INSULIN AND IGF-1 RECEPTORS AND CANCER

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Recent studies have demonstrated a role for both the insulin receptor (IR) and the IGF-1 receptor (IGF-1R) in cancer development, growth and cancer-related mortality. Epidemiological studies showed a relationship between total IGF-1 circulating levels and the relative risk of developing most of the common epithelial cancers including prostate, colon, and breast cancer. In vitro studies have shown an increased expression of the IGF-1R in cancer cells and furthermore, blocking the activation of the IGF-1R inhibits cancer growth both in vitro and in vivo. This has led to the development of numerous humanized IGF-1R blocking antibodies and a number of small tyrosine kinase inhibitors (TKI). Many of these compounds are in preclinical, phase 1 and phase 2 clinical trials. In some studies, complete of partial responses have been seen, though the proportion of patients responding is limited and often the severity of the side-effects have resulted in cessation of the trials. Interestingly, there appears to be some resistance to the blocking effects of the antibodies and studies have demonstrated a compensation by other tyrosine kinase receptors such as the IR, EGFR or PDGFR Studies are also ongoing using a combination of anti-IGF-1R antibodies and other inhibitors of other signaling molecules such as mTOR or PI3'kinase.

On the hand, interest has also focused on the role of insulin in promoting cancer in obesity and Type 2 diabetes (T2D). Again, interest has arisen from epidemiological studies that find an association between c-peptide and serum insulin levels and cancer risk and cancer-related mortality in obesity and/or T2D. In addition, it has been demonstrated that cancer risk in T2D was greater in patients on sulfonylureas or insulin compared to metformin therapy. In the case of breast cancer, studies have convincingly shown that prognosis is worse when the breast cancer samples express higher levels of IR that is activated. In these case the expression of IR-A, a mitogenic sub-type of the IR is also expressed at high levels. To demonstrate the direct causality between endogenous hyperinsulinemia and cancer growth and metastases, we have utilized such a mouse model. Our results show that reducing the hyperinsulinemia or blocking the IR/IGF-1R tyrosine kinases blocks the extra growth of the tumors considered secondary to the hyperinsulinemia. Furthermore, we show an increase that increased metastases is also correlated with hyperinsulinemia.

Thus the increased cancer seen in obese individuals and tyep2 diabetic patients maybe due in part to endogenous hyperinsulinemia.