Seminar on

Understanding metabolic cooperation between tumor and stromal cells

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Seminar Abstract

Tumor stroma interaction is an area of intense investigation and is geared to understand how apparently normal stromal cells become subservient to the metabolic demands of tumor cells. Our recent studies indicate that bone marrow-derived mesenchymal stromal cells (MSCs) exposed to tumor-conditioned medium assume a CAF-like myofibroblastic phenotype and serve as an excellent in vitro model for understanding tumor stroma interactions. More importantly, these cells also exhibit functional properties of CAFs including increased expression of stromal derived factor 1 (SDF-1) and the ability to promote tumor cell growth both in vitro and in an in vivo coimplantation model. Further studies on tumor stroma interactions have revealed that metabolic support from stromal cells is critical for tumor cells to survive and proliferate at the metastatic site. We hypothesize that stromal cells are important for tumor metastasis as they provide critical metabolites via a lactate pyruvate shuttle ensuring tumor growth. Our investigations indicate that a lactate pyruvate shuttle exists between tumor and stromal cells where lactate produced by glycolytic tumor cells is taken up by stromal cells and converted to pyruvate which along with glutamate and gamma amino butyrate is returned to tumor cells as metabolites for continuation of glycolysis as well as for increasing biomass. Such intercellular metabolic coupling may be a means by which tumors secure auxiliary sources of energetic and biosynthetic metabolites, and may synergize with paracrine signaling to robustly promote tumor growth. We propose the following model of reciprocal metabolic cooperation between tumors and their TME that may be developed to identify druggable targets: tumor cells convert glucose to pyruvate, but, rather than use it for oxidative phosphorylation, convert this monocarboxylate to lactate to produce more NAD+, which is necessary for continued glycolysis. To prevent the accumulation of lactate and subsequent Intracellular acidosis the tumor cells efflux this metabolite via MCT4. The stromal CAFs take up the secreted lactate via MCT1, convert it to pyruvate through increased expression of LDH-B, and, as supported by our NMR data, subsequently shunt it into the TCA, thereby fueling their own energetic needs. Paracrine ligands and surplus pyruvate secreted by the stroma are taken up by neighboring tumors to collectively regulate reactive oxygen species and fuel glycolysis. These studies will help identify therapeutic opportunities to disrupt tumor stroma interaction and may result in better tumor suppression.