). Although in another model, AIA, there is synovial infiltration of T $CD4^+$ cells, B lymphocytes, mast cells, and macrophages and therefore is a model which is reasonably close to RA, while type II collagen-induced arthritis is currently the most widely used model because it is more similar to RA than the other models.[4] Mice or rats that are immunized with heterologous type II collagen, present a collagen-dependent, T $CD4^+$ cell mediated immune response. Secondary lesions in this response are similar to those in RA and include synovial inflammation, formation of pannus, cartilage, and bone erosion, and present only mild responses to NSAID therapy.

Other models involve antibody-induced arthritis, in which both anti-type II collagen as well as anti-glucose-6-phosphoisomerase antibodies are injected into the subject.[5,6] These passive models do not require an autoimmune response to induce arthritis and are used to study effector mechanisms. The creation of transgenic mice that overexpress cytokines are essential in the pathogenesis of RA, as is the case with tumor necrosis factor alpha (TNFα) or interleukin 1 (IL-1), providing a system to study the mechanisms of arthritis that depend on those cytokines and test their inhibitors preclinically.[7,8]

In spite of the existence of all of these models, it is well known that no animal model represents RA in its entirety. The artificial induction of arthritis, by over or underexpressing a gene, introducing chemical substances or immunizing with autoantigens, can activate inflammatory pathways which are different to those in humans, making the conclusions reached in these studies the subject of careful analysis.[9-11] In addition, clinical manifestations are different between different strains of mice, even if the same induction protocol is employed, and some of the strains are even selected due to their susceptibility to autoimmunity. The question that one must ask is how representative is an experimental model in a 12-week old lab mouse that has been raised in a germ-free environment for a heterogeneous population of patients with a long history of infections which have modified their immune repertoire. There are large immunologic differences between mice and humans and this has implications in the validity of these models. Therefore, it is important to evaluate the similarities between a certain animal model and the pathogenesis of human disease as an essential requirement before extrapolating the results.

Another point to consider is the elevated frequency of discrepancies in the results that are obtained when the same therapy is tested in different animal models of the same disease. For example, if there are 3 alternative animal models that can be preclinically employed to experiment with treatments destined for RA patients, one could think that the efficacy of this drug should be the same or at least similar to each one of the models. A recent retrospective study concluded that if a treatment was useful in the 2 animal models, AIA and CIA, these results predicted an improved clinical efficacy in patients with RA than if therapy was successful in only one of the 2 models.[12] In any case, these types of results are not always observed in preclinical studies and must not dissuade us from pursuing clinical trials in humans. There are many reasons for these discrepancies and some of these depend on diverse aspects and components of the disease that mimic that specific model. The diverse animal models have generally evolved to imitate only certain aspects of the disease, making a model very efficient in studying the defects in immune cells and another model can be useful for T cell traffic, while a third can be excellent in providing information

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on cell proliferation and death. It is improbable that a single animal model could assume and reproduce human disease in its entirety and oftentimes, little attention is paid to the precise mechanism that is represented by a certain model. For example, if one wishes to prove the potential benefit of a drug that inhibits T cell traffic, it is better to select an animal model in which T cell traffic has shown to be a major feature. This, of course, still leaves the question of whether T cell traffic is important in human disease. This information must be generated in a parallel manner through human cells or tissues that come from patients with the disease.

Because animal models only mimic different aspects of RA, the best use of these models is when questions are raised about the specific mechanisms: for example, does blocking substance X inhibit G cell migration through the endothelium? is a more effective question than, does the blockage of substance X prevent disease in this model? The specific question helps us: *a)* define the objective of the experiment; *b)* select the appropriate model; *c)* better understand the mechanism of therapeutic action; and *d)* interpret the response based on the knowledge of whether the study mechanism is important or not in RA.

All of these considerations explain why only some of the protocols that are effective on mice and rats reach the clinical level. The few cases in which trails with biologic drugs are a great success come in contrast to the long list of failures in which the observed effects in animal models are not reproduced in RA. Anti-histocompatibility molecule treatments, anti-T $CD4^+$ cell or anti-IL-1 treatments have led to contradicting results in patients with RA. For example, it is curious that inhibiting IL-1 is much more effective than inhibiting TNFα in the CIA murine model. Although these studies led us to believe that anti-IL-1 therapy had some promise, subsequent studies proved it to be of little efficacy. Although some authors might argue that maybe the pharmacokinetics of the new drugs does not allow for the efficacious inhibition of IL-1, other authors believe that IL-1 is simply not a central molecule in RA.[13] In addition, in the case of anti-T $CD4^+$ treatment, one can conclude that the depletion of T cells, especially those found in the synovium, is incomplete, or that CIA and AIA models, developed to study the initial autoimmune diseases of RA do not represent the chronic phase of the disease.[14]

In spite of everything that has been commented, animal models adequately reproduced specific aspects of the disease, whether it is regarding its pathogenesis, etiology or clinical course. The use of animal models has allowed us to study and understand the common principles in the chronicity of inflammatory processes and the pathways involved in cartilage and bone erosion and, therefore, have helped identify new therapeutic targets. Also, the CIA model is employed to test new therapies in the preclinical phase. Thanks to all of this, enormous progress has been made in the treatment of RA in the last decade and selective immune modulation has substituted general immunosuppressant therapy.[15] The preclinical results that have been obtained in the mouse models were decisive for the development of treatments with cytokine inhibitors such as IL-1 and TNFα. Anti-TNFα treatment[16,17] is the largest advance in this disease since the discovery of corticosteroids and since then, other immunomodulating selective treatments have started development, such as CTLA4Ig, which inhibits co-stimulating signals in T cells,[18,19] anti-CD20 antibodies which deplete B cells[20,21] or anti IL-6 therapy, another key cytokine in RA pathogenesis.[22-24] These successes teach us that when all of the abovementioned reflections are taken into account, the use of animal models is a valuable weapon that permits the discovery of new mechanisms and new therapeutic principles. And, if we review the recent literature and see the new therapies which have originated after these innovative and original ideas, and which are effective in the animal CIA models, we can expect a clear increase in new treatments for RA in the near future.[25,26]

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