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MORPHOLOGICAL CHANGES IN THE CELLULAR AND VASCULAR STRUCTURE OF THE HEART IN EXPERIMENTAL ANIMALS WITH SIMULATED RHEUMATOID ARTHRITIS

Saidova Mukhabbat Mukhidinovna
Candidate of Medical Sciences, Associate Professor
Bukhara State Medical Institute

Abstract
Rheumatoid arthritis (RA) is a chronic inflammatory joint disease of unknown etiology with a varied clinical course characterized by progressive destruction of synovial joints with cartilage and bone degradation. The onset of the disease peaks between 45-65 years of age and occurs 2-3 times more often in women. Untimely or inadequate treatment may render 30% of patients incapable of work during the first 10 years of the disease.

Keywords: rheumatoid arthritis, cardiovascular risk, prevention, morphology

Relevance

Rheumatoid arthritis (RA) is a chronic, inflammatory and systemic autoimmune disease affecting the connective tissue and primarily the joints. Untreated, RA eventually leads to progressive degeneration of cartilage and bone [1,7]. The etiology of the pathogenesis of RA is unknown, suggesting that its clinical manifestations are heterogeneous and associated with autoantibodies directed against modified native epitopes. Although many RA models already exist for preclinical studies, many current arthritis model systems have limited predictive value because they are either based on animals of phylogenetically distant origin or suffer from overly simplistic in vitro culturing conditions. These limitations pose serious problems for preclinical studies and, therefore, for clinical applications. Here we summarize the most commonly used in vitro RA models and discuss their experimental feasibility and physiological proximity to human RA pathophysiology in order to highlight new avenues of RA research involving humans to expand our knowledge of human pathophysiology and develop effective targeted therapies. Here we summarize the most commonly used in vitro RA models and discuss their experimental feasibility and physiological proximity to human RA pathophysiology to highlight new avenues of research into RA with human involvement to expand our knowledge of human pathophysiology and develop effective targeted therapies [3,9,10].

Purpose of the Study:

Morphological studies of changes in the structure of cells and vessels of the heart in experimental animals with simulated rheumatoid arthritis.

Materials and Methods:

We investigated during 2020-2022. 60 white randomized rats aged from 18 to 24 months in the inpatient conditions of the vivarium of Bukhara State Medical Institute. Complete Freund's adjuvant was used to simulate rheumatoid arthritis.

All animal experiments were performed in compliance with the international principles of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes, as well as in accordance with the "Rules for work with experimental animals". All laboratory animals were divided into 3 groups:

Group 1 - animals with experimentally induced rheumatoid arthritis that did not receive treatment;

Group 2 - animals with experimentally induced rheumatoid arthritis treated with GCS (glucocorticoid model) for 4 weeks;

Group 3 - animals with experimentally induced rheumatoid arthritis treated with cytostatics for 4 weeks;

Group 4 - intact animals that will be kept under standard vivarium conditions. The subject of the study was histological material obtained from different parts of the heart of the experimental animals.

The results of the study showed that animal models are an integral part of the preclinical drug development process and are used to study pathophysiological mechanisms of RA. Although they are extremely useful for testing new intervention approaches in many cases, concerns have been raised about the low success rates in clinical development of investigational drugs. It is important to note that animals do not naturally develop autoimmune diseases such as RA, which is an inherent limitation of these arthritis models.(Table 1). Instead, animal models can be used to study some specific pathophysiological aspects of human disease, such as the destructive pathways involved in articular cartilage and bone erosion. To this end, arthritis can be chemically induced in these animals with soluble agents (e.g., the type II collagen-induced arthritis model) or develop spontaneously after genetic manipulation (e.g., the transgenic human TNF model).Table 1). Although most of these models demonstrate hallmarks of human rheumatoid arthritis, such as inflammatory cell infiltrate, synovial hyperplasia, pannus formation, cartilage destruction, and bone erosions, they also demonstrate specific limitations, such as

development of self-limiting arthritis, development of only arthritis. in susceptible rodent strains and pathophysiology that does not replicate endogenous tolerance disorder and exclude systemic components of the disease [2,6,11]. Mutations used in genetically engineered models of arthritis have not been identified in human rheumatoid arthritis [3, 6]. When comparing mouse and human transcriptional programmes, overlapping but markedly different gene expression patterns were observed. Consequently, therapeutic approaches, such as the use of biologics highly specific to human target proteins, cannot be proven using non-humanised rodent models. Finally, mice and humans differ in their locomotion, lifespan, evolutionary pressures, ecological niches, circadian rhythms, weight load and ratio of leukocyte populations in the blood. Thus, no animal model is able to fully replicate the pathogenesis of RA in humans, which explains the problems observed in clinical interpretation. Current treatment guidelines recommend early and rigorous treatment to achieve low disease activity or remission as soon as possible. Thus, rheumatoid arthritis is currently treated with a wide range of therapeutic agents, ranging from steroidal/nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and disease-modifying anti-rheumatic drugs (DMARDs), such as conventional synthetic DMARDs (e.g. methotrexate), biological and biosimilar DMARDs (e.g. TNF inhibitors or IL-6 inhibitors), and targeted synthetic DMARDs (Janus Kinase Inhibitors (JAK)) affecting specific immune cells, cytokines or proinflammatory pathways [1,8]. Current therapeutic approaches using advanced biologics or JAK inhibitors have been shown to be very successful and effective in most patients with RA, including those with severe disease progression. Despite significant progress in the treatment of RA, there remains an acute unmet medical need, as not all patients achieve sustained clinical remission (less than half of patients with RA) and about 25% still suffer from moderate to even high disease activity [2,4]. Identifying patients with RA (I) who are refractory to available treatments, among patients with RA who are under-treated or not adhering to treatment, (II) identifying objective biomarkers of disease states (e.g. early RA versus established RA) and/or (III) "refractory" states and finally (IV) for conditions response to treatment is still the biggest unmet need in RA. The lack of therapeutic efficacy in patients with true refractoriness may be related to the nature of the universal approach of standardized therapeutic regimens. Thus, the clinical management of patients often ignores their heterogeneity with respect to endogenous circadian rhythms, disease states, subtypes and duration, as well as the pattern of autoantibodies, cytokines and infiltrating immune cells. The identification of objective biomarkers to determine disease subtypes and response to treatment will be necessary to provide a "precision"

individualized treatment strategy for each individual patient, expanding our repertoire in the fight against this potentially devastating disease.

Table 1 Selected rodent models for rheumatoid arthritis (as reviewed in ref.

Animal models of rheumatoid arthritis	**Variety**	**Induction/genetic modification**	**Limitations**
Models of induced arthritis			
Collagen-induced arthritis (CAIA)	Mouse, Rat	Inoculation with heterologous or homologous type II collagen in complete Freund's adjuvant to strains expressing the major histocompatibility complex (MHC) I-Aq haplotype class II	▪ Overall variable frequency, severity, and intergroup inconsistency
Collagen-antibody-induced arthritis (CAIA)	mouse	Anticollagen antibodies have been shown to cause arthritis.	▪ Induced only in susceptible rodent strains
Adjuvant-induced arthritis (AA)	Mouse, rat	A mixture of mineral oils killed by heating mycobacteria and an emulsifier that has been called complete Freund's adjuvant (CFA); also known as incomplete Freund's adjuvant (IFA) when excluding mycobacteria; see also pristane-induced arthritis (PIA)	▪ Low frequency as well as variability in severity of arthritis in c57bl/6 mice
Zymosan-induced arthritis	Mouse, rat	Intra-articular injection of zymosan, a polysaccharide from the cell wall of Saccharomyces cerevisiae, into the knee joints of mice causes proliferative arthritis, including infiltration by immune cells, synovial hypertrophy, and pannus formation.	▪ Acute and self-suppressive polyarthritis in contrast to human RA
Streptococcal cell wall induced arthritis (SCWIA)	Mouse, rat	Streptococcus pyogenes synthesizes a peptidoglycan-polysaccharide (PG-PS) polymer.	▪ Higher incidence in males compared to human RA

Cartilage oligomeric matrix protein (COMP) induced arthritis	Mouse, rat	IFA immunization in combination with native and denatured COMP, which is a large protein synthesized by chondrocytes (see also adjuvant-induced arthritis)	▪ Pathogenesis is not mediated by T- and B-cell response, unlike human RA
Pristane induced arthritis (PIA)	Mouse, rat	Injection of hydrocarbon pristane intraperitoneally in mice	▪ Pathogenesis is induced irrespective of the presence of MHC class II haplotype, unlike human RA
Antigen-induced arthritis (AIA)	Mouse	Inoculation with antigen by intraperitoneal injection	▪ Acute and self-limited polyarthritis unlike human RA
Proteoglycan-induced arthritis	mouse	Intraperitoneal injection of proteoglycan emulsified with adjuvant.	▪ Non-antigenic, but has autoimmune pathophysiology
Glucose-6-phosphatisomerase induced arthritis (G6PI)	mouse	Immunization with the ubiquinone-containing glycolytic enzyme G6PI with CFA for induction of RA	▪ Technical skills required for intra-articular injection in mice
Genetically modified models of spontaneous arthritis			
Model K/BxN	mouse	K/B×N mice were created by crossing mice expressing the A g7 MHC class II molecule with a transgenic KRN T-cell receptor (TCR) line expressing a TCR specific for the G6PI peptide.	▪ Mutations detected only in mice
K/BxN model	mouse	Induction of arthritis due to a point mutation in ZAP-70	▪ Low prevalence of antibodies to g6pi in patients with RA
Transgenic human TNF model	mouse	Human TNF-α transgene	▪ No systemic manifestations or rheumatoid factor production in contrast to human RA

Conclusions

Thus, preclinical models are needed to improve our understanding of pathological mechanisms and to develop and test new therapeutic approaches to meet this unmet medical need. This includes the investigation of human-specific alternatives to identify objective biomarkers for determining disease subtypes and response to treatment, as well as novel targets for controlling immune cell function involved in RA pathogenesis.

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