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Rheumatoid arthritis animal model in mice

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that causes significant disability and has a high recurrence rate. Currently, there is no cure for this disease. Identifying the cause of RA and developing new targeted therapeutic drugs have become priority research areas. Animal models of RA are critical in understanding the disease's pathogenesis and the effectiveness of drug treatments. This review summarizes the most recent progress in developing mouse models of autoimmune arthritis to serve as a reference for the study of experimental animal models that are more similar to the pathological features of human RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease characterized by persistent synovitis, which can occur at any age.[1] The primary pathological features are abnormal proliferation of synovial membranes and surrounding connective tissues, blood vessels formation, and structural damage to ligaments, cartilage, and bone.[2] Clinical manifestations of RA include joint swelling, pain, stiffness, and limited mobility, which can ultimately lead to joint dysfunction or disability.[3] RA can also affect extra-articular organs such as the skin, heart, lungs, and eyes. Accordingly, the unclear pathogenesis of RA, treatment for this disease is limited to slowing its progression; consequently, it has become one of the global research hotspots because there are no preventive or curative drugs available.[4,5] Therefore, establishing of effective animal models during the preclinical stage of drug development is of great significance for conducting research on RA treatment.[6] This review summarizes commonly used mouse models of RA to provide a basis and reference for developing future animal models that more closely resemble human RA disease characteristics.[7]

2. Induced arthritis model

2.1. Collagen-induced arthritis model

Trentham developed the collagen-induced arthritis model (CIA) for animal arthritis research.[8] Type II collagen found in various animals can cause arthritis. Autoantibodies against type II collagen have been found in RA patients' serum and synovial fluid, indicating that type II collagen may play a role in the disease's pathogenesis.[9] The CIA, an endogenous self-antigen-mediated animal model, is primarily regulated by two types of T cells, Th1 and Th2, which reach equilibrium following immunization.[10] When the Th1/Th2 subgroups in the blood are imbalanced, serum levels of IL-1β and tumor necrosis factor (TNF)-α increase due to excessive immune responses mediated by glycan-dependent lymphocyte homing to lymph nodes.[11]

Type II collagen protein (CII) was combined with complete Freund's adjuvant in equal parts to make an emulsion for the first immunization induction. After 21 days, an incomplete Freund's adjuvant was used for booster immunization. Alternatively, booster immunization can be performed using a mixture of emulsions containing equal amounts of type II collagen protein and incomplete Freund's adjuvant. The CIA animal model is more stable over time, but its onset is slower.[12] The disease's peak incidence occurs between days 26 and 35 following the first immunization. DBA/1 mice are commonly used because they respond to type II collagen protein in chickens, cattle, and pigs.[13] According to studies using the CIA model, patients with RA have a high concentration of nuclear rod bacteria, which is positively correlated with the severity of the disease.[14] In this model, baricitinib was found to reduce the severity of arthritis symptoms while also improving neuropsychological symptoms like depression and fatigue.[15]

2.2. Collagen antibody-induced arthritis model

The collagen antibody-induced arthritis model (CAIA) extends the CIA model. This model induces severe arthritis in mice using

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monoclonal antibodies against a specific binding site within type II collagen combined with lipopolysaccharide administration.[16] The clinical and pathological features of the disease are like those of the CIA. However, the disease is primarily defined by the infiltration of macrophages, multinucleated cells, and inflammatory cells rather than by T and B cell responses. This model is ideal for investigating individual gene products and cytokines and screening and testing anti-inflammatory and immunomodulatory drugs.[17]

The method involves injecting monoclonal type II collagen antibodies into mice's peritoneal cavity on day 0, followed by LPS injections from *Escherichia coli* on day 3. After 2–4 days of initial immunization, signs of inflammation appear, followed by severe arthritis on days 6–8. CAIA has a high incidence, reproducibility, and stability, and it can cause arthritis in nearly all mouse strains, including those insensitive to the CIA model.[18,19] Studies have used the CAIA model to investigate the role of LPA signaling.[20] The relationship between changes in tryptophan metabolism and inflammatory diseases was investigated by combining the CAIA model and quantitative tryptophan metabolomics.[21]

2.3. Adjuvant-induced arthritis model

The adjuvant-induced arthritis (AA) model is a traditional RA modeling method that relies primarily on Freund's adjuvant, which includes both complete Freund's adjuvant (CFA) containing heat-killed *Mycobacterium tuberculosis* and incomplete Freund's adjuvant (IFA) lacking bacterial components.[22] A protein in *Mycobacterium tuberculosis* has a structure similar to a glycoprotein molecule found on the synovial membranes of joints. Freund's adjuvant injection activates the immune system, which can trigger T cells to mistakenly attack the joints, resulting in an immune response against the joints.[23] This model resembles human RA regarding disease symptoms, pathological manifestations, and extra-articular symptoms.

The procedure entails injecting Freund's adjuvant into the ankles and surrounding joints of mice. Inflammation symptoms appear 48 h after the initial immunization, with secondary lesions appearing approximately 10–12 days later. C5BL/6 mice, susceptible to unilateral joint symptoms, are commonly used. The AA model was used to investigate coronary endothelial dysfunction associated with myocardial hypertrophy and decreased tolerance to ischemia.[24] The effects of paeoniflorin on RA and neutrophils were studied using an AA mouse model.[25]

2.4. Cartilage oligomeric matrix protein-induced arthritis model

The Cartilage Oligomeric Matrix Protein-Induced Arthritis Model (COMP) is a method for generating arthritis. COMP, or thrombin-sensitive protein, is a non-collagenous glycoprotein.[26] It is found primarily in cartilage, tendons, and synovium, where it catalyzes the formation of collagen I and collagen II fibers and is critical for collagen assembly and extracellular matrix stability.[27] COMP mutations can cause chondrocyte apoptosis, resulting in skeletal system disorders. The pathological mechanism is linked to the immune response of T cells to COMP.[28]

The procedure entails injecting a 1:1 mixture of COMP and CFA/IFA into the base of the mouse skin. On day 35, COMP is added to the IFA to boost immunity.[29] C57BL/6 mice are used in the model. COMP can cause severe arthritis by triggering a strong autoantibody response. However, this model lacks stability and does not cause permanent joint damage.[30,31]

2.5. Pristane-induced arthritis model

T cells and MHC play a role in the chronic arthritis known as pristane-induced arthritis (PIA). Pristane is a non-immunogenic chemical that functions similarly to adjuvants, inducing inflammation and exacerbating immune responses.[32] PIA relies primarily on the activation of $CD4^+$ T lymphocytes to cause inflammation, which is caused by the activation of self-reactive T lymphocytes due to non-specific immune system stimulation.[33]

PIA has high model reproducibility and causes pathological changes in joint tissue like human RA. In mice, PIA can be associated with elevated levels of various autoantibodies.[34] The procedure entails injecting pristane into the abdominal cavity of mice, followed by an additional booster in week 8. Swelling and erythema in mouse feet can be seen after week 17, but severe symptoms appear after week 29. BALB/c mice exhibit chronic development and are commonly used to establish the PIA model. The effect of the Nramp-1 allele on phagocyte activation in the arthritis process is currently being studied using the PIA mouse model.[35] Studies on the genetic background of AIRmin mice revealed varying levels of susceptibility to PIA.[36]

2.6. Streptococcal cell wall-induced arthritis model

Streptococcal cell wall-induced arthritis (SCWA) is an animal model of arthritis caused by streptococcal cell wall peptidoglycan components with pro-inflammatory properties.[37] Streptococci first activate specific B and T lymphocytes, then activate adaptive immune responses, resulting in the development of arthritis in animals.[38] This model shows synovial proliferation, inflammatory cell infiltration, and symmetric joint damage, similar to RA in humans. However, this model lacks high rheumatoid factor (RF) titers and does not produce rheumatoid nodules.[39]

Acute joint swelling appears 24 h after injection of a streptococcal cell wall peptidoglycan polysaccharide components suspension and tends to resolve by week 4. BALB/c and DBA/1 mice can be used to induce unilateral acute arthritis, which, with repeated injections, can progress to chronic arthritis. Studies have found that the mouse CSWA model has a lower success rate than the rat SCWA model.[40]

2.7. Methylated bovine serum albumin-induced arthritis model

The methylated bovine serum albumin-induced arthritis model (AIA) is classified as an antigen-induced arthritis model. Initially, chronic synovitis in rabbits was caused by injecting ovalbumin into the joint cavity.[41] It is a T-cell-dependent arthritis model marked by increased synovial fluid, inflammatory cell infiltration, and vascular opacity formation.[42] This model is appropriate for investigating larger joints with lesions, such as those in rabbits and sheep.[43] The experimental method was later improved and applied to mice.[44,45] The method involves inducing arthritis in mice using methylated bovine serum albumin (mBSA), CFA, and IFA.[46,47]

Other antigen-induced mouse models of arthritis include those induced by ovalbumin,[48] zymosan,[49] and glucose-6-phosphate isomerase (GPI) fragment, which has recently been used in experiments.[50] Many of the antigens in these models need to be modified, which can lead to single-joint onset.

3. Gene-engineered arthritis model

3.1. The tumor necrosis factor (TNF-α) model

Activated macrophages mainly secrete TNF-α, and a small amount is secreted by activated T cells, natural killer cells, and mast cells.[51] TNF-α is an immune regulator of normal and chronic inflammation. In the TNF-α model, the mouse TNF-α gene is replaced with the human TNF-α (hTNF-α) gene. The mouse endogenous promoter regulates the expression of hTNF-α, inducing arthritis like human RA.[52,53]

From week 3, the model mouse begins to show arthritis symptoms, which gradually worsens over time and cannot heal. The model is accompanied by swelling in the ankle from weeks 3 to 4 and peaks from weeks 17 to 21.[54] Therefore, compared with the induced arthritis model, the TNF-α transgenic mouse model has a stable phenotype. The

Table 1
Rheumatoid arthritis mouse model profile.

Classification	Model	Methods	Typical characteristics of model	Cytokine expression	Main applications
Induced model	CIA model	Induced immunity	Symmetrical joint damage and cartilage destruction	TNF-α, IFNγ, IL-1β, IL-6, IL-17, IL-21, IL-23, IL-32, MCP-1, MIP-1, MIP-2	Pathogenesis and therapies of RA
	CAIA model		Cartilage matrix changes	TNF-α, IL-1β, IL-6	Autoantibody effects in arthritis
	AA model		Progressive joint swelling	TNF-α, IFNγ, IL-1β, IL-4, IL-6, IL-17, IL-21, MCP-1, MIP-1	Chronic arthritis drug testing
	COMP model		Unstable joint inflammation	TNF-α, IL-1β	COMP's role in arthritis
	PIA model		Cartilage and bone defects	TNF-α, IFNγ, IL-1β, IL-6, IL-12	Immune response to cartilage
	SCWA model		Symmetrical synovial proliferation	TNF-α, IL-1β, IL-4, IL-6, IL-12, IL-17	Streptococcal arthritis study
	AIA model		Increased synovial fluid	TNF-α, IL-6, IL-17	Antigen-specific arthritis response
Genetic modification model	TNF-α model	Spontaneous immunity	Erosive arthritis	TNF-α, IL-1β	Biological agents research
	K/BxN model		Acute arthritis symptoms	IL-1β, IL-4	Spontaneous arthritis pathogenesis
	SKG model		Cartilage damage	TNF-α, IL-1β, IL-6, IL-17, IL-23	SHIP deficiency in arthritis
	IL-1 model		Synovial inflammation	TNF-α, IFNγ, IL-1, IL-4, IL-6, IL-10	IL-1's role in arthritis

lesions, including joint cartilage damage and fibrous tissue generation, are symmetrical bilateral polyarthritis and these features are very similar to human RA, making it very useful for studying TNF-α-related interventions and can also be used to explore cartilage destruction.[55]

3.2. K/BxN model

The K/BxN model is generated by crossing R28TCR transgenic male mice with non-obese diabetic female mice susceptible to autoimmunity.[56] This model has a large amount of autoantibodies in its serum. The serum of K/BxN mice is transferred to B cell-deficient mice, which results in severe swelling in the joints and other inflammatory symptoms within two days of serum transfer.[57] This model is also known as the K/BxN serum transfer arthritis (K/BxN STA) model.[58] The serum of hybrid offspring mice can induce various mouse models of arthritis. The symptoms of arthritis appear acutely in the model mice from 3 to 4 weeks of their age, similar to clinical signs of RA.[59] The success of this model is determined by symptoms such as elevated levels of inflammatory factors, narrowing of the joint cavity, and inflammatory cell infiltration.[60]

This model has a high incidence rate, with a rapid onset of disease, and is mainly used to study the mechanisms of activation of different innate immune cells, such as neutrophils, macrophages, and mast cells, driven by autoantibodies that cause the formation of immune complex.[61,62]

3.3. SKG model

SKG mice, a new genetic model of RA, which depends on the BALB/c background, develop chronic arthritis spontaneously after being injected with zymosan under specific conditions.[63] This model shares standard features with human RA in terms of female susceptibility, the presence of rheumatoid factors and type II collagen antibodies.[64] It is also a spontaneous arthritis model with a gene harboring hidden mutation that is highly dependent on the expression of IL-17 and other cytokines. The model also presents extra-articular lesions, leading to pneumonia and dermatitis.[65,66]

3.4. IL-1 receptor antagonist knockout model

In the IL-1 receptor antagonist knockout model, the IL-1 receptor antagonist (IL-1Ra) gene is knocked out mice genome, thereby removing the restriction on the activation of its receptor by pro-inflammatory cytokine IL-1, subsequently leading to inflammation.[67] The IL-1Ra gene-deficient mutant mice and their offspring upon crossing with BALB/c mice develop spontaneous arthritis.[68] This model is currently applicable only to BALB/c mice. The pathological phenotype of the IL-1Ra gene knockout mouse model is similar to that observed in human RA and can be used to study the role of cytokines in the onset of RA.[69]

Other arthritis models, include the human/SCID chimeric mouse model[70]and the human DR4-CD4 mouse model.[71,72] These models are more helpful in studying the role of a specific factor or gene in diseases associated with arthritis. The models are hereditary and can be continuously expressed in offspring.

Collectively, abovementioned gene-edited and hereditary arthritis models exhibit superior precision in mimicking disease onset, paving the way for more profound mechanistic explorations and targeted therapeutic breakthroughs. Their striking resemblance to actual arthritic conditions considerably facilitates drug discovery and preclinical evaluations, presenting an exceptional and indispensable platform to delve into the genetic underpinnings of arthritis.

4. Conclusions

In summary, this review summarizes commonly used induced arthritis models as well as newly established arthritis models in recent

years by applying gene editing techniques (Table 1). The pathogenesis of RA is still unclear, and no drug can completely cure this disease; therefore, animal models are still effective and necessary tools for understanding RA. Using mice as models has several advantages, such as simple operation, low cost, easy breeding, and rich biological characteristics. Many inbred and mutant strains of mice have been used widely in the study of human diseases because the arrangement of 93% of the mouse genome is in the same order as the human genome. Induced RA animal models were established early and are well developed with similar or nearly similar characteristics to human RA in terms of clinical manifestations, laboratory indicators, and pathological mechanisms, reflected by specific data, detection indicators, and slices. Gene-engineered mouse models can spontaneously develop arthritis after certain genetic modifications. Targeted engineering of the genes defines more specific and more straightforward spontaneous disease models and can also further elucidate the role of cytokines in the development of RA. RA involves many complex factors, such as environment, immunity, genetics, and infection. However, the vast majority of RA mouse models are established under specific conditions, emphasizing on the selection of one or a few factors, and cannot fully reflect all the properties of RA. With the in-depth study of the etiology and pathogenesis of RA, it is still crucial to adapt and modify animal models to express human diseases better. We ought to endeavor in integrating cutting-edge genetic engineering, immunological analysis, and longitudinal research in order to ultimately devise more precise mouse models of arthritis that better cater to clinical needs.

CRediT authorship contribution statement

Zihong Wei: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Jianfeng Wang:** Writing – original draft, Conceptualization. **Hiroto Kawashima:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The author Jianfeng Wang is an Editorial Board Member for *Animals and Zoonoses* and was not involved in the editorial review or the decision to publish this article.

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