INTEGRATION OF CANCER STEM CELL MAINTENANCE AND LIPID METABOLISM BY SCAVENGER RECEPTORS
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BACKGROUND: Glioblastoma (GBM) contains self-renewing, tumorigenic cancer stem cells (CSCs) which contribute to tumor propagation and therapeutic resistance. While the tumor microenvironment is essential to CSC self-renewal, the mechanisms by which CSCs sense and respond to microenvironmental conditions are poorly understood. Scavenger receptors are a broad class of membrane receptors that are well characterized on immune cells and instrumental in sensing apoptotic cellular debris and modified lipids. METHODS: To interrogate the role of scavenger receptors in GBM, we utilized GBM patient tissue and patient derived xenografts. CSCs were enriched using standard cell surface marker methods and validated using functional assays (proliferation, self-renewal, tumor initiation). The role of scavenger receptors was tested using RNA interference and small molecule approaches in combination with CSC functional assays. The use of scavenger receptors as a biomarker was evaluated using bioinformatics databases and tissue microarray analysis. Lipid metabolism was evaluated by addition of oxidized low density lipoprotein (oxLDL) and de novo lipogenesis was evaluated by following carbon flux from acetate and oleate into phospholipids. RESULTS: We detected the expression of CD36, a major scavenger receptor, in GBM cells in addition to previously described cell types including endothelial cells, macrophages and microglia. CD36 was enriched in CSCs and was able to functionally distinguish self-renewing cells. CD36 was co-expressed with integrin alpha 6, a previously described CSC functional marker, and CD36 reduction by RNA interference resulted in concomitant loss of integrin alpha 6 expression, self-renewal and tumor initiation capacity. These results were confirmed using a novel small molecule inhibitor to CD36. We confirmed that oxidized phospholipids, ligands of CD36, were present in GBM and found that the proliferation of CSCs, but not non-CSCs, increased with exposure to oxLDL. RNA and protein levels of CD36 were informative biomarkers of malignancy and negatively correlated to patient prognosis. An unbiased analysis of GBM patients revealed that higher lipid metabolism correlated to poorer prognosis. To determine if differences in lipid metabolism were present in CSCs versus non-CSCs, we evaluated de novo lipogenesis and fatty acid esterification, both of which were significantly elevated in CSCs and could be attenuated using a CD36 small molecule inhibitor. CONCLUSIONS: Our data demonstrate that CD36 expression is elevated in CSCs, functions to promote self-renewal, and provides CSCs a selective lipid uptake advantage. Taken together, these results provide a paradigm for CSCs to thrive by the enhanced expression of scavenger receptors, providing survival and metabolic advantages. SECONDARY CATEGORY: Preclinical Experimental Therapeutics.