The IGF system in carcinogenesis and its implication for cancer therapy

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The discovery of the insulin-like growth factor (IGF) system occurred half a century ago, in a series of experiments showing that the growth hormone itself exercises no direct metabolic action on skeletal tissues, but rather acts through secondary substances. Those substances were subsequently identified as IGF-I and IGF-II. Since then, a series of substances related to IGF-I and II have been found.

So far, the IGF system has been determined to consist of 2 ligands (IGF-I and -II), 2 receptors (IGF-IR and IGF1R), 6 binding proteins (IGFBP1–6), and 4 IGFBP-related peptides (IGFBP Rp1–4). Components of the IGF system are found throughout the body in various fluids and tissues, and they act on a variety of cells in an endocrine, paracrine, and autocrine manner. The IGF ligands play a critical role in the growth, development, and maintenance of normal homeostasis, but they have a short lifespan unless attached to a binding protein that transports them in the circulation and delivers them to specific tissues. Binding proteins also regulate IGF ligands by modulating their bioavailability to IGF receptors. The balance between free IGF ligands and IGFBP determines the outcome of cells: survival, growth, or apoptosis.

IGF SYSTEM AND CARCINOGENESIS

Many epidemiology studies have indicated that high levels of IGF-I or altered levels of its binding proteins, or both, are associated with an increased risk of the most common cancers, including cancers of the lung, colon and rectum, prostate, and breast. This association may be a result of the binding of IGF-I to its receptor, which triggers a multiparticle cascade with a high potential to protect cancer cells from a variety of apoptotic challenges.

Carcinogenesis in normal tissues occurs usually in several steps, through which genetic and epigenetic aberrations gradually accumulate and result in deregulation of cellular homeostasis. The aberration of cellular homeostasis further develops into an invasive tumour through a series of processes with interactions between various growth factors and their receptors. Accompanying the cancer development, the level of apoptosis in local and surrounding tissues increases in an attempt to limit the expansion of the tumour cell population. However, the high levels of IGF-I in the local and surrounding tissues give the cells with genetic and epigenetic aberrations the ability to escape their apoptotic fate and develop into invasive cancers. The IGF system is also a key proliferation and pro-survival signalling pathway in many malignancies, playing a critical role in the development of resistance to a variety of chemotherapeutic agents. Inhibition of the IGF pathway therefore has the potential to provide clinical benefit in a wide range of malignancies and in a variety of clinically relevant treatment scenarios, including neoadjuvant, adjuvant, maintenance, and palliative therapy.

IMPLICATION FOR CANCER THERAPY

Because the IGF system represents a novel and attractive target for anticancer therapies, a number of strategies to treat cancer by interfering with and inhibiting IGF pathways have been explored. The two most investigated strategies are monoclonal anti–IGF-IR antibody and IGF-IR inhibitor.

Several monoclonal anti–IGF-IR antibodies have reached phase I clinical trials. The early clinical evidence indicated that the anti–IGF-IR antibodies are able to stabilize disease in breast, liver, colorectal, and prostate cancers. In neuroectodermal tumours, the anti–IGF-IR antibodies produced a much better response rate, with some spectacular complete responses and long disease stabilization, indicating that the broad family of neuroectodermal tumours may be susceptible to anti–IGF-IR treatment.

The IGF-IR inhibitors are small-molecule tyrosine kinase inhibitors. Although many tyrosine kinase inhibitors are available for research purposes, only a few have clinical applications. One of these inhibitors, PIP, which has the potential to inhibit human IGF-IR with selectivity 14 times that for the human insulin receptor,
inhibits cell proliferation and induces apoptosis through a mechanism of interference with Akt activation 13. The problem with the IGF-IR receptor inhibitors is their specificity. Because IGF-IR is homologous with the insulin receptor (84% homology within their intracellular tyrosine kinase domains, and 95% at the ATP binding site), it is difficult to design a small-molecule IGF-IR inhibitor that does not interact with the insulin receptor or with other tyrosine kinase receptors. For example, an oral small-molecule IGF-IR inhibitor named INS-18 has recently undergone a phase 1 clinical trial in prostate cancer patients. Although described as an IGF-IR inhibitor and found to inhibit the action of IGF-I, it also inhibited activation of the human epidermal growth factor receptor 2 (HER2) and other receptors 11.

Beyond those two major strategies, scientists have also tried other approaches to stop the interaction between IGF-I and its receptor. For example, a novel IGF-IR antagonist peptide has been demonstrated to have the potential to disrupt that interaction, leading to apoptosis in colorectal cancer cells 14. Because the IGF system and its pathways represent a multifaceted arrangement within cells, the outcomes of interference with this versatile system are highly complex and may be too difficult to control. Other approaches, such as altering the bioavailability of IGF-I to its receptor, have also been explored. For example, our group used a gene transfer approach in ectopic models to overexpress an IGF-I inhibitory binding protein, IGFBP-4, in close proximity to colorectal cancer tissues. That experiment demonstrated that IGFBP-4 reduces IGF-I availability 15, increases colorectal cancer cell apoptosis, and decreases angiogenesis within tumour tissues 16,17.

**SUMMARY**

A higher concentration of IGF-I is associated with an increased risk of common tumours such as cancers of the prostate, colon and rectum, breast, and lung. Although the associations are modest and vary depending on the tumour site, this discovery has major implications for the assessment of cancer risk and offers great potential for the development of a novel therapeutic strategy for treatment of these common cancers.

**CONFLICT OF INTEREST DISCLOSURES**

The authors have no financial conflicts of interest to disclose.

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