The Insulin-like Growth Factor 1 Receptor Pathway in Cancer
An Overview: The IGF1R Pathway Is Necessary for Normal Growth and Tumorigenesis and Represents a Potential Target for Anticancer Therapy

Tumorigenesis is a highly complex pathological process often resulting from aberrant activation or inhibition of key signaling pathways that play essential roles in normal development. One such pathway is the insulin-like growth factor 1 receptor (IGF1R) pathway, which controls cellular proliferation, survival, and metabolism through the binding of the ligands insulin-like growth factor (IGF) 1 and IGF2 to the IGF1R and the downstream activation of the PI3K/Akt and Ras/MAPK signal transduction cascades. A host of studies have determined that the IGF1R pathway is dysregulated in a variety of human cancers, including pancreatic, colorectal, prostate, breast, ovarian, bladder, kidney, and lung, and circulating levels of IGF1 correlate with increased cancer risk. Furthermore, increased IGF1R signaling contributes to the development of resistance to some anticancer agents targeting different signaling pathways that participate in molecular cross talk with the IGF pathway. As such, the IGF1R pathway represents a potential target for anticancer therapy.
IGF1R signaling is predominantly activated by the binding of two structurally related ligands, IGF1 and IGF2. IGF1R is a transmembrane receptor tyrosine kinase (RTK) consisting of two extracellular α-chains and two intracellular β-chains linked by disulfide bonds to form a tetramer. IGF1R shares 60% amino acid sequence homology with the insulin receptor (IR) and each can form homodimers or hybrid heterodimers with the other. Another receptor in this family, IGF2R, is structurally and functionally distinct from IGF1R and IR and has no signaling component associated with it. The ligands IGF1, IGF2, and insulin are capable of binding to homodimeric or hybrid IGF1R and IR with varying affinities; however, the primary ligands for IGF1R are IGF1 and IGF2. IGF1 and IGF2 share 62% homology in amino acid sequence and 40% homology to pro-insulin. IGF1 and IGF2 are produced by multiple tissues, especially the liver, and circulate in the blood where they exert endocrine as well as autocrine and paracrine effects.
IGF1R Signaling Is Modulated by IGF1 and IGF2, Produced Locally and From Distant Sites

Regulation of IGF1R signaling occurs through multiple steps both systemically and locally. Though IGF1 and IGF2 are produced in many tissues, one predominant site of IGF production is the liver, where they are secreted in response to growth hormone (GH). After IGFs are secreted, less than 1% circulate in a free, unbound state; the majority are bound to one of six related high-affinity IGF binding proteins (IGFBPs). Greater than 90% of circulating IGFs are bound specifically to IGFBP-3. Through binding to IGFs, IGFBPs control IGF half-life as well as their availability to bind to receptors. Dissociation of IGFs from IGFBPs allows the ligands to bind to IGF1R in a variety of tissues and also suppresses the production of GH in the pituitary gland as part of a negative feedback loop.
**Activation of IGF1R Triggers Intracellular Signaling Cascades**

IGF1 or IGF2 ligands that are not bound by IGFBP are free to bind to the extracellular α-chains of the IGF1R, resulting in homodimerization of the receptor and autophosphorylation of the intracellular juxtamembrane tyrosine kinase domains at tyrosine 950, creating docking sites for adaptor proteins such as IRS1 and Shc.1 Phosphorylation and binding of adaptor proteins initiates downstream signaling events that result in cell proliferation, survival, and metabolism.2
IGF1R Signaling Regulates Cell Survival, Metabolic Activity, and Proliferation Through Activation of PI3K/Akt and Ras/MAPK Pathways

Activation of the IGF1R pathway and autophosphorylation of the receptor creates docking sites for the adaptor proteins IRS1 and Shc.1,8,9 IRS1 activates the p85 subunit of PI3K, which in turn phosphorylates membrane-bound PIP2 to create PIP3. PIP3 recruits Akt to the membrane where it becomes activated to regulate cell metabolism, promote cell cycle progression, and inhibit pro-apoptotic signaling by impinging upon downstream targets including mTOR, GSK3β, BAD, and FOXO.1,9,10 Shc recruits Grb2 and SOS proteins to activate Ras by stimulating GDP exchange for GTP.8 Activated Ras triggers the classical MAPK pathway, characterized by the sequential activation of the kinases Raf, MEK, and ERK. ERK activation leads to transcription of target genes necessary for cell proliferation, such as cyclin D and Myc.8,11
Rationale for Targeting IGF1R in Cancer: IGF1R Signaling Is Necessary for Tumorigenesis

Overexpression of IGF1, IGF2, and/or IGF1R may contribute to tumor progression in humans. IGF1R has been shown to be overexpressed in a number of human cancers including pancreatic, colorectal, prostate, breast, ovarian, bladder, and lung. IGF1 and IGF2 have also been found to be expressed at higher than normal levels in cancerous tissues and cell lines. IGF1 mRNA levels were higher in human cancerous pancreatic tissue and cell lines compared to normal. There is even evidence for a correlation of increased levels of the binding protein IGFBP-3 (in tumor tissue or in circulation) with increased tumor growth in some types of cancers, including breast, prostate, pancreatic, renal cell, and non-small cell lung cancers. Furthermore, high levels of IGF1R pathway components may be predictive of cancer risk. Experimental and clinical studies have found that elevated plasma concentrations of IGF1 correlates with increased risk of developing breast, colorectal, prostate, and lung cancers.

Increased IGF1R signaling contributes to the development of resistance to some anticancer agents targeting different signaling pathways that participate in molecular crosstalk with the IGF pathway. Thus, the IGF1R pathway represents a potential target in the treatment of cancer worth further investigation.
Summary: The IGF1R Pathway in Cancer

The IGF1R pathway plays a central role in cell proliferation, survival (protection from apoptosis), and the regulation of cellular metabolism. IGF1R signaling is necessary for tumorigenesis. Overexpression of IGF1R pathway components is described in a number of human cancers, such as pancreatic, colorectal, prostate, breast, ovarian, bladder, kidney, and lung. Downstream PI3K/Akt and Ras/MAPK signaling cascades are commonly activated in human cancers by aberrant growth factor signaling and genetic mutation. IGF1R signaling contributes to the development of resistance to various anticancer agents. Thus, the IGF1R pathway represents a potential therapeutic target in cancer.