Humanized mouse models for organ-specific autoimmune diseases

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Murine models for human autoimmune diseases are an essential tool for studying pathogenesis and for identifying new therapeutic targets. Mice are not the natural disease host, and conventional models have proved to be poor predictors of efficacy and safety in recent trials aiming to translate drug and biologic treatments to humans. Evidently, further steps towards recapitulating human diseases are urgently needed, for example using transgenic predisposing human HLA allele(s) plus T-cell receptor(s) implicated in a representative patient's autoimmune disease. The latest development — humanizing most of the immune system by transplanting human hematopoietic stem cells into severely immunodeficient mice — should lead to even better modeling.

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Introduction

Autoimmune diseases are a major cause of morbidity and mortality in humans world-wide, collectively affecting 3–8% of the population [1]. Because their experimental dissection in humans is limited by technical and ethical considerations, biological models are important for understanding the natural underlying mechanisms in patients. To approximate these, researchers have relied mainly on the general homologies between mice and humans, tacitly assuming that any key differences will become obvious and will also shed new light. At best, however, any model can only recapitulate some of the key elements of the human disease.

The most commonly used model organism is the inbred mouse. Starting from a limited founder population of wild animals in the early 1900s, it has been developed into the present range of inbred strains with their distinct homozygous genomes [2]. These have been the primary laboratory animal for proof-of-concept experiments, and are increasingly used to assess potential therapies. However, the incomplete overlap between murine and human immunology clearly imposes major limitations in predicting their applicability in humans; examples of this include findings in conventional models for multiple sclerosis (MS; e.g. experimental autoimmune encephalomyelitis [EAE]), type 1 diabetes (T1D; e.g. nonobese diabetic mouse [NOD]) and rheumatoid arthritis (RA; e.g. collagen-induced arthritis [CIA]) [3–9].

Rapid translation of new immunological concepts into clinical treatments is limited by the paradox that we need to understand fully the genetics and pathogenesis of any disease before we can develop optimal models for it. For example, the premature assumption that MS was exclusively Th1-mediated led many groups to underestimate the potential of IL-17 producing Th cells and $CD8^+$ T cells [10,11]. To improve prediction, researchers have used evolving technologies to generate transgenic mice (since the early 1980s), to knockout specific molecules (since ~1990) and then to introduce human genes in place of their murine counterparts to better reproduce a human milieu [12]. However, this is fraught with the further problems of any venture into the unknown (Table 1). In this review, we discuss the limitations of such models for studying autoimmune diseases, the key mouse–human differences and how they could be minimized.

Current approaches in humanizing animal models for autoimmune diseases

Transgenic mice that express HLA class I and HLA class II susceptibility genes

The most widely used approach to humanize mice has been to introduce HLA class II transgenes. Obviously, this depends on prior proof that the disease truly is associated with the suspect class II allele rather than with one of its fellow travelers. Several groups have used such mice to identify auto-epitopes presented by the HLA alleles and have then compared them with those in the patients (reviewed in [12]). HLA class II-transgenic mouse models have also been established for imitating MS, RA, T1D, dermatitis herpetiformis or idiopathic dilated cardiomyopathy [12–14] (Table 2). Even though these models are not perfect, they mimic important

Table 1

Categories of mouse–human differences potentially relevant to autoimmune diseases.

Hematopoietic differences	Stromal differences
Antigen processing	Host autoantigen expression and cross-reaction
Epitope presentation by MHC	Host microbial flora, infections and diet
TCR repertoire and dominance	Thymic epithelium and selection
Ig V_H and V_L repertoires	Host BM and germinal centers
Complement components, receptors and regulators	Complement receptors and regulators
Cytokines and chemokines	Host cytokine and chemokine receptors
Co-receptor, co-stimulatory, adhesion and homing molecules	Host endothelium and stroma
Distribution of key molecules, e.g. MHC class II, CD40 on hematopoietic cells	Distribution of key molecules, e.g. MHC class II, CD40 on stromal cells

General factors: outbreeding, longevity, antigen experience, estrus and circadian cycles

aspects of the respective human diseases. They are now also being used to address more specific questions about the pathogenesis of autoimmune diseases. In an HLA-DR4-transgenic mouse model for RA, collagen type II-autoreactive T cells were detectable mainly in the joints early in the disease course [15]. Notably, that is consistent with the reported difficulty in detecting collagen-specific T cells in blood from patients who have ongoing RA. It argues instead for focusing on pre-treatment patients with early rather than established RA, and on synovial T cells in newly affected joints. Furthermore, in an HLA-DR1-transgenic mouse model for RA, there is more stringent regulation of processing of the arthritogenic glycosylated CII(261–273) epitope, which is implicated in the induction of autoimmune arthritis, than of its non-glycosylated form [16]. Mechanisms of this regulation might constitute novel therapeutic targets in RA.

Few autoimmune diseases show associations with MHC class I alleles, but the association between HLA-B27 and spondyloarthropathies, a group of seronegative inflammatory arthritis characterised by involvement of the spine, peripheral arthritis and enthesitis, are particularly strong and are thought to be $CD8^+$ T cell-mediated [17]. Again, in rats and mice transgenic for HLA-B27, this MHC class I allele is strongly implicated in the disease pathogenesis; rats with a high copy number of HLA-B*2705 transgenes show a syndrome similar to spondyloarthropathies, with peripheral and axial arthritis, gut inflammation, and genital and skin lesions [18]. Recent studies that have focused more on underlying mechanisms have shown that HLA-B27 misfolding is associated with intestinal inflammation in transgenic rats, whereas their arthropathy apparently has an independent pathogenesis [19].

Previously, $CD8^+$ T cells were considered irrelevant in most autoimmune diseases; recently, however, their importance has been highlighted as effector cells and in chronic phases of, for example, MS [11] and T1D [20,21]. Interestingly, the HLA class I region is implicated in both diseases, and recent studies in NOD mice transgenic for the associated HLA-A*0201 allele show earlier diabetes onset than those in conventional NOD mice [22]. Moreover, $CD8^+$ T cells kill both HLA-$A*0201^+$ murine and human islet cells, indicating both presentation of shared natural auto-epitopes by HLA-A*0201 and its potential relevance to T1D [23•]. This relevance is underlined by a report that autoantigen-reactive $CD8^+$ T cells are associated with β cell destruction in T1D patients [21].

$CD8^+$ T cells have also been implicated at earlier stages in idiopathic dilated cardiomyopathy — another disease that is, apparently, autoimmune. Similar pathology develops

Table 2

Examples of humanized models for autoimmune diseases expressing HLA transgenes.

Disease	HLA allele(s)	References
Multiple sclerosis	HLA-DRB1*1501	[25,48]
	HLA-DRB1*0401	[26,49]
Rheumatoid arthritis	HLA-DRB1*0401	[50]
	HLA-DRB*0101	[51]
Type 1 diabetes	HLA-DQB1*0302	[52]
	HLA-A*0201	[22]
Celiac disease/dermatitis herpetiformis	HLA-DQB1*0302	[13,53]
Spondyloarthropathy	HLA-B*2705	[18,54]
Thyroiditis	HLA-DQB1*0602 (H2-A^k)	[27]
Autoimmune cardiomyopathy	HLA-DQB1*0302	[14]