LOSS OF PUTATIVE TUMOR SUPPRESSOR EPHB2 INDUCES LIPID DROPLETS ACCUMULATION AND PROLIFERATION IN PROSTATE CANCER CELLS

Introduction: To sustain the constant demand of energy associated with a proliferative phenotype, cancer cells undergo metabolic re-programming by increasing their rate of fatty acid (FA) synthesis and storage in lipid droplets (LD). Dysregulation of receptor tyrosine kinase (RTK) signaling can result in aberrant metabolism through disruption of critical metabolic pathways. Here, we show a novel role of EPHB2, an RTK member of the Ephrin family, on LD biogenesis and subsequent accumulation associated with increased prostate cancer (PCa) cell proliferation.

Method: Expression of EPHB2 and LD density was assessed in PCa specimens and PCa cell lines with different degrees of tumorigenicity. EPHB2 silencing was performed in PCa cells. The accumulation and size of LDs were assessed under basal and obesogenic (Oleic acid, OA) environments using a combination of flow cytometry and microscopy. Key molecules involved in lipogenesis and lipolysis were assessed. The biological effects of EPHB2 knock down were tested in vitro.

Results: High grade PCa accumulate significantly more neutral lipid than lower grade tumors. EPHB2 staining of prostate specimens showed a distinct strong membrane expression in benign epithelial glands, compared to diffuse and weak expression in areas with PCa. Expression of EPHB2 was inversely associated with PCa cells tumorigenicity. EPHB2 silencing had a positive effect on PCa cells proliferation. Increased accumulation of LD in the cytoplasmic and nuclear compartments were observed in cells with EPHB2 knock down. LD changes were associated with differential expression of key molecules involved in lipogenesis and lipolysis, notably DGAT1, DGAT2 and ATGL. Inhibition of lipogenesis using a DGAT1-specific inhibitor abolished the effects on LD metabolism induced by EPHB2 loss in PCa cells.

Conclusions: Decreased EPHB2 expression observed in PCa may play a key role in the excessive accumulation of neutral lipids within LDs in cancer cells. PCa cells can use this lipid-rich environment as a source of energy to fuel a more aggressive phenotype. Several DGAT1 inhibitors are currently being evaluated in clinical trials as anti-obesity agents, showing promising results, therefore, the potential anti-tumorigenic utility in high-risk PCa patients with altered ephrin levels requires further study.