The pathological hallmark of rheumatoid arthritis (RA) is a synovial pannus that comprises proliferating and invasive fibroblast-like synoviocytes, infiltrating inflammatory cells, and an associated neoangiogenic response. Animal models have been established to study these pathological features of human RA. Spontaneous and induced animal models of RA primarily reflect inflammatory aspects of the disease. Among various induced animal models, collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA) models are widely used to study the pathogenesis of RA. Improved transplantation techniques for severe combined immunodeficiency (SCID) mouse models of RA can be used to evaluate the effectiveness of potential therapeutics in human tissues and cells. This review provides basic information on various animal models of RA, including CIA and CAIA. In addition, we describe a SCID mouse coimplantation model that can measure the long-distance migration of human RA synoviocytes and cartilage destruction induced by these cells.

Keywords: Animal models; Cell movement; Rheumatoid arthritis; Severe combined immunodeficient mice; Synoviocytes

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disorder that affects approximately 1% of the global population. It is characterized by tumor-like expansion of the synovium, angiogenesis, and destruction of the articular cartilage and bone [1]. Despite the advent of anticytokine therapies that ameliorate the inflammatory manifestations of RA, there is no curative treatment and the pathogenesis of the disease is not fully understood. In RA joints, various cell populations, including innate immune cells, adaptive immune cells, endothelial cells, and fibroblast-like synoviocytes (FLSs), are activated [1]. Resident synoviocytes participate in the chronic inflammatory response and joint destruction in RA, and in fact, these cells represent the major cell population in the invasive pannus [2]. RA-FLSs have the potential to secrete matrix-degrading enzymes (matrix metalloproteinase 3 [MMP3] and MMP9), pro-inflammatory cytokines (interleukin 1 [IL-1] and IL-6), chemokines (IL-8 and C-C motif chemokine ligand 2), and angiogenic factors (vascular endothelial growth factor and placental growth factor) [2]. Moreover, although RA synoviocytes are primary cells, they proliferate abnormally and display resistance to Fas-mediated apoptosis, similar to cancer cells [2,3]. During RA development, the phenotype of RA-FLSs is altered to an invasive and aggressive behavior, with increased migratory ability and reduced attachment-dependent growth, leading to articular cartilage destruction [2,4]. RA-FLSs can spread by migrating from the af-
fected site to distant unaffected joints in immune-deficient mice [5]. In this regard, antimigratory agents targeting RA synoviocytes may be of therapeutic benefit. Despite the importance of FLSs in RA pathogenesis, no attempt has been made to develop an animal model capable of specifically identifying FLS migration and invasiveness. This review summarizes the immunological properties of mouse models of RA and describes humanized models that are capable of measuring the migration and invasiveness of human synoviocytes.

**Ethical statements:** This study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Catholic University of Korea (IACUC No: CUMC-2020-0182) and the Institutional Review Board (IRB) of the Catholic Medical Center, the Catholic University of Korea (IRB No: KC14TASI0898).

### Murine models of rheumatoid arthritis

As RA is an autoimmune disease characterized by joint destruction, careful consideration is needed when choosing the correct animal model for different in vivo experiments. Therefore, careful analysis of specific aspects of the disease and specific knowledge targeted in each study must be considered when choosing an RA animal model. Animal models of RA can be broadly divided into induced and spontaneous models, including mutant and genetically altered strains. The induced models may be polyarticular (systemic response), which is more likely to be severe, or monooarticular (local response). Spontaneous models progress naturally and generally involve nonresolving, chronic conditions. In this study, we have summarized the involvement of immune cells and cytokines in these models (Table 1).

#### 1. Induced models of rheumatoid arthritis

RA in animals is induced by treatment with agents, such as antigens, antibodies, adjuvants, and serum. Examples of induced mouse models of RA include collagen-induced arthritis (CIA), adjuvant-induced arthritis, proteoglycan-induced arthritis (PGIA), and collagen antibody-induced arthritis (CAIA).

1. **Collagen-induced arthritis**

   CIA is the most frequently used animal model of RA because it shares both immunological and pathological features with human RA, including symmetric joint involvement, synovitis, and cartilage and bone destruction [2,5]. It is elicited in genetically susceptible mouse strains by immunization with type II collagen (CII) emulsified in complete Freund’s adjuvant (CFA). The requirement of T and B cells in the development of CIA is clear [6]. The autoimmune response to CII is characterized by both the stimulation of CII-specific T cells and secretion of specific immunogens and autoantigens [6]. Moreover, CD4+ T cells are believed to participate in the induction phase of the disease, supporting the activation of collagen-specific B cells [6,7].

   Various cytokines have been implicated in the pathogenesis of RA through time-dependent immune system activation [8]. At the time of the clinical onset of arthritis, proinflammatory mediators (tumor necrosis factor alpha [TNF-α], IL-1β, and IL-6) and anti-inflammatory mediators (IL-10, IL-1 receptor antagonist [IL-1Ra], and transforming growth factor-beta isoforms [TGF-β1, TGF-β2, and TGF-β3]) can be detected in CIA joints [6-10]. Because interferon gamma (IFN-γ) inhibits Th17 cell development, IFN-γ receptor-knockout mice develop CIA more readily [11]. IL-23 is also required for the induction of joint inflammation by mediators including IL-17 [12,13].

2. **Antigen-induced arthritis**

   Virtually any animal species can be used to generate antigen-in-

### Table 1. Involvement of immune cells and cytokines in mouse models of arthritis

| Model                          | Immune cell                                      | Cytokine |
|-------------------------------|--------------------------------------------------|----------|
| Collagen-induced arthritis    | Monocytes/macrophages, dendritic cells, granulocytes, synoviocytes, T cells, B cells | TNF-α, IL-1β, IL-6, IL-17, IL-23, IL-32, MCP-1, MIP1 |
| Antigen-induced arthritis     | Monocytes/macrophages, dendritic cells, granulocytes, synoviocytes, T cells, B cells | TNF-α, IL-1β, IL-6, IL-17, IFN-γ |
| Proteoglycan-induced arthritis| Monocytes/macrophages, granulocytes, synoviocytes, T cells, B cells | TNF-α, IL-1β, IL-6, IL-12, MCP-1, MIP1α, MIP-2 |
| Collagen antibody-induced arthritis | Monocytes/macrophages, synoviocytes | IL-1β, IL-6, TNF |
| HuTNF transgenic mice          | Monocytes/macrophages, granulocytes | TNF-α, IL-1β |
| IL-1 receptor antagonist knockout mice | Monocytes/macrophages, synoviocytes | IL-1, IL-17 |

TNF, tumor necrosis factor; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; IFN, interferon; HuTNF, human tumor necrosis factor.

24  https://doi.org/10.12701/jyms.2022.00773
duced arthritis (AIA) models. In mice, ovalbumin and bovine serum albumin (BSA) are commonly used, and modified antigens (e.g., methylated antigens) can induce chronic arthritis [14]. Antigens, such as methylated BSA, are cationic substances that bind negatively to cartilage [14,15]. When antigens are injected into one or multiple joints, inflammation progresses quickly and complement is activated locally, resulting in cartilage destruction [14]. AIA is T cell-dependent in hypothymic nu/nu mice [14]. In a recent study, both IL-23p19−/− and IL-17Ra−/− mice displayed significantly milder arthritis than wild-type mice, demonstrating that AIA progression is dependent on IL-23 and IL-17Ra signaling [16,17].

3) Proteoglycan-induced arthritis

PGIA is a progressive polyarthritis characterized by symmetrical synovitis, marginal erosion, pannus formation, and synovial infiltration of immune cells [18]. It is induced by the injection of human cartilage proteoglycans (PGs) into BALB/c (H-2d) mice, which exhibit remission and exacerbation. The first and fourth injections contain PG/CFA, the second and third injections contain PG/incomplete Freund’s adjuvant (IFA), and arthritis develops on approximately day 11 and reaches maximum severity 2 to 4 weeks after the last PG injection [19]. Mice with PGIA display CD4+ T cell responses along with an antibody response to PG, and immunoglobulin G (IgG) 2a antibody levels are correlated with disease severity [18]. Although PGIA is a predominantly Th1-type arthritis model, it has been reported that IL-4 deficiency increases the severity of PGIA [20]. In addition, treatment with IL-4 or IFN deficiency suppresses PGIA [21].

4) Collagen antibody-induced arthritis

CAIA can be induced in many susceptible mouse strains, and clinical signs of arthritis generally appear a few days after antibody administration [22]. A cocktail of anti-CII monoclonal antibodies is administered to induce arthritis in the mice. Intraarticular injection of lipopolysaccharide increases disease severity and the incidence of arthritis; however, it is not essential for disease induction [22].

Disease initiation in CAIA models occurs mainly independently of B and T cells; however, immune cells modulate inflammation during the effector phase [23]. The main effector cells appear to be neutrophils and macrophages, which are activated by immune complexes formed in the joints via binding of CII antibodies to cartilage surfaces [23]. Typical pathological changes observed in RA, such as synovitis, pannus formation, and cartilage and bone destruction, are observed in the joints of animals with CAIA [24,25]. Although the cytokines involved in the pathogenesis of CAIA have not been studied in detail, the involvement of IL-1β, IL-6, and TNF is anticipated [24,26].

2. Genetically modified models of rheumatoid arthritis

Genetic manipulations that affect the pathogenesis of arthritis can lead to arthritis in a variety of mice.

1) Human tumor necrosis factor transgenic mice

The first TNF transgenic mouse model was generated by Kefler et al. in 1991 [27]. They generated transgenic mice expressing wild-type and 3′-modified human TNF-α transgenes [27]. In this mouse model, synovial hyperplasia and inflammatory cell infiltration were observed in the joints after 3 to 4 weeks of age, and pannus formation, cartilage destruction, and bone erosion were observed in the mice at approximately 10 weeks of age [28,29]. This model highlights the importance of TNF-α in the pathogenesis of arthritis and can be used for the development of TNF inhibitors.

2) Interleukin-1 receptor antagonist knockout mice

IL-1 is an important inflammatory cytokine produced by a variety of cell types, including activated monocytes, macrophages, fibroblasts, and synovial cells [30]. In contrast, the IL-1 inhibitor IL-1Ra regulates the activity of IL-1 as an anti-inflammatory protein that binds to the IL-1 receptor [31,32]. It has been reported that IL-1Ra knockout mice develop spontaneous arthritis mediated by the amplification of Th17-dependent inflammation [32,33]. In a BALB/c background, polyarthritis develops starting at 5 weeks of age, and by 12 weeks of age, almost all mice are affected [33].

Histopathological analysis revealed marked synovial and periarticular inflammation, with articular destruction caused by the invasion of granulation tissues, closely resembling RA in humans [32]. Moreover, high levels of antibodies against IgG, CII, and double-stranded DNA were detectable in the sera of these mice [32,33].

3. Collagen-induced versus collagen antibody-induced arthritis

The most commonly used mouse models are CIA and CAIA. CAIA bypasses the host’s generation of autoantibodies to CII; thus, it can be induced in mice that do not possess CIA-susceptible major histocompatibility complex haplotypes (H-2q and H-2r), such as BALB/c and C57BL/6 mice [22,24]. Therefore, CAIA can be induced in most mouse strains, including transgenic and knockout mice, with an arthritis incidence approaching 100% [22]. This model is ideal for screening and evaluating anti-inflammatory agents without the effects of CFA or IFA, which strongly
affect the host’s immune response.

Table 2 presents the similarities and differences between the CIA and CAIA models, and a time comparison.

### Humanized models of rheumatoid arthritis

Mouse models of RA have been used for decades to study the immunopathogenesis of the disease and to explore therapeutic strategies. Nevertheless, differences in the immune systems of humans and mice have limited confidence in the success of disease treatments. To overcome this issue, severe combined immunodeficiency (SCID) mice have been used to investigate human tissues in autoimmune disease \[^{34-37}\].

The use of SCID mice provides a novel model for studying tissues and cells from patients with RA \[^{5,36}\]. In this review, we introduce a method that can measure cell migration and the ability to destroy human cartilage by applying synovial cells isolated from patients with RA in SCID mice.

1. **Model using synoviocyte migration in severe combined immunodeficiency mice**

FLSs, which are components of the synovial membrane, play a critical role in RA pathogenesis through aggressive migration and matrix invasion \[^{2,4}\]. A model for measuring the migration of synoviocytes to the site of inflammation was established by subcutaneous induction of inflammation with CFA in SCID mice and then injecting synoviocytes from patients with RA around the site of inflammation \[^{38}\]. One day after the CFA injection, RA-FLSs labeled with fluorescent dyes were implanted intradermally into the mice at a fixed distance (1.2 cm) from the injection site (Fig. 1). Five days after implantation, skin samples were obtained from the FLS-implanted site, CFA-injected site, and a region between these two sites (sites a, c, and b in Fig. 1). The migration of synoviocytes was analyzed according to the presence or absence of human leukocyte antigen class I (+) cells in each tissue site obtained at the end of the experiment \[^{38}\].

2. **Model using synoviocyte migration and invasion in severe combined immunodeficiency mice**

RA starts in a few joints; however, as the disease progresses, it can affect all joints \[^{5}\]. Interestingly, it has been reported that RA synoviocytes in a SCID mouse model can travel long distances through the bloodstream and migrate toward, attach to, and invade the distant cartilage matrix \[^{5}\]. This model may be useful for elucidating the role and mechanism of an agent targeting activated synoviocytes in RA. In this section, we summarize the protocol for developing a synoviocyte migration and invasion model in SCID mice.

![Fig. 1. Schematic of model using synoviocyte migration in severe combined immunodeficiency mice. Skin inflammation was induced by subcutaneously injecting CFA (120 µg) into site a. One day after the CFA injection, rheumatoid arthritis-FLSs were implanted intradermally in site c. Five days after human FLSs implantation, skin samples were obtained from site b. CFA, complete Freund’s adjuvant; FLS, fibroblast-like synoviocyte.](https://doi.org/10.12701/jyms.2022.00773)

| Variable                  | CIA                                      | CAIA                                      |
|---------------------------|------------------------------------------|-------------------------------------------|
| Induction method          | Type II collagen/CFA                     | Type II collagen monoclonal antibodies    |
| Period                    | 7–8 weeks                                | 1–2 weeks                                 |
| Mouse strains             | Restricted to select mouse strains       | Many mouse strains                        |
| Feature of arthritis      | Polyarthritis                            | Polyarthritis                             |
| RF and ACPA               | Positive                                 | Negative                                  |

CIA, collagen-induced arthritis; CAIA, collagen antibody-induced arthritis; CFA, complete Freund’s adjuvant; RF, rheumatoid factor; ACPA, anticitrullinated protein/peptide antibodies.
1) Implantation experiments

FLSs were prepared from synovial tissues of patients with RA [4,38]. Normal human cartilage was obtained from the nonarthritic knee joints of patients undergoing amputation [5,39]. Cartilage and RA synoviocytes in sponges were coimplanted into SCID mice at the primary site (6–8 weeks), and cartilage without synoviocytes was implanted at the contralateral site [5,35,39]. After 60 days, the implants were removed and either immediately embedded in a snap-frozen medium or fixed in 4% buffered formalin for paraffin embedding [5,37,39]. Using standard hematoxylin and eosin staining, each specimen was evaluated for invasion and perichondrocytic cartilage degradation in the implanted cartilage.

A procedural overview of the current model is shown in Fig. 2.

2) Histological score

The cartilage invasion was evaluated on a 0-to-3-point scale indicating the depth of cell invasion (0, no or minimal invasion; 1, visible invasion [2 cell depths]; 2, invasion [5 cell depths]; and 3, deep invasion [10 cell depths]).

Perichondrocytic cartilage degradation was assessed by scoring the diameter of the chondron (0, no degradation and sharp halo; 1, visible degradation [1 diameter of the chondron]; 2, degradation [1–2 diameters of the chondron]; and 3, intensive degradation [2 diameters of the chondron]) [36,39].

Conclusion

The careful selection, design, and implementation of animal models are important strategies for RA treatment. In this review article, we describe a variety of mouse models that are widely used or that exhibit pathologies similar to those of arthritis in humans. These models were divided into induced and genetically modified groups. This summary of the characteristics of each model will help researchers to select the best animal model for evaluating the effectiveness of experimental treatments for RA. Furthermore, humanized models are extremely important for investigating the role and mechanism of RA-FLSs targeting these cells.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by grants from the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (2019R1A2C2010897).

Author contributions

Conceptualization, Data curation, Resources, Software: all authors; Formal analysis: SAY, GHJ; Funding acquisition, Validation: SAY, JSK; Methodology, Investigation, Project administration, Visualization, Supervision: SAY; Writing-original draft: SAY; Writing-review & editing: SAY, JSK.

ORCID

Jin-Sun Kong, https://orcid.org/0000-0003-4878-8733
Gi Heon Jeong, https://orcid.org/0000-0003-2935-0293
Seung-Ah Yoo, https://orcid.org/0000-0003-4878-8733

References

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.
2. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effec-
tor cells in rheumatoid arthritis. Immunol Rev 2010;233:233–55.
3. Matsuno H, Yudoh K, Nakazawa F, Sawai T, Uzuki M, Nishioka K, et al. Anti-rheumatic effects of humanized anti-Fas monoclonal antibody in human rheumatoid arthritis/SCID mouse chimera. J Rheumatol 2002;29:1609–14.
4. Yoo SA, Park JH, Hwang SH, Oh SM, Lee S, Cicatiello V, et al. Placental growth factor-1 and -2 induce hyperplasia and invasiveness of primary rheumatoid synoviocytes. J Immunol 2015;194:2513–21.
5. Lefèvre S, Knedla A, Tennie C, Kampmann A, Wunrau C, Dinser R, et al. Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. Nat Med 2009;15:1414–20.
6. Inglis JJ, Notley CA, Essex D, Wilson AW, Feldmann M, Anand P, et al. Collagen-induced arthritis as a model of hyperalgesia: functional and cellular analysis of the analgesic actions of tumor necrosis factor blockade. Arthritis Rheum 2007;56:4015–23.
7. Taneya V, Taneya N, Paisansinsup T, Behrens M, Griffiths M, Luthra H, et al. CD4 and CD8 T cells in susceptibility/protection to collagen-induced arthritis in HLA-DQ8 transgenic mice: implications for rheumatoid arthritis. J Immunol 2002;168:5867–75.
8. Marinova-Mutafchieva L, Gabay C, Funakawa K, Williams RO. Reversal of collagen-induced arthritis is associated with high levels of transforming growth factor-beta expression in the joint. Clin Exp Immunol 2006;146:287–93.
9. Lee KM, Zhang Z, Achuthan A, Fleetwood AJ, Smith JE, Hamilton JA, et al. IL-23 in arthritic and inflammatory pain development in mice. Arthritis Res Ther 2020;22:123.
10. Kannan K, Ortmann RA, Kimpel D. Animal models of rheumatoid arthritis and their relevance to human disease. Pathophysiology 2005;12:167–81.
11. Chu CQ, Song Z, Mayton L, Wu B, Wooley PH. IFNgamma deficient C57BL/6 (H-2b) mice develop collagen induced arthritis with predominant usage of T cell receptor Vbeta6 and Vbeta8 in arthritic joints. Ann Rheum Dis 2003;62:983–90.
12. Murphy CA, Langrish CL, Chen Y, Blumenwirth W, McClanahan T, Kastelein RA, et al. Divergent pro- and antiinflammatory roles for IL-17 and IL-12 in joint autoimmune inflammation. J Exp Med 2003;198:1951–7.
13. Lubberts E, Koenders MI, Oppers-Walgren B, van den Besselaar L, Coenen-de Roo CJ, Joosten LA, et al. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum 2004;50:650–9.
14. Brackertz D, Mitchell GF, Mackay IR. Antigen-induced arthritis in mice: I. Induction of arthritis in various strains of mice. Arthritis Rheum 1977;20:841–50.
15. Bendele A. Animal models of rheumatoid arthritis. J Musculoskeletal Neuronal Interact 2001;1:377–85.
16. Razaway W, Asamwidjaja PS, Mus AM, Salieska N, Davelaar N, Kops N, et al. CD4+ CCR6+ T cells, but not γδ T cells, are important for the IL-23R-dependent progression of antigen-induced inflammatory arthritis in mice. Eur J Immunol 2020;50:245–55.
17. Cornelissen F, Mus AM, Asamwidjaja PS, van Hamburg JP, Tocker J, Lubberts E. Interleukin-23 is critical for full-blow expression of a non-autoimmune destructive arthritis and regulates interleukin-17A and RORgammat in gammadelta T cells. Arthritis Res Ther 2009;11:R194.
18. Glant TT, Mikecz K, Bartlett RR, Deak F, Thonar EJ, Williams JM, et al. Immunomodulation of proteoglycan-induced progressive polyarthritis by leflunomide. Immunopharmacology 1992;23:105–16.
19. Mikecz K, Glant TT, Poole AR. Immunity to cartilage proteoglycans in BALB/c mice with progressive polyarthritis and ankylosing spondylitis induced by injection of human cartilage proteoglycan. Arthritis Rheum 1987;30:306–18.
20. Kaplan C, Valdez JC, Chandrasekaran R, Ebel H, Mikecz K, Glant TT, et al. Th1 and Th2 cytokines regulate proteoglycan-specific autoantibody isotypes and arthritis. Arthritis Res Ther 2002;4:54–8.
21. Doodes PD, Cao Y, Hamel KM, Wang Y, Rodeghero RL, Mikecz K, et al. IFN-gamma regulates the requirement for IL-17 in proteoglycan-induced arthritis. J Immunol 2010;184:1552–9.
22. Nandakumar KS, Holmdahl R. Efficient promotion of collagen antibody induced arthritis (CAIA) using four monoclonal antibodies specific for the major epitopes recognized in both collagen induced arthritis and rheumatoid arthritis. J Immunol Methods 2005;304:126–36.
23. Nandakumar KS, Bäcklund J, Vestberg M, Holmdahl R. Collagen type II (CII)-specific antibodies induce arthritis in the absence of T or B cells but the arthritis progression is enhanced by CII-reactive T cells. Arthritis Res Ther 2004;6:R544–50.
24. Moore AR, Allden S, Bourne T, Denis MG, Kranidioti K, Okoye R, et al. Collagen II antibody-induced arthritis in Tg1278TNFko mice: optimization of a novel model to assess treatments targeting human TNFa in rheumatoid arthritis. J Transl Med 2014;12:285.
25. Zhao T, Xie Z, Xi Y, Liu L, Li Z, Qin D. How to model rheumatoid arthritis in animals: from rodents to non-human primates. Front Immunol 2022;13:887460.
ates inflammation and oxidation in mice with collagen antibody-induced arthritis via TLR4/NF-κB signaling. Mol Med Rep 2016;14:1365–70.

27. Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kiousis D, et al. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J 1991;10:4025–31.

28. Williams RO, Feldmann M, Maini RN. Cartilage destruction and bone erosion in arthritis: the role of tumour necrosis factor alpha. Ann Rheum Dis 2000;59(Suppl 1):i75–80.

29. Joe B, Griffiths MM, Remmers EF, Wilder RL. Animal models of rheumatoid arthritis and related inflammation. Curr Rheumatol Rep 1999;1:139–48.

30. Kinne RW, Stuhlmüller B, Burmester GR. Cells of the synovium in rheumatoid arthritis. Macrophages. Arthritis Res Ther 2007;9:224.

31. Horai R, Nakajima A, Habiro K, Kotani M, Nakae S, Matsuki T, et al. TNF-alpha is crucial for the development of autoimmune arthritis in IL-1 receptor antagonist-deficient mice. J Clin Invest 2004;114:1603–11.

32. Horai R, Saijo S, Tanioka H, Nakae S, Sudo K, Okahara A, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. J Exp Med 2000;191:313–20.

33. Nakae S, Saijo S, Horai R, Sudo K, Mori S, Iwakura Y. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. Proc Natl Acad Sci U S A 2003;100:5986–90.

34. Duchosal MA. SCID mice in the study of human autoimmune diseases. Springer Semin Immunopathol 1992;14:159–77.

35. Elkon KB, Ashany D. The SCID mouse as a vehicle to study autoimmunity. Br J Rheumatol 1993;32:4–12.

36. Schinnerling K, Rosas C, Soto L, Thomas R, Aguillón JC. Humanized mouse models of rheumatoid arthritis for studies on immunopathogenesis and preclinical testing of cell-based therapies. Front Immunol 2019;10:203.

37. Müller-Ladner U, Kriegsmann J, Franklin BN, Matsumoto S, Geiler T, Gay RE, et al. Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. Am J Pathol 1996;149:1607–15.

38. You S, Yoo SA, Choi S, Kim JY, Park SJ, Ji JD, et al. Identification of key regulators for the migration and invasion of rheumatoid synoviocytes through a systems approach. Proc Natl Acad Sci U S A 2014;111:550–5.

39. Dang J, Zhu S, Wang J. A protocol for humanized synovitis mice model. Am J Clin Exp Immunol 2019;8:47–52.