and metastasis. An important feature of this metabolic flexibility is conversion of glutamine to glutamate, an amino acid integral to protection of cells from oxidative stress. Consistent with this, we show multiple cellular models of ER+, endocrine resistant breast cancer cells markedly increase glutamate release and upregulate expression of essential glutamine/glutamate metabolic enzymes and transporters, including the glutamate/cystine antiporter xCT, glutamate dehydrogenase (GLUD1/2), and/or the glutamine importer SLC1A5. Riluzole (RIL) is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS), and has several proposed mechanisms of action, including suppression of glutamate release and increased glutamate uptake. We show ER+, endocrine responsive and resistant breast cancer cells are growth-inhibited by RIL. This is due to an increase in cell death, particularly in endocrine resistant breast cancer cells, and cell cycle arrest. Interestingly, histologic subtype confers a different cell cycle arrest profile, with invasive ductal cancer (IDC) models arresting in G1 but invasive lobular cancer (ILC) models arresting in G2/M. Isobologram analysis of RIL plus SERMs or SERDs shows additive-to-synergistic activity in a subset of ER+ cell line models, and preliminary studies show combination activity in patient-derived explants (PDEs). Mechanistically, we tested whether signaling through metabotropic glutamate receptors (mGluRs, GRMs) and/or cystine import contribute to RIL's growth-inhibitory phenotype. Antagonists of mGluRs/GRMs don't phenocopy the effects of RIL, suggesting extracellular glutamate signaling through these receptors is not a key mechanism. Rescue experiments with β-mercaptoethanol to promote cystine uptake through transporters other than xCT show partial reversal of RIL-mediated cell cycle arrest in some cells, suggesting xCT may contribute to RIL-induced growth inhibition. In summary, we show RIL may be a viable addition to endocrine therapy in ER+ breast cancer. Ongoing studies will test additional mechanism(s) by which RIL may attenuate the growth of ER+ breast cancer models *in vitro*, including inhibition of protein kinase C and casein kinase 1 delta. We are further testing RIL efficacy alone and in combination with a SERD in primary tumors and lung metastases in a ER+ patient-derived xenograft (PDX) model.

Diabetes Mellitus and Glucose Metabolism

GESTATIONAL DIABETES, DIABETES IN PREGNANCY, AND IN UTERO EXPOSURES

Profiling of Activation Patterns of Placental mTOR in Pregnancies Complicated by Gestational Diabetes Mellitus

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The mammalian target of rapamycin (mTOR) couples' energy and nutrient abundance to cell growth and is critically involved in the onset and progression of diabetes, cancer and ageing. Placental mTOR is involved in nutrient sensing and transfer to the fetus; animal models suggest that placental mTOR is upregulated in pregnancies complicated by hyperglycaemia (1). In this study we investigated expression patterns and activation of placental mTOR and possible effects of gestational diabetes (GDM). Our study consisted of GDM-mothers (n=28) and their offspring and ii) mothers (n=33) with normal pregnancies (non-GDM) and their infants. Total and phospho-mTOR (Ser2448) expression were determined in placental biopsies using either immunoblotting and immunohistochemistry (IHC) analysis. Newborn anthropometric parameters were also determined at delivery. GDM pregnant women presented with higher fasting glucose levels than non-GDM (98.12±22.82mg/dL; 73.61±9.89mg/dL; $p<0.001$). No significant difference was found in birth weight or baby length between GDM and non-GDM infants. IHC analysis showed that both total and activated mTOR were predominantly expressed in trophoblasts and to a lesser extend in syncytiotrophoblasts, in both GDM and non-GDM placentas. GDM placentas exhibited a higher mTOR H-score (2) compared to non-GDM ($p<0.012$), and WB analysis showed a higher phosphor-mTOR signal intensity ($p=0.047$) in the same group, most likely due to increased total mTOR expression. mTOR expression was also increased in both GDM syncytiotrophoblasts and endothelial cells compared to non-GDM ($p<0.001$) whereas a reduced signal was detected in stromal phospho-mTOR ($p=0.004$). No difference was found in trophoblasts or endothelial cells between the 2 study groups suggesting that activation of this kinase is tightly regulated and is relatively independent of changes in total kinase levels. Interestingly bivariate correlation analysis identified an extensive network of significant associations in the expression levels of total, phosphor-mTOR and P/T mTOR between trophoblasts, stroma, endothelial and syncytiotrophoblastsin control placental biopsies; this network was significantly disrupted in GDM placentas, identifying a disheveled regulation of placental mTOR activity. In conclusion, placental mTOR/PmTOR expression is differentially regulated across different placental cell types and is sensitive to hyperglycaemia associated with gestational diabetes mellitus.(1)M. Castillo-Castrejon and TL. Powell. Front Endocrinol (Lausanne). 2017; 8: 306. (2) E. Lakiotaki, et al., Scientific Reports 2016; 6, 21252.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

The Burdens of Adrenal Insufficiency: A Survey Study from Two Tertiary Care Centers in the United States

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