European Journal of Pharmacology 759 (2015) 278–286

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Animal models of rheumatoid arthritis: How informative are they?

Kay McNamee [a], Richard Williams [a,*], Michael Seed [b]

[a] Kennedy Institute of Rheumatology, University of Oxford, Roosevelt Drive, Oxford OX3 7FY, UK
[b] School of Health, Sport and Bioscience, University of East London, Water Lane, London E15 4LZ, UK

ARTICLE INFO

Article history:
Received 29 January 2015
Received in revised form
6 March 2015
Accepted 12 March 2015
Available online 27 March 2015

Keywords:
Rheumatoid arthritis
Animal models
Drug therapy
Biologics

ABSTRACT

Animal models of arthritis are widely used to de-convolute disease pathways and to identify novel drug targets and therapeutic approaches. However, the high attrition rates of drugs in Phase II/III rates means that a relatively small number of drugs reach the market, despite showing efficacy in pre-clinical models. There is also increasing awareness of the ethical issues surrounding the use of animal models of disease and it is timely, therefore, to review the relevance and translatability of animal models of arthritis. In this paper we review the most commonly used animal models in terms of their pathological similarities to human rheumatoid arthritis as well as their response to drug therapy. In general, the ability of animal models to predict efficacy of biologics in man has been good. However, the predictive power of animal models for small molecules has been variable, probably because of differences in the levels of target knockdown achievable in vivo.

1. Introduction

Animal models of arthritis have been used extensively to test identify drug targets for rheumatoid arthritis (RA) and test potential therapeutics. However, concerns about low clinical development success rates for investigational drugs (Hay et al., 2014), coupled with increasing awareness of the ethical issues surrounding the use of animal models, have led many to question their utility. It is timely, therefore, to review the most commonly used models in terms of their pathological relevance to human RA and in terms of their response to therapeutic intervention.

2. Overview of RA

RA affects 0.5–1% of the population in the UK and has a lifetime risk of 4% for women and 2% for men. For many, RA is a painful and disabling disease associated with chronic inflammation. RA is one of the most common causes of disability in the western world with the age of onset typically between 25 and 50, although it can occur at any age. The principal pathological features of the disease include inflammatory erosive synovitis that ultimately leads to destruction of cartilage, bone and soft tissues, resulting in long-term deformity and loss of joint function. Although joints are the main target of the disease process in RA, patients may present with extra-articular features, including sub-cutaneous nodules, vasculitis and pulmonary fibrosis, especially in the more severe cases.

Conventional treatment choices RA include corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) and for patients who fail to respond adequately to these drugs the additional use of biopharmaceuticals, in particular TNF inhibitors, offers greater opportunities for disease management. However, despite the undoubted success of anti-TNFα, only a quarter of patients treated with a combination of a TNFα inhibitor plus methotrexate achieve disease remission (defined as a DAS-28 score of less than 2.6). In addition, up to 50% of primary responders lose their response within 12 months of the start of therapy (Buch et al., 2007). Hence, there remains a need for more effective anti-arthritic medicines.

The search for new drugs goes hand-in-hand with attempts to understand the aetiopathogenesis of RA and genetic factors are known to play an important role in determining susceptibility to the disease. Indeed, the association between RA susceptibility and specific HLA DRB1 alleles has been demonstrated in a number of populations around the world (Silman and Pearson, 2002). A concept emerged more than a quarter of a century ago suggesting that $CD4^+$ T cells play an important role in the pathogenesis of the disease (Janossy et al., 1981), due to the presence of large numbers of T cells in the joints of RA patients and the association of MHC class II with RA, for which the only known function is to present peptide antigens to $CD4^+$ T cells.

This has developed further with the increased understanding that RA patients present with different synovial pathological

* Corresponding author.
E-mail address: Richard.williams@kennedy.ox.ac.uk (R. Williams).

http://dx.doi.org/10.1016/j.ejphar.2015.03.047
0014-2999/

features that may relate to different RA phenotypes (Pitzalis et al., 2013a). The complexities of 'antigen drift' as the disease develops, and accompanying differences in emphasis between cell types, such as $CD4^+$, Th17, and B-cells during this evolution is making RA a disease that has increasing potential for personalised medicine. The prediction of clinical efficacy from RA animal models should therefore be accompanied with a deep understanding of the mechanisms employed and how they relate to the human disease (Pitzalis et al., 2013b).

3. Models commonly used for drug testing

3.1. Collagen-induced arthritis (CIA)

Arthritis is induced in susceptible strains of rats and mice by immunisation with type II collagen in incomplete Freund's adjuvant (IFA) or complete Freund's adjuvant (CFA), respectively (Holmdahl et al., 1989; Trentham, 1982). Both T helper (Th) 1 and (Th17) responses are induced in CIA, but Th17 cells appear to play the dominant pathological role (Murphy et al., 2003). The histology of CIA resembles RA in terms of the infiltrating cells in synovial tissue and destruction of bone and cartilage. CIA susceptibility is linked to the I-A region of the $H\text{-}2^q$ and $H\text{-}2^r$ haplotypes in mice. Analysis of the I-A chains of alleles from susceptible and resistant strain (B10.Q) indicated that susceptibility is associated with a four-amino-acid sequence in the I-Aβ chain (Nabozny et al., 1994). This sequence is located in a region associated with binding antigenic peptide, analogous to the genetic susceptibility observed in RA in humans conferred by the DRβ chain. The induction of arthritis in mice of a C57BL/6 ($H\text{-}2^b$) background (Campbell et al., 2000; Inglis et al., 2007a) has facilitated the use of gene knockout mice and a more recent development of this has been the generation of the congenic C57Bl/6N.Q strain, that expresses the arthritis susceptible q haplotype of the MHC class II region (Backlund et al., 2013). Rat collagen arthritis is the next most common model used, and is likewise based on the rat equivalent to murine Class 1a, namely MHC Class II RT1 complex, with susceptibility being dominant.

3.2. Adjuvant-induced arthritis

The adjuvant-induced arthritis (AIA) model was established following the finding that certain strains of rats develop arthritis following administration of CFA (Pearson, 1956). It was initially thought that components of the mycobacteria cross-reacted with joint-specific self-antigens, such as heat shock proteins (van Eden et al., 1988). However, even non-antigenic adjuvants, such as muramyl dipeptide, incomplete Freund's adjuvant and CP20961 can also induce arthritis and it was suggested that these adjuvants may enhance reactivity to self-antigens in the joint (Kohashi et al., 1982). The mechanisms underlying induction of AIA are not fully understood but the fact that susceptibility is linked to certain MHC class alleles (Lorentzen and Klareskog, 1996; Vingsbo et al., 1995) and that antibodies to CD4 and MHC class II molecules can inhibit disease (Holmdahl et al., 1992; Larsson et al., 1985) confirms the importance of $CD4^+$ T cells. The mechanisms underlying CFA and the mineral oil arthritides are different, with the sensitisation to mycobacterial antigens playing a large role in the former. A difference between adjuvant and collagen arthritis is that resistance is dominant in adjuvant disease, and MHC playing a lesser role, though still significant. Non-MHC phenotypes contribute significantly, such as the *Aia1, Aia2, and Aia3* regions (Joe et al., 2002). A difference between AIA and RA is that AIA displays a fairly rapid remission while human RA is a chronic disease. In contrast, arthritis induced by the lipid, pristane (2,6,10,14-tetramethylpentadecane), follows a more chronic relapsing disease course (Bedwell et al., 1987).

3.3. Antigen-induced arthritis

Antigen-induced arthritis is seen in mice, rats and rabbits following intra-articular injection of protein antigen (e.g. methylated bovine serum albumin) into the knee joints of animals that have previously immunised with the same antigen (Brackertz et al., 1977; Dumonde and Glynn, 1962). The cellular basis is very similar to CIA, but with more tightly defined sensitisation and challenge steps that can be exploited. It is $CD4^+$ T-cell dependent. The histopathological appearance of antigen-induced arthritis bears similarities to RA, including synovial lining layer hyperplasia, perivascular infiltration with lymphocytes and plasma cells, lymphoid follicles, pannus and cartilage erosions. Indeed repeated injections of antigen can induce ectopic lymphoid structures (ELS) similar in appearance to those seen in RA patient subsets. The erosiveness is related to the ability of the antigen to bind cartilage. However, unlike RA, antigen-induced arthritis is a monoarticular disease that affects only the injected joints. Susceptibility to antigen-induced arthritis is not MHC class II restricted and this makes the model useful for studies involving transgenic and gene knock-out mice.

3.4. Bacterial cell wall-induced arthritis

Injection of bacterial cell wall structures can induce arthritis in susceptible strains of rats which is clinically similar to human RA. A single intraperitoneal injection of cell walls may induce a cycle of exacerbation and remission of arthritis. The development of arthritis is thought to be due to accumulation of bacterial cell wall fragments in the joints and once disease is initiated, recurrence can be triggered by microbial superantigens that activate T cells with specific *Vβ* genes in an antigen-independent manner (Schwab et al., 1993).

3.5. Spontaneous models

Arthritis occurs spontaneously in mice expressing a modified transgene encoding human TNFα which has been dysregulated by the replacement of the 3′ AU rich region with the 3′ untranslated region of the human β-globin gene (Keffer et al., 1991). Synovial cells of the joint are a major source of the transgenic TNFα expression.

The K/BxN model arose from transgenic expression of a TCR specific for a peptide from bovine pancreatic ribonuclease. These mice spontaneously developed arthritis when bred on to the NOD background (Kouskoff et al., 1996). Further studies revealed that the development of arthritis in K/BxN mice was dependent on I-Ag7 MHC class II molecules and could be blocked by treatment non-depleting anti-CD4 mAb (Korganow et al., 1999; Kouskoff et al., 1996; Mangialaio et al., 1999). Although this is highly suggestive that the disease is driven by $CD4^+$ T cells, it was also found that the development of arthritis required the presence of B lymphocytes (Korganow et al., 1999; Kouskoff et al., 1996). Furthermore, transient arthritis could be transferred by injecting naive mice with serum IgG from arthritic mice in a complement-dependent and FcγR-dependent manner, indicating the pathological role played by autoantibodies in this model (Corr and Crain, 2002; Korganow et al., 1999; Solomon et al., 2002). The molecular target of the autoantibodies was identified as glucose-6-phosphate isomerase (GPI), a ubiquitous cytoplasmic enzyme in the context of I-Ag7 MHC class II molecules (Matsumoto et al., 1999).

Sakaguchi et al. (2003) described a model of arthritis that occurred spontaneously in mice carrying a point mutation of the gene encoding ZAP-70, a key signal transduction molecule in T cells. It was proposed that altered T-cell receptor signalling as a