Chapter 13

Animal Models of Rheumatoid Arthritis

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Abstract

Autoimmunity is a condition in which the host organizes an immune response against its own antigens. Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, characterized by the presence of chronic inflammatory infiltrates, the development of destructive arthropathy, bone erosion, and degradation of the articular cartilage and subchondral bone. There is currently no treatment that resolves the disease, only the use of palliatives, and not all patients respond to pharmacologic therapy. According to RA multifactorial origin, several in vivo models have been used to evaluate its pathophysiology as well as to identify the usefulness of biomarkers to predict, to diagnose, or to evaluate the prognosis of the disease. This chapter focuses on the most common in vivo models used for the study of RA, including those related with genetic, immunological, hormonal, and environmental interactions. Similarly, the potential of these models to understand RA pathogenesis and to test preventive and therapeutic strategies of autoimmune disorder is also highlighted. In conclusion, of all the animal models discussed, the CIA model could be considered the most successful by generating arthritis using type II collagen and adjuvants and evaluating therapeutic compounds both intra-articularly and systemically.

Keywords: autoimmune disease, rheumatoid arthritis, animal models, biomarkers, therapeutic alternative

1. Introduction

Traditionally the immune system has been considered as a set of structures (molecules, cells, and specialized tissues) and biological processes responsible for the defense against aggression by a variety of infectious agents, chemicals, and tumor cells. One of the fundamental characteristics of the immune system is its ability to discriminate foreign antigens [1]. Autoimmunity is a multifactorial condition in which the host organizes an immune response against its own antigens [2]. Autoimmunity is associated with genetic, immunological, hormonal, and environmental factors, with it being classified as organ-specific and systemic, of which RA is one of the most representative.

RA has an incidence of 5 per 100,000 adults and occurs in 0.5–1% of the population in industrialized countries [3]. The RA can manifest as pain, stiffness, swelling, and loss of mobility. There are different strategies for the study of RA, including experimental animal models that help elucidate different aspects of the disease, as well as evaluate compounds that can reduce the inflammation that triggers the disease. An ideal animal model for RA should reproduce as close as possible the complex pathogenesis and symptoms that underlie the disease, including the presence of chronic inflammatory infiltrates, the development of destructive arthropathy, bone erosion, and degradation of the articular cartilage and subchondral bone [4]. Current RA animal models are highly reproducible and of short duration, having similar patterns to those occurring in human disease although they present some differences, such as (1) faster progression of the disease, characterized by an acute inflammatory response and (2) rodents have a tendency to marked resorption and bone formation (especially of the periosteum/endosteum) in response to joint inflammation. The use of animal models has contributed significantly to the knowledge of processes and mediators that generate inflammation and bone and cartilage damage and, in this sense, can be used as an intermediary to provide knowledge and for the evaluation of therapeutic molecules to correct these disorders [5]. There are numerous therapeutic alternatives for RA; however, the duration of these therapies and the side effects associated with some of these drugs mean that until now, there is no effective therapy for this disease.

2. The human immune system and manifestations of RA

2.1. Primary and secondary lymphoid organs and defense mechanism

The immune system is responsible for protecting the human body from external and potentially pathogenic organisms. It is made up of a series of cells, tissues, and organs distributed widely throughout the body. From the point of view of its structural characteristics, there are organs such as the thymus, spleen, and lymph nodes and tubular structures such as the lymphatic vessels that are intercommunicated. If the functions performed are taken into account, they can be classified into primary and secondary lymphoid organs. The primary lymphoid organs

(thymus and bone marrow) produce T and B lymphocytes, while secondary lymphoid organs include lymph nodes (LNs), spleen, Peyer's patches (PPs), and mucosal tissues, nasal-associated lymphoid tissue (NALT), adenoids, and tonsils, which also harbor perifollicular areas [6].

The immune system has two lines of defense, specific and nonspecific (adaptive and innate), which are responsible for keeping the body free from pathogens or, if present, can eliminate them as well as their residue [7, 8]. The innate, nonspecific antigen response destroys microorganisms and triggers an inflammatory process that blocks the spread of infection. If microorganisms get past this first barrier, antigen-specific adaptive immunity composed of T and B lymphocytes can produce antibodies and killer cells that destroy infected cells [9]. The innate immunity is constituted of external barriers such as mucous and skin; the inflammatory process; cells such as macrophages, natural killer (NK) cells, and phagocytic cells; and chemicals. In relation to adaptive immunity, this is generated only after exposure of inducing agents, and two distinct responses are generated, the cellular response, in which T lymphocytes are responsible for generating this reaction and the humoral response, carried out by B lymphocytes, which in turn are responsible for producing antibodies against the agents that cause damage [10].

2.2. Autoimmune disease as an imbalance in immunoregulation

Autoimmune diseases have been classified according to the organ and tissues affected by the impaired immune response. Nearly 80 autoimmune diseases have been reported to date, and a prevalence of 5–6% worldwide has been stated [11].

An autoimmune manifestation is triggered by antigens that are generated naturally in an individual, and most of the time, these autoimmune events are devoid of pathological character. A large number of people worldwide have autoantibodies to different parts of the body, which are activated when a viral or pathogen infection is present. These diseases are usually the result of an imbalance of immunoregulation [12].

The process by which autoimmune disease is triggered follows different pathways including infection with viruses or bacteria, the use of drugs, the use of irritant chemicals, and environmental factors that damage health. The infection is capable of generating enzymatic changes which in turn alter cell membranes exposed to hidden antigens or may expose new antigenic sites [13]. Also the viral infection can induce new antigens that are released or expressed on its cell surface [14].

Among the first signs of autoimmune disease are pain, swelling, heat, and inflammation [15]. The affection of these diseases will depend on the target organ, since any part of the body, such as the eyes, heart, joints, or brain, can be attacked [16].

Aging and molecular haptens are also associated with the formation of new antigens or the appearance of those that are hidden; in the haptens a response is triggered both against them and the protein to which they bind [17]. Such antigens may be obtained from diet or generated from virus cross reactions with antigens that are present in the individual which force the immune system to react against them.

There are several theories which consider that these types of autoimmunity are due to the loss of tolerance of T lymphocytes or their inability to effectively suppress the reaction that is generated against their own antigens or harmless agents [18].

Autoimmunity is triggered when the response is persistent and leads to the development of uncontrolled cells that react aggressively against any component of the body [19]. These processes require the entry of effector cells into the target organ, whereby there are changes in blood vessels due to the inflammatory substances that are released into the blood [20]. There are different associated factors that trigger an autoimmune disease such as those shown in **Figure 1**.

Recognition of the major histocompatibility complex (MHC) II by the T-lymphocyte receptor (TCR) will produce a clustering with other surface receptors that activate a signaling cascade, which in turn alters the T-lymphocyte transcriptional program. These events produce tissue destruction and loss of function of affected organs during the course of the autoimmune disease. There is evidence that CD4+ T cells are active in local inflammation and cell infiltration that result in inflammation [21].

2.3. Rheumatoid arthritis, its causes and prognosis

RA is a chronic inflammatory disease characterized by synovitis with a symmetrical distribution that causes severe joint destruction [22]. RA is a common autoimmune systemic inflammatory disease that affects approximately 1% of the worldwide population and its incidence is 0.5–1% [3]. Cohort studies have shown that people with arthritis are 54% more likely to die than a healthy person, and there are data that indicate that this frequency is directly associated with the severity of the disease [23]. The process was reported in 1909 by Nichols and Richardson, and among the symptoms of RA are a prodromal period preceded by overt asthenia, general malaise, diffuse myalgia, fever, and anorexia, weight loss, pain, stiffness, and swelling in affected joints [24].

RA initiates as an inflammation of synovial fluid, in which rheumatoid factor (RF), IgM and IgG, and anti-CCP antibodies are present in serum and joints. Complement is activated within the synovial fluid, with C3a and C5a being the most important components found [9]. The disease is perpetuated by the production of cytokines and the action of extracellular matrix metalloproteinases (MMP) [25].

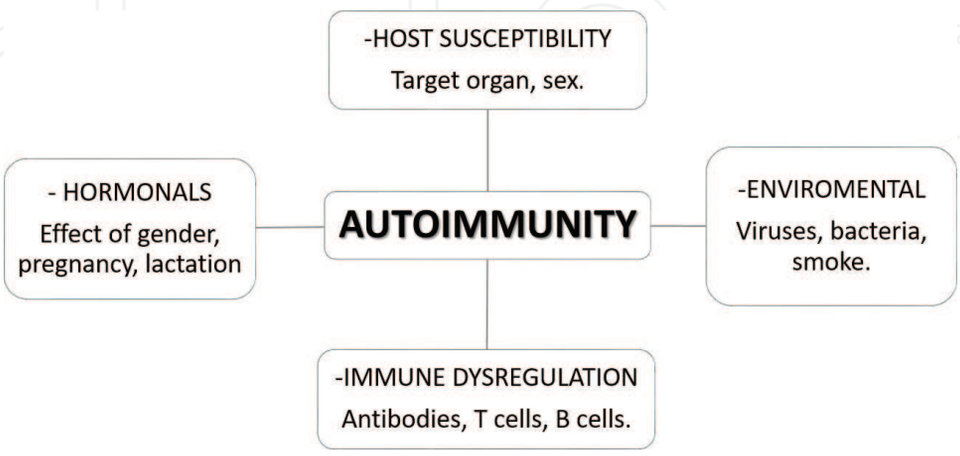

Figure 1. Factors associated with the development of autoimmunity. There are several important factors that are considered the trigger of an autoimmune disease, since the true etiology is not currently known. These include hormonal, immunological, environmental, or genetic factors (susceptibility).

After the onset of the disease, the synovial membrane of patients with RA, which is generally hypocellular, becomes hyperplastic, containing a large number of cells, such as polymorphonuclear leukocytes surrounding immune complexes and complement molecules [26].

Chronic inflammation in hypertrophic synovium is maintained by activated cell groups such as synovial fibroblasts and macrophages, as well as an area containing a clear cell infiltrate: mast cells, CD4+ and CD8+ T lymphocytes, NK cells, B lymphocytes, and plasma cells (the latter produce RF against altered IgGs), along with invasive mesenchymal cells. This accumulation of complexes and cells forms what is called pannus [26].

Once the presence of inflammatory arthritis is recognized, a preliminary diagnosis is made; other diagnoses of arthritis (lupus, psoriatic arthritis, spondyloarthritis, among others) are ruled out. Finally, the risk of developing persistent and/or erosive arthritis is assessed. Patients with early RA develop symmetrical polyarthritis, and its appearance is associated with the presence of positive rheumatoid factor (RF) and/or anti-citrullinated (anti-CCP) antibodies. RF corresponds to antibodies that are directed against immunoglobulins IgG, IgM, and IgA and are usually present in 80% of the patients who suffer this disease [27]. In RA, the inflammatory process is mediated primarily by the action of pro-inflammatory cytokines. In addition to enhancing the activity of IL-1 and TNF-α, IL-17 has a direct effect on the evolution of the disease, since it stimulates osteoclast differentiation and promotes the destruction of the cartilage and bone [28].

Until a few years ago, Th1 cells were considered to be the main cause of tissue damage in autoimmune diseases, but Th17 is currently considered to be the major inducer of autoimmune disease. It migrates more rapidly than Th1 to the areas of lesion. Once there, it stimulates the inflammatory response and is able to recruit other complementary cells, including Th1, which is necessarily associated with Th17 for inflammation and tissue destruction [29].

The onset of RA involves certain components such as T cells (CD4+), monocytes, fibroblasts, B cells, dendritic cells, mast cells, and neutrophils [30]. The synovium of patients with RA usually presents a certain red coloration due to the strong inflammation that is present. Chemokines are usually very important in the pathogenesis of the disease, being the most representative of the CXC family which is a strong promoter of angiogenesis [31].

Cytokines are implicated in the pathogenesis of RA, which triggers and perpetuates autoimmunity, maintaining chronic inflammatory synovitis and directing the destruction of connective tissue. Therefore, they integrate the regulatory immune events and destruction of the tissues that are observed in the clinical progression of RA. Cytokines that play an important pro-inflammatory role in arthritis are TNFα, IL-1β, IL-6, and IL-17 [32].

3. In vivo models for RA

RA is a cosmopolitan disease that affects 60 million people, making it a big problem for the health sector [33]. The etiology and pathophysiology of RA remain poorly understood, but it is generally accepted that genetic, immunological, hormonal, and environmental factors could lead to chronic inflammatory infiltrates, the development of destructive arthropathy, and the manifestation of clinical symptoms [34].

Since 1806, RA has been associated with a certain degree of inheritance; its relationship with genetic and environmental components has not been neglected in greater proportion [35]. There are different experimental models that generate basic knowledge of the pathophysiology of RA for the development of diagnostic kits through the discovery of biological markers. These are grouped in genetic, immunological, hormonal and environmental characteristics; that is, these factors are always associated with most autoimmune diseases.

3.1. Genetic models

The first RA-associated gene appeared in 1978 with the elucidation of HLA association with the disease. Nowadays, it is a clear complex of predisposition to suffer RA [36].

The first set of studies aimed at demonstrating the genetic susceptibility to RA was performed in twins, in which the environment and the genome were similar. This led to the hypothesis that 60% of the changes are attributable to genetic components. One of the best strategies has been to link polymorphisms with RA; despite these efforts, only HLA and PTPN22 factors have been linked with accurate results, hence the importance of genetically modified animal models [3, 37].

The collagen-induced arthritis (CIA) model was developed through the induction of type II collagen although the usefulness of other types of collagen has been demonstrated [38]. This model has become the most effective genetic biomarker. Among the targets that have been evaluated are immunoglobulin-producing B cells which attack type II collagen. Additionally, TCR transgenic mice in which the development of arthritis has been generated by immunoglobulins have also been evaluated [39, 40].

The way in which the transgenic mice model is developed is by injecting a construct that weighs an expression promoter, the gene or molecule of interest, and, commonly, a reporter gene, which will facilitate the exact location of the construction generated by immunofluorescence techniques. Once this construction is obtained, it is introduced into a pronucleus of a fertilized egg. The mouse that will be obtained will be able to express the gene of interest and transmit it to its descendants [41].

The therapeutic targets evaluated in CIA models or transgenic mice with adjuvants (from DBA/1 strain) are genes that code for T lymphocytes, within which the generation of a polymorphism has been associated with the development of RA. Finally, CMH, whose association with RA was reported in 1978, has been assigned to different loci such as HLA-DQ and HLA-DR, as well as to the H-2q region of HCM, demonstrating involvement in animal models with transgenic mice. Despite efforts to detect altered genes in this complex, to date, the exact pathway in which the pathogenesis is produced and the precise effect of this complex on the disease are unknown [42]. **Table 1** summarizes the animal models used for the genetic model of RA.

3.2. Immunological models

Among the immunological factors, commonly considered biomarkers are cytokines, chemokines, immune response cells, and adhesion molecules.

Model	Inbred strain and mechanism	Genotypic characteristics	Limitation	Advantage	Reference
IL-6R	The genetic background is with strain C57BL / 6 and the model is generated due to a mutation generated in the amino acid tyrosine in the IL-6 receptor.	gp130$^{F759/F759}$	A high frequency of B cells is generated, which could result in an increase in the humoral response.	Mutation in GP130 enhances IL-6 expression.	[4, 43, 44]
IL-1Ra	The strain used is C57BL / 6J and said mice are deficient in the gene that enconding for the IL-1Ra receptor antagonist.	B6.129S-*IL1rn*^{tm1Dih}/J	Fail to respond to IL-1 and exhibit an altered immune response to many different target proteins.	Exhibit altered inflammatory responses.	[4, 43, 45]
K/BxN	For this model, the strains of NOD and C57BL/6 are used, in which autoimmunity against the GPI is generated after its crossing.	B6.TCR. C$\alpha^{-/-}$.H-2^{bxg7}	-Number of experimental mice obtained from very small crosses. -Controls may generate arthritis -Additional care due to complexity of the model.	-Obtain control mice, arthritic and experimental at the same time. -Development of early arthritis and RF production.	[4, 43, 46, 47]
SKG	A mutation occurs in the SH2 region of the ZAP 70 protein, which is the result of an error in the selection of T cells, the mouse model is the BALB / c	ZAP-70^{W163C}	-Do not develop lymphadenopathy or lupus-like diseases. -Arthritis is significantly reduced when the mice are rendered TNF-α, IL-1 or IL-6 deficient.	-Develop RF and anti-CCP antibody. -Mutation in the SH2 domain of Zap 70. -Spontaneous arthritis.	[4, 43, 48]
TNF-α-transgenic	The animal strain used is C57BL / 6 in which an overexpression of the human TNF-α gene is generated	Tg197	Have impaired fertility and therefore it is very difficult to obtain offspring from this model.	-Increased TNF-α production. -May lead to the discovery of novel treatment and prevention alternatives. -Develops an erosive polyarthritis.	[4, 43, 49, 50]

CCP, cyclic citrullinated peptide; RF, rheumatoid factor; TNF, tumor necrosis factor; IL, interleukin; α, alpha; SKG, Sakaguchi; BL, black; ZAP 70, zeta-chain associated protein 70; SH_2, Src homology 2; GP130, glycoprotein 130; R, receptor; Ra, receptor antagonist; NOD, nonobese diabetic; TCR, T cell receptor.

Table 1. Genetic models for RA.

Cytokines often provide valuable information within the role of soluble factors that develop in RA. IL-1 β, TNF-α, IL-6, IL-15, and IL-18 are the most documented cytokines that play a regulatory role in RA, depending on the immune response or inflammatory processes.

The mice strains that are used for evaluation of some cytokines or regions of the TCR are knockout mice or transgenic mice, which have a deficiency of the molecule to be studied. Typically, these strains develop the CIA model more easily than other strains such as C57BL/6 [51].

In addition, different therapeutic targets such as chemokines, signaling molecules, and cellular trafficking can be evaluated in arthritis models like collagen-induced arthritis (CIA), streptococcal cell wall (SCW), adjuvant-induced arthritis (AIA), and models in chemokine-deficient knockout mice. On the other hand, immune response cells (NK, monocytes, etc.) are evaluated in K/BxN mice with CIA, which must be pre-stimulated with LPS to inhibit Fc receptors. Adhesion molecules, whose function resides in leukocyte trafficking, have been referred to be evaluated in SCW models with BALB/c mice and among the markers found are P-selectin, ICAM-1, and VCAM-1 [52].

For this model, K/BxN mice, which will jointly express the cell receptor T and the CMH II allele, are usually used. These mice typically develop no problem with a severe form of arthritis, when they are inoculated with serum antibodies due to high levels of GPI. Two mice are required to generate the model: one from the C57BL/6 strain that has the KRN and NOD/Lt transgene carrying the CMH II allele [53].

3.3. Environmental models

One marker that has been associated with RA is a low socioeconomic level, from which unhealthy diets are derived. It has recently been found that the consumption of certain vitamins and minerals from healthy food provides protection and reduces the effects of RA in patients [54, 55].

In animal models, the first link in which the association of the environment in arthritis was observed was when the HLA-B27 complex was evaluated in transgenic rats with spondyloarthritis. The rats did not develop the disease, so it was deduced that normal intestinal flora in B27 plays an important role [56]. Among the main environmental links with RA are smoking, the presence of infections, antibodies to rheumatoid factor, and anti-cyclic citrullinated peptides [57].

Cigarette smoke is strongly associated with RA, and during a study in 2011 in which mice of the DBA/1 J strain were in contact with condensed smoke, an increase in the induction of RA mediated in the CIA model. This strongly suggests that smoking may be an etiologic cause of this pathology [58].

4. Implication of hormones in animal models

Sex hormones are linked to RA because they function normally as inhibitors or suppressors of the immune response. Over the last few years, it has been speculated that the appearance

Animal model	Characteristics	Species	Limitations
Streptococcal cell wall arthritis	Peptidoglycans in the cell walls of bacteria (*Streptococcus* sp., *Lactobacillus* sp.) are responsible for inducing the model. Biphasic arthritis is generated, and it persists for several months. The model is generated in Lewis rats	Rat	The most important limitation is that the arthritis that is generated is monoarticular, and because the inflammation is generated by injecting intra-articularly, the systemic effects cannot be effectively evaluated
Passive transfer of CIA antibodies	The induction is performed by injecting type II collagen. The generation of specific antibodies for type II collagen is well characterized. Mice used are B-cell deficient and resistant to developing CIA	Mouse	It does not generate B- or T-cell responses, which are important factors to evaluate in RA despite having macrophages and polymorphonuclear cell infiltrates
Collagen-induced arthritis	This model is inducible in susceptible mice and rats; it is the gold standard and causes polyarthritis. Animals are inoculated with collagen II and coadjuvant; a re-restriction of MHC II is generated. The most commonly used strain of mice is DBA 1/J	Rat, mouse	Prior experience is required to perform the injection of the agents to evaluate intra-articularly. Arthritis characterized by polyarthritic does not meet all the characteristics, and results generated are variable. The arthritis that is triggered is acute
Immune complex-induced arthritis	Is generated for passive transfer of anti-isozyme antibodies in mice, which are injected into the knee with poly-L-lysine-lysozyme	Rat, mouse	The model does not comply with endogenous factors that are generated, and it is very difficult to resemble certain models such as CIA. Reactivity is generated by the presence of type II collagen and increases the production of factors that trigger inflammation
Spontaneous arthritis in knockout or transgenic mice	Mutations generated in the model are only generated in mice 4–5 weeks of age. Arthritis is mild and can be induced by serum transfer and induces changes in the MHC	Mouse	These models require specific environmental stimulants, which are very sensitive to the changes; therefore they are usually models with considerably high costs. Another limitation is that antibodies to anti-glucose-6-phosphate isomerase are generated that mostly cause pathogenic effects

RA, rheumatoid arthritis; CIA, collagen-induced arthritis; MHC, major histocompatibility complex.

Table 2. In vivo models for the study of RA.

of polymorphisms in genes encoding testosterone, progesterone, and androgens is what trigger an imbalance in the hormone complex with immune system and thus be associated with RA [59].

A higher prevalence of arthritis is present in females, but in murine models, it has been shown that for CIA and antibody-induced arthritis models, male mice and rats (CIA only) exhibit a higher prevalence. Castration of male mice produces a high prevalence of arthritis in the SCW model [60].

Another hormone that can also be a marker is cortisol secreted during periods of stress. In mice it has been shown to reduce the sensitivity to be induced in the CIA model; therefore, it usually confers some protection [61]. **Tables 2** and **3** summarize the in vivo models for the study of RA and the information of the genetic, immunological, and environmental animal models used in RA, respectively.

Characteristic	**Model**		
	Genetic	**Immunological**	**Environmental**
Model genetic background	Transgenic mice deficient in a specific gene to evaluate the effect of this in the murine model.	Arthritis is induced by transfer of antibodies in the serum to susceptible mice, transgenic mice and induced by adjuvants	When in contact with external pollutants, in the animal model, the induction of RA in the CIA model increases.
Advantages	-A specific genetic model allows studying how the disease is developed during prolonged periods and with possibility of repetition. -It allows knowing the functioning of the genes involved in RA.	Generates knowledge about several inflammation-related molecules and their implications in its signaling pathways.	This model gives the facility to know how the environmental influences the intestinal flora and the development of RA.
Year of development	In 1991 the first genetic model was developed, which was of mice that overexpressed the human TNF-α gene	The model of adjuvant arthritis was the first to be described in 1956	The main environmental risk factor for the development of arthritis is smoking and the first murine model of this factor was described in 1992.
Limitation	- Place of indeterminate integration. - Expensive model. -Variable gene expression	- Evaluation of a single gene at a time. - It is generated in inducible models and less in transgenic mice	- There are very few genes or alterations that are evaluated in this model for RA so it is almost obsolete.
Phenotypic expression	Transgenic mice	C57BL/6, K/BxN	DBA 1/J
Reference	[42, 62]	[51, 62]	[58, 63, 64]

RA, rheumatoid arthritis; CIA, collagen induced arthritis.

Table 3. Comparison of animal models for the study of RA.

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5. Therapeutic strategies

Over the years, different RA therapies have been developed; one of the most representatives is TNF blockers, which, although effective, generate some notable side effects. The importance of animal models serves to generate the knowledge and evaluation of new therapies [52]. All these models are intended to induce inflammation and subsequent destruction of one or more peripheral joints in different animal species, with rodent species, such as mice and rats, being the most frequently used. The most common administration routes for evaluation of compounds in murine RA models are two, as shown in **Figure 2**. The most common administration route used for molecules including viral vectors such as lentivirus, retrovirus, and adeno-associated virus is intra-articular, which consists of administering a vector that contains a gene with regulatory effects on some mechanism of RA in the joint of the animal model being evaluated. Recently, murine models have been evaluated in which the viral vector is administered systemically (intravenously), and these have been able to reduce the inflammation generated by the disease as well as other clinical symptoms, without decreasing the effectiveness associated with the route of administration [52].

Some of the therapeutical goals of drugs, irrespective of their route of administration, include regularizing cytokine levels, since there is an overproduction of these, adjusting the expression levels of transcriptional products that cause inflammation and bone degradation, and decreasing chemokines and adhesion molecules, all of which are determinants of RA pathogenesis [52].

The models most used for the evaluation of exogenous substances that help reduce the disease are varied [65]; besides they depend on the animal model, as thus illustrated.

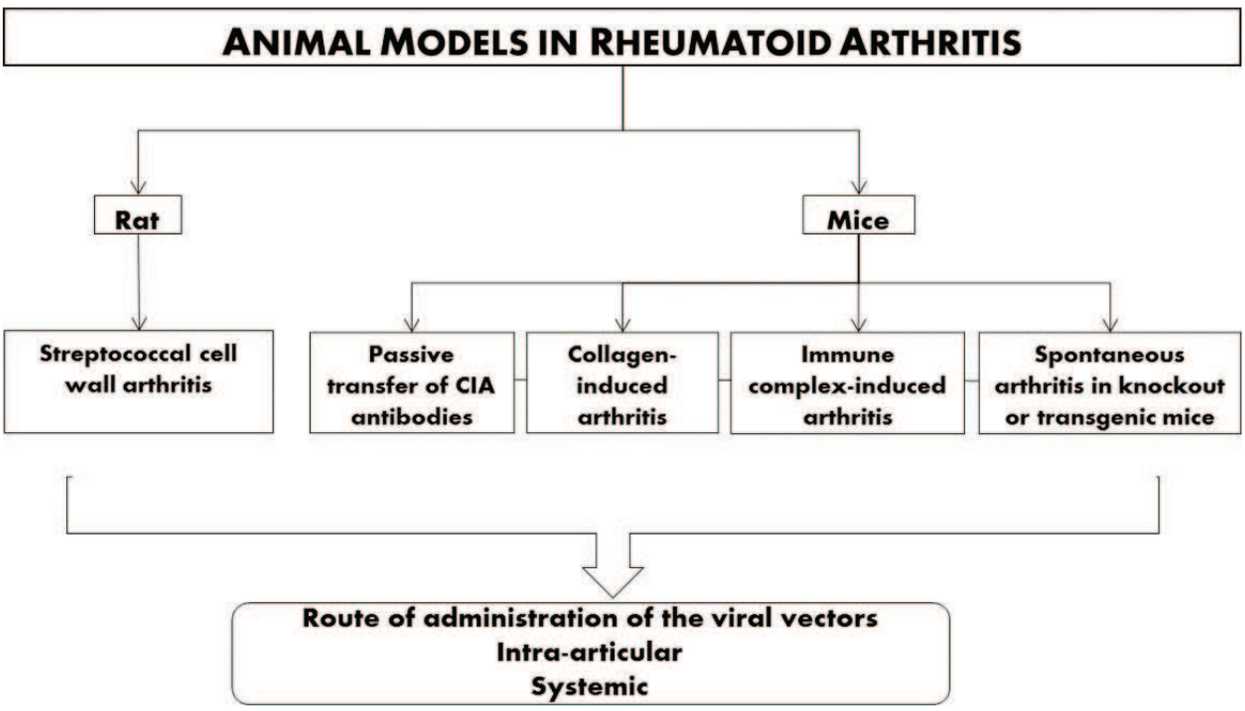

Figure 2. Animal models in RA. The models that are currently used for the generation of RA in mice and rats are varied and depend on the purpose. This can be generated by adjuvants with susceptible animals or spontaneously with genetically modified animals. There are several routes of administration which depend on the vehicle to be administered; for gene therapy the most used are the intra-articular and systemic routes.

5.1. Rat models

5.1.1. Streptococcal cell wall (SCW) arthritis

The SCW arthritis rat model is an experimentally induced inflammatory model with many features which resembles RA in humans. This model is used for studies of pathogenesis, therapy, and obtaining genetic knowledge in the acute and chronic phases of inflammation. Arthritis is induced in strains of rats that are susceptible (Lewis rat strain) and is performed by intraperitoneal injection of peptidoglycan polysaccharide polymers, which are obtained from the cell wall of *Streptococcus pyogenes* group A, D58 strain. This model representatively generates the severity of the arthritis and also generates granulomas in the liver, spleen, and peritoneum, granulomatous enterocolitis, and uveitis [66].

Commonly the streptococcal walls are formed by peptidoglycans (PG) bound to specific polysaccharides. These peptidoglycans have the function of triggering chronic arthritis, followed by a systemic response. Once these PGs are deposited in aqueous solution, three events may occur, which may be deposited in articular tissues. These may last a long time that stimulate the macrophages and pro-inflammatory mechanisms of T-cell activation [67].

The SWC model with Lewis rats (endogenous strain that is highly susceptible) is initiated after injection of the PGs in aqueous form. Once the inoculation takes place, it is necessary to observe the animals daily to verify the development of arthritis during the first 6 days, after this they can be checked every 2–3 days for at least 6–8 weeks. The acute response of this model develops from the first 48 hours to the next 10–21 days; finally, the chronic phase is triggered, which persists for several months in the animal model [67].

The conventional way of generating the model is using a systemic approach, which is obtained by intraperitoneal injection. But there are other alternatives that have been used in later years, such as injection of the cell wall intra-articularly. Strategic application will cause local inflammation with edema in 24 hours and after 3 weeks; the inflammation will be very little noticeable but will be accompanied by synovial infiltration of monocytes and remnant lymphocytes. The presence and importance of Th1 cells in the generation of arthritis for this inflammation model have been strongly suggested [68]. A single intraperitoneal administration of the cell wall is sufficient to generate arthritis and cause remission, although early experiments suggest that systemic administration was performed [69]. Among the main therapeutic targets to be evaluated in this model are direct components of the immune system such as cytokines. There are different studies in which inhibiting the IL-37 and P2X7 receptor, regulating the function of IL-10, and decreasing IL-21 production will produce resistance to joint inflammation when presented with this SCW model [70–72].

5.2. Mouse model

5.2.1. Passive transfer of CIA antibodies

The gold standard animal model for the study of RA is arthritis induced by collagen (CIA). The induction is performed by injecting type II collagen, which is the most predominant constituent

protein of the joint cartilage, and its induction with native collagen and adjuvants produces polyarthritis of a cross-immune response to the homologous collagen. The susceptibility of CIA is linked to the expression of certain complexes such as MHC II, which plays a primordial role in T cells [73].

The generation of antibodies specific for type II collagen is highly characterized. Mice used are B-cell deficient and resistant to developing CIA. The antibodies were shown to induce CIA in the DBA1/J mice strain although the arthritis generated is very mild [74].

For the generation of this AR model, it is necessary to obtain anti-collagen type II antibodies, which are obtained from a CIA model. These antibodies can be extracted from different biological matrices such as serum.

These antibodies are important for the generation of CIA pathogenesis. This transfer shows that arthritis is identical in mice with restriction of T cells. Several studies confirm that the development of the model depends on the joint response of B and T cells toward anti-CII antibodies [75].

The importance of knowing RF in RA is not well understood. It is believed to serve in the formation of immune complexes and in the formation of the complement system, which in turn attracts neutrophils to the site of inflammation [76]. The information is unclear to date, and arthritis is also believed to be induced by the binding of citrullinated peptide epitopes or by cross-reactivity [77].

This model is discussed in DBA1/J type mice, and since it is generated from a serum with antibodies in a CIA model, its targets are generally the same as IL-1β and TNF-α, although other therapies have also been discussed and approved, such as the inhibition of CTLA41g-stimulated T cells and the decrease in B cells with anti-CD20 [78].

5.2.2. Collagen-induced arthritis

CIA is an autoimmune disease that is generated in rodents that are usually genetically predisposed to present features very similar to arthritis, with these being immunized with type II collagen emulsified with complete Freund's adjuvant [34]. CIA in mice exhibits a restriction to MHC II in animals expressing H-2q and H-2r molecules [79]. Trentham et al. (1980), described the administration of type II collagen from chicken, emulsified in complete Freund's adjuvant (CFA) is capable of producing rat arthritis [80]. It was later described that this disease can also be induced in mice [81].

This experimental model of arthritis was designed and described primarily in rats, but currently a mouse strain with genetic predisposition to arthritis, strain DBA/1, is used [11]. Due to its restriction to MHC II, it is obvious that T lymphocytes play a prominent role in the autoimmune response, both in the production and regulation of pro-inflammatory cytokines and in the modulation of the B-cell response [79]. Activated T lymphocytes also activate macrophages to produce pro-inflammatory cytokines, TNFα, IL-1, and IL-6, among others, inducing the expression of chemokines and adhesion molecules with the consequent infiltration of polymorphonuclear cells, MN and formation of pannus.

Histologically, the CIA presents intense synovitis that correlates with the development of the disease. About 5 weeks after application of type II collagen, the animals develop a polyarthritis

similar to RA that occurs in humans. In general, there is fibrosis and ankylosis of the involved joints, and among the histological alterations, erosion of the subchondral bone and formation of pannus can be observed, also autoantibody formation.

All these immunopathological processes of CIA involve a response of T and B lymphocytes. The administration of type II collagen induces a strong activation of cooperating T lymphocytes, which stimulate B lymphocytes to produce antibodies against this protein, and later, a series of antibodies that will interact with cartilage constitutive proteins also activate the complement system. In the serum of arthritic animals, antibodies to different proteins have been detected, in addition to type II collagen [82].

The first antigenic determinants of type II collagen, in the case of DBA 1 mice, have been identified with the H-2q haplotype; the antigenic determinant is between amino acids (aa) 257 and 270 of the protein and in mice with the haplotype H-2r; it is between aa 442 and 456 [83].

Pro-inflammatory cytokines induce synovial cells such as chondrocytes, fibroblasts, and osteoclasts to produce MMPs and other effector molecules, all of which are responsible for cartilage degradation, bone erosion, and fibrosis [84].

B cells also play a key role in the development of CIA. It has been shown that the transfer of immune serum from arthritic mice to healthy mice induces severe inflammation, and although the antibody is no longer detected, the inflammatory response persists. This indicates that the humoral response is capable of triggering more factors that have an important role in establishing the autoimmune response in this model [77].

For the CIA model in rats, the therapeutic agents that have been evaluated are methotrexate and corticosteroids, and for biological targets, it is most common to evaluate the soluble receptor of TNF and IL-1, which have had effective results in decreasing the inflammation generated in the model [85].

CIA model but with mice which is currently the most commonly used with the DBA1/J strain because it has been shown that IL-1β boosts inflammation and perpetuates TNF-α, which have become the main therapeutic targets. Analogous collagen system peptides are currently evaluated for good results by reducing the symptoms of the disease in the murine model [86, 87].

The main route of administration for evaluation of therapeutic compounds, used for this model, is intra-articular; despite being the most used, it has caused controversy in its applicability when used in patients. Therefore, in recent years, efforts have been made to replace it by other means such as the system, which, despite being used recently, has shown favorable results.

5.2.3. Immune complex-induced arthritis (IC)

There are certain important events in RA as the formation of immunocomplexes. These immunocomplexes have been found in the synovium and joint cartilage of patients with RA [88]. The appearance of such complexes has been associated with the severity of the disease.

The most commonly used experimental models of RA, the antigen-induced arthritis, and the adjuvant-induced arthritis exhibit close resemblance to the pathophysiology of RA. However, they do not allow a precise investigation of the isolated contribution of IC to the development

of arthritis. In the case of articular lesions, it is important to note that there is no evidence of a significant increase in the prevalence of this type of disease on IC formation although the recruitment and activation of these cells in IC-induced lesions are considered essential to the full-blown development of the reaction [89].

This model has the advantage that its mechanism of action or effector molecules are generated in a simple way and knowledge of the pathogenesis of the disease is obtained quickly. Among the associated molecules are cytokines IL-1 and TNF-α, essential for the development of the disease, as well as macrophages, neutrophils, and mast cells [90, 91].

To generate the induction of RA, FcR, present in mast cells, neutrophils, and macrophages are very important. Activation of the complement pathway, mainly the C5a fragment, which functions as a chemoattractant factor, is also necessary [92, 93]. Also, innate components of the immune system often play an important role in the development of the CIA model. One example is the specificity of the K/BxN model, despite the omnipresence of autoantigen GPI [94].

In this model, the cationic retention principle is used in the passive transfer of anti-lysozyme antibodies in mice, which are injected into the knee with poly-L-lysine-lysozyme. This compound is large enough to be retained in the joints for a prolonged time and contributes to the joint destruction and chronicity of the disease produced by the model. The models with DBA/1 mice show a strong dependence on IL-1, and TNF blockade is usually very ineffective [95].

In this model, immunocomplexes will generate arthritis-like inflammation, which can be triggered in mice and rats (although in a lesser proportion). It is known that complement factors are usually a therapeutic target in this model and have recently added neutrophils, FcRy, and opsonic components which play a key role in RA inflammation [96].

5.2.4. Spontaneous arthritis in knockout or transgenic mice

Mice that are genetically modified will have various uses, such as the removal or introduction of genes for some receptor, cytokines, or other factors that help trigger immune mechanisms in the etiology of RA. Sometimes, spontaneous inflammation occurs, resulting in arthritis or another inflammatory disorder [52].

These models are much discussed at present, due to their ability to generate the disease, without the need to inoculate the animal with adjuvants, antibodies, or some external agent as in the CIA, SWC, and AIA models.

The K/BxN mouse (transgenic KRN T-cell receptor mouse on the background C57BL/6 x NOD) spontaneously develops chronic and progressive inflammation [97]. Clinically visible joint inflammation is observed from the third week of disease onset and thereafter evolves into a chronic and severe type of problem. T cells and B cells generate autoantibodies that promote the perpetuation of disease and joint destruction [98]. In addition to T-cell involvement, B cells secrete autoantibodies that promote joint destruction. Like arthritis with immunocomplexes or passive antibody transfer, and similarly to the CIA model, arthritis can be induced by serum transfer and induces changes in the MHC. Arthritis is mild and nondurable and requires persistence in the injection of serum with anti-CII antibodies. The fragment of Fc immunoglobulins plays an important factor in this model. The K/BxN model is thus an important tool to

study the role of antibodies in the development of RA [66]. This model alone demonstrates that a specific molecule or antibody is not required to generate arthritis. The receptor of the T cells of the KRN strain recognizes the GPI and, on the other hand, the MHC [99]. This immune recognition of G6PI gives rise to autoantibodies to the isomerase which, when purified, can transfer disease. The relevance of this reactivity to the etiology of RA is unclear. Recognition of G6PI is first obtained by antibodies, and subsequently these can be transferred, although the relevancy of this discovery does not really generate knowledge toward RA.

The transgenic T-cell receptor of the krn strain was originally generated to recognize a bovine-type antigen; its discovery was totally serendipity. Different authors have performed different series of studies to define the mechanism of action, the effector phases, as well as the evaluation of cells involved in this animal model of RA [99].

On the other hand, immunization with G6PI induces an inflammatory arthritis that is dependent on T cells in mice that have not been studied, generating clues about the knowledge and use of such a model [100].

In this model, arthritis is produced by transfer of serum antibodies from a previous arthritis model; mice are genetically modified to develop RA when it is induced. The targets in this model are cytokines and chemokines. The absence of these molecules is analyzed to verify if they generate protection or induction of RA and additional information such as the signaling pathway that it alters. The TRANCE/RANKL factor was one of the most used for evaluation of the NF-kB pathway with TNF [101]. The phenotypic characteristics of the major animal models are shown in **Figure 3**.

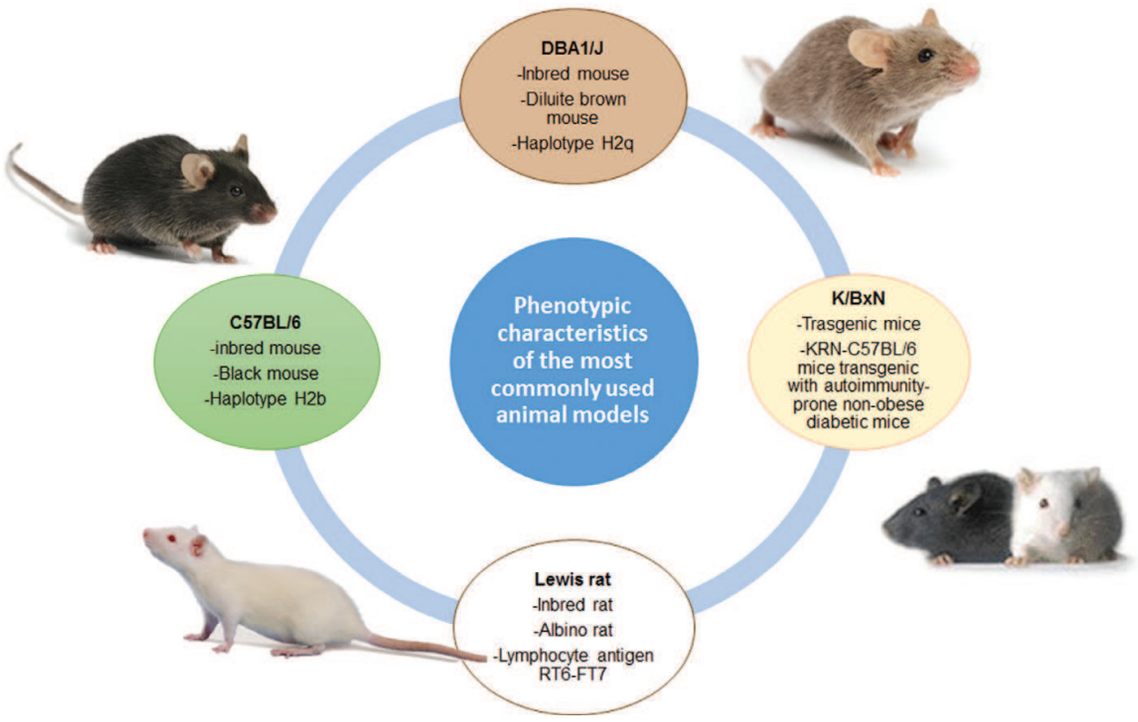

Figure 3. Phenotypic characteristics of animal models. There are different strains of mice and rats used as models for the evaluation of RA; among them the most representative strains are Lewis, DBA 1/J, C57BL/6, and K BxN, which respond to different genotypic and phenotypic characteristics.

6. Future prospect

Animal models, as we have already commented, still are the strongest link to evaluate therapeutic compounds, at least in autoimmune diseases, such as rheumatoid arthritis. In general, each model provides different information about the disease, and it is suggested that for more reliable results, the evaluated compounds have been tested in two different models to have a little more certainty of the effects generated by the molecules that are determined in each experiment.

Efforts are currently directed to find a model that can more accurately reproduce the symptoms and signs of RA taking the security of continuing to obtain reliable results. Another strategy is that the route of administration is as aggressive and invasive as possible but reproduces precise results, so other routes are being evaluated such as systemic to thus discontinue intra-articular injection.

These studies are carried out with the aim of using as few animals as possible and, in turn, with the least suffering, due to the techniques to inoculate the therapeutic agent to be evaluated, in addition to the fact that the population decline does not interfere in the test results.

7. Conclusion

Despite decades of research to eradicate the disease, RA remains one of the most prevalent diseases within its scope and even with a well-defined and unknown etiology. Currently, animal models continue to be an effective and necessary tool for the generation of knowledge on most autoimmune diseases including RA. Currently the animal models are still the main link to understand how the immune system attacks its own components (cells or organs), as well as the evaluation of molecules with therapeutic objectives.

Animal models, inducible (CIA models, passive antibody, or streptococcal wall transfer) or spontaneous (knockout mice), have been shown to be useful in understanding unknown processes. For spontaneous models, it is difficult to perceive the mechanism by which the disease in which the therapeutic compounds are evaluated is triggered. In the same way, no animal model shows all the characteristics of the disease and the route by which the therapeutic agent is introduced can generate variation in the results, so this information should be complementary with the evaluation of more routes of administration. It is envisaged that the generation of new molecular techniques will help to determine the complexity of the functioning of RA as well as to evaluate the different routes of administration of therapeutic compounds pending the attainment of low toxicity and wide benefit therapies that are determined and used for clinical phases.

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