RECEPTOR FOR LACTATE DEHYDROGENASE V IS A NOVEL THERAPEUTIC TARGET FOR GLIOBLASTOMA

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In order develop effective immunotherapies for cancer it is important to understand the crosstalk between the tumor and the tumor-supportive immune cells in the microenvironment. In patients with aggressive brain tumors, such as the Grade IV glioblastoma (GBM), myeloid cell accumulation supports local immunosuppression, angiogenesis, and chemoresistance. We have recently shown that extracellular, GBM-derived lactate dehydrogenase 5 (LDH5) influences gene expression in myeloid cells to generate a natural killer cell-suppressive phenotype. Although extracellular LDH5 is not known to have a role in cell signaling, we hypothesized that LDH5 found in the highly necrotic tumor, mediates crosstalk between tumor cells and myeloid cells, influencing the functions of both populations. We found that macrophages, monocytes, and GBM cells all internalize LDH5 in a manner consistent with receptor mediated endocytosis, a function that can be blocked with a monoclonal antibody against LDH5. We found that LDH5 alters the metabolic phenotype of macrophages by increasing ATP production, lactate export, and glycolytic rate following oligomycin administration. Monocytes treated for 24 hours with LDH5 have decreased levels of intracellular reactive oxygen species and a depolarized mitochondrial membrane potential with no change in viability. GBM tumor cells treated with LDH5 also exhibit depolarized mitochondria, without changes in mitochondrial mass or cell viability. Interestingly, under hypoxic conditions, exposure of these cells to LDH5 causes increased levels of intracellular GTP, while under normoxic conditions, GTP is reduced by LDH5. This suggests that LDH5 helps to tolerize tumor and immune cells to an environment with extensive necrosis and reduced oxygen, both hallmarks of GBM. Our data indicate a receptor for LDH5 that could act as a therapeutic target by altering metabolic functions of tumor cells and associated immunosuppressive myeloid cells in the tumor microenvironment.