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Post-genome research in kidney diseases: a kidney-specific serpin gene, megsin

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Glomerular injury is the most common cause of end-stage renal disease (ESRD), which is dramatically increasing in the developed countries. As dialysis is an expensive measure to save the life of patients, ESRD is now a critical subject both medically and economically. Glomerular mesangial cells play an important role in maintaining a structure and function of the glomerulus and in the pathogenesis of glomerular injury of various kidney diseases. We hypothesized that a specific gene expressed in mesangial cells contributes to pathophysiological functions of glomerulus. The purposes of the present study were 1) to identify genes expressed specifically/predominantly in mesangial cells and 2) to elucidate molecular mechanism leading to progressive glomerular disorders. We obtained the “gene profile” of cultured human mesangial cells, and discovered five unknown genes predominantly expressed in mesangial cells. “Megsin” is one of these novel genes and is now classified into the serpin (serine protease inhibitor) superfamily. The characteristics of megsin as a function of serpin are highly conserved among different species, including mice and rats. Expression of megsin is up-regulated in a variety of diseases with glomerular mesangial injury in humans and in animal models. Of note, transgenic mice overexpressing megsin developed glomerular injury, e.g., mesangial expansion and hypercellularity, which was associated with glomerular immune complex deposition. The diabetic mice overexpressing megsin showed early development of severe diabetic nephropathy associated with nodule-like lesions, whose phenotypes closely resembled those in advanced diabetic nephropathy in humans. In vitro assays identified that plasmin is one of candidate targets of megsin, although it is likely that megsin has other biological ligands in vivo. The resent results suggest that megsin plays an essential role in modulating the biological functions of mesangial cells. Megsin may play a role in the regulation of a wide variety of processes in mesangial cells, such as matrix metabolism, cell proliferation, and apoptosis. Identification of the exact biological functions and target proteases of megsin will lead us to develop novel therapeutic approaches to glomerular diseases.