세미나 초록

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발표 주제	Exploring the molecular mechanisms to connect metabolism, DNA damage response, and Aging
발표 내용	Aging is considered a process of declining organismal function, which results in the collapse of body homeostasis. It increases the susceptibility to age-related diseases, including neurodegenerative diseases and cardiovascular diseases. One of the attractions of studying the mechanism of aging is to make aging slower. One strategy to appeal is calorie restriction, which is thought to regulate life span based on scientific evidence. However, the detailed mechanism is not precise. Calorie restriction activates Sirt1 and induces autophagy. Autophagy is a self-eating system that degrades intracellular compartments in cells. It degrades protein aggregates and damaged organelles as a defense mechanism when cells are stressed, such as through starvation, hypoxia, and DNA damage. We showed that Sirt1, an NAD+-dependent deacetylase interacts with autophagy-related proteins (Atgs) and regulates the acetylation status of several essential Atg proteins such as Atg5,7,8 and 12 in vivo as well as in vitro. In other words, Sirt1 is a positive regulator of autophagy. Sirt1 and autophagy are essential in preventing aging and age-related diseases such as cancer, neurodegenerative diseases, diabetes, and so on. Growing evidence indicates that metabolic signaling pathways are interconnected to DNA damage response (DDR). However, factors that link metabolism to DDR remain incompletely understood. SIRT1, an NAD+-dependent deacetylase that regulates metabolism and aging, has been shown to protect cells from DDR. Here we demonstrate that SIRT1 protects cells from oxidative stress-dependent DDR by binding and deacetylating Checkpoint Kinase 2 (CHK2). We first showed that essential proteins in DDR were hyper-acetylated in Sirt1-deficient cells and that the level of acetylated CHK2 was highly increased among them. We found that Sirt1 formed molecular complexes with BRCA1/BRCA2-associated helicase 1 (BACH1), H2AX, Tumor suppressor p53-binding protein 1 (53BP1), and CHK2, which are key factors of DDR. We then demonstrated that CHK2 was normally inhibited by SIRT1 via deacetylation but dissociated with SIRT1 under oxidative stress conditions. This led to acetylation and activation of CHK2, which increased cell death under oxidative stress conditions. Our data also indicated that SIRT1 deacetylated K235 and K249 residues of CHK2, whose acetylation increased cell death in response to oxidative stress. Thus, SIRT1, a metabolic sensor, protects cells from oxidative stress-dependent DDR by deacetylation of CHK2. Our finding suggests a crucial function of SIRT1 that inhibits CHK2 as a potential therapeutic target for cancer treatment.