has a 5-year survival rate of only 10% in 2020. Using human and mouse pancreatic cancer cells and RNA and protein expression analyses by RT-qPCR, ELISA, and western-blot, we identified that (i) GH upregulates specific ABC-transporter expressions in a drug-context specific manner, (ii) GH upregulates EMT transcription factors, (iii) GH activates specific oncogenic signaling pathways, and (iii) GH action increases cytochrome P450 members involved in hepatic drug metabolism. The GH antagonist, Pegvisomant, significantly inhibited these effects. Additionally, we confirmed the effects of these molecular changes by specific assays. For example, GH increases basement membrane invasion, viability of circulating tumor cells, and drug efflux; while inhibition of GHR by pegvisomant in pancreatic cancer cells reversed this aggressive tumor phenotype and sensitized the tumor cells to chemotherapy. Cell viability assays confirmed a decreased IC50 of gemcitabine, doxorubicin, and erlotinib in pancreatic cancer cells treated with pegvisomant and an increase in IC50 cells treated with GH. We further verified our results using in silico analyses of TCGA datasets for pancreatic cancer - which provided robust confirmation of our experimental findings. Presently we are validating our observation in nude mice with human pancreatic cancer cell xenografts. In conclusion, our *in vitro* results confirm that GHR antagonism can drastically sensitize human pancreatic cancer cells by blocking mechanisms of drug resistance, thus providing a valuable window for improved efficacy of available chemo- and targeted therapy.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Halting Retrograde Transport Excludes ErbB-2 From the Nucleus Abrogating Tumor Growth in Triple Negative Breast Cancer

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Triple negative breast cancer (TNBC) refers to a subtype of tumors with poor prognosis, devoid of hormone receptors and of membrane overexpression or gene amplification of ErbB-2. Due to its molecular heterogeneity, TNBC represents a major clinical challenge. In this regard, clinical biomarkers and targeted therapies remain elusive, and chemotherapy has been the standard of care for early and metastatic TNBC. ErbB-2, a member of the ErbB family of tyrosine kinase receptors, is a major player in the BC scenario. While it is a cell membrane-bound receptor, it migrates to the nucleus (NErbB-2) where it acts as a transcription factor or coactivator. We recently found that both the canonical (wild-type, WT) ErbB-2 and the alternative isoform c are located in the nucleus of TNBC, a scenario with an aggressive oncogenic potential. The route of intracellular transport from the plasma membrane to the trans Golgi network (TGN) and the endoplasmic reticulum (ER) is termed retrograde trafficking, and constitutes the pathway by which ErbB-2 migrates to the nucleus. The retrograde transport route is also hijacked by toxins and viruses to access the ER and exert their deleterious effects. Retro-2, a small molecule inhibitor, was shown to protect cells from toxin and virus effects by blocking their retrograde trafficking. Given the high levels of NErbB-2 in TNBC cells, we explored whether treatment with Retro-2 modulates localization of ErbB-2 and proliferation in TNBC.

We found that Retro-2 treatment decreased the levels of both WT ErbB-2 and isoform c in the nucleus of TNBC cells demonstrating that Retro-2 effects are not limited to a particular ErbB-2 isoform. Indeed, immunofluorescence assays revealed accumulation of ErbB-2 in the Golgi after Retro-2 treatment further preventing its sorting to the ER. We previously demonstrated that growth factors induce ErbB-2 migration into the nucleus in ErbB-2-positive BC cells. Consistently, we observed that Retro-2 prevents growth factor-induced NErbB-2 in ErbB-2-positive BC cells. Retro-2 treatment resulted in a dose-dependent decrease in cell proliferation in a panel of TNBC cells, whilst did not inhibit cell proliferation in the ErbB-2-negative MCF10A normal breast cell line. Moreover, disruption of retrograde transport by Retro-2 decreased the expression of cell cycle related NErbB-2 target genes (*i.e.* Erk5 and cyclin D1) therefore inducing cell cycle arrest at the G0/G1 phase. Most importantly, Retro-2 excluded ErbB-2 from the nucleus and abrogated tumor growth in preclinical models of TNBC.

Collectively, our findings reveal Retro-2, a non-toxic inhibitor of the retrograde transport route, as a candidate novel therapeutic agent for TNBC based on its ability to evict ErbB-2 from the nucleus and to abrogate TNBC growth.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Heterogeneous Nuclear Ribonucleoprotein K Is Involved in the Estrogen-Signaling Pathway

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Heterogeneous nuclear ribonucleoprotein K (hnRNPK) has been found in the nucleus, cytoplasm, and mitochondria. It is implicated in chromatin remodeling, transcription, splicing, and translation processes. Although hnRNPK has reportedly been associated with poor prognosis in colon cancer patients, it is beneficial in gastric cancer as it inhibits cancer cell proliferation. Expression of hnRNPK in ER (Estrogen receptor) -positive/PR (Progesterone receptor) -positive breast cancer was higher than other subtypes; however, the biological functions of hnRNPK in the ER-mediated signaling pathway have not been identified. In this study, we investigated the functions of hnRNPK in the estrogen-signaling pathway. We initially evaluated