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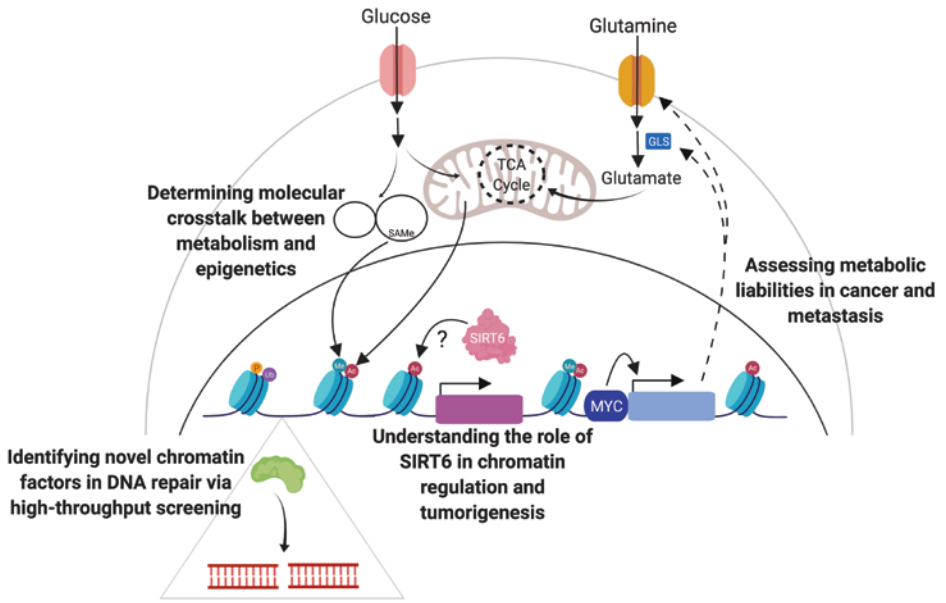
Research in **the Mostoslavsky laboratory** focuses on the crosstalk between chromatin dynamics and cellular metabolism. In particular, we have focused on sirtuins, a family of proteins first discovered in yeast that plays a critical role in many human diseases, including cancer. Most of our previous work involves the Sir2 mammalian homolog known as SIRT6, an enzyme with roles in compacting the DNA scaffolding structure known as chromatin. Our research indicates that SIRT6 modulates glucose metabolism and DNA repair and functions as a strong tumor suppressor gene. Using transgenic mouse models and other experimental systems, we are exploring the role of SIRT6 and metabolism in tumorigenesis and other disease processes, as well as trying to understand the crosstalk between metabolism and epigenetics. Our current projects involve understanding the molecular roles of chromatin in DNA repair, identifying chromatin and metabolic drivers of metastatic disease, and the crosstalk between metabolic pathways and chromatin structure.

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, they need a finely tuned system to modulate chromatin dynamics in order to respond to metabolic cues. Reciprocally, chromatin changes necessary for cellular functions need as well to be coupled to metabolic adaptations.

Our lab is interested in understanding the influence of chromatin on nuclear processes (gene transcription, DNA recombination and DNA repair) and the relationship between chromatin dynamics and the metabolic adaptation of cells. One of our interests is on the study of a group of proteins called SIRTs, the mammalian homologues of the yeast Sir2. In particular, our work has focused on the mammalian Sir2 homologue, SIRT6. In recent years, we have identified SIRT6 as a key modulator of metabolism. Mice lacking SIRT6 exhibit severe metabolic defects, including severe hypoglycemia. SIRT6 functions as a histone H3K9 deacetylase to silence glycolytic genes; in this way directing glucose away from the TCA cycle to reduce intracellular ROS levels. This function appears critical for glucose homeostasis, as SIRT6 deficient animals die early in life from hypoglycemia. Remarkably, SIRT6 acts as a tumor suppressor in multiple cancers, regulating cancer metabolism through mechanisms that bypass 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



Understanding the crosstalk between metabolism and Epigenetics

Image Credit: Lara Roach

(i.e., the Warburg effect), the molecular mechanisms behind this metabolic switch remained a mystery. We found that SIRT6 is a critical epigenetic modulator of the Warburg effect, providing a long-sought molecular explanation to this phenomenon. Importantly, new work from the lab suggests that such metabolic adaptation occurs in a rare population of cells, indicating that tumors exhibit metabolic heterogeneity. We have also uncovered key roles for SIRT6 in DNA repair (anchoring the chromatin remodeler SNF2H to DNA breaks) and early development (acting as a repressor of pluripotent genes), indicating broad biological functions for this chromatin deacetylase. Lastly, we have also identified SIRT6 as a robust tumor suppressor in pancreatic cancer, where it silences the oncofetal protein Lin28b, protecting against aggressive tumor phenotypes. As such, SIRT6 represents an example of a chromatin factor modulated in cancer cells to acquire "epigenetic plasticity".

In recent years, we have broadened our research to explore roles of one carbon metabolism (1C) in chromatin dynamics, exploring novel metabolic liabilities in cancer (uncovering a novel adaptation to bypass glutamine deprivation), new chromatin modulators of DNA repair, where we discovered a new factor that modulates Homologous Recombination, explaining some features of a human syndrome, and the use of screening strategies to identify novel epigenetic/metabolic drivers of metastatic disease. We use a number of experimental systems, including biochemical and biological approaches, as well as genetically engineered mouse models.

Specific projects:

1. Determining the role of SIRT6 in tumorigenesis using mouse models
2. Elucidating the role of histone modifications and chromatin dynamics in DNA repair
3. Determining molecular crosstalk between epigenetics and metabolism
4. Discovering non-genetic (epigenetic and metabolic) drivers of metastases

Selected Publications:

Choi-J, Sebastian C, Ferrer C, Lewis C, Sade-Feldman M, Lasalle T, Gonye A, Lopez BCG, Abdelmoula W, Regan MS, Cetinbas, M, Pascual G, Wojtkiewicz GR, Silveira GG, Boon R, Ross KN, Tirosh I, Saladi SV, Ellisen LW, Sadreyev RI, Benitah SA, Agar NYR, Hacohen N, and **Mostoslavsky R.** A unique subset of glycolytic tumor propagating cells drives squamous cell carcinoma. *Nature Metab.* 2021, 3, 182-195.

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Etchegaray J-P, Zhong L, Li C, Henriques T, Ablondi E, Nakadai T, Van Rechem C, Ferrer, C, Ross KN, Choi J-E, Samarakkody A, Ji F, Chang A, Sadreyev RI, Ramaswamy S, Nechaev S, Whetstine JR, Roeder RG, Adelman K, Goren A, and **Mostoslavsky R**. (2019). The histone deacetylase SIRT6 restrains transcription elongation via promoter-proximal pausing. *Molecular Cell.* 2019 Jul 20. pii: S1097-2765(19)30491-5.

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Toiber D, Erdel F, Bouazoune K, Silberman DM, Zhong L, Mulligan P, Sebastian C, Cosentino C, Martinez-Pastor B, Giacosa S, D'Urso A, Naar AM, Kingston R, Rippe K, and **Mostoslavsky R**. SIRT6 recruits SNF2H to DNA break sites, preventing genomic instability through chromatin remodeling. *Molecular Cell.* 2013 Aug 22;51(4):454-68.

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