Title: IGF and Insulin system in regulating hallmarks of cancer

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The Insulin-like growth factor (IGF) system is implicated in various cancers and is known to regulate cell growth, proliferation, and metabolism. Type 1 IGF receptor (IGF-1R) targeting strategies have been unsuccessful, probably due to its characteristic to form heterotetrameric hybrids with the homologous insulin receptor (IR). This introduces multiple IGF-1 binding sites and draws focus on IR and its isoforms – IR-A and IR-B, as potential therapeutic targets. A high IR-A to IR-B ratio is observed in various tumors including breast cancer. IR-A dominates fetal growth and development while IR-B is predominantly found in liver and skeletal muscle where glucose uptake is regulated via glucose transporter GLUT4. IR's important role in maintaining physiological metabolism necessitates delineating IR isoform roles to develop efficient targeted strategies. The side effects of anti-IGF-1R therapy–hyperinsulinemia and hyperglycemia–warrant strategy development to manage the toxicity associated with non-specific IR targeting. Ideally, targeting IR-A specifically, and leaving IR-B unaffected, might be an effective IGF and insulin system targeting approach. Our group developed IR K/O MCF-7L (ER+ breast cancer cell line) and introduced IR-A or IR-B to generate isoform-specific cell lines. The real-time ATP production rates suggest IGF-1 promotes glycolytic ATP production in MCF-7L, MCF-7L IR K/O, IRB-C9, and MDA MB 231 (TNBC) while, insulin at physiological concentration doesn't affect ATP production. Therefore, IR-B may maintain the metabolic demand of ER+ breast cancer cells when activated by IGF-1. Additionally, IR inactivation and metabolic stimulation via IGF-1 suggest investigating alternative fuels. We are interested in investigating glutamine as it promotes tumorigenesis by acting as a nitrogen source for amino acid and nucleotide biosynthesis and carbon source to replenish tricarboxylic acid (TCA cycle) and lipid biosynthesis. Glutamine metabolism has pleiotropic effects including mTOR activation and reactive oxygen species (ROS) maintenance. This further supports proliferation, metastasis, and drug resistance. Preliminary experiments indicate the dependency of MCF-7L on both fuels to maintain the glycolytic phenotype when stimulated with IGF-1. IGF-1 also stimulated migration in MCF-7L and MDA MB 231 cell lines while insulin promoted this phenotype in MDA MB 231 only. Further investigation will elucidate IR isoform roles in cellular hallmarks of cancer.