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HLA Transgenic Mice as Humanized Mouse Models of Disease and Immunity

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The application of molecular genetics to human disease in the past decade has been helpful in elucidating the genetic influences involved in the induction and pathogenesis of various autoimmune diseases. Among the numerous genes studied for their role in disease development, polymorphisms within HLA class I and class II loci play a significant role in predisposition to disease. HLA molecules are encoded by genes on the short arm of chromosome 6. Crystal structures of MHC molecules show a peptide binding cleft which contains the variable region of MHC molecules. Genetic polymorphism at the MHC determines the specificity and affinity of peptide binding and T cell recognition.

HLA molecules play a pivotal role in T cell repertoire selection in the thymus and antigen presentation in the periphery. Analysis of T cell responses in humans has involved the use of T cell lines or clones in vitro from naturally primed individuals. On the other hand, MHC restriction, mapping of epitope recognition, and T cell function in murine systems have been determined by in vivo studies. Various experimental animal models of autoimmune diseases have been studied, contributing greatly to our basic understanding of the disease. For example, type II collagen-induced arthritis (CIA)¹ in mice and rats has been used as an experimental model for RA. Even though the model differs in the manner polyarthritis is induced, disease expression is broadly similar to RA, with the occurrence of symmetrical peripheral polyarthritis and systemic inflammation.

Although growing knowledge of the functions of T and B cells in the immune response has shed light on their role in disease induction, the pathogenic mechanisms of most autoimmune diseases remain unresolved. There are many unanswered questions as to how tolerance to self is usually maintained, because autoreactive T cells can be found in normal as well as diseased individuals. How is tolerance broken in autoimmunity? Do specific autoantigens trigger the immune

system to mount tissue-destructive responses? These questions need to be solved for most of the autoimmune diseases.

Although the strongest MHC association with an autoimmune disease is between HLA class I B27 and spondyloarthropathies, class II alleles are implicated in most other cases. For example, RA is strongly associated with alleles of the DRB1 locus, whereas diabetes shows a stronger association with DQB1 alleles. HLA-DR and -DQ alleles are inherited en bloc and are known to occur in linkage disequilibrium. To better understand the role of HLA molecules in autoimmune diseases, transgenic animals expressing human HLA genes associated with disease have been developed. The generation of transgenic mice expressing functional HLA molecules has been an important step toward the creation of an in vivo model for enhancing our understanding of the function of human molecules in disease induction and predisposition.

The potential value of HLA transgenic animals as a "humanized" disease model was first illustrated in the HLA-B27 transgenic rat, which developed a disease resembling human spondyloarthropathies (1). Recently, spontaneous inflammatory arthritis was reported in B27 transgenic mice lacking β 2 microglobulin (2). To make the model analogous to human disease, the mouse β 2m was replaced with human β 2m. These studies emphasized the role of free class I MHC heavy chains present on the cell surface in the disease process (3). Thus, studies with HLA transgenic mice may solve some of the mysteries associated with human disease. This *Perspective* focuses on disease studies in transgenic mice expressing HLA-DR and HLA-DQ genes.

HLA-DR and HLA-DQ transgenic mice

MHC class II alleles determine the T cell repertoire in the thymus by presentation of self peptides. HLA-DR molecule has been shown to be a major restriction molecule for antigen presentation to T cells. However, very little is known about biologic function of the HLA-DQ molecule. Although HLA-DQ molecules occur in linkage with DR molecules, most of the human disease studies have concentrated on the association with DR molecules. Studies showing DQ association are limited to a few diseases. On the other hand, in the murine system the HLA-DQ analogous H2-A locus has a dominant role in immune responsiveness.

To determine the functional role of HLA class II molecules, several laboratories initiated the production of transgenic mice. The DR α transgene was expressed in the B10 mice, and paired with the endogenous H2-E β chain. The hybrid molecule was able to present MTV superantigen (4). A DQ6 β transgene in H2^f (H2-E negative) mice resulted in the expression of DQ6 β A α molecule capable of deleting T cell receptor V β 11 and V β 5 bearing lymphocytes (5, 6). These studies showed that the human class II chain can pair with mouse class II chains and effectively interact with mouse CD4. Double transgenic mice expressing DR3 α and DR3 β showed nega-

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1. Abbreviations used in this paper: CIA, collagen-induced arthritis; GAD65, glutamic acid decarboxylase 65; HT, Hashimoto's thyroiditis; NOD, nonobese diabetic; Tg, thyroglobulin; ZP3, zona pellucida 3.

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tive and positive selection similar to the H2E molecule, although with different efficiency (7). In contrast, in DQ6 $\alpha\beta$ double transgenic mice an antigen-specific response could not be generated (8).

Because CD4 T cells interact with the $\beta 2$ domain of class II molecules (9, 10), the possibility that there might be a species barrier for mouse CD4 interaction with human class II raised serious concerns for using HLA class II transgenic mice as models to study human diseases. However, comparison of HLA-restricted responses to a human MBP peptide in triple transgenic mice expressing DRA, DRB, and CD4 showed no difference between the Hu CD4⁺ and Hu CD4⁻ littermates. This supported the notion that, for some responses, the requirement for species-matched CD4 may not be absolute (11). In DR51 (DRB5*0102) and DQ6 transgenic mice, HLA-restricted response to peptides indicated that CD4 on murine T cells can function as an accessory molecule during peptide presentation by human HLA class II molecules (12). Fugger et al. (13) recovered a human class II-restricted response in DR4 (α and β) transgenic mice by coexpressing the human CD4 transgene under the control of the murine CD3- δ promoter. Thus Hu-CD4 was expressed on all cells that express murine CD3. These mice showed T cell repertoire selection, and an HLA-DR-restricted CD4⁺ T cell response to peptides. Similarly, transgenic mice expressing human CD4 and HLA-DQ6 molecules on an endogenous CD4/CD8-deficient background restored some human class II-restricted immune responses (14). However, success in generating consistent HLA class II-restricted responses in these transgenic mice was limited.

The xenogeneic barrier was circumvented by producing a human/mouse chimeric DR/H2-E chain in which the $\alpha 1$ and $\beta 1$ domains were from DR molecules, and the $\alpha 2$ and $\beta 2$ domains were derived from the H2-E molecule, so that murine CD4 molecules could interact with the $\beta 2$ domain of H2-E. Using this system, a human-mouse chimeric (HLA-DR4/H2E transgenic mice) was generated. Expression of these chimeric class II molecules influenced selection of the mouse T cell repertoire intrathymically, and such mice were capable of mounting DR-restricted immune response to either peptide or whole protein antigens (15). These animal models provide a powerful tool to study the role of HLA class II molecules in various autoimmune diseases. However, these mice are unable to mount pathologic immune responses. Furthermore, these mice expressed endogenous mouse class II molecules, a problematic issue in deciphering the role of transgenic HLA molecules in these animals.

HLA.DQ8.A β o transgenic mice are susceptible to CIA

An alternative approach to generate HLA class II-restricted responses in mice was to express HLA class II transgenes in animals deficient for endogenous class II expression. By disrupting the A β gene, Gosgrove et al. (16) generated mice that could not express H2A molecule (A β o). Because these mice were of the H2^b haplotype and lacked functional H2-E molecule, no class II molecules were expressed on the cell surface. Introduction of HLA transgenes into these mice could potentially generate disease models, because the only expressed class II molecules would be human derived. Transgenic mice were generated expressing a functional HLA-DQ8 (DQA1*0301, DQB1*0302) molecule on the class II-deficient A β o background (17). The only class II molecules expressed in these transgenic animals were encoded by the HLA-DQ8 α

and β genes. These mice showed a good expression of HLA-DQ, restored development of CD4⁺ T cells, and positively selected T cells expressing the various V β T cell receptors. Because the HLA-DQ8 gene occurs in linkage with DR4, an allele known to be associated with susceptibility to RA, this was an attractive model for studying the role of DQ molecules in joint inflammation. For the first time, the induction of a pathogenic autoimmune response in mice expressing a human MHC class II molecule was shown (18). Immunization of HLA-DQ8.A β o mice with bovine type II collagen (CII) led to a severe, RA-like polyarthritis. In addition, these mice could mount a strong DQ8-restricted and CD4-mediated response against the immunizing antigen. Not only did these mice produce antibodies to bovine CII but also to mouse CII which could have been crucial in the disease process. These findings established a novel humanized animal model to study autoimmune arthritis and suggested that HLA-DQ molecule might have an important role in determining susceptibility to RA. The demonstration that, in HLA transgenic A β o mice, human class II can function as an antigen-presenting molecule leading to a pathogenic response paved the way to explore the basis for the predisposition of HLA class II molecules to various autoimmune diseases.

DRB1 "shared epitope" shapes T cell repertoire

Studies in the mouse CIA model had shown that DR homologous H2-E molecules play a protective role (19). This protection seems to be mediated by the HV3 region of E β gene, the homologue of the region of the DRB1 that contains the shared epitope (20). A new hypothesis was proposed by Zanelli et al. (21), suggesting that the shared epitope shaped the T cell repertoire by serving as a self peptide for DQ molecules. Thus, high-affinity DR peptides binding to DQ molecules would negatively select an autoreactive T cell, while a low-affinity DR peptide would positively select the T cell. In fact, peptides from DR molecules are found naturally in the antigen-binding groove of DQ molecule. This hypothesis was explored in the DQ8.A β o transgenic mice, and the data showed that HV3 peptides derived from the non-RA-associated DRB1 molecules are highly immunogenic, while those derived from the RA-associated DRB1 alleles fail to induce a DQ8-restricted T cell response (22). Together these data suggested that polymorphism within DQ alleles can determine predisposition to RA while DRB1 molecules associated with susceptibility to RA may appear to play a permissive role. The notion was thus introduced that the combination of HLA-DQ and DR alleles (susceptibility inducing DQ and permissive DR) is responsible for the association of the HLA class II region with RA. Indirect support for this hypothesis comes from binding studies that show that DQ molecules bind multiple CII peptides as compared with DR molecules (23). Linkage studies have shown that the RA-associated DR haplotypes carry DQ4, DQ7, DQ8, and DQ9 alleles. Interestingly, the antigen-binding P1 pocket is identical in all of the four RA-associated DQ molecules, thus enabling them to present a common set of peptides (24). The hypothesis that polymorphisms within DQ molecules are important in determining disease susceptibility was confirmed when transgenic mice expressing DQA1*0103, DQB1*0601 (DQ6).A β o, an allele associated with resistance to RA, was also resistant to CIA (25). Similar to RA in HLA heterozygous human patients, double transgenic mice expressing both DQ6 and DQ8 molecules developed moderate CIA.

HLA-DR transgenic mice and CIA

Role of DRB1 polymorphism in RA was investigated using transgenic mice expressing the DR genes. The expression of the DR-homologous mouse H2-E molecule protected DQ8.A β mice against arthritis (26). Furthermore, the DR2 transgene introduced into CIA-susceptible H2-A^q mice was also protective (27). Whether DRB1 polymorphism could really alter the T cell repertoire and influence the outcome of DQ-restricted CIA was addressed using the HLA-DQ and -DR transgenic mice. Since DR and DQ genes are coexpressed in humans, the appropriate mouse should express both DR and DQ genes in A β mice. Therefore, we introduced both DR2 (DRB1*1502), an allele known to be associated with protection against RA in some populations, and DR3 (DRA1*0301, DQB1*0301), a neutral allele in most populations, into mouse class II negative A β mice. Studies using HLA-DQ8/DR2/A β and DQ8/DR3/A β mice showed clearly that DRB1 polymorphism can lead to differences in T cell repertoire selection and influence DQ-restricted arthritis. While DR2 protected DQ8 mice against arthritis significantly, the DR3 molecule did not alter the incidence of arthritis in DQ8 mice (28). The single transgenic DR2 and DR3 mice are resistant to CIA. These findings demonstrated the value of using double transgenic/knockout mice to study the interactive role of DR and DQ molecules in human disease. Studies with DQ8/DR4/A β mice would further shed light on this subject.

Recently, a role for DR1 in susceptibility to RA was studied in a transgenic mouse model of CIA using a chimeric DR molecule (29). The investigators showed severe arthritis and HLA-restricted responses in these transgenic animals. These animals express the endogenous mouse molecule (A^f), which can present CII arthritogenic peptides even though it does not itself induce disease. Thus, a possible interaction of mouse A^f with human DR in the disease induction cannot be ruled out. For example, the DR molecules in these mice may positively select autoreactive T cells which can then expand after presentation of the arthritogenic CII peptides by both A^f and DR and cause the tissue damage. Recently, we have made transgenic mice expressing the DRA1*0103, DRB1*0401 (DR4) molecule in mice deficient in endogenous class II molecules (our unpublished observations). The DR4 β 2 domain carries a mutation that promotes optimal interaction with mouse CD4. These mice can mount strong HLA-restricted responses to DR4-binding peptides showing that DR4 is functional. Immunization of these mice with bovine CII led to induction of mild arthritis. Introduction of DR4(DRB1*0401) gene into H2-A^q mice made them susceptible to severe arthritis induced by porcine CII. H2-A^q mice are resistant to porcine-induced CIA but can present porcine CII peptides. These studies suggest that certain DR molecules can cause mild arthritis, but require H2-A or HLA-DQ for severe arthritis. DQ8/DR4 transgenic mice currently being generated will further elucidate the role of DQ and DR in CIA to shed more light on RA.

Hashimoto's thyroiditis (HT)

Another human autoimmune disease with a well-known murine model is HT. Susceptibility to murine experimental autoimmune thyroiditis, a model for HT, is linked to H2-A molecules. In human patients, studies have not revealed a clear HLA association with HT, although a weak and controversial association with DR3 has been reported. Using DRB1*0301 and DRB1*1502 transgenic mice it was shown that a DRB1

polymorphism is a determining factor in susceptibility to autoimmune thyroiditis (30). Introduction of the DR3 gene in experimental autoimmune thyroiditis-resistant B10.M mice made them susceptible to the disease. Immunization with either mouse or human thyroglobulin (Tg) resulted in severe thyroiditis. Similarly in DR3.A β mice, immunization with Tg resulted in high antibody titers to mouse Tg and a severe disease. In contrast, DR2 transgenic mice were unresponsive to mouse Tg and resistant to thyroiditis. These data show the importance of using a humanized model to identify the potential autoantigens and mapping the epitopes involved in human disease.

Insulin-dependent diabetes mellitus

Predisposition to type 1 diabetes is strongly associated with the presence of DQ8, while DQ6 has been found to be protective. The nonobese diabetic (NOD) mouse is an animal model for spontaneous diabetes. To determine if HLA-DQ6 can protect against glycosuria and insulinitis, NOD mice expressing DQ6 transgene were studied. A lower incidence of glycosuria and insulinitis was observed in mice carrying the HLA transgene (31). Glutamic acid decarboxylase 65 (GAD65) is thought to be a potential autoantigen in disease development in human diabetes and NOD mice. Using DR4 transgenic mice, T cell epitopes of human GAD65 were mapped (32, 33). Wicker et al. (32) identified two naturally processed, DR4-restricted T cell epitopes from human GAD65. We studied transgenic mice expressing HLA-DQ8 and DQ6 to elucidate the T cell determinants on a putative islet cell target antigen, insulin. Differential recognition of epitopes on human preproinsulin polypeptide presented by the HLA-DQ8 allele as compared with DQ6 was observed (34). These studies suggest that transgenic mice can be used to define T cell epitopes to potential autoantigen which are relevant in the disease and that a strategy to downmodulate the autoimmune response can be formulated.

Multiple sclerosis

A well characterized autoimmune disease in which putative autoantigens (MBP and PLP) are known is multiple sclerosis. These autoantigens are known to cause experimental allergic encephalomyelitis in mice and rats. In most populations HLA-DRB1*1502/*1501 have been associated with disease, but HLA-DR4 is another allele which occurs with significant frequency in multiple sclerosis in some populations. Transgenic mice expressing HLA-DR4/H2-E chimeric class II molecules develop inflammatory lesions in white matter of the CNS (35). Although these results suggest a direct role of MHC class II molecules, the association was not clear since a chimeric molecule was used. Experiments using A β mice expressing transgenes DR3, DQ8, and DQ8/DR3 demonstrated an initial role for DR3 molecule and a supportive role for DQ8. DR3 mice get a mild disease, whereas A β .DQ8 mice are resistant to induction of disease upon immunization with MBP. However, the DQ molecule adds to the severity of disease, as DQ8/DR3 mice show very severe experimental allergic encephalomyelitis (36).

HLA transgenic mice in vaccine development

Another important and interesting area for use of HLA class II transgenic mice is in vaccine development. Individual MHC haplotypes dictate the response to a given antigen. Since the

antigen specificity of CD4⁺ T cells in humans is strongly controlled by HLA class II (DR) polymorphism, the immunogenicity and protective efficacy of candidate vaccines need to be defined in the context of HLA-DR polymorphism. A major challenge in human vaccine design is to overcome the variation in the immune response in a genetically heterogeneous outbred population. Human zona pellucida 3 (ZP3) is a target antigen for a contraceptive vaccine. However, immunization with ZP3 in primates has shown side effects. Immunogenicity and contraceptive potential of a chimeric peptide consisting of a native ZP3 B cell epitope and a known helper T cell epitope were evaluated in mice expressing HLA-DR3, DQ6, and DQ8 molecules (37). IgG antibodies were detected in mice expressing the human transgene upon immunization with human ZP3 peptide, proving that a T cell response can occur to the peptide when presented by each of these class II molecules. Thus, HLA transgenic mice provide a tool to evaluate the immunogenicity of a human peptide without human immunization. The widely used tuberculosis vaccine strain *Mycobacterium bovis* BCG remains among the most controversial vaccines today because of its varied protective efficacy. HLA transgenic mice may represent useful models for design of novel vaccines. HLA-DR3.Aβ mice immunized with *Mycobacterium tuberculosis* antigens hsp65 and BCG85 develop T cell responses to *M. tuberculosis* comparable to BCG immunization (38). The

same immunodominant epitopes are recognized by T cells from DR3.Aβ mice and DR3 humans, regardless of the mode of immunization, thus emphasizing the role of HLA class II molecules in controlling specificity of the T cell responses to the mycobacterium and underscoring the potential of HLA transgenic mice in design of novel vaccines.

Allergy

Another effective use of HLA transgenic mice has been to test allergies in different HLA haplotypes. Allergy affects ~20–25% of the population. Some allergic responses have been found to be associated with HLA class II alleles. House dust mite, *Dermatophagoides pteronyssinus* (*Der p*), is a source of allergens, causing symptoms ranging from atopic dermatitis to extrinsic asthma and allergic rhinitis. HLA-DQ8.Aβ mice are capable of mounting a DQ-restricted response to *Der p* antigens (39). Another common allergen is rye grass, which has been characterized as a major cause of hay fever. The responses of Aβ DQ6 and DQ8 mice to rye grass allergen showed that different epitopes were being recognized by the two DQ molecules (40). The use of HLA transgenic mice to determine HLA restriction of the allergen-specific T cell response will aid in understanding T cell involvement in the regulation of the allergic response, and in developing antagonist peptides for immunointervention.

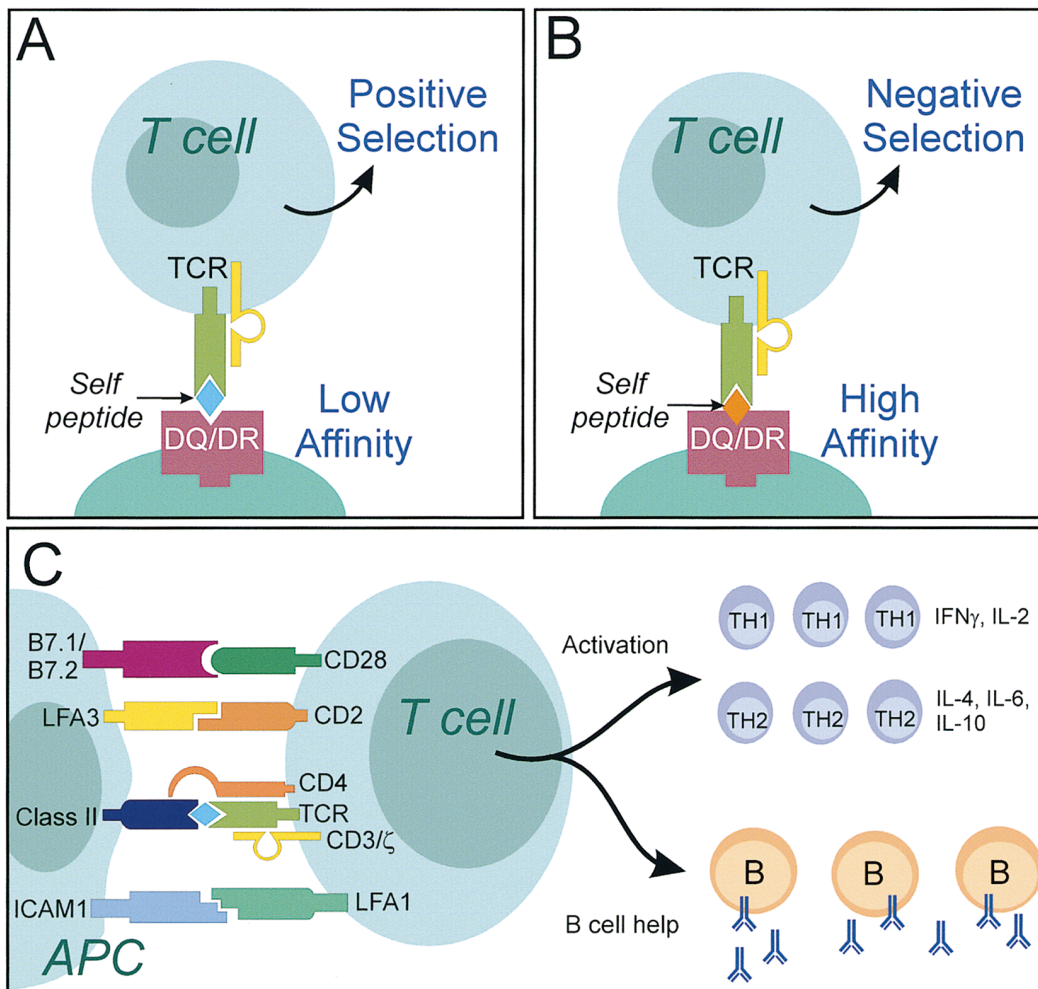


Figure 1. HLA molecules in transgenic mice lacking endogenous class II molecules can shape the T cell repertoire in the thymus of mice. (A) A self peptide with low binding affinity with HLA molecules can lead to positive selection of T cells in thymus, while (B) one with high affinity can lead to negative selection of T cells. (C) In the periphery, the positively selected CD4⁺ T cells can be activated by antigens being presented in the context of HLA class II molecules. Costimulatory and accessory molecules help in activation of T cells leading to Th1 or Th2 type response and also can provide B cell help to produce antibodies. A peripheral tolerance to HLA class II is maintained. Thus, in these mice HLA class II molecules act as “self MHC” molecules. Illustration by Naba Bora, Medical College of Georgia.

Thus, a new tool to study human disease has arrived. HLA transgenic mice used as disease models are one step closer to the human system than most conventional animal models, because the MHC molecules in these mice are the same ones involved in human disease. In the absence of endogenous class II molecules, the human class II molecules become the self-MHC in these mice. In the thymus, they interact with T cells and positively/negatively select T cells expressing various antigen receptors (Fig. 1). The costimulatory and accessory molecules treat the HLA molecules as self and interact with them. Thus, these transgenic mice provide an important tool for exploring much needed insight into pathophysiologic role of HLA class II molecules in various autoimmune diseases. The availability of such mice will allow us to explore the role of HLA class II molecules in shaping the T cell repertoire by presenting self peptides in the thymus. The trigger for the onset of disease in humans can be investigated by testing candidate autoantigens for presentation by the HLA molecules. The potential autoantigens could be evaluated for their capacity to induce disease. The epitopes on these antigens involved in the disease can be identified. Finally they can be used to evaluate potential therapeutic protocols and development of vaccines.

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