특별강연

Mechanistic Insights and Therapeutic Opportunities of IGF System in Metabolic Syndrome and Cancer

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The IGF system plays a significant role in an array of diseases including kidney disease, cardiovascular disease, obesity, insulin resistance and cancer. IGF action has to be either activated or suppressed for the therapeutic purpose depending upon the role of IGF system in the disease. Recombinant human IGF-I is administered for the treatment of short children with severe IGF-I deficiency and reversal of catabolic states in diseases such as cystic fibrosis, coeliac disease, anorexia nervosa, myotonic dystrophy and in HIV patients. IGF-I also show therapeutic potential for insulin resistance since IGF-I directly lower blood glucose by inhibiting renal gluconeogenesis and inhibits GH secretion, thereby blocking antagonistic effect of GH on insulin action and improving glucose homeostasis as a whole.

On the other hand, inhibition of IGF action is necessary for the treatment of cardiovascular disease and cancer. The potential mechanisms for inhibiting IGF action include: (1) inhibition of IGF binding to the IGF-IR using monoclonal antibodies against the ligands IGF-I and IGF-II and IGFBP fragments; (2) inhibition of the activation of the IGF-IR signaling pathway using monoclonal antibodies against IGF-IR and IGF-IR specific tyrosine kinase inhibitors; (3) regulation of IGF bioavailability to the IGF receptors using IGFBPs; and (4) induction of IGF-independent actions of IGFBPs using recombinant IGFBPs which prevents/inhibits progression of a specific disease. The most actively investigated component as a therapeutic target in the system is the IGF-IR, and studies have been pursued to inhibit IGF-IR by the administration of monoclonal antibodies and tyrosine kinase inhibitors in a variety of human cancers. Several monoclonal antibodies are currently in clinical trials and some show very promising results.

In addition, recent findings on IGF-independent actions of IGFBPs imply therapeutic potential of IGFBPs in a variety of human diseases. In particular, IGFBP-3 has great potential for the treatment of inflammatory disease, cancer, cardiovascular disease and insulin resistance. Recent studies have implicated interaction of IGFBP-3 with a variety of proteins or signaling cascades critical to cell cycle control and apoptosis, however, the actual mechanism of IGFBP-3 action is still unclear. We have recently identified an authentic IGFBP-3 receptor which mediates most of biological actions of IGFBP-3 in cancer cells. We also found that IGFBP-3 interferes with the pro-inflammatory and antiapoptotic NF-κB signaling cascade in human normal and malignant cells and alterations in IGFBP-3/IGFBP-3R levels are implicated in the pathogenesis of cancer and inflammatory disease including asthma.

Taken together, therapeutic potential of IGF system is very promising and indeed, some therapeutic candidates are undergoing clinical investigations and have gained commercial importance in the past decade. However much more research needs to be done to identify specific mechanisms involved, reduce any side effects and increase the efficiency of the drugs.