Molecular Approach to Glomerular Diseases : IgA Nephropathy and Diabetic Nephropathy

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IgA nephropathy and diabetic nephropathy are two major causes of end stage renal diseases in Japan where more than 190,000 patients are treated with dialysis. The pathogenesis of these diseases is different, but the mechanism of glomerular sclerosis is assumed to share common mediators, which will be useful for development of effective treatement. Since there have been numerous reports concerning cytokines and other chemical mediators responsible for glomerular sclerosis in these diseases, the aim of this study was to uncover the difference of molecular aberrations occurring in end stage renal disease in IgA nephropathy and diabetic nephropathy.

In preliminary experiments, it was demonstrated that IL-6, PDGF and TGF-beta were expressed in renal biopsy specimens in parallel with the progression of these two diseases. Furthermore, results of in situ hybridization analysis revealed that the major lesion of such expression in renal tissues was in the interstitium including proximal tubular walls. However, the degree of expression of these cytokines in the glomeruli paralleled the tissue damage in patients with IgA nephropathy, but an inverse relationship was observed in diabetic nephropathy.

To solve this dichotomy, AGE (advanced glycated endproduct) was analysed in renal biopsy specimens in these patients. There was a significant increase in AGE in the glomeruli from patients with diabetic nephropathy. The sources of the AGE in diabetic patients were both sugar and lipid moieties in diabetic patients, but only a slight increase in lipid-derived AGE was observed in patients with IgA nephropathy. There was a significant relationship between the decrease in cytokine and metaloproteinase expressions and the increase in AGE in the glomeruli of patients with diabetic nephropathy. It is postulated that accumulation of AGE in the diabetic glomeruli might interfere with the metabolism of extracellular matrix while inflammatory stimulation in the glomeruli with IgA nephropathy might accelerate the chronic inflammatory response.

A few other differences in molecular mechanisms in the development and progression of IgA nephropathy and diabetic nephropathy have been observed. These differences included activation of NK cells followed by production of IFN-gamma and several point mutations in IgA class switch genes in patients with IgA nephropathy. Recent advances in gene tips specifically prepared for analysis of renal biopsy specimens are shedding more light on molecular aberrations of major glomerular diseases. Further studies on molecular mechanisms in the development and progression of glomerular diseases are warranted to explore specific treatments for IgA nephropathy and diabetic nephropathy.