

Metabolic coupling of hypoxia to intratumoral heterogeneity

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Abstract: Intratumoral phenotypic heterogeneity represents a major obstacle for effective cancer treatment. In particular, subpopulations of tumor cells with dedifferentiated, stem-like features can resist cytotoxic therapies and repopulate tumors. These cancer stem-like cells (CSCs) often reside in poorly vascularized, hypoxic regions of tumors, but the mechanisms by which the hypoxic tumor microenvironment induces and influences the CSC phenotype remain poorly defined. We identified a previously unknown metabolic pathway wherein malignant cells produce the metabolite L-2-hydroxyglutarate (L-2HG) in response to hypoxia. Analogous to the stemness-promoting effects its enantiomer D-2HG in IDH-mutant malignancies, we show that L-2HG inhibits alpha-ketoglutarate-dependent enzymes resulting in stabilization of hypoxia-inducible factor, accumulation of repressive chromatin marks, and impairment of stem and progenitor cell differentiation. Moreover, we find that L-2HG appears to be necessary and sufficient to induce epigenetic heterogeneity within hypoxic regions of tumors. Thus, we hypothesize that L-2HG functions as a metabolic signal coupling the hypoxic tumor microenvironment to heterogeneous induction of a stem-like phenotype in subpopulations of genetically similar tumor cells. We will test this hypothesis in pancreatic ductal adenocarcinoma (PDAC), a cancer with an abysmal prognosis that exhibits a poorly vascularized, hypoxic tumor microenvironment and extensive intratumoral heterogeneity, as determined by our pilot single-cell RNA sequencing data. We will employ novel genetic approaches to selectively manipulate L-2HG levels in organoids, genetically engineered mice, and patient-derived xenografts to investigate the mechanisms through which L-2HG influences intratumoral heterogeneity. These efforts will determine whether targeting L-2HG metabolism could be translated into a new therapeutic strategy for PDAC and other solid tumors.