研究課題

進行性紫斑病性腎炎の遺伝子解析と進行因子の臨床および分子生物学的検討

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研究発表

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研究成果

1. **Deletion polymorphism of the angiotensin-converting enzyme gene predicts persistent proteinuria in childhood Henoch-Shönlein purpura nephritis. A comparative study with IgA nephropathy**

Deletion polymorphism of angiotensin-converting enzyme gene predicts persistent proteinuria in Henoch-Shönlein purpura nephritis. -A comparative study with IgA nephropathy- Deletion polymorphism of the 16th intron of the angiotensin-converting enzyme (ACE) gene has been shown to be associated with the progression of some glomerular and non-renal diseases. The genetic significance of this gene polymorphism on clinical manifestations of Henoch-Schönlein purpura nephritis (HSPN) in children (4-15 yr at onset, followed for 2 to 22 yr, n=40) was compared with that in children with IgA nephropathy (4-15 yr at onset, followed for 2 to 18 yr, n=78). Homozygotes for the deletion allele (DD) were found in 20 % and 13 % of patients with HSPN and IgA nephropathy, respectively. The degree of proteinuria and other clinical manifestations (hematuria, systolic and diastolic blood pressures, and degree of crescent formation) at the onset of both diseases were not different among homozygotes for insertion (II), heterozygotes (ID) and DD genotypes. In HSPN, the incidence of moderate to heavy proteinuria (urine protein excretion rate >0.5 g/day) at 4 and 8 years after onset was significantly higher in DD than in II genotype, and that in the ID genotype was intermediate. In contrast, no such trend was observed in IgA nephropathy. The number of patients in whom proteinuria resolved (<0.1 g/day) at 4 and 8 years after onset was significantly lower in DD compared to II and ID genotypes. Again, no difference was detected among 3 genotypes in patients with IgA nephropathy. Other clinical parameters were not associated with the ACE genotypes in both HSPN and IgA nephropathy. Serum ACE activities in patients with DD genotype were significantly elevated (on average, 230 % higher than the non-DD genotypes). Thus, the ACE DD genotype predicts persistent proteinuria in HSPN. The proteinuria may be related to a deviated angiotensin system which is genetically determined by the D/I polymorphism. In contrast, such genetic characteristics may not be an unique determinant of prolonged proteinuria in children with IgA nephropathy.

2. **Glomerular endotheria linjury associated with free radical production induced by a fungal cell wall component, (1→3) β-D glucan.**

Clinical evidence suggest that microangiopathy may be induced by a fungal infection. The present study evaluated toxic effect of (1→3) β-D

glucan, a major component of the cell wall, on cultured transformed glomerular endothelial cells (TF-GEN). When TF-GEN were exposed to increasing concentrations of (1→3) β-D glucan (β-DG; 115 to 430 pg/ml) for 1 to 3 hours, there was a concentration and a time-dependent increase in hydroxyl radical production assessed by an electron paramagnetic resonance using 5, 5-dimethyl-1pyrrolyne-N-oxide as a spin trap agent. The amount of radicals produced by 230 or 430 ng/ml β-DG was comparable to those produced by E. coli LPS (1 or 10 μg/ml). The b-DG induced free radical production was associated with a subsequent increase in LDH release from TF-GEN. When TF-GEN pretreated with U78517F (0.1 or 1.0 μM) which is a lipophilic antioxidant were stimulated with LPS (1 or 10 μg/ml) or b-DG (230 pg/ml) for 3 hours, the free radical production by TF-GEN was significantly reduced in cells pretreated with the higher concentration of U78517F. Thus, fungal (1Æ3) b-D glucan induces glomerular endothelial injury by stimulating cellular free radical production. Such a mechanism may underlie microangiopathies in systemic fungal infections.