Cells need to maintain their nuclear DNA accurately in order to function properly. Indeed, defects in DNA integrity are associated with cancer, aging and immunodeficiency. Therefore, numerous DNA repair systems in mammalian cells function to endow us with long and relatively tumor-free lives. The DNA and the histones are arranged in the nucleus in a highly condensed structure known as chromatin. Cellular processes that unwind the double helix—such as transcription, replication and DNA repair—have to overcome this natural barrier to DNA accessibility.

Multicellular organisms also need to control their use of cellular energy stores. Glucose metabolism plays a crucial role in organismal homeostasis, influencing energy consumption, cell proliferation, stress resistance and lifespan. Defective glucose utilization causes numerous diseases ranging from diabetes to an increased tendency to develop tumors. For cells to respond appropriately to changes in energy status or to DNA damage, a close coupling of DNA repair, chromatin remodelling and metabolic pathways is likely to be involved.

Our lab is interested in understanding the influence of chromatin on DNA repair and the relationship between the DNA damage response and the metabolic adaptation of cells. We focus on the study of a group of proteins called SIRTs, the mammalian homologues of the yeast Sir2. Sir2 is a chromatin silencer that functions as an NAD-dependent histone deacetylase to inhibit DNA transcription and recombination. Although we have several collaborations involving the mammalian SIRT1 protein, most of our work has focused on another mammalian Sir2 homologue, SIRT6. We found that SIRT6 binds to chromatin and likely regulates DNA repair functioning as an anchor of chromatin remodeling proteins. In addition, we have shown that SIRT6 regulates metabolic responses in cells and that mice lacking SIRT6 exhibit severe metabolic defects, including hypoglycemia and hypoinsulinemia. SIRT6 appears to modulate glucose flux inside the cells, functioning as a histone H3K9 deacetylase to silence glycolytic genes acting as a coexpressor of Hif1alpha, in this way directing glucose away from glycolysis to other pathways.

Research in the Mostoslavsky laboratory focuses on a family of proteins first discovered in yeast that plays a critical role in many human diseases, including cancer. The yeast protein Sir2 enables yeast cells to survive under conditions of nutrient stress and functions as a modulator of lifespan.

While recent studies indicate that some of the mammalian sirtuin (SIRT) homologues also play a role in stress resistance and metabolic homeostasis, their precise molecular functions remain unclear. Most of our work involves the Sir2 mammalian homolog known as SIRT6. Our research suggests that SIRT6 modulates glucose metabolism and DNA repair and may function as a tumor suppressor gene. Using transgenic mouse models and other experimental systems, we are exploring the role of SIRT6 in tumorigenesis and other disease processes.
reduce intracellular ROS levels. This function appears critical for glucose homeostasis, as SIRT6 deficient animals die early in life from hypoglycemia.Remarkably, our recent studies implicate SIRT6 as a tumor suppressor that regulates cancer metabolism through mechanisms that by-pass known oncogenic pathways. Cancer cells prefer fermentation (i.e., lactate production) to respiration. Despite being described by biochemist and Nobel laureate Otto Warburg decades ago (i.e., the Warburg effect), the molecular mechanisms behind this metabolic switch remain a mystery. We believe SIRT6 may function as a critical modulator of the Warburg effect, providing a long-sought molecular explanation to this phenomenon.

Our current studies are directed at determining how the DNA repair and metabolic functions of SIRT6 may be related to each other. We use a number of experimental systems, including biochemical and biological approaches, as well as genetically engineered mouse models.

Projects:

1. Defining which enzymatic activity is critical for SIRT6 function and determining the proteins targeted by this activity
2. Deciphering how SIRT6 regulates chromatin structure
3. Determining whether SIRT6 plays a direct role in regulating glucose metabolism in specific organs
4. Determining the role of SIRT6 in DNA repair and tumorigenesis using mouse models
5. Elucidating the role of histone modifications and chromatin dynamics in DNA repair

Selected Publications:


