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Review

A methodological review of induced animal models of autoimmune diseases

Xinhua Yu [a,b,*], Frank Petersen [a]

[a] Research Center Borstel, Airway Research Center North (ARCN), Members of the German Center for Lung Research (DZL), 23845 Borstel, Germany
[b] Xiamen-Borstel Joint Laboratory of Autoimmunity, Medical College of Xiamen University, Xiamen, 361102, China

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ABSTRACT

Autoimmune disorders are characterized by a loss of immune tolerance and consequent autoimmunity-mediated disease manifestation. Experimental models are invaluable research tools helping us to understand disease pathogenesis and to search for novel therapeutics. Animal models of autoimmune diseases consist of two groups, spontaneous and induced models. In this review article, we focus on the induced models of autoimmune diseases. Due to the complex nature of autoimmune disorders, many strategies have been applied for the induction of corresponding experimental models in animals like monkeys, rabbits, rats, and mice. Methodologically, these strategies can be categorized into three categories, namely immunization with autoantigen, transfer of autoimmunity, and induction by environmental factors. In this review article, we aim to provide a comprehensive overview of the field of induced experimental autoimmune diseases. On the one hand, we describe and summarize the different strategies used for induction of experimental autoimmune disease. On the other hand, we discuss how to select a strategy for modeling human disease, including the choice of an appropriate species and method for such an approach.

Contents

* Corresponding author at: Research Center Borstel, Parkallee 22, D-23845 Borstel, Germany.
E-mail address: xinhuayu@fz-borstel.de (X. Yu).

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1. Introduction

Autoimmune diseases are characterized by a loss of self tolerance and consequent autoimmune attack against target tissues in the body. So far, more than 80 autoimmune disorders have been identified, affecting more than 10% of the population worldwide [1]. Experimental models are powerful research tools to explore the pathogenesis as well as for the search for novel therapeutics [2,3]. The first evidence of experimental autoimmune disease can be traced back to 1888, when some patients showed paralysis after repeatedly receiving rabbit virulent cord as rabies vaccination [4]. However, this important evidence was not recognized until 1933, when Rivers et al. demonstrated that repeated injection with healthy rabbit brain induced demyelization and paralysis in macaques [5]. This breakthrough and the invention of complete Freund's adjuvant [6] opened a new field of animal models of autoimmune diseases.

Animal models of autoimmune diseases refer to two groups, spontaneous and induced models. In the former group, animals with or without genetic modifications develop disease spontaneously [7], while in the latter group disease is artificially induced [8]. In this review, we focus on the group of induced models. Due to the complexity of autoimmune disorders in etiology and pathology, many strategies have been applied to induce autoimmune diseases in animals. According to their principle, those strategies can be grouped into three categories, namely immunization with autoantigen, transfer of autoimmunity, and induction by environmental factors (Table 1). To establish an animal model for a specific disease, the selection of an appropriate strategy and a suitable species are of great importance. In this methodological review, we aimed to provide a comprehensive overview of those strategies and a guide in the field of induction of experimental autoimmune diseases.

2. Strategies for the induction of experimental autoimmune diseases

2.1. Immunization with autoantigens

2.1.1. Immunization with tissue extracts

In 1947, Kabat and colleagues reported that the rapid and acute disseminated encephalomyelitis (now termed as experimental autoimmune encephalomyelitis, EAE) was induced in rhesus monkeys by immunization with heterologous and homologous brain tissue extract in presence of CFA [9], demonstrating for the first time that experimental autoimmune disease can be induced by immunization with whole target tissue extract. Since then, immunization with tissue extracts has been applied to induce various autoimmune disorders, including multiple sclerosis (MS) [10], autoimmune hepatitis (AIH) [11], autoimmune thyroiditis (AIT) [12], glomerulonephritis [13] myasthenia gravis (MG) [14], and autoimmune myocarditis (AIM) [15]. Interestingly, all abovementioned experimental models can be induced with homologous tissue extracts [9–12,15], with only one exception [13] where this issue has not been addressed. This phenomenon suggests that using whole tissue extract as antigen for immunization is an advantage for breaking the immune tolerance.

Table 1
Summary of strategies for induction of experimental autoimmune diseases.

Category	Strategies	Reference
Immunization with autoantigen	Immunization with tissue extracts	[9–15]
	Immunization with cells/cell extracts	[16–18]
	Immunization with specific protein	[21–31]
	Immunization with peptide	[32–37]
	Immunization of knock out animals with the outknocked protein	[38–40]
	Genetic immunization	[42]
	Virus immunization	[45]
Adoptive transfer of autoimmunity	Transfer of immune cells	[46–55,57–62]
	Transfer of serum/autoantibodies	[63–66]
Induction by environmental factors	Induction by infection	[73–75]
	Induction by drugs	[71,78,79]
	Induction by adjuvant	[69,81–83]

2.1.2. Immunization with cells

Some autoimmune diseases do not affect tissue or organs but target specific types of cells. For example, autoimmune thrombocytopenia (AITP) is a disorder of low blood platelet counts in which platelets are destroyed by autoantibodies [16]. To establish animal model for AITP, Musaji and colleagues immunized mice with rat platelets by repeated intraperitoneal injection [17]. After the immunization, mice developed a transient thrombocytopenia and autoantibodies capable of binding to and destroying platelets, which demonstrates the effectiveness of this immunization strategy.

Beside autoimmune diseases with a defined target cell, immunization with cells allows also modeling of disorders with cells which are putative candidates as autoimmune targets. In 2005, Taraseviciene-Stewart et al. reported that rats immunized with human umbilical vein endothelial cells (HUVEC) produce autoantibodies against EC and develop autoimmune emphysema [18]. Although emphysema is not regarded as an primary autoimmune disorder, autoantibodies against pulmonary EC present in sera of the patients and autoimmunity are suspected to be involved in the disease manifestation [19,20]. This model does not only demonstrate that autoimmunity could play a role in the pathogenesis of emphysema, but also provides an interesting idea how to model an autoimmune disease without clearly defined autoantigens.

2.1.3. Immunization with specific protein

Since tissue extracts and cells consist of a complex mixture of different potential antigens, immunization with such material is hampered by a low specificity of the induced model and these strategies also preclude the clear identification of the pathogenic autoantigen. Therefore, the identification of pathogenic autoantigen will help to increase the specificity in the established experimental models. In 1962, Laatsch et al. reported that immunizing guinea pigs with myelin basic protein (MBP) could induce EAE [21], suggesting that MBP is one critical encephalomyelitic autoantigen and resulting in the first animal model of autoimmune disease mediated by immunization with a single protein. Subsequent studies demonstrated that EAE can also be induced in mice by murine MBP [22], demonstrating that immunization with homologues autoantigen can break immune tolerance. However, due to the self-tolerance, induction of experimental autoimmune diseases by immunization with homologous autoantigen is limited [22,23].

Most proteins used as antigens for immunization are either heterologous or modified homologous proteins. Due to their immunological differences to the homologous antigens which help to break immune tolerance, heterologous antigens have been extensively used for immunization to induced animal models of many autoimmune diseases, including MG [24], rheumatoid arthritis [25], autoimmune uveitis [26], glomerulonephritis [27], and pemphigus vulgaris (PV) [28]. Beside heterologous antigens, homologous antigens with chemical modifications have been used for immunization. For example, recombinant homologous antigens supplemented with a GST-tag have been used for induction of experimental epidermolysis bullosa acquisita (EBA) [29] and experimental bullous pemphigoid (BP) [30]. In addition, immunization with homologous antigen conjugated to a peptide containing a T cells epitope has also been reported to be efficient for induce autoimmunity [31].

2.1.4. Peptide-based immunizations

Induction of autoimmune disease with specific proteins provides a chance for the identification of pathogenic epitopes recognized by T cells and autoantibodies. The identification of pathogenically relevant antigenic determinants can enable the establishment of animal models based on immunization with peptides. Due to their advantages in flexibility and availability, chemically synthesized peptides are widely used

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