Project Description:

Alteration in energy metabolism is a characteristic hallmark of human cancers, and the mechanisms driving this reprogramming are under intense investigation. In cancer the mitochondria, which are the power generators of the cell, become less efficient at generating energy from oxygen, while alternative pathways such as aerobic glycolysis are utilized instead. We have recently identified a new system for regulation of expression of the genes coded by the mitochondrial genome, involving modification of bases within the genome. In the nucleus, analogous epigenetic modification of DNA is a powerful mechanism for regulating gene expression. We have determined that the enzymes responsible for this control mechanism in the mitochondria are regulated by cancer-related genes, such as the tumor suppressor p53. We have therefore proposed that epigenetic regulation of mitochondrial gene expression plays an important role in modulating mitochondrial function during the metabolic reprogramming seen in oncogenesis. The studies proposed here will apply biochemical, biophysical and structural methods to understand the details of how modified DNA affects normal functioning of the proteins involved in transcription of the genes encoded in this genome. The information generated will allow an assessment of the importance of mitochondrial DNA modification to metabolic reprogramming, as well as a deeper understanding of the details of the normal interaction between DNA and proteins required for transcription. The experiments proposed are specifically designed to provide the necessary data for a multi-investigator RO1 grant application.