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ANIMAL MODEL OF HUMAN DISEASE

Murine Chronic Graft-Versus-Host Disease as a Model for Lupus Nephritis

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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is an autoimmune disease characterized by the formation of antibodies directed against an array of auto-antigens. Any organ in the body may be affected. The most common cause of death is renal failure, limiting the five-year survival rate to 77% of patients.[1]

The pathogenetic mechanism responsible for lupus nephritis is still not fully known. Research into the pathogenesis of SLE has been hampered by sparsity of well-defined animal models. The most widely accepted models are the spontaneous murine models (eg, NZB/W, MLR).[2] In these mouse strains, an SLE-like syndrome develops spontaneously and at a late life onset. Therefore, these models are not easy to manipulate experimentally, and their use is relatively time-consuming. The need for less time-consuming, inducible models exists.

Animal Model

An SLE-like disease evoked by the abnormal T-B cell cooperation of the graft-versus-host reaction has been described.[3-8] For the induction of chronic graft-versus-host disease (GvHD), 8–10-week-old (C57B1/10 × DBA/2) F_1 hybrids (Olac 1976 Ltd, Bicester, UK) are used as recipients of DBA/2 donor (Olac) lymphocytes.[7] Single-cell suspensions containing a mixture of thymus, spleen, and lymph-node donor cells (the last orginating from mesenteric, inguinal, and axillary lymph nodes) are injected intravenously 4 times at 3–4-day intervals. The recipient mice develop a variety of pathologic alterations associated with the formation of auto-antibodies.[3,8] Therefore, murine GvHD has been proposed as a model for human SLE.

Comparison With Human Disease

As in human SLE, during GvHD autoantibodies directed against nuclear antigens (eg, anti-double-stranded DNA) and auto-antibodies against erythrocytes are elicited. Corresponding to human lupus nephritis, antinuclear antibodies are thought to play a pathogenetic role in renal involvement.[3,6,8] Twelve to 14 weeks after injection of "parental" lymphocytes, light microscopy shows glomerular mesangial, segmental, and diffuse proliferation as well as membranous nephritis and, in the most severe cases, global glomerular sclerosis (Figure 1). These lesions are typical of human lupus nephritis and have been classified by the World Health Organization (WHO).[9] As in human SLE, the majority of the animals show a proliferative type of glomerular lesion.

Deposits of immunoglobulin and complement are observed in a granular pattern along the glomerular

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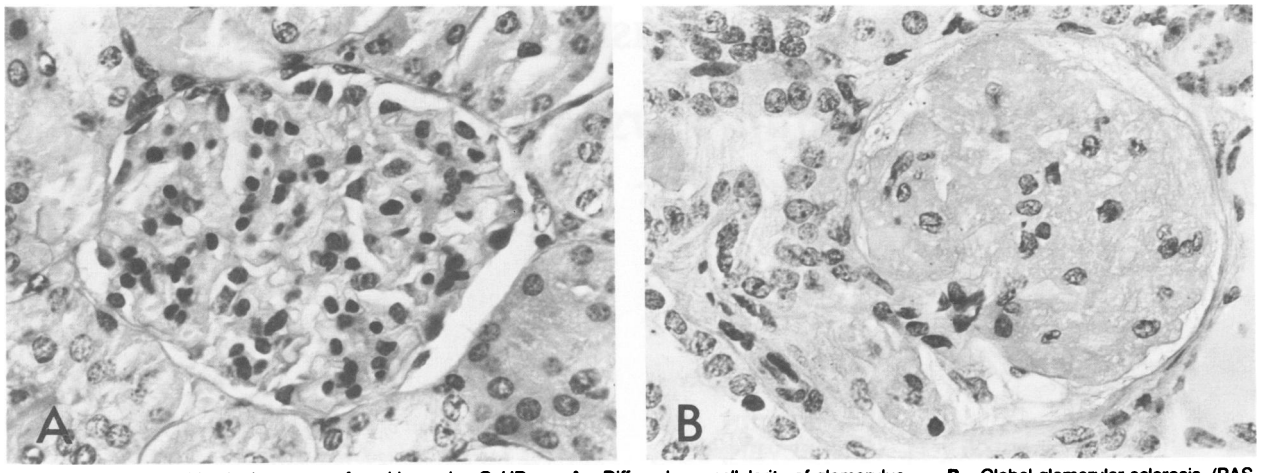

Figure 1—Glomerular histologic patterns found in murine GvHD. **A**—Diffuse hypercellularity of glomerulus. **B**—Global glomerular sclerosis. (PAS, ×480)

capillary wall (mostly IgG) and in the mesangium (IgM) (Figure 2). Electron microscopy reveals the presence of mesangial and subepithelial electron-dense deposits with varying degrees of spike formation and incorporation of electron-dense material in the glomerular basement membrane (Figure 3A). Kidneys of animals with proliferative alterations have electron-dense deposits in subendothelial localizations as well (Figure 3B). These features are comparable to lesions characterizing human lupus nephritis.[9]

Albuminuria, measured by rocket electrophoresis,[10] increases markedly in the affected animals (Table 1), causing hypoalbuminemia (Table 1) and frequently edema. Furthermore, creatinine clearance decreases and uremia develops (Table 1), eventually leading to death of the animals.

Usefulness of the Model

This experimental model has two advantages over other models of SLE. The disease can be induced experimentally, and it develops relatively rapidly. This makes it appropriate for experimental work. The combination of DBA/2 and (C57B1/10 × DBA/2) F_1 mouse strains was found to be suitable for this purpose. Lymphocytes of strain DBA/2 fail to induce the severe depression of lymphoid tissue that is characteristic of acute GvHD.[7] In contrast, pathologic changes in the animals closely resemble those in human SLE, such as persistent lymphoid hyperplasia, formation of auto-antibodies, and development of similar lesions.[3] Renal morphologic alterations can be classified according to the WHO morphologic classification of

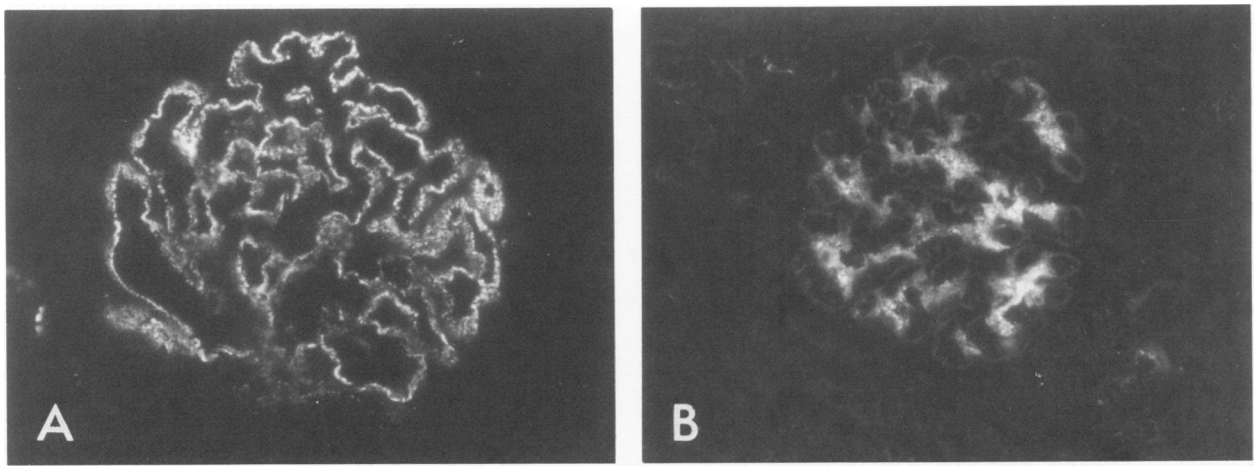

Figure 2—Immunofluorescence of the kidney of a GvHD mouse shows granular distribution of IgG along the glomerular capillary wall (**A**) and IgM in a mesangial pattern (**B**). (×480)

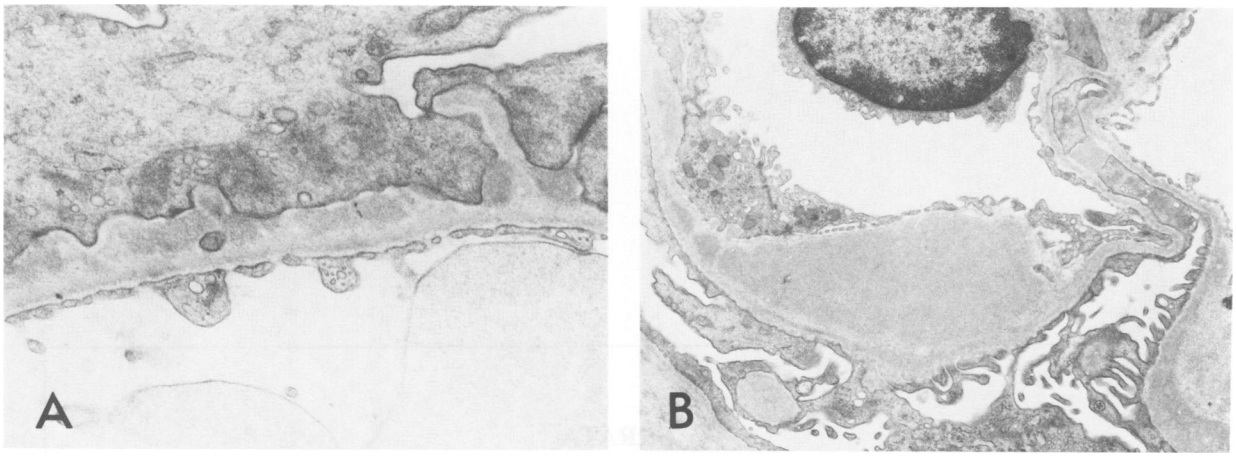

Figure 3—Electron micrograph of the kidney of a GvHD mouse suffering from membranous glomerulonephritis illustrating subepithelial electron-dense deposits with spike formation and incorporation of deposits (**A**) (×20,000); subendothelial aggregates are seen in mice with proliferative lesions (**B**) (×10,000).

Table 1—Renal Functional Changes in Murine GvHD Determined 14 Weeks After Injection of Parental Lymphocytes

	Experimental	Control
Urine albumin (μg/18 hr)	11,300 ± 2140	10 ± 2
Plasma albumin (g/l)	11.0 ± 0.8	22.5 ± 0.5
Plasma urea (mmol/l)	21.6 ± 7.0	7.9 ± 0.4
Plasma creatinine (μmol/l)	142 ± 13	33 ± 2
Creatinine clearance (μl/min)	15.2 ± 2.2	91.5 ± 7.9

All results are expressed as means ± SEM. All differences between control and experimental animals are statistically significant ($P < 0.05$; Student *t* test for unpaired data).

lupus nephritis. Severe kidney dysfunction develops and has a fatal outcome.

These mice offer an excellent model for studies on the pathogenesis (eg, genetic and immunologic aspects), prevention, and treatment of lupus nephritis, which is a major complication of and cause of death in human SLE.

Availability

C57B1/10, DBA/2, and (C57B1/10 × DBA/2) F_1 hybrids can be purchased from several commercial animal breeders.

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