CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170619

Project Title:
An Unexpected Oncometabolic Axis: Exposing Novel Regulators of Cardiac Remodeling in Leukemia

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Acute myeloid leukemia (AML) affects 20,000 Americans annually and is the most common cancer in children. Improved treatments have increased patient survival, but despite these efforts survivors have a five-fold higher risk for developing heart failure. Recent advances in clinical and basic research studies have found that deteriorating cardiovascular events occur in survivors independent of the type of cancer treatment. This underscores the need for innovative therapeutic strategies to target leukemia cells and to ultimately protect the heart. Specific metabolic activities provide benefits to cancer cells and drive tumor growth. Two genes called IDH1 and IDH2 are mutated in 20% of AML cases, making them important contributors to the metabolic transformation in this cancer. IDH mutations drive the formation and release of an oncometabolite, D-2-hydroxyglutarate (D2-HG) into the bloodstream, which leads to enlargement and impaired function of the heart. Our extensive studies showed that D2-HG can directly impair cardiac metabolism and function by redirecting the Krebs cycle, a key metabolic pathway that is responsible for energy provision in every mammalian cell. This pathway is also critical for the growth of cancer cells, and possibly involved in a maladaptive process in the heart. We hypothesize that D2-HG promotes metabolic and structural remodeling in muscle cells. We will study this remodeling using cell culture and mathematical models that we have developed. Our goal is to identify metabolic pathways and specific proteins that can be targeted to slow cancer growth and at the same time protect heart and skeletal muscle cells. We anticipate that these studies will have broad implications for our understanding of how IDH-mutant cancers reprogram the metabolism of other cells and will identify novel therapeutic targets for AML and heart failure. Our long-term goal is to translate these findings into clinical studies and to optimize treatments of AML patients.