Review

Association of MHC and rheumatoid arthritis
Why is rheumatoid arthritis associated with the MHC genetic region? An introduction

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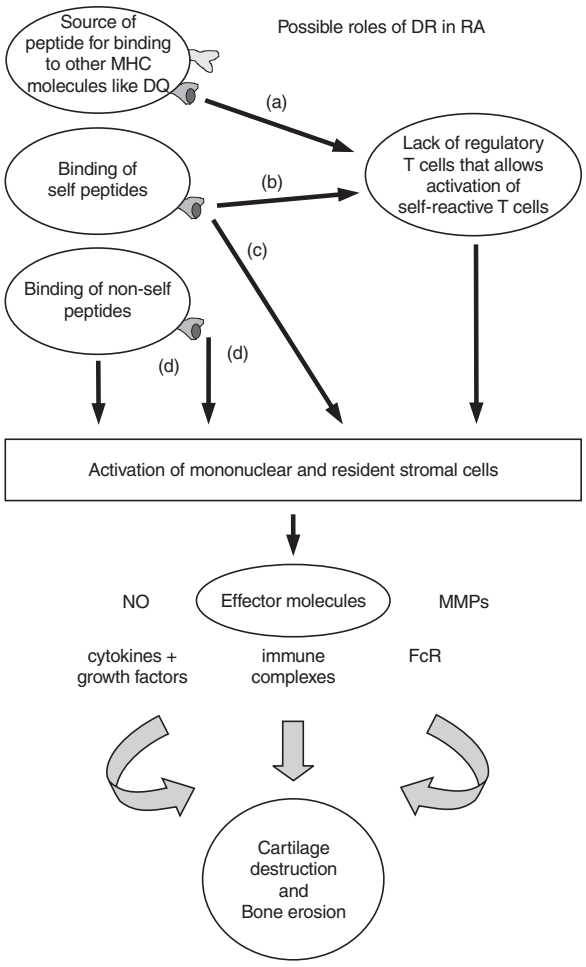
The apparent association of rheumatoid arthritis (RA) with the MHC region and, in particular, with the shared epitope present in the peptide-binding cleft of certain DR molecules has always amazed me. It is amazing because it suggests a narrow specificity of immune responses in RA whereas other observations suggest there should not be. Nevertheless, it is one of the few clear and unarguable findings that give us one end of a thread to unwind this complex disease. The MHC association was discovered decades ago and has been the subject of numerous investigations, but the mechanism is still not known. In fact, there is no indisputable evidence for which MHC gene or genes is responsible for the association. This is the time of unraveling the entire human genome sequence and, accordingly, there are expectations to find the genes that control our most common diseases. The MHC region was the first to be sequenced but this did not elucidate the mystery of its genes. Still, there are good candidates and, in fact, the shared epitope hypothesis gives strong arguments for a role of the DR molecule. It is under dispute whether other class II molecules are involved, such as DQ, or even other MHC molecules, such as tumor necrosis factor α, but let us say that the DR molecule (in particular, specific structures in its peptide binding pocket) does play an important role in the disease.

So, what does that mean? Several mechanisms have been proposed, all supported by circumstantial evidence (summarized in Fig. 1). Some of these thoughts and arguments [1–4] are collected in this *Arthritis Research* issue. All accept the role of the shared epitope of the DR molecule but, in Taneja and David's view [1], the role of the DR molecule is rather to deliver peptides to be bound to the DQ molecule. The shared epitope peptide fails to bind to the disease associated DQ molecules, which are then available to bind self-peptides of importance for the development of arthritis. Thus, DQ is the disease-associated molecule, as supported by mouse experiments, in which the expression of DQ8 is permissive for development of collagen induced arthritis (CIA). This is opposed by Fugger and Svejgaard [2], who argue that there is no evidence for a role for DQ in RA and that the expression of DR1 and DR4, with shared epitope, in mice also permits the development of CIA. However, neither of the alternatives, DR or both DR and DQ, directly explains the role of MHC in RA, although they cast some light on the mouse model of CIA.

It is easy to be enthusiastic about the possibility of directly humanizing animal models but I think there are reasons to treat them with great caution. The insertion of foreign genes will certainly give erroneous results that are easy to accept if they fit our thinking but difficult to explain if they do not. The mouse models will, however, give significant information by themselves. In the mouse model, it has been shown that a bottleneck in the pathogenesis is the T cell response to an immunodominant peptide bound to the murine A^q molecule, a finding reproduced by the human DR1 and DR4 which, in fact, have quite similar peptide-binding pockets. It leaves important questions, such as those about tolerance of collagen-reactive T cells and the downstream effector pathways, but it definitely provides a workable model. This model may, however, have little to do with RA or may reflect only one of the many pathways that can lead to RA. Weyand and Goronzy [3] point out one very important fact about RA, which tends to be forgotten in discussing mechanisms – that RA is most likely not a disease, but a syndrome that could be caused by many different diseases. This needs clearly to be taken into account when discussing the role of MHC. Thus, different DR alleles seem to be associated with different subforms of RA. And this is probably only the beginning of the dissection of RA in different specific diseases controlled by various sets of genes.

CIA = collagen induced arthritis; RA = rheumatoid arthritis

Figure 1



Some of the mechanisms proposed for the role of DR in RA. **(a)** DR molecules provides peptides for binding to other MHC molecules which will trigger T cells that regulate pahogenic T cells. **(b)** DR- self peptide complexes select the T cell repertoire that may have a regulatory impact on the activation of pathogenic T cells. **(c)** DR molecules bind self peptides, which may or may not be derived from joint tissue, that trigger pathogenic T cells. **(d)** Another possibility is that DR molecules binds peptides derived from infectious agents that may persist in the joints or give rise to a self cross-reactive T cells. Subsequently the activated T cells could induce, modulate or regulate the erosive destruction of the joints.

Thus, there is room for different mechanisms for how the MHC is involved in the pathogenesis of RA. One, very attractive, such explanation is the shaping of the T cell repertoire as proposed by Roudier [4]. Specific DR alleles do have an impact on the T cell repertoire and so have specific combinations of peptides bound to class II, which provides room for several attractive possibilities of cross-reactive responses to peptides from various infectious organisms. However, these connections need to be proven. Also, the role of a skewed T cell repertoire needs to be formulated and shown, although numerous experiments in experimental systems demonstrate the importance of regulatory cells selected in the thymus. Experimental models for RA are needed to test this point. Unfortunately, the presently used limited number of animal models has failed to show an importance of at least the genetically selected polymorphism of the T cell repertoire [5], but there are still experimental systems in which a somatic selected repertoire could be of importance [6]. However, as in all investigations of the pathogenesis of RA, it is difficult to sort out the hen and the egg, and the RA process in itself clearly results in a contracted T cell repertoire [7].

The solution of the MHC enigma is a Gordian knot in understanding RA, and it is still far from being cut. The role of MHC alleles in the subtypes of RA definitely needs to be known more precisely, and also the role at different phases of the disease. Maybe their role is to determine the self-perpetuative events rather than the susceptibility as such or, alternatively, to control the downstream effector phases of the disease. Such differences have been observed not only in RA, but also in various animal models [8,9]. Ways are also needed to directly address and prove our hypotheses. Some animal models, like CIA, have suggested a clearer proposal that needs to be challenged, and workable models for other hypotheses also need to be developed in order to test these possibilities. In this way we can further our understanding and improve our attempts at therapy for the various subsets of RA.

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