Bar-Ilan University
Faculty of Medicine

אוניברסיטת בר-אילן
הפקולטה לרפואה

Faculty Seminar

Targeting NAD metabolism and sirtuins in cancer and metabolic disorders

By

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Abstract

Metabolic disorders, such as obesity and type-2 diabetes afflict increasing numbers of the population and pose a constant health challenge. These conditions are also linked to increased risks of developing cancer, cardiovascular and neurodegenerative disorders, highlighting the critical need for better therapy options. My current research program is focused on determining the potential health benefits of modulating intracellular NAD/nicotinamide levels and Sirt2 activity in metabolic disorders, cancer and aging. Nicotinamide and its metabolite, NAD, have emerged in the past decade as key players in various human diseases, including metabolic disorders, cancer and neurodegeneration. The intracellular NAD/nicotinamide ratio exerts its physiological effects primarily through modulating the activity of NAD-consumer proteins, such as sirtuins and poly(ADP-ribose) polymerases (PARPs), which use NAD as a cofactor in protein deacetylation and poly-ADP ribosylation, respectively. Both activities result in the production of nicotinamide, which acts as a feedback inhibitor to these enzymes. Nicotinamide-metabolizing enzymes, such as nicotinamidase and nicotinamide phosphoribosyl transferase (NAMPT) promote sirtuin and PARP activities by decreasing cellular nicotinamide levels, while increasing NAD synthesis. Sirtuins are evolutionary conserved NAD+-dependent protein deacetylases involved in the regulation of numerous cellular processes, including oxidative-stress and DNAdamage responses, metabolism and aging. Though described initially as class-III histone deacetylases, they have been shown to deacetylate and regulate a large array of proteins involved in stress response and apoptosis, such as p53, NF-κB and FoxO and in metabolism, e.g., PGC-1a, PPAR-γ, GDH, and LXR. Activation and increased expression of certain sirtuins has been shown to extend lifespan and to hold health benefits in various animal models. We demonstrated that overexpression of nicotinamidase in flies extends lifespan in a sirtuindependent manner and our recent results indicate that its expression in mammals increases the activities of sirtuins and PARPs, resulting in increased resistance to various stress insults, including UV and γ-radiation, oxidative stress and DNA-damaging agents. We also reported recently that the cytoplasmic sirtuin, Sirt2, plays a critical role in insulin signaling and demonstrated that its activation sensitizes cells to insulin. This study identified Sirt2 as a target of AMP-activated kinase, the main target of the first-line anti-diabetic drug, metformin, providing a potential link to diabetes treatment. Our initial results also show that Sirt2 attenuates TNF signaling to JNK, which is considered a key effector in initiating insulin resistance in obese and inflammatory stress conditions. We postulate that increasing nicotinamidase and Sirt2 activities could result in significant health benefits in mammals, especially in metabolic disorders and cancer where accumulation of oxidative and inflammatory damage play a central role in disease pathogenesis. We have established recently two unique transgenic mouse models for testing this hypothesis and I will discuss our expectations for the potential health benefits of targeting NAD metabolism and sirtuins in metabolic disorders and cancer.