Review Article

A Short Review on Preclinical Models for Inducing Rheumatoid Arthritis in Laboratory Animals

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ABSTRACT

Rheumatoid arthritis is an autoimmune disorder which is seen more commonly in women rather than men. Its major symptoms are pain, swelling, and stiffness in multiple joints. It is typically triggered by a combination of genetic factors and environmental influences. Genetic factors, such as HLA-DR1 and HLA-DR4, may predispose individuals to this condition, whenever they exposed to environmental toxins like cigarette smoke or specific pathogens, may leading to the activation of CD4+ T-helper cells and subsequent production of autoantibodies by plasma cells. These autoantibodies, along with T-helper cells, migrate to the joints where they induce inflammation. T-cells release cytokines like interferon-γ and interleukin-17, recruiting inflammatory cells such as proteases that degrade the articular cartilage. Diagnosis is done by observing four factors in arthritis, swelling of small or large joints, serologic test to find out rheumatoid factors and anti-CCP antibodies, disease duration not less than 6 weeks, and erythrocyte sedimentation rate and CRP are evaluated and assigned weighted scores. A total score of 6 or higher out of 10 indicates definite rheumatoid arthritis. Major goal of the Rheumatoid arthritis is focus on suppression of joint inflammation, pain, improving joint function, as well as preventing joint destruction and deformity, may often involving rest as part of the management strategy. Treatment with conventional medicine for rheumatoid arthritis can lead to mortality rates of approximately 10 to 20% due to cardiac complications and 60 to 80% due to pulmonary issues associated with the disease. The present review is mainly focused on the various etiological factors, diagnosis, treatment various preclinical models available for rheumatoid arthritis screening.

Keywords: Rheumatoid arthritis, inflammation, Interleukins, DMARD, preclinical models.

INTRODUCTION

Rheumatoid arthritis (RA) is an enduring, inflammatory autoimmune condition characterized by symmetrical joint inflammation, initially affecting small joints before progressing to larger ones, and potentially impacting the skin, eyes, heart, kidneys, and lungs. The term "rheumatism" originates from a Greek word dating back 2500 years, denoting a "Flowing current," symbolizing the widespread joint involvement throughout the body. Historical records dating back 2500 years mention the pain-alleviating effects of consuming a decoction made from European white willow bark. Salicin, identified as a constituent of the bark, was discovered in the nineteenth century.

The destruction of bone and cartilage in joints, along with weakened tendons and ligaments, often leads to deformities and bone erosion, causing significant pain for patients. Rheumatoid arthritis typically manifests between the ages of 35 and 60, characterized by periods of remission and exacerbation. It can also affect children, known as juvenile RA (JRA), before the age of 16, which shares similarities with RA but lacks rheumatoid factor effects on the lungs, heart, or immune system. Another distinction is that RA patients experience persistent morning stiffness lasting at least one hour. Treatment goals for RA focus on reducing joint inflammation and pain, improving joint function, and preventing joint destruction and deformity, often involving rest as part of the management strategy[1]. Women aged between 30 and 50 are frequently affected by a condition with an incidence rate of 1 in 150. The combination of pharmaceuticals, weight-bearing exercise, and patient education is often an effective strategy for managing various health issues, especially those related to musculoskeletal disorders, metabolic diseases, and chronic conditions, leading to pain, swelling, and stiffness in multiple joints. In 1853, Gerhardt synthesized acetylsalicylic acid, which showed greater in-vivo stability compared to salicin.

It wasn't until 1897 that acetylsalicylic acid was introduced to the market as a tablet for arthralgia by Hoffman. In the late 20th century, rheumatoid arthritis came to be understood as an autoimmune disease primarily characterized by polyarthritis[2]. Key mediators of disease, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), have been identified as pivotal targets for breakthrough therapies. Despite the expanding range of treatment options, a significant number of patients still experience insufficient responses to therapy or encounter intolerable adverse effects[3]. Typically, rheumatoid arthritis exhibits a bilateral and symmetrical pattern of disease advancement, impacting corresponding joints on both sides of the body, such as both hands or both knees. Additionally, RA can extend to extra-articular locations, involving areas like the eyes, mouth, lungs, and heart[4]. While rheumatoid arthritis primarily affects the joints, it should be regarded as a syndrome encompassing extra-articular symptoms like rheumatoid nodules, pulmonary

complications or vasculitis, and systemic comorbidities[5]. Treatment with conventional medicine for rheumatoid arthritis can lead to mortality rates of approximately 10 to 20% due to cardiac complications and 60 to 80% due to pulmonary issues associated with the disease. Rheumatoid arthritis is linked to molecules of the major histocompatibility complex, which trigger T cell responses. Certain natural compounds, such as brazilin, cardamom in, bufalin, and curcumin, exhibit anti-rheumatic properties. The joint damage in this condition results from complex interactions among immune modulators[6]. Rheumatoid arthritis (RA) significantly reduces quality of life (QoL) due to pain, fatigue, and disability, leading to mood disturbances like anxiety and depression. The disease activity score using 28 joints (DAS28) is a commonly employed tool for assessing a patient's response, incorporating parameters such as tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and patient visual analogue score (VAS). The primary advantage of the DAS28 score lies in its reliance on subjective components, particularly the patient's VAS and TJC, within the scoring system[7].

India, with its vast population of 1.2 billion people and considerable landmass, can be described as a subcontinent. It boasts socio-cultural diversity, including over 20 official languages. Understanding the epidemiology of rheumatoid arthritis (RA) in India is crucial for devising effective management strategies. Untreated RA can lead to joint deterioration, severe disability, diminished quality of life, the onset of various comorbidities, and premature mortality. These potential comorbidities encompass cardiovascular disease (CVD), cancer (specifically lymphoma, lymphoproliferative diseases, lung cancer, and melanoma), infections, depression, and gastrointestinal ailments. Notably, CVD disproportionately affects RA patients[8].

Etiology: A typical healthy joint consists of two bones covered with articular cartilage, a specialized connective tissue that acts as a protective cushion and facilitates smooth bone movement. These joints, known as synovial joints, are connected by a fibrous joint capsule that extends from the outer layer of periosteum. An example of a synovial joint is the knee joint, found in the lower limb. Within this fibrous capsule lies a synovial membrane, which produces synovial fluid to lubricate the joint and remove debris. Rheumatoid arthritis, an autoimmune disorder, is typically triggered by a combination of genetic factors and environmental influences. Certain genes, such as HLA-DR1 and HLA-DR4, may predispose individuals to this condition, particularly when exposed to environmental toxins like cigarette smoke or specific pathogens. These environmental factors can lead to modifications in our own antigens, such as IgG antibodies, type-II collagen, and vimentin, through a process called Citrullination. In rheumatoid arthritis, the immune system may fail to recognize these modified antigens as self, leading to the activation of CD4+ T-helper cells and subsequent production of autoantibodies by plasma cells. These autoantibodies, along with T-helper cells, migrate to the joints where they induce inflammation. T-cells release cytokines like interferon-γ and interleukin-17, recruiting inflammatory cells such as proteases that degrade the articular cartilage.

Furthermore, inflammatory cytokines upregulate the expression of RANKL on T-cells, facilitating their interaction with osteoclasts and subsequent bone resorption. Antibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (CCP) form immune complexes in the synovial fluid, activating the complement system and exacerbating joint inflammation. Chronic inflammation prompts angiogenesis around the joints, allowing more inflammatory cells to infiltrate. As the disease progresses, multiple joints become inflamed and damaged. Macrophages enter the joint space and produce inflammatory cytokines like tumour necrosis factor-α, interleukin-1, and interleukin-6, stimulating synovial cell proliferation. This results in the formation of Pannus, a thickened synovial membrane composed of various cell types, which contributes to cartilage and bone damage over time.[9]

Pathophysiology

The exact cause of rheumatoid arthritis (RA) remains unclear, but it's believed to involve a combination of genetic predisposition and external triggers like cigarette smoking, infections, or trauma. This interplay sets off an autoimmune response, resulting in inflammation of the synovial membrane within joints and potentially affecting other body tissues. The progression from pre-RA to clinically apparent RA involves several phases:

1. Phase I: Genetic and environmental factors interact, increasing the risk of RA.

2. Phase II: Production of RA-specific autoantibodies like rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP).

3. Phase III: Onset of symptoms such as joint stiffness or arthralgia without visible joint inflammation.

4. Phase IV: Initial development of arthritis in one or two joints, termed early undifferentiated arthritis; intermittent episodes of arthritis at this stage may be referred to as palindromic rheumatism.

5. Phase V: Progression to established RA, characterized by chronic joint inflammation and potential extra-articular manifestations.

These phases reflect the gradual evolution of RA from initial genetic and environmental influences to the development of autoantibodies, symptoms, and ultimately, established disease. Not all individuals follow a uniform progression through the phases of rheumatoid arthritis (RA), prompting ongoing research to identify those at risk of disease progression and explore strategies for delaying or preventing RA onset. Early in the pathological process of RA, hyperplasia of synovial cells

and activation of endothelial cells initiate inflammation, culminating in cartilage and bone destruction. Genetic predisposition and immune system dysregulation contribute to disease development. Key cellular players in RA pathophysiology include CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils, while B cells produce autoantibodies like rheumatoid factors.

Abnormal production of various inflammatory mediators, such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, IL-8, transforming growth factor beta (TGF-ß), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), is observed in RA patients. Ultimately, inflammation and excessive synovial proliferation (referred to as pannus) lead to tissue destruction, including cartilage, bone, tendons, ligaments, and blood vessels. Although the joints are primarily affected in RA, other tissues may also be involved. Ongoing research aims to better understand these processes and develop targeted interventions to mitigate disease progression and tissue damage in RA patients.[10]

Epidemiology

Globally, rheumatoid arthritis (RA) has an annual incidence of around 3 cases per 10,000 people and a prevalence rate of approximately 1%, with its occurrence rising with age and peaking between 35 and 50 years old. While RA affects all populations, its prevalence varies, being higher in certain groups, such as some Native American populations (5-6%), and lower in others, like Black individuals from the Caribbean region. Individuals with a first-degree relative with RA have a 2- to 3-fold higher risk of developing the disease, indicating a genetic component, although nongenetic factors also play a significant role. Despite the relatively consistent frequency of RA worldwide, there is speculation that a common infectious agent may contribute to its etiology.

Women are affected by RA approximately three times more often than men. For instance, a study in Norway found a prevalence of 1.10% in women compared to 0.46% in men. However, sex differences in RA prevalence diminish in older age groups. Research investigating potential reproductive risk factors found that women who had given birth to only one child had a higher RA rate than those with two or three offspring. Interestingly, nulliparous women or those with a history of miscarriages did not show increased RA rates. Additionally, there appears to be a decreased risk of RA during the first five years postpartum, even among those with higher-risk genetic markers. [11]

Diagnosis

The rheumatoid arthritis classification criteria established jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 are commonly utilized for diagnosis. These criteria aim to identify persistent and potentially destructive arthritis, distinguishing it from other types of arthritis.

Arthritis that develops soon after onset requires prompt treatment with disease-modifying antirheumatic drugs (DMARDs). The diagnostic process involves excluding various diseases like connective tissue disorders, osteoarthritis, spondylarthritis, and crystal-induced arthritis in the initial step. Then, four factors—arthritis (swelling of small or large joints), serologic test results (rheumatoid factors and anti-CCP antibodies), disease duration (at least 6 weeks), and acute-phase reaction (erythrocyte sedimentation rate and CRP)—are evaluated and assigned weighted scores. A total score of 6 or higher out of 10 indicates definite rheumatoid arthritis.

Additionally, if arthritis is present in one or more joints accompanied by typical bone erosion, it is classified as rheumatoid arthritis regardless of the score. Upon comprehensive diagnosis based on classification criteria, DMARD treatment is initiated to potentially prevent joint damage. Disease activity assessment is crucial for planning treatment strategies. The 28-joint Disease Activity Score (DAS28), which considers tender or swollen joints, erythrocyte sedimentation rate, and patient-reported disease activity, is commonly used. DAS28 scores are interpreted as follows: > 5.1 indicates high disease activity, 3.2–5.1 suggests moderate disease activity, < 3.2 indicates low disease activity, and < 2.6 denotes remission. Similarly, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are commonly utilized for assessing rheumatoid arthritis (RA). In terms of physical impairment evaluation, the Health Assessment Questionnaire Disability Index (HAQ-DI) is extensively employed worldwide. [12]

Consisting of 20 questions across 8 categories pertaining to physical functioning in daily activities, it serves as a valuable tool in assessing disability. RA often manifests with extra-articular involvement, affecting various organs such as the eyes, oral cavity, blood, lungs, heart, skin, nerves, kidneys, and lymph nodes. Lung disorders notably impact prognosis, with chest computed tomography (CT) being instrumental in identifying them in about 70% of patients. Among these cases, approximately 50% exhibit nonspecific changes, 30% present with interstitial pneumonia, and 20% show signs of chronic infection or chronic obstructive pulmonary disease. Other potential pathological conditions include pleurisy, pulmonary alveolar haemorrhage, and bronchiectasis.

In instances of rheumatoid vasculitis, characterized by progressive arthritis coupled with systemic vasculitis affecting various organs like the skin, gastrointestinal tract, heart, lungs, spleen, and pleura, interstitial pneumonia may also be present. Additionally, as RA activity escalates, there's a likelihood of concurrent lymphoproliferative disease. Patients may also develop autoimmune conditions like Hashimoto's disease, other thyroid disorders, and secondary Sjögren's syndrome. It's crucial to differentiate between organ dysfunction associated with RA pathology, other comorbidities, concurrent bacterial

and viral infections, and drug-related adverse events in all cases.

Treatment:

1. First-line management (NSAIDs and corticosteroids):

The overall goal of first-line treatment is to relieve pain and decrease inflammation

Non-steroidal anti-inflammatory drugs: These medications are considered to be fast acting.

NSAIDs include- Acetyl salicylate (aspirin)

Naproxen (Naprosyn)

Ibuprofen (Advil & Motrin)

Etodolac (Lodine)

NSAIDs function by inhibiting cyclo-oxygenase to halt the production of prostaglandins, prostacyclin, and thromboxane's. Aspirin, one of the earliest NSAIDs, is highly effective in treating joint pain and is particularly beneficial for rheumatoid arthritis when administered in high doses. A newer NSAID, celecoxib, acts as a selective COX-2 inhibitor and is specifically used for rheumatoid arthritis. [13]

Corticosteroids:

Corticosteroids, on the other hand, are more potent anti-inflammatory agents compared to NSAIDs but carry a higher risk of side effects. Consequently, they are typically prescribed at low doses for short durations. Intra-articular corticosteroid injections can target localized inflammation symptoms. These medications function by suppressing the release of phospholipids and reducing the activity of eosinophils, thereby mitigating inflammation

2.Second-line management (DMARD):

The primary objective of second-line treatments is to induce remission by slowing down or halting the advancement of joint damage and deformity. These medications are termed slow-acting as they require several weeks to months to exhibit their effectiveness

- **Methotrexate:** Serving as the initial choice for second-line therapy, methotrexate acts as an analogue to folic acid. Its mechanism involves inhibiting the binding of dihydrofolic acid (FH2) to the enzyme responsible for converting FH2 into FH4 (folinic acid). This DMARD is highly effective, boasting a lower incidence of side effects compared to other DMARDs, and offers dosing flexibility.

- **Hydro chloroquine (Plaquenil):** Originally an anti-malarial medication, hydro chloroquine finds utility in long-term rheumatoid arthritis treatment. Its adverse effects may manifest in gastrointestinal and central nervous system complications.

- **Sulfasalazine (Azulfidine):** Primarily utilized for treating irritable bowel disease, sulfasalazine becomes an adjunct in rheumatoid arthritis therapy when combined with anti-inflammatory drugs.

- Gold salts such as Aurothioglucose (solganal)

  Auranofin (Ridaura),

  Gold sodium thiomalate (myochrysine)

3. Newer Medications:

Biologic's: Biological DMARDs, or biologics, are swiftly effective in slowing down joint damage progression in rheumatoid arthritis. They offer a more targeted and precise approach to treatment. However, they carry the risk of side effects such as neurological disorders like multiple sclerosis and lymphoma

Tumor Necrosis Factor (TNF): Biological DMARDs, or biologics, are swiftly effective in slowing down joint damage progression in rheumatoid arthritis. They offer a more targeted and precise approach to treatment. However, they carry the risk of side effects such as neurological disorders like multiple sclerosis and lymphoma.

4.Surgery – Surgery is typically considered a final option in the treatment of rheumatoid arthritis. While joint surgeries saw a peak in the 1990s among patients with this condition, a study in 2010 revealed a decline in surgery rates among individuals aged 40 to 59. Conversely, there was an increase in surgery rates among those over 60. Surgical intervention should be tailored to the individual's specific needs, given the diverse range of surgical procedures available.

A ten synovectomy involves removing inflamed tendon sheaths or repairing recent tendon ruptures, primarily in the hand.

Radio synovectomy, an alternative to surgical synovectomy, entails injecting small radioactive particles directly into the joints. It is cost-effective and capable of treating multiple joints simultaneously.

A total joint replacement procedure entails the extraction of the affected joint and substituting it with a prosthetic device made of metallic, plastic, or ceramic materials. This procedure is frequently performed in various joints such as the shoulder, elbow, wrist, hip, knee, and ankle. The primary factor prohibiting surgical joint replacements is the existence of an ongoing systemic articular infection.

Risk factors

Factors contributing to the risk of developing Rheumatoid Arthritis (RA) can be broadly categorized into those related to the individual (host) and those related to the surrounding environment. Host-related factors implicated in RA development can be subdivided into genetic influences, epigenetic mechanisms, hormonal, reproductive, and neuroendocrine factors, as well as

concurrent health conditions. Meanwhile, environmental risk factors encompass smoking and exposure to other airborne substances, microbiota and infectious agents, dietary patterns, and socioeconomic conditions. [14]

Host Factors:

Similar to numerous other immune-mediated conditions, the individual's characteristics play a significant role in the susceptibility to developing Rheumatoid Arthritis (RA). Primarily, genetic factors represent a substantial portion of the risk for the disease.

Genetic Factors:

Evidence supporting a genetic influence on Rheumatoid Arthritis (RA) initially emerged from studies involving families and twins. Notably, monozygotic twins of RA patients have a significantly higher risk of developing RA compared to dizygotic twins, with a risk ranging from 9% to 15%, which is up to four times greater than that observed in the general population. Moreover, the risk of RA is elevated by 1.5 to 3 times in individuals who are offspring of parents affected by other immune-mediated inflammatory disorders such as systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis, or Hashimoto thyroiditis.

Epigenetic Factors:

In recent years, there has been increasing attention on the role of epigenetics in the development of rheumatoid arthritis (RA). Epigenetic mechanisms are responsible for heritable changes in gene expression without altering the underlying DNA sequence. Key epigenetic changes implicated in RA include DNA methylation, modifications to histone proteins, and the involvement of non-coding RNAs. These mechanisms have been shown to contribute to the susceptibility of individuals to RA. Specifically, differences in DNA methylation patterns have been observed in both peripheral blood mononuclear cells (PBMCs) and fibroblast-like synoviocytes (FLSs) among RA patients.

While DNA methylation has been extensively studied, our understanding of histone modifications in RA remains limited. Histone proteins can undergo various modifications, such as acetylation, methylation, phosphorylation, and citrullination, which can influence chromatin structure and, consequently, gene transcription. Additionally, non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), represent another layer of epigenetic regulation that has been thoroughly investigated in relation to RA susceptibility, severity, and response to treatment.

Hormonal, Reproductive and Neuroendocrine Factors:

The prevalence of rheumatoid arthritis (RA) shows a notable skew towards females, prompting extensive investigation into the role of hormonal and sex-related factors in predisposing individuals to the disease. Traditionally, the imbalance has been attributed to the pro-inflammatory nature of estrogen, counter to the anti-inflammatory effects of progesterone and androgens, which are typically lower in RA patients of both sexes. However, the actions of these hormones are intricate, with estrogen also exhibiting anti-inflammatory properties in various cells and tissues. The overall impact likely hinges on factors such as hormone levels in the bloodstream and tissues, prevalent cell types, types of estrogen receptors engaged, and the stage of reproductive life. Understanding these mechanisms is crucial to deciphering the conflicting research findings on the influence of hormonal and reproductive factors on RA risk. Beyond hormones, numerous environmental, dietary, and lifestyle factors have been linked to RA. Smoking, in particular, has been repeatedly associated with increased odds of developing RA, with some studies suggesting that exposure to smoking may contribute to as much as 20-30% of the environmental risk for RA. [15]

Environmental Factors: Environmental factors can be roughly grouped into four categories: airborne exposures, notably including: 1. Smoking

2. microbiota and infectious agents;

3. diet; and socioeconomic factors.

Smoking and Other Airborne Exposures

A significant advancement in understanding rheumatoid arthritis (RA) has been the recognition of the lungs as a crucial site for early disease-related events. This is evidenced by the strong correlation between several harmful airborne substances and RA. Numerous studies have revealed odds ratios linking smoking to RA that exceed 2, suggesting that approximately 20–30% of the environmental risk for RA can be attributed to smoking. For instance, it is hypothesized that smoking might increase citrullination, which, in individuals with certain genetic predispositions, could lead to the presentation of citrullinated proteins and the production of anti-citrullinated protein antibodies (ACPA). However, it's essential to acknowledge that smoking tobacco has various other local and systemic effects that could also impact immunity.

Microbiota and Infectious Agents: The concept of the "infectious hypothesis" has long been suggested as a potential explanation for the initiation or aggravation of rheumatoid arthritis (RA). This theory found support from both epidemiological and translational research involving a variety of viruses, bacteria, and other microorganisms, indicating their possible involvement in RA development through mechanisms like non-specific immune activation or molecular mimicry. However, despite decades of extensive investigation, no single infectious agent has been consistently identified as the primary cause or a significant risk factor for RA. In recent years, there has been an increasing acknowledgment of the role of mucosal immunity, oral/intestinal dysbiosis, and chronic infections in the etiology and pathogenesis of RA. An important consideration is periodontitis, a condition

arising from an imbalance in the oral microbiota, which has been associated with a heightened risk of rheumatoid arthritis (RA). The interplay between these two ailments is intricate and mutual, with RA patients exhibiting an increased likelihood of developing periodontitis, and vice versa. This correlation is emphasized by common genetic factors (such as HLA-SE alleles) and environmental triggers (such as smoking and dietary factors) shared between RA and periodontitis. Both conditions share characteristics of chronic inflammation, bone erosion, and tissue damage.

The documented decrease in rheumatoid arthritis (RA) occurrence across different populations subsequent to enhancements in general health and hygiene indirectly reinforces the idea of a connection between RA and conditions such as periodontitis. Nonetheless, despite these observations, the exact mechanisms governing the interaction among microbiota, infectious agents, and RA are yet to be completely understood. [16]

Diet: Extensive epidemiological research has explored the correlation between dietary factors and rheumatoid arthritis (RA). Moderate alcohol consumption has been shown to offer a protective effect against the development of RA, with a meta-analysis of cohort or nested case-control studies indicating a 14% decrease in risk. Similarly, adopting a generally healthy diet has been linked to a lower risk of RA. Conversely, an essential aspect of a nutritious diet involves the consumption of foods high in polyunsaturated oils, such as omega-3 fatty acids found in fish and olive oil. Fruits and vegetables, which are key components of a balanced diet and abundant sources of fiber and antioxidants like vitamin C, have also been associated with a reduced risk of RA in well-established prospective studies.

Socioeconomic: Additionally, early life socioeconomic factors play a role, with lower parental household education and adverse early life conditions such as food insecurity and young maternal age being associated with a higher likelihood of developing RA in adulthood.

Animal models used for rheumatoid arthritis

Utilizing animals for scientific experimentation has been a longstanding tradition in biological research and medical studies. The notable similarities in anatomy and physiology between humans and animals, particularly mammals, have motivated researchers to explore various mechanisms and test new treatments in animal models before implementing their findings in human studies.

Selection criteria for animal models used for the study are based on:

- Smallest animal species
- Strains specific characteristics desirable to require for the specific there proposed(resemblance)
- Lower cost
- Mortality rate
- Find commercial vendors (easily availability)

There are various types of models used for RA but the standard models used for RA are (16,17)

- Adjuvant arthritis
- Collagen induced arthritis
- Arthus reaction
- Antigen induced arthritis
- Proteoglycan induced arthritis
- Collagen antibody induced arthritis
- Genetically modified models of rheumatoid arthritis
- Collagen induced versus collagen antibody-induced arthritis

1.Adjuvant Arthritis

Adjuvant-induced arthritis involves inducing arthritis in rats by immunizing them with complete Freund's adjuvant containing either Mycobacterium tuberculosis, Mycobacterium or Staphylococcus epidermidis. This model is commonly utilized as a representation of Rheumatoid Arthritis (RA). [17]

Mechanism: The mechanism behind this involves the presence of peptidoglycan in the Mycobacterium cell wall membrane, which contains muramyl dipeptide. Muramyl dipeptide activates macrophages, leading to increased cytokine production. Consequently, this activation triggers beta cells and T-cells (MHC), ultimately resulting in the development of RA in rats.

2.Collagen- induced arthritis:

Collagen-induced arthritis is initiated by injecting rats intradermally with type-II collagen mixed with incomplete Freund's adjuvant. This model is favoured due to the resemblance of symptoms observed in rats to those seen in human disease. It serves as a valuable tool for evaluating the anti-inflammatory and immunosuppressive effects of experimental compounds.

Mechanism: The mechanism underlying this model is supported by the presence of antibodies against collagen in patients suffering from rheumatic polyarthritis. This indicates a potential role of autoimmunity in the pathophysiology of synovitis and joint damage.

Arthus Reaction: The Arthus reaction induced by immune complexes involves inflammatory components that are associated with acute responses observed in the joints of patients with rheumatic conditions. Activation of complement and polymorphonuclear neutrophils occurs upon the formation of antigen-antibody complexes, triggering an inflammatory focal point characterized by swelling, bleeding, and inflammation of blood vessels. The

immediate type of Arthus reaction reaches its peak intensity within 2 to 8 hours after induction.

3) Proteoglycan-induced arthritis

Progressive polyarthritis, known as PGIA, is characterized by symmetrical inflammation of the synovium, along with the development of marginal erosion, pannus formation, and infiltration of immune cells into the synovial tissue. This condition is induced in BALB/c (H-2d) mice through the injection of human cartilage proteoglycans (PGs), which leads to cycles of remission and exacerbation.

The protocol involves four injections, with the first and fourth injections containing PG mixed with complete Freund's adjuvant (CFA), while the second and third injections contain PG mixed with incomplete Freund's adjuvant (IFA). Arthritis typically manifests around day 11 following the injections and peaks in severity 2 to 4 weeks after the final PG injection.

Mice experiencing PGIA exhibit responses from CD4+ T cells and produce antibodies against PG, particularly showing elevated levels of immunoglobulin G (IgG) 2a antibodies, which correlate with disease severity. Although PGIA primarily represents a Th1-type arthritis model, it has been noted that the absence of interleukin-4 (IL-4) exacerbates the condition. Conversely, deficiency in either IL-4 or interferon (IFN) has been found to suppress PGIA. [18-20]

4) Collagen antibody-induced arthritis

In the induction of arthritis in mice, a combination of anti-collagen type II (CII) monoclonal antibodies is administered. Although lipopolysaccharide injected intraperitoneally can enhance disease severity and the occurrence of arthritis, it is not indispensable for initiating the condition. Disease onset in models of collagen antibody-induced arthritis (CAIA) primarily occurs independently of B and T cells, but immune cells play a role in modulating inflammation during the effector phase.

Neutrophils and macrophages are the primary effector cells, activated by immune complexes formed within the joints through the binding of CII antibodies to cartilage surfaces. Pathological changes typical of rheumatoid arthritis (RA), including synovitis, pannus formation, and damage to cartilage and bone, are observed in the affected joints of animals with CAIA.

Although the specific cytokines implicated in CAIA pathogenesis have not been extensively studied, it is anticipated that IL-1β, IL-6, and TNF play significant roles. This model can be induced in various mouse strains, and clinical signs of arthritis typically manifest a few days after antibody administration. [21-23]

5. Genetically modified models of rheumatoid arthritis: Various genetic alterations affecting arthritis pathogenesis can lead to arthritis development in different mouse models.

a) Human Tumor Necrosis Factor Transgenic Mice: The initial TNF transgenic mouse model, created by Keffer et al. in 1991, involved the introduction of wild-type and 3'-modified human TNF-α transgenes. This model demonstrated synovial hyperplasia and infiltration of inflammatory cells in the joints at 3 to 4 weeks of age, progressing to pannus formation, cartilage degradation, and bone erosion by approximately 10 weeks of age. It underscores the significance of TNF-α in arthritis pathogenesis and serves as a valuable tool for developing TNF inhibitors. [24]

b) Interleukin-1 Receptor Antagonist Knockout Mice: Interleukin-1 (IL-1) is a crucial inflammatory cytokine produced by various cell types, while the IL-1 inhibitor IL1Ra acts as an anti-inflammatory protein by binding to the IL-1 receptor. Knockout of IL-1Ra results in spontaneous arthritis characterized by amplified Th17-dependent inflammation. In BALB/c mice, polyarthritis onset occurs from 5 weeks of age, affecting nearly all mice by 12 weeks. Histopathological examination reveals substantial synovial and periarticular inflammation, accompanied by articular tissue destruction due to granulation tissue invasion, closely resembling human RA. Additionally, elevated levels of antibodies against IgG, CII, and double-stranded DNA are detectable in the sera of these mice.

6. Collagen-induced versus collagen antibody-induced arthritis

The CIA and CAIA mouse models are commonly utilized in arthritis research. CAIA, unlike CIA, doesn't rely on the host's production of autoantibodies to collagen type II (CII), making it feasible to induce arthritis in mice lacking CIA-susceptible major histocompatibility complex haplotypes (H-2q and H-2r), such as BALB/c and C57BL/6 mice. Consequently, CAIA can be induced in nearly all mouse strains, including transgenic and knockout mice, with a high incidence of arthritis close to 100%. This model serves as an excellent tool for screening and assessing anti-inflammatory agents, as it circumvents the influence of complete or incomplete Freund's adjuvants (CFA or IFA), which can strongly impact the host's immune response. [25-7]

CONCLUSION

Consensus across various literature underscores the crucial importance of early diagnosis, swift treatment initiation, and achieving remission targets promptly in rheumatoid arthritis (RA), as these actions offer a unique opportunity to alter the disease's trajectory, improving functional, radiographic, socioeconomic, and prognostic outcomes. RA, being a chronic condition, necessitates interventions aimed at modifying disease progression. Notably, the most recent RA guidelines, issued by ACR in 2015 and EULAR in 2016, exhibit specific discrepancies reflecting variations in the studied regions/populations. For screening of NCE against RA is very complicated in preclinical due complex nature in autoimmune disorder. Hence, we summarized the major screening models with

their advantages. It could be useful for people who are interested to do research on this area. Future updates of the ACR guidelines may likely incorporate commentary on the roles of baricitinib, sarilumab, and other promising therapies for RA.

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