특별강연

Insulin-like Growth Factor (IGF)-IGF Binding Protein Axis in Chronic Kidney Disease

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The insulin-like growth factor (IGF) system plays a significant role not only in somatic growth but also in diseases such as cancer, diabetes and malnutrition by serving as endocrine, autocrine, and paracrine stimulators of mitogenesis, differentiation, survival and cellular transformation. The IGF system encompasses ligands (IGF-I and IGF-II), receptors (IGF-IR and IGF-IIR), and a family of high- and low-affinity binding proteins (IGFBPs and IGFBP-related proteins). The mitogenic actions of IGFs are mediated largely through IGF-IR, which is a heterotetrameric membrane-spanning tyrosine kinase. The IGFBPs bind IGF-I and IGF-II with high affinity and are essential to transport IGFs, prolong their half-lives and regulate the availability of free IGFs for interaction with IGFRs, thereby modulating the biological effects of IGFs. In recent years, ample evidence demonstrates that IGFBPs have unique intrinsic biological activities beyond their ability to interact with the IGF-IGFR axis, termed the "IGF-independent" actions. In particular, IGFBP-3, the major IGFBP species in circulation, has been recognized as an important growth-inhibitory, cell differentiation or anti-inflammatory factor in various cell systems through an IGF-independent mechanism. Due to its pleural biological actions and therapeutic potential, the IGF system has become the focus of research in a variety of diseases. Any disruption in the IGF system has its implications on growth retardation, cardiovascular disease, obesity, insulin resistance and cancer. The IGF system also has significant effects on renal function and has been implicated in renal development and hypertrophy as well as kidney disease including chronic kidney disease (CKD).

CKD is a common disorder, exhibiting a common final pathophysiology, despite differences in the primary cause for loss of kidney function. CKD is largely caused by diabetes, hypertension, glomerulonephritis, obesity and metabolic syndrome. CKD results in complex metabolic and hormonal disturbances, particularly in the GH-IGF-IGFBP axis. Perturbations in this somatotropic hormone axis are responsible for many important complications seen in CKD, such as growth retardation and catabolism, as well as disease progression. Recent studies demonstrate that growth failure in children with CKD is due to a relative GH insensitivity and functional IGF deficiency. The latter appears to be attributed to increased circulating levels of IGFBPs due to increased production and reduced clearance with impaired kidney function, which results in decreased IGF bioactivity of CKD serum despite normal total IGF levels. On the other hand, the functional IGF deficiency in nephritic syndrome appears to result from low levels of serum IGFBPs as well as serum IGFs due to increased urinary losses of serum IGF-IGFBP complexes. Therefore, use of IGFs, IGF agonists and IGFBP displacer that increases IGF bioactivity in circulation would hold promise as therapeutic agents in kidney disease.

Furthermore, the systemic inflammatory response appears to be a key player for progression of CKD, and how to prevent and treat this response is currently of great interest. Since recent studies demonstrate

existence of IGFBP-3 receptor (IGFBP-3R) and IGF-independent anti-inflammatory action of the IGFBP-3/IGFBP-3R axis, these findings reinforce the concept in support of the clinical significance of the IGFBP-3/IGFBP-3R axis in the assessment of pathophysiology of kidney disease and its therapeutic potential for CKD.