The Relevance of Nonhuman Primates as Preclinical Model of Human Autoimmune Diseases

Introduction

Nonhuman primates are the closest living relatives of man. It can be envisaged that therefore a high degree of similarity exists between the immune systems of man and nonhuman primate species that are kept in laboratories for biomedical research. For example, based on genetic analysis the age of the shared ancestor of man and chimpanzees is estimated at \( \pm 5 \), of man and macaques at \( \pm 35 \) and man and marmosets at \( \pm 55 \) million years (Fig. 1). When plotted on the same scale man and rodents are more than 80 million years apart. Two loci within the highly polymorphic major histocompatibility complex, \( MHC-DR \) and \( -DQ \), have been implicated as major regulatory elements in various chronic autoimmune diseases (1). Both loci are shared between various primate species and even the sharing of allelic lineages has been documented (2). This close phylogenetic relationship with man, make disease models in macaques a valuable tool for the systematic dissection of genetic and immunological mechanisms that contribute to the induction and development of chronic autoimmune diseases.

Besides for its relevance in basic research, disease models in nonhuman primates are also important to test the safety and efficacy of new therapies (3, 4). In autoimmune diseases — like multiple sclerosis, autoimmune diabetes, rheumatoid arthritis and others — the mechanisms that in healthy individuals control the reactivity of the immune system towards the body’s own tissues are dysfunctioning. Such diseases have usually been treated with immunosuppressive therapies, such as with corticosteroids. However, systemic immunosuppression may put the patient at increased risk increased to infections with pathogenic micro-organisms or cancer. The increased understanding of the pathophysiological pathways that result in clinical expression of the various types of autoimmune diseases has led to the idea that more specific therapies can be developed to eliminate the ‘bad’ processes, while keeping the ‘good’ ones intact. With the help of biotechnological methods specific biological molecules (biologicals) — such as monoclonal antibodies, cytokines, cytokine antagonists etc. — can now be produced in sufficiently large quantities for clinical application.

The high species-specificity of most biologicals causes that, of molecules which show promising effects \textit{in vitro} and in rodent disease models, primate-specific versions need to be constructed for clinical application (Fig.2). When tested in humans
Fig. 1. The evolutionary relationship of nonhuman primate species is represented as a tree. The age of the shared ancestors of species is given in million years.

Fig. 2. Safety and efficacy tests in nonhuman primates often form the last preclinical step before new therapies are tested in the clinic.
a new complication emerged, namely that the \textit{in vivo} effects of the vast majority of biological molecules is seriously hampered by the induction of neutralising immune responses. This problem is now addressed by engineering the compounds to form human-like molecules. It can be envisaged that most rodent disease models are invalid to test the safety, immunogenicity and efficacy of primate-specific humanised molecules. In the past decade the interest in valid nonhuman primate models of human diseases has therefore strongly increased.

Spontaneous manifestation of chronic autoimmune diseases in wild populations of nonhuman primates, in particular of arthritides, has been documented. However, under laboratory conditions the incidence is too low to be of use as experimental model and therefore experimentally-induced models have been developed.

Collagen-induced arthritis (CIA) is one of the various experimental models for human arthritic diseases. CIA has been successfully induced in Old World monkey species, in particular macaques, by immunisation with heterologous type II collagen, from bovine or fowl origin. In contrast to some rodent strains, nonhuman primates seem resistant to arthritis induced with bacterial antigens (5). The clinical expression of CIA in rhesus macaques \textit{(Macaca mulatta)} shares various features with human rheumatoid arthritis (RA).

The majority of CIA-affected monkeys develop a symmetrical polyarthritis, which is most prominently expressed in the (meta)carpal and (meta)tarsal joints and in the interphalangeal joints of hands and feet. At a later stage the arthritis can progress to the larger synovial joints, such as knees, elbows and hips. Spondylitis is only rarely found. At the histological level, early stages of CIA are characterised by hyperplasia of the synovium, which is also infiltrated by large numbers of mononuclear cells. At that stage substantial degradation of the cartilage surface by overgrowing pannus-like tissue is taking place. At end-stage arthritis almost complete degradation of the cartilage and remodelling of bone is usually found (6). The possibility to monitor longitudinally the severity of inflammation and destruction of joint-tissues in a quantitative manner makes the model particularly attractive for preclinical testing of new anti-arthritic therapies (6).

All rhesus monkeys in the self-sustaining nonhuman primate colonies that are kept at BPRC are typed for MHC class I and II alleles. This has enabled us to associate the MHC class I and II alleles with clinical expression of autoimmune diseases, such as \textit{Mamu-DPB*01} with susceptibility to experimental autoimmune encephalomyelitis (7) and the MHC class I allele \textit{Mamu-A26} with resistance to CIA (8). The availability of genetically identifiable CIA-susceptible and -resistant monkeys has been very helpful in the identification of immunological and diagnostic parameters of CIA. As in rodent model of CIA the clinical expression of arthritis in rhesus monkeys results from the synergistic action of humoral and cellular autoimmune component. The failure to evoke arthritis was found associated with the incapacity to generate anti-type II collagen antibodies of the IgM isotype (9, 10). CIA in rhesus monkeys is essentially monophasic, implicating that after a disease period of 1 to 3 weeks spontaneous remission of the clinical signs takes place. In a minority of the monkeys a relapse of the clinical signs could be induced by booster-immunisation with type II collagen in incomplete adjuvant. Both the occurrence of disease-remission and exacerbation
appeared related to the *in vitro* responsiveness of peripheral blood mononuclear cells to the CIA inciting antigen (10).

To date it is not understood how the presence of a MHC class I allele (*Mamu-A26*) controls disease resistance in the rhesus monkey CIA model. DNA sequencing of *Mamu-A26* has shown that it is a MHC-B allele. The intriguing possibility that the strong positive association of HLA-B27 with ankylosing spondylitis and the negative association of *Mamu-A26* with CIA are functionally linked justifies detailed investigation. Importantly, the presence of *Mamu-A26* has no effect on the susceptibility to EAE (7) pointing at an antigen-specific phenomenon, implicating that the protective effect is likely exerted by the *Mamu-A26* molecule or the product of a closely linked gene. It is tempting to speculate that the resistance is based on molecular interaction between a MHC class II molecule binding a motif within the Mamu-A26 molecule. A similar model has been proposed by Zanelli and co-workers, namely the cognate interaction between HLA-DQ and -DR molecules in susceptibility regulation of rheumatoid arthritis (1). Experiments are now in progress to identify the ‘resistance’ motif and to test if this peptide induces resistance to CIA in *Mamu-A26*-negative monkeys.

**Concluding remarks**

According to the law on animal experimentation, nonhuman primates should not be used for experimentation when the same information can be obtained in rodents. The necessity to use nonhuman primates for a particular experiment should therefore always be seriously considered. In recent years the use of nonhuman primates in biomedical research has considerably increased. One of the main reasons is that many of the newly developed therapies, including those for treatment of chronic diseases, are exclusively reactive in man and closely related nonhuman primate species. However, refinement of the existing models is demanded to reduce the discomfort to the animals as much as possible. This could be reached by the development of non-invasive techniques to monitor the disease progression. The fact that we are now able to monitor joint-destruction in the rhesus monkey CIA model by measuring excretion of collagen split-products in the urine is an important step in that direction.

**References**


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