CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140672

Project Title:
Mutant KRAS Reprograms Lipid Metabolism Exposing Beta- Oxidation as a Novel Therapeutic Target in Lung Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Lung cancer is the leading cause of cancer-related death inTexas. This cancer type is often diagnosed in an advanced stage and is resistant to conventional therapy. As a result, the long-term survival of cancer patients is dismal. The KRAS oncogene is mutated in ~30% of non-small cell lung cancers, the most common form of this disease. The presence of mutant KRAS is associated with aggressive disease, poor outcome and an overall survival of about 15%. To make progress towards the generation of new therapies, we performed experiments to identify the cellular networks that cancer cells use to generate energy and building blocks. Our preliminary experiments indicate that mutant KRAS lung cancer cells use fatty acids to generate energy (i.e burn fat, a process ordinarily used by liver and muscle). Furthermore, we found that inactivation of the Acyl-CoA synthetase, an enzyme that regulates this process leads to death of cancer cells. There is a growing appreciation that lot of metabolic changes occur in cancer cells to meet the energy demands for rapid growth. However, this feature of cancer cells has not been exploited yet in cancer therapy. We propose the innovative concept that inhibition of the key enzymes, which regulate the utilization of fat in cells for the generation of energy will lead to antitumor effects. For this purpose we will conduct experiments both in human lung cancer cells in culture and in mouse models of lung cancer. If successful, this research will provide the rationale for the use of same set of drugs in lung cancer therapy that are currently being used to inhibit the cellular utilization of fat in heart disease. The requested funding from CPRIT will be instrumental to provide the resources needed to develop this novel area of research in our lab and to provide the rationale to test its therapeutic potential in lung cancer.