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REVIEW ARTICLE

Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance

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Abstract One of the greatest obstacles to current cancer treatment efforts is the development of drug resistance by tumors. Despite recent advances in diagnostic practices and surgical interventions, many neoplasms demonstrate poor response to adjuvant or neoadjuvant radiation and chemotherapy. As a result, the prognosis for many patients afflicted with these aggressive cancers remains bleak. The insulin-like growth factor (IGF) signaling axis has been shown to play critical role in the development and progression of various tumors. Many basic science and translational studies have shown that IGF pathway modulators can have promising effects when used to treat various malignancies. There also exists a substantial body of recent evidence implicating IGF signaling dysregulation in the dwindling response of tumors to current standard-of-care therapy. By better understanding both the IGF-dependent and -independent mechanisms by which pathway members can influence drug sensitivity, we can eventually aim to use modulators of IGF signaling to augment the effects of current therapy. This review

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summarizes and synthesizes numerous recent investigations looking at the role of the IGF pathway in drug resistance. We offer a brief overview of IGF signaling and its general role in neoplasia, and then delve into detail about the many types of human cancer that have been shown to have IGF pathway involvement in resistance and/or sensitization to therapy. Ultimately, our hope is that such a compilation of evidence will compel investigators to carry out much needed studies looking at combination treatment with IGF signaling modulators to overcome current therapy resistance.

Introduction

The insulin-like growth factor (IGF) signaling axis is critical to the growth, development, and maintenance of many tissues within the human body.[1] It is particularly important during neonatal and pubertal growth, and essentially carries out its effects by simulating cell proliferation and interrupting programmed cell death.[1,2] The IGF system is comprised of two ligands, IGF-1 and IGF-2, which exhibit their effects through binding to IGF-1R (primarily), IGF-2R, and the insulin receptor (IR), all belonging to the tyrosine kinase receptor family.[1]

Upon binding the IGF ligand, IGF-1R is activated through autophosporylation, and subsequently phosphorylates insulin receptor substrate 1 (IRS-1).[2] Activated phosphoinositide 3-kinase (PI3K) then leads to increased phosphatidylinositol 3,4,5-trisphosphate (PIP3), which results in the activation of the critical protein AKT/PKB (AKT for short) through phosphorylation.[3] AKT then performs a variety of functions, such as releasing the anti-apoptotic protein Bcl-2 from Bad, activating protein synthesis through mTOR, and promoting glucose metabolism by inhibiting GSK-3β.[3,4] This is commonly referred to as the PI3K/AKT pathway of IGF-1R signaling and is ultimately responsible for preventing cell death (Fig. 1).[5]

In parallel, IGF-1R signaling also promotes cell differentiation proliferation via the Ras/MAPK pathway (Fig. 1).[3] IGF-1R activates the IRS protein SHC, which then stimulates Raf through the GTPase Ras. Raf then triggers a kinase cascade eventually resulting in the activation of mitogen-activated protein kinases (MAPKs), ERK1 and ERK2. These MAPKs go on to phosphorylate and activate several targets, notably the transcription factor ELK1 which promotes gene expression and therefore cell growth.[3,6,7]

The activity of the IGF ligands and receptors is modulated in a complex fashion by six IGF binding proteins (IGFBPs), named IGFBP-1 through IGFBP-6, respectively. The IGFBPs are usually bound directly to IGF-1 (or IGF-2) in extracellular fluids, serving to mediate the half-life and localized availability of the ligands in circulation.[8] Furthermore, extensive evidence has recently elucidated that the IGFBPs have many IGF-independent actions. By associating directly with many extracellular and cell-surface markers, these binding proteins are able to cause a variety of unique effects involving growth and differentiation.[8]

Taken as a whole, the IGF signaling axis has vast implications for cellular proliferation, apoptosis, and interactions with the microenvironment. Though these processes are critical for normal development and maintenance of tissues, it has also become increasingly evident that dysregulation of this pathway contributes significantly to abnormal growth and disease states.

IGF signaling in cancer and the development of drug resistance

Numerous cancers have been shown to be associated with aberrant IGF signaling, including colon cancer, prostate cancer, pancreatic cancer, melanoma, osteosarcoma, and childhood malignancies, among many others.[9] Numerous *in vitro*, *in vivo*, and clinical studies have shown that increased IGF-1R activity is implicated in cancer cell proliferation, migration, and invasion.[9,10] IGF ligand appears to be delivered not only from distant sources (i.e. endocrine signaling), but also through paracrine/autocrine signaling in more aggressive tumors.[10] In addition, increased serum levels of IGF-1 have been observed in cancers of the lung, colon, prostate, and breast.[11–14] Many other IGF pathway members are also thought to play a role in malignancies. From increased circulating levels of IGF-2 in colorectal cancer to suppressed activity of IGFBP-5 in osteosarcoma, it is clear that the IGF axis serves as an important lens to better understand and address the underlying mechanisms of neoplasia.[15–17] In fact, several IGF signaling modulators have undergone significant basic science and translational investigations with promising results; currently, monoclonal antibodies to IGF-1R are undergoing clinical trials.[18] However, it has become clear that the IGF axis is part of a much larger network of cellular signaling that ultimately results in the highly proliferative and invasive cancer phenotypes.[19]

Current non-surgical forms of cancer treatment are largely limited by severe systemic side effects and acquired resistance, resulting in increased morbidity and decreased survival. Of the many processes that are thought to play a role in the resistance of neoplasms to radiation or chemotherapy, the IGF signaling axis has been recurrently deemed as a culprit.[20] Here, we review recent literature implicating IGF signaling in resistance to therapy among various types of human cancer. With a better grasp of the underlying mechanisms, we can one day hope to augment the efficacy