Role of sirtuin proteins in metabolic regulation.

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ABSTRACT

The sirtuins are a highly conserved family of NAD1-dependent enzymes that regulate lifespan in lower organisms. Recently,the mammalian sirtuins have been connected to an ever widening circle of activities that encompass cellular stress resistance, genomic stability, tumorigenesis and energy metabolism. Here we review the recent progress in sirtuin biology, the role these proteins have in various age-related diseases and the tantalizing notion that the activity of this family of enzymes somehow regulates how long we live. Sirtuins in metabolic regulation in mammals include, blood glucose concentration is maintained within a narrow range under a variety of physiological conditions. During starvation, maintenance of serum glucose is achieved in part by implementing a program of hepatic gluconeogenesis. Increasing evidence suggests an important role for sirtuins in this physiological adaptation. The peroxisome proliferator-activated receptor gammacoactivator-1a (PGC-1a) is a known target of SIRT1-dependent deacetylation, and this coactivator also plays a fundamental part in regulating gluconeogenesis and fatty acid oxidation pathways within the liver. The ability of PGC-1a to modulate these latter two pathways appears to require SIRT1. Recently, distinct roles for protein acetylation and SIRT1-dependent deacetylation have been shown to regulate the hepatic response to both short term (,6 h) and long term (.18 h) fasting. In this case, the opposing actions of SIRT1 and the p300/CBP acetyltransferase choreograph hepatic glucose production in the setting of nutrient stress. Finally,the observation that SIRT6-deficient mice demonstrate severe hypoglycaemia suggests a potential role for other sirtuins in glucose production and homeostasis Although the role of sirtuins in regulating metabolism has centred on key metabolic organs, such as liver and pancreas, early studies in human subjects undergoing voluntary caloric restriction suggest that levels of SIRT1 rise in tissues as diverse as skeletal muscle and circulating mononuclear cells. The role of sirtuins in the metabolic adaptation of these cell types is largely unexplored. The intriguing connection between SIRT1 and circadian rhythms provides a glimpse. The observation that SIRT1 can directly deacetylate core components of the circadian clock machinery is particularly fascinating, as the ultimate goal of such rhythms is to coordinate the sleep-wake cycle of an organism with environmental cues, including coordinating and matching intracellular metabolism to external food availability.

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