

IGFR: New Anti-Cancer Target for SCCHN

Summary of the Article: Insulin-like Growth Factor Receptor as a Therapeutic Target in Head and Neck Cancer; Barnes CJ. et al. *Clinical Cancer Res* 2007; 13(14).

Squamous cell carcinoma of the head and neck (SCCHN) is the fifth most common cancer worldwide and contributes considerably to the mortality and morbidity rate in the United States. There is currently no highly successful way to improve SCCHN patient survival, recurrence of primary tumors, or rate of metastases. One anti-tumor strategy that has shown to reduce the aggressive phenotype of SCCHN tumors is the use of blocking antibodies to inhibit the activation of cell surface receptors, particularly the epidermal growth factor receptor (EGFR). Although this is an advance in molecular-targeted therapy, it has only proven successful in a subset of patients.

Recently, the insulin-like growth factor type I receptor (IGF-IR) has emerged as a new target in preclinical investigations. Systemic increases in the IGF ligand, IGF-I, and the high cellular expression levels of IGFIR have been correlated to the development and progression of certain types of cancers. The binding of IGF-1 to IGFIR initiates signaling downstream that includes the autophosphorylation of the receptor and subsequent activation of the Ras-Raf-MAPK and the P13K-Akt signaling cascades, which are all important for cancer cell survival and proliferation. The proliferative and antiapoptotic effects of IGF-IR signaling are also mediated through an adaptor protein called insulin receptor substrate 1 (IRS-1), which is tyrosine phosphorylated by IGFIR. IRS-1 ultimately facilitates cell motility and invasion.

The authors first investigate the expression and function of IGF-IR in human head and neck cancer. An increase in the expression of the IGF receptor was discovered across a variety of human head and neck cancer cell lines. Additionally, when comparing normal and tumor tissue from tongue cancer patients, elevated levels of IGF were found in all cases. The use of IMC-A12 (A12), a known blocking antibody to the IGF receptor, decreased progression through the cell cycle (G1 arrest), downstream receptor signaling, cellular motility based on wound-healing assays, and anchorage-independent cell growth, illustrating the importance of IGFIR signaling to the cancer cell survival and proliferation. Another important finding was that stimulation of the cancerous cells with IGF also led to the activation of the EGF receptor. However, this signaling axis is not bi-directional since stimulation with EGF does not result in IGFIR phosphorylation. Immunoprecipitating the IGF type 1 receptor with an antibody also pulled down the EGFR, suggesting a heterodimer of these two receptors that exist endogenously. When A12 and a similar blocking antibody to the EGF receptor (C225) were combined, it proved more efficacious than each of the single agents alone when SCCHN xenographs were analyzed. Taken together, the authors establish a potential biological significance for targeting the IGF receptor and using inhibitory agents to both the IGFIR and EGFR as a likely combination treatment.