Insulin-like growth factor signaling as a therapeutic target in pancreatic cancer.

Abstract:
Insulin-like growth factor-1 (IGF-1) leads via its receptor IGF-1R to the activation of the PI3K/Akt pathway, providing anti-apoptotic signals to pre-malignant and malignant cells. In pancreatic cancer, IGF-1 and its receptor are constitutively overexpressed. Mammalian target of rapamycin (mTOR) is the main mediator of mitogenic stimuli transduced by PI3K/Akt. Interestingly, inhibition of mTOR activates PI3K/Akt by up-regulating IGF-1R signaling. Several targeted agents have been developed to inhibit the activity of IGF-1 or to block IGF-1R. These pharmaceuticals may offer additional ways of stimulating apoptosis in neoplastic cells. Yet, there are difficulties in targeting this pathway: The ideal anti-cancer drug target is expressed only in cancer cells; however, IGF-1 and its receptor IGF-1R are ubiquitously expressed throughout the body. Moreover, when using antibodies against IGF-1R, the structurally similar insulin receptor might also be blocked, leading to hyperglycemia as a severe side effect. There are currently several phase I/II trials investigating IGF-1 and its receptor as a drug target in various kinds of cancer. Specifically, therapeutic effects on pancreatic cancer by combining a humanized monoclonal antibody against IGF-1R with other chemotherapeutics are being investigated. To improve the clinical outcome of mTOR inhibitors such as everolimus, it has been suggested to use combination...
therapies of mTOR inhibitors and IGF-1/IGF-1R inhibitors. In theory, this would counterbalance the feedback effects of mTOR inhibition on IGF-1 signaling. In conclusion, IGF-1 and its receptor are promising new drug targets in cancer therapy. Combination therapies of IGF-1/IGF-1R inhibitors and mTOR inhibitors could improve the clinical outcome.