Award ID:
RP140452

Project Title:
Inactivating Mutation of D2HGDH Establishes a Novel Link Between Metabolism, Alpha-KG Dependent Dioxygenases and Epigenetic Reprograming in B Cell Lymphoma

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
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Lay Summary:

Cancer cells have a unique metabolism. However, debate still exists as to whether this altered cellular metabolism can cause cancer, or if it is simply a byproduct of the fast growth pattern that typifies malignant cells. Studying B cell lymphomas, we discovered the presence of inactivating mutations in the gene D2HGDH, which encodes an important metabolic enzyme. This finding supported the idea that metabolic aberrations can directly cause cancer. To start to examine how inactivation of D2HGDH may contribute to the development and/or maintenance of tumor cells, we quantified the molecules that are processed by this enzyme. Cells containing the defective D2HGDH gene had abnormally lower levels of a metabolite called alpha-ketoglutarate (a-KG). Herein, we propose to test the hypothesis that the lower levels of a-KG caused by the D2HGDH mutation will inhibit the function of a class of proteins (the a-KG dependent dioyxygenases) that work in concerted fashion to prevent malignant transformation. Thus, cells carrying a defective D2HGDH will be at an increased risk of becoming cancerous, and will display a specific chemical signature, hypermethylation, at DNA and histone protein levels. Confirming this hypothesis will provide the blueprint for the rapid development for several initiatives that directly benefit patients with cancer, including: the quantification of a-KG with diagnostic intent or to monitor therapy response (biomarker), and the use of specific therapeutic agents (e.g., DNA demethylating compounds) in patients with D2HGDH-mutant tumors. Finally, beyond B cell lymphomas, which are common and often fatal cancers, we also encountered evidence for mutations in the D2HGDH gene in a small but significant fraction of lung and colorectal cancers, thus indicating that the relevance of our findings may be even broader than initially appreciated.