arthritis research&therapy

EDITORIAL

Characterization of a novel and spontaneous mouse model of inflammatory arthritis

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Abstract

Arthritis is a heterogeneous disease comprising a group of inflammatory and non-inflammatory conditions that can cause pain, stiffness and swelling in the joints. Mouse models of rheumatoid arthritis (RA) have been critical for identifying genetic and cellular mechanisms of RA and several new mouse models have been produced. Various methods have been applied to induce experimental models of arthritis in animals that would provide important insights into the etiopathogenetic mechanisms of human RA. Adipue and colleagues recently discovered that mice in their breeding colony spontaneously developed inflamed joints reminiscent of RA and may, therefore, have found a new model to examine pathogenic mechanisms and test new treatments for this human inflammatory disease.

Mouse model of rheumatoid arthritis

Adipue and colleagues [1] have characterized the novel IIJ (inherited inflamed joints) mouse strain, a new murine model of inflammatory, possibly autoimmune, arthritis that is similar both histologically and serologically to human rheumatoid arthritis (RA) and other murine models of autoimmune arthritis [1]. RA is a chronic and progressive inflammatory disorder characterized by synovitis and severe joint destruction. The pathogenesis of RA is a complex process, involving synovial cell proliferation and fibrosis, pannus formation, and cartilage and bone erosion [2]. Rodent models of RA have been used extensively to evaluate potential new therapeutic agents.

Arthritis in the mouse can be induced, can occur spontaneously in some inbred strains, or can result from single gene mutations (Table 1). Induced murine arthritis models include immunization with type II collagen (DBA/1LacJ), or treatment with pristane (BALB/c), thymocytes (C3H/He), mycoplasma (CBA), or a high fat diet (C57BL). Spontaneous models can be grouped according to their origin: development of autoimmune-prone strains by selective mixing of previously existing inbred strains (for example, the MRL/lpr strain [3]); targeted gene manipulation (for example, the TCR transgenic K/BxN model [4], TNF-α overexpression models [5], the IL-1Ra knock-out model [6], and the gp130Y759F-induced mutant); and identification of spontaneous mutants from breeding colonies (for example, SKG mice with a point mutation in Zap-70 [7]).

Despite the existence of all of these models, it is well known that no animal model represents RA in its entirety. In addition, clinical manifestations are different between different strains of mice, even if the same induction protocol is employed, and some of the strains are even selected because of their susceptibility to autoimmunity. Even though it is improbable that a single animal model could assume and reproduce human disease in its entirety and consistently, animal models have allowed us to understand common principles of the induction and persistence of inflammatory processes and the pathways involved in cartilage and bone erosion and, therefore, have helped identify new therapeutic targets (Table 2).

Characterization of a novel and spontaneous mouse model of inflammatory arthritis

Adipue and colleagues [1] describe a new strain of mouse that spontaneously develops a chronic inflammatory, possibly autoimmune, arthritis that shares many similarities with human RA and other mouse models of arthritis. The authors point out that arthritis incidence in IIJ mice also displays the sex bias common to many complex autoimmune diseases such as RA, multiple sclerosis, and systemic lupus erythematosus [8]. The sex bias appears to be specific for the arthritis phenotype since the incidence of typhlocolitis was similar between male and female IIJ mice. As most models reach 100% incidence in both sexes, no other spontaneous mouse model of arthritis has displayed such a sex bias, although more severe arthritis

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Table 1. Animal models of arthritis

Model	Abbreviation	Species	Feature
Induced models			
Non-specific immune stimuli			
Adjuvant-induced arthritis	AA	Lewis rat	Autoimmune
Oil-induced arthritis	OIA	DA rat	Autoimmune
Pristane-induced arthritis	PIA	DA ra	Autoimmune
Cartilage directed autoimmunity			
Collagen-induced arthritis	CIA	DBA mouse	CII AI
Proteoglycan-induced arthritis	PGIA	Balb/c mouse	PG AI
Infectious agents/exogenous triggers			
Streptococcal cell wall arthritis	SCW-A	Lewis rat	Persistent bacteria AI
Flare	SCW-F	Mouse	Th17
Antigen-induced arthritis	AIA	Rabbit, mouse	Persistent antigen
Flare	AIA-F	Mouse	Th17
Transgenic spontaneous models			
HTLV-induced arthritis	HTLV	Mouse	Viral tax antigen
KRN arthritis	KRN	K/BxN mouse	GPI AI
SKG arthritis	SKG	Mouse	ZAP-70 T cell defect
GP130 arthritis	GP130	Mouse	STAT3, T cell defect
TNF transgenic arthritis	TNFtg	Mouse	TNF overexpression
IL-1ra transgenic arthritis	IL-1ra-/-	Balb/c mouse	Autoimmune T cells
IL-1 transgenic arthritis	IL-1tg	Mouse	IL-1 overexpression
Immune complex models			
Collagen type II	CAIA	DBA mouse	Mouse CII antibody
KRN serum	GPI	Balb/c mouse	Mouse GPI antibody
Poly-L-lysine-lysozyme	PLL-L	DBA mouse	Cationic antigen
New animal model			
Spontaneous			
Inherited inflamed joints strain	IIJ	Arthritic male mouse crossed with SJL/J females	Autoimmune arthritis (for understanding the female bias)

AI, autoimmunity; CII, collagen type II; GPI, glucose-6-phosphate isomerase; HTLV, human T-lymphotropic virus; IL, interleukin; KRN, C57Bl/6 mice carrying the KRN transgene heterozygously; PG, proteoglycan; SKG, SKG strain, derived from closed breeding colony of BALB/c mice, spontaneously develops chronic arthritis; TNF, tumor necrosis factor.

in females has been reported for both the SKG [7] and gp130Y759F models [9]. A female bias in incidence was also observed in collagen-induced arthritis in humanized HLA-DR4-transgenic mice [10] and was attributed to both hyperactive B cells and HLA-DR4 restricted antigen presentation in female mice and increased numbers of T and B regulatory cells in male mice [11]. In particular, Adipue and colleagues emphasize that the histopathology in IIJ mice is similar to that described in previously published mouse models of autoimmune arthritis [7,9]. In addition, the predominantly neutrophilic and lymphocytic infiltration into the inflamed IIJ joints parallels the large numbers of neutrophils and T cells present in the inflamed synovial fluid of RA patients [12]. Finally, the IIJ mice also share serological similarities with RA and some other mouse models.

Conclusion

Adipue and colleagues have identified the IIJ strain as a new murine model of inflammatory, possibly autoimmune, arthritis. The IIJ strain is similar both histologically and serologically to RA and other murine models of autoimmune arthritis. Moreover, the increased incidence of arthritis in female IIJ mice makes it a potentially important model to study the underlying causes of sex bias in autoimmunity.

Abbreviations

IIJ, inherited inflamed joint; IL, interleukin; RA, rheumatoid arthritis.

Competing interests

The author declares that they have no competing interests.

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Table 2. Drugs used to treat arthritis

Type of drug	Name of drug	Use
Drugs that affect symptoms of the disease (analgesics)	Acetaminophen	Relieves pain
	Aspirin	Reduces inflammation and relieves pain
Oral nonsteroidal anti-inflammatory drugs (NSAIDs)	Diclofenac	Reduces inflammation and relieves pain
	Diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin	All NSAIDs treat the symptoms and decrease inflammation but do not alter the course of the disease
COX-2 inhibitors	Celecoxib, valdecoxib	Reduces inflammation and relieves pain
Narcotic/analgesics	Propoxyphene	Relieves pain
	Tramadol	Relieves pain
Corticosteroids	Methylprednisolone, prednisone, injectable corticosteroids	Suppresses inflammation in severe organ disease or life-threatening disease
Disease-modifying antirheumatic drugs (DMARDs)[a]	Auranofin (oral gold), cyclosporine, gold salts (injectable), hydroxychloroquine, leflunomide, methotrexate, penicillamine, sulfasalazine	All DMARDs can slow progression of joint damage as well as gradually decrease pain and swelling
Biologics		
Anti-TNF compounds	Adalimumab, etanercept, infliximab, certolizumab, golimumab	Suppresses inflammation and inhibit the progress of joint damage
IL-1 inhibitor	Anakinra	Treats moderate to severe RA in people who do not respond to DMARDs
B-cell-depleting agent	Rituximab	Treats RA unresponsive to TNF inhibitors
T-cell co-stimulation antagonist	Abatacept	Treats RA unresponsive to DMARD therapy
IL-6 antagonist	Tocilizumab	Treats RA unresponsive to TNF inhibitors

COX, cyclooxygenase; DMARD, disease-modifying anti-rheumatic drug; IL, interleukin; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

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