IGF 1 and IGF 2

64

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Contents

Abstract

Insulin-like growth factor-1 (IGF-1) and IGF-2 are circulating peptide growth factor hormones important in normal growth and development. Their biological effects are mediated by specific cell surface receptors, the type I IGF receptor (IGF1R) and the insulin receptor. In cancer, preclinical and epidemiological evidence support a role for these growth factors in regulating cancer risk and tumor biology. Thus, neutralization of these growth factors could play a role in cancer prevention and therapy.

Keywords

Growth Factor • Insulin-like growth factors

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Target: Insulin-Like Growth Factor I and II (IGF-I and IGF-II)

IGF-I and IGF-II are polypeptide hormones important in normal growth and development (Baker et al. 1993). As their name implies, they are homologous in structure to insulin (Bell et al. 1984; Jansen et al. 1983). Like insulin, both hormones interact with specific heterotetrameric transmembrane tyrosine kinase receptors. IGF-I has the highest affinity for the type I IGF receptor (IGF1R). IGF-II can activate this receptor but also has high affinity for the fetal form of the insulin receptor (insulin receptor A, IRA) (Frasca et al. 1999).

Biology of the Target

IGF-I expression is increased during puberty by action of growth hormone on the liver (Mauras 2001). Once produced, IGF-I circulates bound to a high-affinity binding protein (IGF binding protein-3) and is further stabilized by the "acid labile subunit" in a ternary complex (Martin and Baxter 2011; Domene et al. 2009). High levels of serum IGF-I are found in adult life, but most of it is bound in the ternary complex and not available for receptor binding. During periods of stress, IGF binding protein-specific protease can cleave the binding protein and release IGF-I to interact with receptors. Thus, adults have a substantial reservoir of IGF-I in the circulation. IGF-I can also be found in the bone matrix in complex with other IGF binding proteins (Govoni et al. 2005).

IGF-II has an important function in fetal growth. In mice, IGF-II is necessary for normal fetal development. In rodents, IGF-II levels drop shortly after birth. However, humans maintain high levels of IGF-II during adult life and its function is not understood.

IGF1R activation requires binding by either IGF-I or IGF-II to signal. Thus, ligand production and receptor binding are necessary for activation of this receptor system.

Target Assessment

IGF-I and IGF-II can be measured by commercially available ELISA assays (Frystyk et al. 2010). "Free" IGF-I (unbound to IGF binding proteins) has been reported to predict outcome in some clinical trials of anti-IGF1R drugs. This assay is not commercially available.

Role of the Target in Cancer

Rank: 5

High-Level Overview

Diagnostic, Prognostic, and Predictive

The level of IGF-I and insulin is associated with increased cancer risk (Vigneri et al. 2009; Renehan et al. 2004). In preliminary reports, levels of free IGF-I are associated with benefit from IGF1R inhibition by the monoclonal antibody figitumumab in non-small cell lung cancer trials (Gualberto et al. 2009).

Therapeutics

Since hepatic IGF-I is under the control of growth hormone, disruption of growth hormone action could be a cancer therapy. This possibility is supported by the clinical observation that humans with mutation in growth hormone receptor are unable to respond to growth hormone, have low levels of IGF-I and IGF-II, and rarely, if ever, get cancer. Strategies to disrupt growth hormone releasing hormone or growth hormone receptor have been described (Schally et al. 2008; Divisova et al. 2006). A polyethylene glycol-conjugated mutant of growth hormone is available for treatment of growth hormone access (acromegaly). This drug, pegvisomant, has been evaluated in normal subjects (Yin et al. 2007). However, its development in cancer was discontinued by the manufacturer.

Monoclonal antibodies that bind both IGF-I and IGF-II have been described (Dransfield et al. 2010; Goya et al. 2004). A ligand-binding antibody is currently in phase I clinical trial (NCT00816361).

Preclinical Summary

Substantial preclinical data in cell culture and mouse model systems have shown that IGF-I is a potent mitogen for cancer cells. Expression of IGF-I can accelerate tumorigenesis in mouse model systems (Kleinberg et al. 2008). IGF-II is an imprinted gene. Loss of imprinting allowing biallelic expression has been linked to cancer development and progression (Hu et al. 2011; Kaneda et al. 2007).

Clinical Summary

Humans who lack the ability to produce IGF-I do not get cancer (Steuerman et al. 2011; Guevara-Aguirre et al. 2011). Studies examining lowering of IGF-I and IGF-II levels by neutralizing antibodies have not yet been reported.

Anticipated High Impact Results

Publication of phase I and II results from IGF-I and IGF-II neutralizing antibody clinical trials.

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