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).

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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...
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 Al                   |
| Proteoglycan-induced arthritis             | PGIA         | Balb/c mouse    | PG Al                    |
| Infectious agents/exogenous triggers      |              |                 |                          |
| Staphylococcal cell wall arthritis         | SCW-A        | Lewis rat       | Persistent bacteria Al   |
| 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 Al                   |
| SKG arthritis                              | SKG          | Mouse           | ZAP-70 T cell defect     |
| GP130 arthritis                            | GP1 30       | Mouse           | STAT3, T cell defect     |
| TNF transgenic arthritis                   | TNFtg        | Mouse           | TNF overexpression       |
| IL-1α transgenic arthritis                 | IL-1α/-      | 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                           |              |                 |                          |
| 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, tolfenin | 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)‡    | 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                                         | Adalimumab, etanercept, infliximab, certolizumab, golimumab | Suppresses inflammation and inhibits the progress of joint damage |
| Anti-TNF compounds                                | Anakinra                              | Treats moderate to severe RA in people who do not respond to DMARDs |
| IL-1 inhibitor                                    | Rituximab                             | Treats RA unresponsive to TNF inhibitors                            |
| B-cell-depleting agent                            | Abatacept                             | Treats RA unresponsive to DMARD therapy                             |
| T-cell co-stimulation antagonist                  | Tocilizumab                           | Treats RA unresponsive to TNF inhibitors                            |
| IL-6 antagonist                                   |                                      |                                                                    |

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

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