Pathogenesis of Vasculitis in env-pX Rats

Akihiro Ishizu, MD, PhD,¹ and Takashi Yoshiki, MD, PhD²,³

Transgenic rats carrying the env-pX gene of human T-cell leukemia virus type I (HTLV-I) develop various collagen vascular diseases such as arthritis resembling rheumatoid arthritis, sialoadenitis resembling Sjögren’s syndrome, vasculitis, thrombosis, myocarditis, myositis, and dermatitis.¹-³) In the serum of these env-pX rats, various antibodies such as the anti-nuclear antibody, rheumatoid factor, and anti-phospholipid antibody are detected, suggesting that autoimmune mechanisms are involved in the development of collagen vascular diseases observed in env-pX rats. The histopathological findings of vasculitis are those of necrotizing angiitis such as fibrinoid necrosis of the vascular walls and infiltration of inflammatory cells such as monocytes and neutrophils in the medium- and small-sized vessels. IgM deposition is present in the vascular walls of the lesion while IgG deposition shows perivascular leakage, and no complement element deposition is observed. The anti-neutrophil cytoplasmic antibody (ANCA) is negative, and there is no lesion in the renal glomeruli. These findings suggest that vasculitis developing in env-pX rats closely resembles human polyarteritis nodosa (PN). In this review, we provide an outline of the developmental mechanism of vasculitis in env-pX rats that has been clarified by previous studies, and discuss the pathogenesis of human necrotizing angiitis.

INTRODUCTION

Transgenic rats carrying the env-pX gene of human T-cell leukemia virus type I (HTLV-I) develop various collagen vascular diseases such as arthritis resembling rheumatoid arthritis, sialoadenitis resembling Sjögren’s syndrome, vasculitis, thrombosis, myocarditis, myositis, and dermatitis.¹-³) In the serum of these env-pX rats, various antibodies such as the anti-nuclear antibody, rheumatoid factor, and anti-phospholipid antibody are detected, suggesting that autoimmune mechanisms are involved in the development of collagen vascular diseases observed in env-pX rats. The histopathological findings of vasculitis are those of necrotizing angiitis such as fibrinoid necrosis of the vascular walls and infiltration of inflammatory cells such as monocytes and neutrophils in the medium- and small-sized vessels. IgM deposition is present in the vascular walls of the lesion while IgG deposition shows perivascular leakage, and no complement element deposition is observed. The anti-neutrophil cytoplasmic antibody (ANCA) is negative, and there is no lesion in the renal glomeruli. These findings suggest that vasculitis developing in env-pX rats closely resembles human polyarteritis nodosa (PN). In this review, we provide an outline of the developmental mechanism of vasculitis in env-pX rats that has been clarified by previous studies, and discuss the pathogenesis of human necrotizing angiitis.

INvolvement of the thymus in the Development of Vasculitis in Env-pX Rats

Transgene expression in env-pX rats is controlled by the LTR promoter of HTLV-I itself, and, therefore, observed constitutively in all organs and cells. To determine whether the cause of various disorders in env-pX rats is present in blood cells represented by lymphocytes or the target tissue expressing the env-pX gene, we performed blood cell replacement experiments by the transfer of bone marrow cells or splenic cells between env-pX rats that had not yet developed disorders and wild-type rats of the same strain. As a result, the developmental mechanisms of various disorders observed in env-pX rats differed according to the target organ. For example, dermatitis could be induced in wild-type rats by transferring bone marrow cells or splenic cells of env-pX rats, which suggested the importance of blood cells such as lymphocytes expressing the env-pX gene in the development of dermatitis.⁴) However, arthritis was not induced in wild-type rats using bone marrow or splenic cells of
env-pX rats, while env-pX rats developed arthritis even after the replacement of their blood cells by cells derived from wild-type rats. These findings suggest the primary role of the target tissue such as the synovial membrane expressing the env-pX gene in the development of arthritis.\(^5,6\) Vasculitis developed in wild-type rats to which splenic cells of env-pX rats were transferred. However, no vasculitis developed in wild-type rats after replacement of their blood cells by bone marrow cells of env-pX rats. Splenic cells used for transfer contain T cells selected in the donor’s thymus, while T-cell precursors derived from the bone marrow used for transfer are selected in the recipient’s thymus. Based on these findings, we speculate that the thymus expressing the env-pX gene plays an important role in the development of vasculitis in env-pX rats. Therefore, we produced rats expressing the env-pX gene only in the thymus framework by combining bone marrow transplantation and thymus replacement, and observed the development of vasculitis in these rats similar to that observed in env-pX rats.\(^7\) These results suggested that when bone marrow-derived T-cell precursors pass the thymic framework expressing the env-pX gene in env-pX rats, certain abnormality in T-cell selection occurs, and autoreactive T cells against the self blood vessels appear in the periphery, inducing vasculitis (Fig. 1).

**Abnormalities of Inhibitory T Cells in env-pX Rats**

In env-pX rats, functional disorder in Foxp3-positive, CD25-positive, CD4-positive T cells that inhibit autoimmune responses in the periphery has been reported.\(^8,9\) This functional disorder may not always be indispensable for the development of necrotizing angiitis, but there is a possibility that it maintains or enhances autoimmune responses targeting the blood vessels.

**Establishment of an Autoreactive T-Cell Clone against Self Vascular Endothelial Cells**

When premorbid env-pX rats were immunized with rat vascular endothelial cells (RECs) derived from wild-type rats, the development of vasculitis was promoted (Fig. 2). This result also supported the presence of autoreactive T cells against the self blood vessels in the blood of env-pX rats. We obtained lymph node cells from env-pX rats immunized with RECs, repeatedly stimulated these cells with RECs in vitro, and established a T-cell clone (VASC-1) showing the promotion of proliferation, depending on RECs. Intravenous VASC-1 administration to wild-type rats of the same strain induced vasculitis in the lungs and systemic connective tissues, confirming the vasculitis inducibility of VASC-1.

**Pathogenesis of Necrotizing Angiitis**

Concerning the pathogenesis of human necrotizing angiitis, some hypotheses have been proposed based on analysis in animal models. In B/W F1 mice obtained by crossing New Zealand Black mice with New Zealand White mice, necrotizing angiitis develops due to the deposition of the immune complexes of gp70 as an endogenous retrovirus envelope glycoprotein and the anti-gp70 antibody in the vascular walls.\(^10\) Therefore, necrotizing angiitis in B/W F1 mice is considered to be...
due to a type III allergic mechanism. In SL/Ni mice, necrotizing angiitis is considered to develop due to the budding of endogenous retrovirus particles in the smooth muscle of the tunica media of the vascular walls and host’s humoral immune responses to it, i.e., by a type II allergic mechanism.11) These mechanisms resemble the pathogenesis of some of the vasculitides such as necrotizing angiitis observed in systemic lupus erythematosus and that observed in Goodpasture’s syndrome, respectively. However, there are still many other types of necrotizing angiitis such as PN in which the involvement of humoral immunity observed in type II and III allergic reactions is unclear. There is a possibility that the pathogenesis of necrotizing angiitis observed in env-pX rats, i.e., the mechanism mainly involving cellular immunity, will be a new concept that can explain the pathogenesis of necrotizing angiitis with an unknown cause such as PN.

**Conclusions**

Autoreactive T cell-mediated vascular injury could be implicated in the development of necrotizing angiitis in env-pX rats. Although further studies are needed to identify the REC antigens recognized by VASC-1 and the mechanism of induction of vascular injury by VASC-1 that reacted with REC antigens, similar mechanisms may be involved in the pathogenesis of human necrotizing angiitis with an unknown cause such as PN.

**References**


5) Abe A, Ishizu A, Ikeda H, et al. Bone marrow cells carrying the env-pX transgene play a role in the severity but not prolongation of arthritis in human T-cell...


