Vasculitis Syndrome—Molecular Biological Research to Clinical Aspects*

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1. Etiopathogenesis of Necrotizing Vasculitis

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Vasculitis syndrome includes a wide spectrum of inflammatory vascular diseases, affecting large elastic vessels in Takayasu arteritis and temporal arteritis, medium to small muscular arteries in polyarteritis nodosa (PN) and Wegener's granulomatosis and small arteries and capillaries in microscopic polyangiitis (MPA). Allergic granulomatous angitis and Kawasaki disease are suggested to be pathogenetically related to allergic reactions, bacterial and/or viral infections. Vasculitis syndrome also includes a variety of vascular diseases associated with autoimmune and related diseases. In spite of the recent progress in molecular biology techniques, the etiopathogenesis of vasculitis syndrome in man has been largely unknown. In order to understand the etiopathogenesis of vasculitis syndrome, especially of necrotizing vasculitis in man, appropriate animal models mimicking human diseases are needed. Here, three animal models of necrotizing vasculitis in man are presented.

(NZBxNZW) F1 mouse

The (NZBxNZW) F1 mice spontaneously develop a spectrum of autoimmune disorders that mimic human SLE. All the

(NZBxNZW) F1 mice develop florid glomerular lesions closely resembling those seen in human lupus nephritis. Immune complexes are heavily deposited in the glomerular lesions. (NZBxNZW) F1 mice also manifest necrotizing vasculitis (1). The vessels most frequently affected are the medium to small sized arteries of the ovary, uterus, gallbladder, and kidney. The early change is the accumulation of fibrinoid materials in the subendothelial space. In the advanced stage, the internal elastic membrane is disrupted and a cellular infiltrate containing neutrophils, lymphocytes, plasma cells, and histiocytes surrounds the affected vessels. Host immunoglobulins, IgG and IgM, and C3 are as granules deposited in the affected lesions. (NZBxNZW) F1 mice carry endogenous retrovirus of xenotropic type throughout life. An extremely high concentration of viral envelope glycoprotein, gp70 is found in the serum. (NZBxNZW) F1 mice are shown to produce IgG autoantibodies to gp70 by aging. Large amounts of gp70 immune complexes are accumulated in the circulation and deposited in the vessel walls as well as in the glomeruli, resulting in necrotizing vasculitis and lupus nephritis.

SL/Ni mouse

SL/Ni mice show spontaneous manifestations of necrotizing arteritis and chronic glomerulonephritis (2). Starting at about 9 months of age, SL/Ni mice manifest necrotizing arteritis at

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acute and chronic stages in a single mouse. The vessels most frequently affected are the medium to small sized arteries of the ovary, uterus, parotis, kidney, spleen, and pancreas. The early changes are fibrinoid degeneration of the muscular media. A cellular infiltrate containing neutrophils, lymphocytes, histiocytes, eosinophils and plasma cells surround the affected blood vessels. By immunofluorescence, host immunoglobulins, IgM and IgG, are found to be deposited as granules in the muscular media of affected vessels. Intramural deposits of C3 are also found. Along with the deposits of immunoglobulins and C3, retroviral structural proteins, gp70, p30, and p15 (E) are found deposited. An electromicroscopic study demonstrated numerous retrovirus particles in the matrix of the muscular media just before or at the appearance of vascular lesions, and virus particles budding from the muscular cells are frequently seen. It was found that SL/Ni mice produce humoral antibodies against viral p70 and p30 by aging. The collective evidence indicates that locally expressed retroviral structural proteins, gp70 and p30 on the vascular myocytes were the target molecules for humoral antibodies. This was followed by myocyte injury mediated through complement-dependent cellular cytotoxicity (CDCC), finally resulting in the development of necrotizing arteritis in SL/Ni mice. At present, SL/Ni mice do not manifest necrotizing vasculitis.

Transgenic rats carrying HTLV-1LTR-env-pX gene (env-pX rat)

Human T lymphocyte virus type-1 (HTLV-1) is associated with a number of clinical disorders, including adult T cell leukemia, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-1 uveitis, HTLV-1 associated arthropathy, and probably Sjögren syndrome, T cell alveolitis, polymyositis and infective dermatitis. We successfully introduced the HTLV-1 env-pX gene under control of HTLV-1 long terminal repeat (LTR) into inbred WKAH rats. Env-pX rats begin to develop unilateral or bilateral swelling of the ankle joints with redness or swelling of footpad near the ankle which occurs as early as 5 weeks of age. Histology of the swollen joint shows marked synovial lining hyperplasia, a mixed inflammatory infiltrate consisting lymphocytes, plasma cells, neutrophils and histiocytes, erosion of articular cartilage and destruction of contiguous bones by pannus forming granulation tissues. Overall the histological features resemble rheumatoid arthritis (RA) in humans. Env-pX rats also manifest a series of collagen vascular diseases, including necrotizing arteritis resembling polyarteritis nodosa, polymyositis, myocarditis, dermatitis and chronic sialoadenitis mimicking Sjögren syndrome (3). The vessels affected are the medium to small sized arteries in the connective tissue around the thymus, salivary glands, testis, pancreas, and dermis and subcutaneous fatty tissues. Panarteritic and periarteritic inflammation with a cellular infiltrate containing neutrophils, lymphocytes, plasma cells and histiocytes surrounding the affected artery are observed and the media shows fibrinoid necrosis, and thus the affected arteries resemble polyarteritis nodosa in humans. Fresh and organized thrombi and reparative fibrosis are observed. In order to

clarify the pathogenetic roles of the transgene, 3 sets of reciprocal cell transfer experiments, which consist of bone marrow cell transfer (BMT), spleen cell transfer (SCT) and a combination of BMT and the exchange of thymus framework between env-pX and non-transgenic rats were carried out. The result can be summarized as follows: 1) Necrotizing arteritis develops in lethally irradiated non-transgenic rats receiving SCT from env-pX rat. 2) Necrotizing arteritis develops in thymectomized non-transgenic rats with thymus framework transplant from env-pX rats, followed by normal BMC reconstitution. The collective evidence strongly suggests that autoreactive T cells may play a major pathogenetic role in this type of necrotizing arteritis. Molecules constitutively expressed in the normal arterial wall are likely to be the target for cellular autoimmunity. In addition, functional abnormality of the thymus framework induced by the transgene appears to play a key role in the development of necrotizing arteritis of env-pX rats. 3) Dermatitis develops in non-transgenic rats receiving either BMT or SCT from env-pX rats, suggesting that lymphocytes carrying the env-pX gene may play a major role in the development of dermatitis. 4) Expression of the transgene in the target joint tissues is a necessary prerequisite for the development of RA-like arthritis. Local autoimmune response by env-pX positive T cells may also play a pathogenic role.

In summary, 3 animal models for necrotizing vasculitis are presented in this paper. In all 3 models, retrovirus infections are directly or indirectly involved in the etiopathogenesis of necrotizing vasculitis. It is to be noted that the pathogenetic pathways of necrotizing vasculitis in 3 models clearly differ. In (NZBxNZW) F1 mice, circulating retroviral gp70 immune complexes are deposited in the subendothelial space and these pathogenic immune complexes induce necrotizing vasculitis by a type III allergic reaction. With SL/Ni mice, endogenous retrovirus structural proteins, gp70 and p30 being expressed on the vascular myocytes are the major target molecules for humoral antibodies. This type II allergic reaction mediated by CDCC in the arterial wall causes necrotizing arteritis. It is of particular interest that necrotizing vasculitis in env-pX rats may be initiated by autoreactive T cells which escaped from intrathymic negative selection. However, it remains to be determined whether the type IV allergic reaction is actively involved in the pathogenetic pathways of necrotizing vasculitis. Establishment of T cell clones, which can induce necrotizing vasculitis *in vivo*, is essential to prove this hypothesis.

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