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Growth Hormone & IGF Research

Review

Impact of targeting insulin-like growth factor signaling in head and neck cancers

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ABSTRACT

The IGF system has been shown to have either negative or negligible impact on clinical outcomes of tumor development depending on specific tumor sites or stages. This review focuses on the clinical impact of IGF signaling in head and neck cancer, the effects of IGF targeted therapies, and the multi-dimensional role of IRS 1/2 signaling as a potential mechanism in resistance to targeted therapies. Similar to other tumor sites, both negative and positive correlations between levels of IGF-1/IGF-1-R and clinical outcomes in head and neck cancer have been reported. In addition, utilization of IGF targeted therapies has not demonstrated significant clinical benefit; therefore the prognostic impact of the IGF system on head and neck cancer remains uncertain.

1. Introduction

The insulin-like growth factor (IGF) pathway is involved in growth and development of normal tissue at both cellular and organism levels [1]. IGF ligands and its superfamily of receptors are ubiquitously expressed in higher eukaryotes and are among the first signaling factors secreted by the liver in the developing embryo [1]. Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-1 receptor (IGF-1-R) are required for cell cycle progression and have been shown to play a role in proliferation, differentiation, cell survival, transformation, tumor invasion, metastasis and inhibition of apoptosis [2–9]. IGF-1-R has tyrosine kinase activity and upon activation by ligand (IGF-1 or IGF-2) it leads to the phosphorylation of insulin receptor substrate (IRS) proteins and the activation of numerous signaling cascades including MAPK, AKT, and mTOR [1]. There are six distinct IRS proteins (IRS-1–6) with IRS-1 and IRS-2 having the broadest tissue distribution and mediating most of the signaling downstream of IGF-1 [10,11]. Following ligand stimulation, IRS-1 levels have been shown to gradually decline beginning around 4 h and this process is dependent on phosphatidylinositol 3-kinase

(PI3K) and proteasome activities [12]. Interestingly, addition of epidermal growth factor (EGF) to IGF-1 stimulation has been demonstrated to prevent IRS-1 degradation [12]. Regulation of IRS-1 is also accomplished through phosphorylation, with tyrosine sites promoting downstream signaling and serine sites facilitating negative feedback loops to terminate signaling (Fig. 1). Receptor activation leading to phosphorylation of tyrosine^{896} on IRS-1 promotes binding of Grb2 and subsequent activation of MAPK signaling. Phosphorylation of tyrosine^{612} on IRS-1 promotes binding of PI3K and subsequent activation of PKB/Akt signaling. mTor signaling leads to phosphorylation of IRS-1 on serine^{636}, which serves as a negative feedback loop to decrease activation of the PI3K/Akt pathway [13,14]. Treatment with rapamycin reduces mTor/S6K signaling and alleviates this inhibitory phosphorylation leading to increased Akt phosphorylation [13,15]. Metformin treatment activates AMPK which phosphorylates IRS-1 on serine^{789}. While both rapamycin and metformin are able to reduce mTor activation, metformin treatment does not lead to Akt activation since the inhibitory phosphorylation of IRS-1 remains [16]. Activation of IGF signaling is primarily regulated by at least six insulin-like growth factor binding proteins (IGFBPs), among which IGFBP-3 binds to >95% of IGFs in circulation thus reducing its bioavailability [3,5,17,18]. IGFBP-3 has also been shown to inhibit cell growth independent of IGF-1 [5,18].

2. Negative impact of IGF signaling on clinical outcomes of tumor development

Over the last few decades, several studies have searched for a connection between the IGF system and its potential role in cancer development. In general, it has been hypothesized that high levels

of IGF-1 correlate with elevated risk of developing cancer due to its mitogenic function [2,9,19,20]. A study on colorectal cancer [21] reported that the role of IGF-1 was to contribute to a more aggressive malignant phenotype in a subset of colorectal cancers. This study also found a correlation between elevated expression of IGF-1-R and more advanced stages of cancer. Interestingly, a different study [22] found high levels of IGF-1 to be positively correlated with the presence of colorectal adenomas; however, after the adenomas were removed, serum levels of IGF-1 were inversely correlated with adenoma recurrence. In a small case–control study on ovarian cancer [6], serum IGF-1 levels in cancer patients did not correlate in a significant manner compared to controls; however, after normalizing to age, IGF-1 levels strongly correlated with higher risk of ovarian cancer in patients younger than 55 years. In this study IGFBP-3 showed no relation to risk of developing ovarian cancer. Collectively, these studies suggest that IGFs promote an environment where tumor development at specific sites is successful.

3. Negligible impact of IGF signaling on clinical outcomes of tumor development

Conversely to the previously mentioned studies, in a case–control study conducted within a cancer prevention study [23], it was reported that low concentrations of IGF-1 were correlated with higher risk of developing glioma, while IGFBP-3 showed no correlation. Another case control study within the European Prospective Investigation into Cancer and Nutrition cohort reported no association between circulating IGF-1 or IGFBP3 levels and pancreatic cancer risk [7]. Similarly, several reports have shown conflicting results when trying to establish a relationship between IGF-1, IGF-1-R and IGFBP-3 and risk of developing prostate cancer. While some of these studies found no association between IGF-1 or IGFBP-3 and risk of prostate cancer [24,25], another study reported that elevated levels of IGFBP-3 were related to a modest decrease in risk [26], although no statistical significance was shown. In an effort to clarify this uncertainty, a prospective case control analysis within the ProtecT trial was initiated to determine the association between IGFs and prostate cancer in 6000 men (3000 cases and 3000 controls) who underwent PSA screening [27]. This report did not find a positive association between IGF-1 and PSA detected prostate cancer. Furthermore, the authors conducted a meta-analysis of all citations evaluating IGF-1 and PSA detected prostate cancer which also did not find any positive associations. The authors concluded that IGF-1 may not have a key role in the development of early stage cancers; however it cannot be concluded to have no role in progression of clinically identified prostate cancers [27]. Collectively, these studies suggest that IGF levels have little impact on the development of certain tumor types.

4. Impact of IGF signaling on head and neck cancers

Head and neck cancer encompasses tumors that develop in the pharynx, oral cavity, tongue, larynx, nasal cavity and salivary gland with a majority of cases in the first three listed sites [28]. Typical genetic alterations observed in these cancers include mutations of p53 and overexpression of epidermal growth factor receptor (EGFR) [29]; however more recent work has investigated the impact of the IGF system. Intratumoral expression of IGF-1-R does not affect time to progression in head and neck squamous cell carcinoma (HNSCC); however elevated expression of IGFBP-3 was associated with a shorter time to progression [30]. In addition, the combination of elevated IGF-1-R and IGFBP-3 had the shortest time to progression in these patients [30]. Elevated levels of IGFBP-3 have also been reported in metastatic melanoma and targeted silencing of IGFBP-3 expression through siRNA leads to a reduction in proliferation [31]. This suggests that elevated IGFBP-3 contributes to increased proliferation in late stages of cancer development. Serum levels of IGFBP-2 have also been reported to be elevated in head and neck cancer patients when compared to healthy controls [32]. Conversely, this same study reported no differences in serum levels of IGF-1, IGF-2 and IGFBP-3 between these two populations [32]. In oral cavity squamous cell carcinoma (OCSCC), elevated intratumoral expression of IGF-1-R was significantly higher in patients with grades II–III when compared to patients with grade I disease [33]. However, IGF-1-R expression was not predictive of tumor treatment response across all grades of OCSCC disease [33]. In patients with advanced OCSCC (grades III–IV), elevated IGF-1-R expression was correlated with poorer survival [33]. Evaluation of patients with head and neck cancer that developed second primary tumors has demonstrated that high levels of IGF-1 and extremely low or high levels of IGFBP-3 represent positive risk factors [34]. This suggests that IGFBP-3 levels have a U-shaped curve effect, with the greatest inhibition of IGF signaling at intermediate concentrations. Salivary gland tumors are a small subset of the total head and neck cancer cases and contain a heterogeneous histopathology and considerable variability in the molecular signatures of these cancers [35]. Due to the rarity of these tumors clinically, the importance of IGF signaling in salivary tumor biology has largely been studied in model systems. Transgenic mice bearing an inducible IGF-1-R fusion receptor spontaneously developed invasive
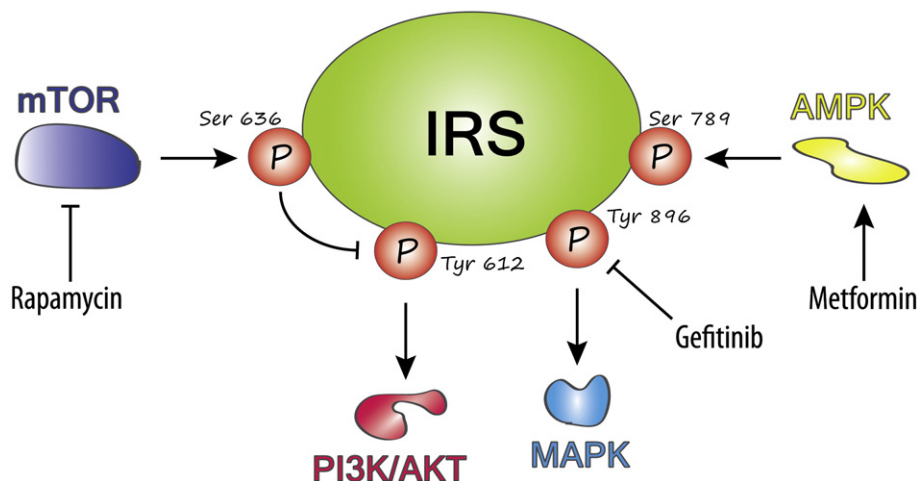

Fig. 1. Select IRS-1 phosphorylation sites and activation or inhibition of downstream pathways.