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REVIEW ARTICLE

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The SCID–HuRAg mouse as a model for rheumatoid arthritis

Abstract Many animal models have been developed for a study of rheumatoid arthritis (RA). However, RA animal models are not always similar to RA patients in their response to antirheumatic drugs. Recently, humanized monoclonal antibody (mAb) has been developed for the treatment of RA, but at present there is no animal model on which to screen this mAb therapy because of problems with cross-reactivity. We therefore considered the development of a novel animal model for the screening of antirheumatic drugs using the severe combined immunodeficiency (SCID) mouse in order to prevent the rejection of human transplant cells. Following subcutaneous implantation of synovial tissue in the SCID mouse, all target cells within the SCID–HuRAg mouse were of human origin, having migrated from the implanted tissue. Moreover, human interlukin-6 and rheumatoid factor were detected in this mouse serum. We therefore propose that this SCID–HuRAg mouse is a novel, useful animal model for the study and development of new drugs for RA patients. This novel RA animal model is reviewed in this chapter.

Key words Animal model · Monoclonal antibody · Rheumatoid arthritis · SCID mouse · Treatment

Particulars of SCID–HuRAg mouse development

A severe combined immunodeficiency (SCID) mouse is a mutant mouse from the C.B.-17 strain, which is a congenic strain of the BALB/c-Icr mouse.[1] In SCID mice there is a defect in the VDJ recombinase system which impairs their ability to rearrange immunoglobulin and T cell receptor genes. As a consequence, SCID mice fail to develop mature T or B lymphocytes and lack the associated immune responses. Therefore, they are unable to reject allogenic and xenogenic grafts. Consequently, SCID mice are considered to be a useful animal model for human diseases, since many human cells or tissues may be successfully grafted into SCID mice. There are two methods of transplanting human cells into SCID mice: one is by injecting human peripheral blood cells into the mice,[2,3] and the other is by grafting human tissue directly onto the mice.[4] These two transplanting methods are referred to as the PBL–SCID mouse and the SCID–hu mouse, respectively.

Adams et al.[5] were the first to report that RA synovial tissue could be transplanted into SCID mice. Following this, Rendt et al.[6] analyzed the model in detail and reported that this animal model was useful for studying the pathogenesis of RA and the development of antirheumatic drugs. The initial studies[5–7] (Table 1) were carried out with small pieces of synovium transplanted beneath the renal capsule in the mice. This meant that very few lymphocytes were transplanted with the tissue, which limited the usefulness of the model, since they are the main inflammatory cells in RA. We therefore considered that a mouse model whose pathological state was more analogous to that in human RA should be developed. The transplantation area was changed to the subcutaneous tissue on the back of the mouse, a technique which had already been used in the cancer field.[8] This improved the model because a much larger piece of tissue could be implanted using this method. Thus, a novel RA animal model, the SCID–HuRAg mouse, was developed in our laboratory.[9,10] We combined articular cartilage and bone in the synovial tissue grafts because bone and cartilage destruction were also investigated with the SCID–HuRAg mouse. Sack et al.[11] also reported that lymphocytes transplantation with RA synovium into SCID mice was more successful using other transplantation methods.

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Table 1. Phenotypic histological analysis of implanted tissues on SCID–hu mice

Procedure (reference)	Positive cells				
	+++	++	+	±	−
Under renal capsule (Rendt et al.[6])	Fibroblasts, vessels CD14, CD44, CD54 CD29, CD71	CD7, CD4, CD8 T cell receptor HLA-DR	CD2, CD58, CD11a, CD25	MMP-1, MMP-3	CD20
Under renal capsule; partially subcutaneous (Geiler et al.[7])	Fibroblasts CD14, CD68 MMP-2 (type IV collagen)			Lymphocytes	
Mouse knee (Sack et al.[11])	CD68, CD20 HLA-DR			CD3	CD19, CD22
Subcutaneous (Matsuno et al.[10])	Fibroblasts, vessels CD4, CD20, CD68 MMP-9 IL-6, TNF-α HLA-DR	MMP-1 CD8 Osteoclasts			

Preparation of SCID–HuRAg mouse

Six- to seven-week-old male SCID mice (CB.17/Icr, Charles River Japan, Japan), which had been bred under the specific pathogen-free conditions at our University Animal Center, were used for the experiments. Pannus tissue from synovial membrane, articular cartilage, and bone, collected together from RA patient at the time of surgery, was used for implantation. The size of the transplant tissue was trimmed to a block about 4–8 mm in diameter prior to implantation. The tissue implants were grafted subcutaneously on the back of the mouse. Successful transplantation required all operative procedures to be completed within 1 h. After the subcutaneous tissue was exposed, the oblique ext abdominal muscle was scraped with a scalpel until it bled. The graft was then placed on the muscle at the level of the 4th–6th lumbar vertebra of the mouse. All surgical procedures were performed under sterile conditions. Successful implantation of human RA tissue was observed by visual assessment 4 weeks after implantation, when experimentation becomes possible.

Histological findings of SCID–HuRAg mice

As in previous RA animal models, visual observation of the mouse arthritis was impossible in the SCID–HuRAg mouse because the arthritis does not appear in the mouse joints.[12,13] However, the histological characteristics of the implant tissue in this mouse were very similar to those of human RA,[14] and all implanted cells were of human origin. These were the advantages of using this animal model.

The histologic features of human RA were observed in SCID–HuRAg mice. Pathological features such as the proliferation of inflammatory cells (CD4-, CD8-, CD20-, and CD68-positive cells) and lymphoid follicle formation were observed in the implanted tissues. Pannus formation was maintained in the implanted tissue, and proliferative synovial fibroblasts, osteoclasts, and hyaluronic acid-positive articular cartilage were also observed. In addition, the presence of cytokines (TNF-α, IL-1, and IL-6) and matrix metalloproteinases (MMP-1 and -9) was confirmed in the SCID–HuRAg mouse model. Levels of both human rheumatoid factor and IL-6 in the serum of mice were increased following the implantation. Therefore, the features of the implanted tissue in the SCID–HuRAg mouse model appeared to be very similar to the those of joint tissue in humans with RA.[10,15]

The SCID–HuRAg mouse as an experimental model for anti-RA drugs

Many animal models have been developed for the study of RA. However, previous animal RA models did not always show a similar response to antirheumatic drugs when compared with RA patients.[16] In addition, monoclonal antibody (mAb) therapy has recently been used for RA pateints.[17–20] However frequent administration of mouse-type mAb to patients creates an unacceptable risk, since mouse mAb is an immunogenic protein for humans.[21,22] Therefore, chimeric, humanised, or human-type mAb is recommended for mAb treatment. A chimeric mAb was produced by substituting the mouse light chain with that of a human. Homology with human immunoglobulin molecules is about 67%. The humanized mAb is reconstructed by recombination of the complementarity-determining region of the human immunoglobulin molecule, and the homology is about 90% (Fig. 1). However, when the mAb is reshaped to the human form, the affinity and avidity of the mAb sometimes differ from those of the original mouse mAb.[23,24] Moreover, the monkey is the only animal model in which there is a reaction to the reshaped human mAb. For this reason, the development of novel models is necessary before an extensive study of reshaped human mAb treatment can be conducted.

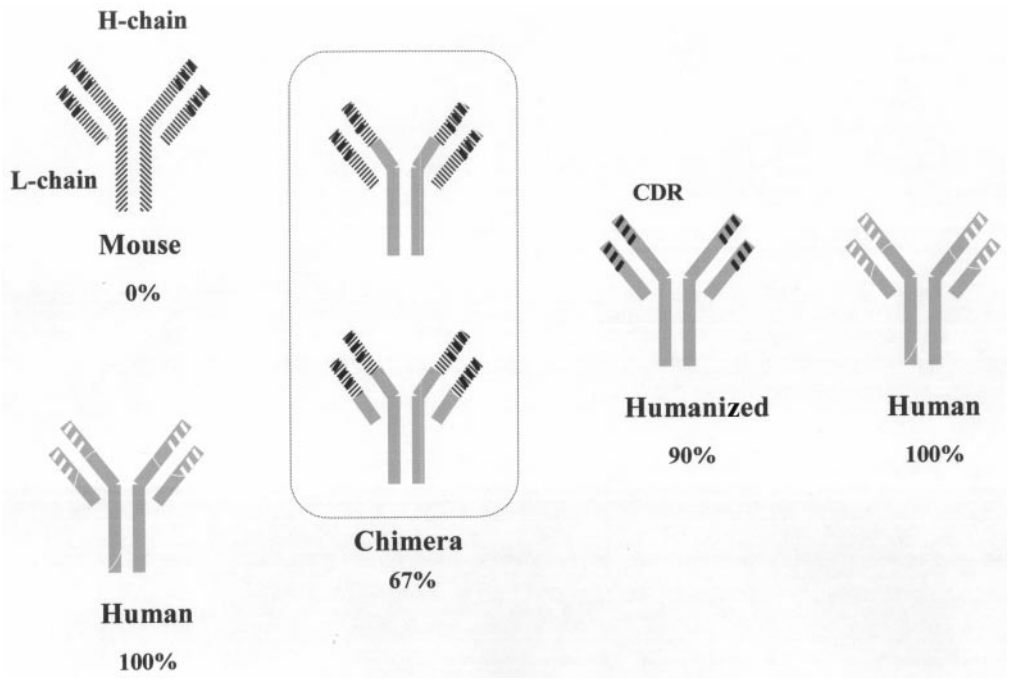

Fig. 1. The chimeric-type mAb is produced to substitute the mouse light chain for the human chain, and the agreement rate with humans is about 67%. The humanized mAb is reshaped by recombination of the complementarity-determining region of the human immunoglobulin, and the agreement rate is about 90%

Since all the transplanted tissues and cells have originated from human tissue, the SCID–HuRAg mouse is an effective model for screening this reshaped human mAb. We have already tested some reshaped human mAbs (anti-IL-6 receptor mAb, -TNF-αmAb, and -Fas mAb) in the SCID–HuRAg mouse model and have obtained good results.[10,15,17] In addition, we have recently confirmed that gene therapy screening is also possible using this model.[25] Therefore, we expect that the demand for SCID–HuRAg mice will increase in the future because they can be used to evaluate reshaped human mAbs. In conclusion, the SCID–HuRAg mouse is a useful animal model with which to evaluate the effectiveness of reshaped human mAbs in RA therapy.

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