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The Autophagic Tumor Stroma Model of Cancer: Role of Oxidative Stress and Ketone Production in Fueling Tumor Cell Metabolism

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A loss of stromal caveolin-1 (Cav-1) in the tumor fibroblast compartment is associated with early tumor recurrence, lymphnode metastasis and tamoxifen-resistance, resulting in poor clinical outcome in breast cancer patients. Here, we have used Cav-1 (-/-) null mice as a pre-clinical model for this ?lethal tumor micro-environment?. Metabolic profiling of Cav-1 (-/-) mammary fat pads revealed the upregulation of numerous metabolites (nearly 100), indicative of a major catabolic phenotype. Our results are consistent with the induction of oxidative stress, mitochondrial dysfunction and autophagy/ mitophagy. The two most prominent metabolites that emerged from this analysis were ADMA (asymmetric dimethyl arginine) and BHB (beta-hydroxybutyrate; a ketone body), which are markers of oxidative stress and mitochondrial dysfunction, respectively. Transcriptional profiling of Cav-1 (-/-) stromal cells and human tumor stroma from breast cancer patients directly supported an association with oxidative stress, mitochondrial dysfunction and autophagy/mitophagy, as well as ADMA and ketone production. MircoRNA profiling of Cav-1 (-/-) stromal cells revealed the upregulation of two key cancer-related miR?s, namely miR-31 and miR-34c.

Consistent with our metabolic findings, these miR?s are associated with oxidative stress (miR- 34c) or activation of the hypoxic response/HIF1a (miR-31), which is sufficient to drive authophagy/mitophagy. Thus, via an unbiased comprehensive analysis of a lethal tumor micro-environment, we have identified a number of candidate biomarkers (ADMA, ketones and miR-31/34c) that could be used to identify high-risk cancer patients at diagnosis, for treatment stratification and/or for evaluating therapeutic efficacy during anti-cancer therapy.

We propose that the levels of these key biomarkers (ADMA, ketones/BHB, miR-31 and miR-34c) could be (i) assayed using serum or plasma from cancer patients or (ii) performed directly on excised tumor tissue. Importantly, induction of oxidative stress and autophagy/mitophagy in the tumor stromal compartment provides a means by which epithelial cancer cells can directly ?feed off? of stromal-derived essential nutrients, chemical building blocks (amino acids, nucleotides) and energy-rich metabolites (glutamine, pyruvate, ketones/BHB), driving tumor progression and metastasis.

Essentially, aggressive cancer cells are ?eating? the cancer-associated fibroblasts via autophagy/mitophagy in the tumor micro-environment. Lastly, we discuss that this ?Autophagic Tumor Stroma Model of Cancer Metabolism? provides a viable solution to the ?Autophagy Paradox? in cancer etiology and chemo-therapy.