SIRTUINS, NAD and AGING

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SIR2 and related genes (sirtuins) are NAD-dependent deacetylases that link metabolism, protein acetylation and aging in a variety of species. Sirtuins are also involved in the longevity conferred by dietary or calorie restriction (CR). The mammalian sirtuins SIRT1-7 are involved in changes in stress resistance and metabolism that are triggered by CR, which not only extends life span, but also protects against many diseases of aging, including the major neurodegenerative diseases. In this talk, I will describe how mamamlian SIRT1 impacts tissue maintenance and diseases of aging by deacetyling nuclear transcription factors that govern key physiological pathways. Moreover, I will also describe new data showing the importance of NAD metabolism in aging, and demonstrate that declining NAD during aging may limit health span and life span because it results in sirtuin inactivation. This relies on a new class of mutations in the NAD-binding domain, which may allow Sir2 orthologs to function at sub-optimal NAD levels in cells. Finally, I will also present new data, which demonstrate that SIRT1 in intestinal cells is critical for those cells to respond to dietary signals sent by the niche cells, Paneth cells. This pathway is required for CR mediated responses in the gut, and is mediated by mTOR in Paneth cells (Yilmaz et al., Nature 2012) and SIRT1 in the stem cells.

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