

SIRT1: roles in aging and cancer

Eun-Joo Kim¹ & Soo-Jong Um^{2,*}

¹Department of Molecular Biology, Dankook University, Yongin-si, Gyeonggi-do 448-701, Korea, ²Department of Bioscience and Biotechnology/Institute of Bioscience, Sejong University, Seoul 143-747, Korea

Aging and cancer both occur as a result of accumulated cellular damage, and both are related to the regulation of specific genes in the damage response. Recent research has unveiled connections between the mechanisms of aging and cancer, but how to prevent the development of cancer and increase longevity remain unknown. SIRT1 (the mammalian Sir2), which has NAD⁺-dependent class III histone deacetylase activity, may be a key gene linking the modulation of cancer and aging. SIRT1 has broad biological functions in growth regulation, stress response, tumorigenesis, endocrine signaling, and extended lifespan. Here, we focus on the current knowledge regarding the role of SIRT1 in aging and cancer, and discuss the implications of SIRT1 as a therapeutic target for the optimal balance between anti-aging and anti-cancer activities. [BMB reports 2008; 41(11): 751-756]

The mammalian sirtuins

The Sir family of proteins (sirtuins) is a group of nicotinamide (NAD⁺)-dependent deacetylases/ADP-ribosyltransferases initially discovered in yeast that are conserved in diverse organisms including yeast, bacteria, and humans (1, 2). Sir2 regulates longevity in yeast, flies, and worms. In mammals, there are seven homologues of the yeast Sir2 gene (SIRT1-7) that localize to the nucleus, cytoplasm, or mitochondria, and which utilize various substrates and exhibit a broad spectrum of functions (Table 1) (3).

SIRT1, SIRT6, and SIRT7 are functionally distinct nuclear proteins enriched in the nucleoplasm, heterochromatin, and nucleoli (4). SIRT1 is the best-characterized mammalian Sir2 ortholog; this protein is involved in chromatin remodeling that culminates in gene silencing, DNA damage response, and an extended lifespan following calorie restriction (CR) (5-7). Similar to yeast Sir2, human SIRT1 modifies chromatin and silences transcription by heterochromatin formation (8). Mouse SIRT6 exhibits robust ADP-ribosyltransferase activity *in vitro*, but lacks

deacetylase activity (9). In addition, in mouse cells SIRT6 is required for DNA repair in association with base excision repair and maintenance of genomic instability. SIRT6-deficient mice develop a degenerative defect that mimics an aging-like phenotype (10). However, human SIRT6 deacetylates histone H3 lysine 9 (H3K9), which modulates telomeric chromatin (11). SIRT7 is a broadly expressed nucleolar protein that activates RNA polymerase I transcription and prevents apoptosis in response to stress response in the heart (12, 13).

Only SIRT2 is reported as a cytoplasmic protein; there it binds and deacetylates α -tubulin and interacts with HDAC6 (14). SIRT2 also deacetylates histone H4 lysine 16 during mitosis (15). Inhibition of SIRT2 modulates α -synuclein-mediated toxicity in a cellular model of Parkinson's disease (16), whereas overexpression of the protein suppresses adipogenesis in 3T3-L1 cells through the deacetylation of transcription factor FOXO1 (17). The mitochondrial localization of SIRT3, SIRT4, and SIRT5 is especially interesting because mitochondrial dysfunction is associated with both aging and cancer (18). SIRT3 is a mitochondrial deacetylase that regulates energy metabolism (19-22). SIRT4 is an ADP-ribosylase that plays an important role in pancreatic β -cells by inhibiting glutamate dehydrogenase activity (23). To date, the cellular substrate and biological role of SIRT5 remains unknown, although its structure suggests a deacetylase function. Based on these observations, sirtuins may provide beneficial effects in human diseases.

SIRT1 and aging

Sirtuins mediate lifespan regulation by CR in organisms as varied as yeast and mammals (24). CR reduces age-related chronic disorders and extends the lifespan of different organisms. In yeast, Sir2- and NAD⁺-dependent CR-mediated lowering of glucose concentration extends lifespan (25). Sir2p deacetylates histones at the ribosomal DNA (rDNA) locus, thereby increasing rDNA silencing, which is linked to increased lifespan and repressed production of toxic rDNA circles (26). Sir-2.1 extends the lifespan of *Caenorhabditis elegans* by up to 50% and binds to 14-3-3 proteins to activate forkhead transcription factor DAF-16 by down-regulating insulin signaling (27, 28). The activation of the Sir2 ortholog by resveratrol and other sirtuin activators mimics CR and increases the lifespan in *Drosophila melanogaster* (29).

*Corresponding author. Tel: 82-2-3408-3641; Fax: 82-2-3408-4334; E-mail: umsj@sejong.ac.kr

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Table 1. Cellular localization and function of mammalian sirtuins

Sirtuin	Localization	Enzyme activity	Function
SIRT1	Nucleus	NAD-dependent Deacetylase	Metabolism/Aging/Cancer/Neural differentiation/rRNA synthesis
SIRT2	Cytoplasm	NAD-dependent Deacetylase	Cell cycle/Adipogenesis/Neurodegeneration
SIRT3	Mitochondria	NAD-dependent Deacetylase	Mitochondrial deacetylation
SIRT4	Mitochondria	ADP-ribosyltransferase	Mitochondrial deacetylation/Insulin metabolism
SIRT5	Mitochondria	NAD-dependent Deacetylase	Mitochondrial deacetylation
SIRT6	Nucleus	NAD-dependent Deacetylase	Genome instability/Telomeric chromatin
SIRT7	Nucleus	ADP-ribosyltransferase ?	Stress resistance (heart)/RNA pol1 Transcription

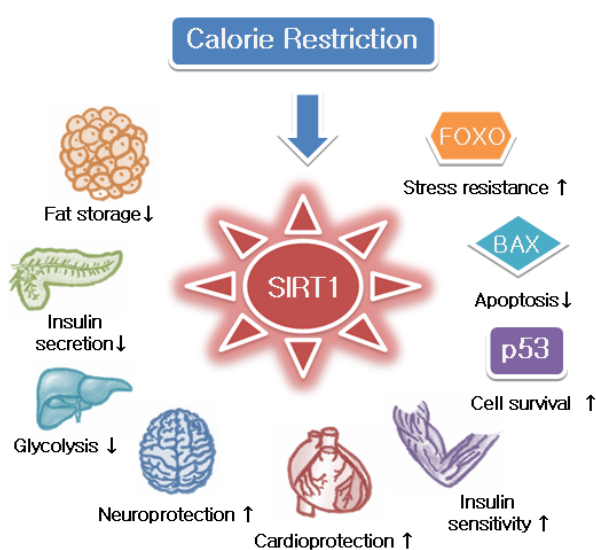


Fig. 1. SIRT1 effects in mammals. CR or cellular stress increases SIRT1 activity. SIRT1 regulation of age-related metabolic changes including fat storage, insulin secretion, glycolysis, neuroprotection, cardioprotection, and cell survival leads to the potentiation of stress resistance and extended longevity.

In mammals, CR effects have more complicated mechanisms because they are associated with various tissues and metabolisms. SIRT1 is connected to important metabolic changes and regulatory proteins in the response to CR (Fig. 1). SIRT1 is induced in CR rats, and treatment of human cells with serum from these animals deacetylates the DNA repair factor Ku70, thereby inhibiting stress-induced apoptosis (30). CR induces endothelial nitric oxide synthase production, and promotes mitochondrial biogenesis and SIRT1 expression in several metabolic tissues including liver, muscle, and brain (31, 32). Moreover, CR leads to decreased insulin production in pancreatic β -cells, reduced fat storage in white adipose tissue, and increased insulin sensitivity in liver and muscles (33). SIRT1 promotes glucose-stimulated insulin secretion by repressing UCP2 in pancreatic β -cells (34, 35) and regulates glucose homeostasis through deacetylation of PGC-1 α in the liver in response to fasting signals (36, 37).

Furthermore, SIRT1 attenuates adipogenesis by repressing peroxisome proliferator-activated receptor alpha and increases fat mobilization in white adipose tissue (38). SIRT1 also has a role in the protection of cardiac myocytes against ischemia-induced apoptosis (39, 40) and links to neuroprotection in axonal degeneration and Alzheimer's disease (41-43). SIRT1 may also influence the redox-dependent fate of neural progenitor cells (44) and regulation of apoptosis and Nanog expression in mouse embryonic stem cells in response to reactive oxygen species (45). These results suggest that SIRT1 may be functionally linked to stem cell aging. Recent findings have directly related SIRT1 function and the physiological effects of CR in mice. Using SIRT1 knockout mice, it was shown that SIRT1 is required for the induction of physical activity by CR; wild-type mice had a 5- to 10-fold increase in physical activity in response to CR, whereas knockout mice did not display any increase in activity (46). In addition, SIRT1 transgenic mice exhibit some phenotypes similar to those of mice on a calorie-restricted diet (47). The above studies support the notion that SIRT1 regulates important physiological processes triggered by CR-induced longevity in mammals.

SIRT1 and cancer

As cancer is an aging-related disease, several investigations have implicated SIRT1 in the epigenetic regulation of gene expression in cancer cells. In many cancers, SIRT1 localizes to the promoters of several aberrantly silenced tumor suppressor genes whose DNA is hypermethylated (48). Furthermore, the inhibition of SIRT1 increases H4-K16 and H3-K9 acetylation at endogenous promoters and suffices to induce gene re-expression in breast and colon cancer cells (49). SIRT1 also regulates heterochromatin formation via deacetylation of histone H1-K26 and promotes the loss of H3K79me2, a marker associated with transcriptionally active chromatin. SIRT1 binds directly to and deacetylates SUV39H1, and contributes to elevated SUV39H1 activity that results in increased levels of H3K9me3 modification (50). These reports have speculated that SIRT1 has a role associated with the epigenetic hallmarks of cancer. In addition to histones, SIRT1 also deacetylates non-histone proteins including various transcription factors involved in growth regulation, stress response, and apoptosis in

the fundamental progression of cancer. SIRT1 negatively regulates p53-dependent apoptosis by deacetylation of p53 in response to cellular damage (51, 52) and localizes to promyelocytic leukemia bodies to inhibit p53-dependent cellular senescence (53). Other substrates of SIRT1 including DNA repair protein Ku70, FOXO family proteins (54, 55), and nuclear factor kappa B (56) are also involved in stress response and apoptosis. Tumor suppressor HIC1 binds directly to the SIRT1 promoter and attenuates its transcription, modulating p53-dependent DNA damage responses (57). The level of SIRT1 is also highly elevated in several cancer cell types. SIRT1 binds to and deacetylates the androgen receptor and represses dihydrotestosterone-induced androgen receptor signaling in human prostate cancer (58), and SIRT1 silencing induces growth arrest and/or apoptosis in human epithelial cancer cells (59). The ectopic induction of SIRT1 in a β -catenin-driven mouse model of colon cancer significantly reduces tumor formation, proliferation, and animal morbidity (60). Whether SIRT1 acts as an oncogene or as a tumor suppressor remains to be determined; nevertheless, these findings provide strong evidence that SIRT1 may be a critical regulator of cancer development (Fig. 2) (61).

Therapeutic potential of SIRT1

SIRT1 has emerged as a drug development target for treating age-dependent diseases. The SIRT1 activator resveratrol mimics the health benefits of CR in lower organisms and in mice fed a high-fat diet (62). A novel small molecule activator of SIRT1 that is 1,000-fold more potent than resveratrol improves

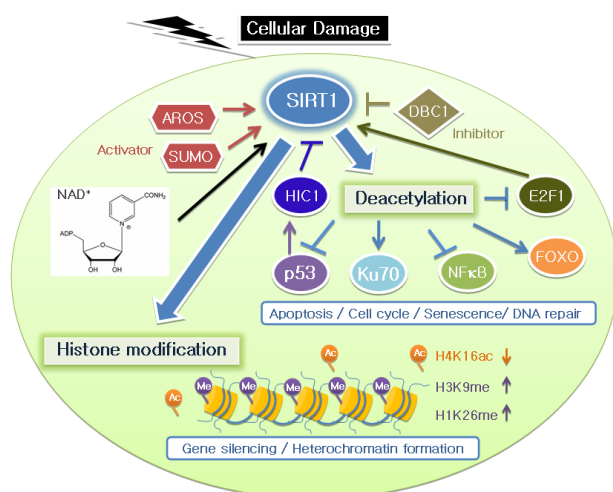


Fig. 2. SIRT1 pathways in cancer. SIRT1 deacetylates various transcription factors involved in senescence, cell cycle progression, and apoptosis that underlie cancer. Sumoylation or the binding of AROS activates SIRT1, and DBC1 represses SIRT1 activity. Epigenetic regulation by SIRT1 promotes gene silencing and heterochromatin formation.

glucose homeostasis and insulin sensitivity in fat, skeletal muscle, and liver (63). This compound is a promising new therapeutic agent for treating type 2 diabetes. Sumoylation of SIRT1 at lysine 734 increases its deacetylase activity and regulates the cellular response to genotoxic stress (64). In addition, a recently identified endogenous activator of SIRT1 designated AROS binds to the N-terminus of SIRT1 and potentiates its deacetylase activity toward p53 in the damage response (65). Inhibitors such as sirtinol, splitomycin, and nicotinamide have been used in the laboratory to probe SIRT1 function (66). Tenovin was discovered as a potent SIRT1 and SIRT2 inhibitor that indirectly activates p53, implicating sirtuins in the development of chemotherapeutic drugs (67, 68). Deleted in breast cancer 1 (DBC1) is a negative regulator of SIRT1 (69, 70) that interacts directly with the deacetylation domain of SIRT1 and inhibits the access of substrates to the catalytic site. These studies suggest that the control of SIRT1 activity either by chemicals or protein regulators is essential for the therapeutic prevention of aging and cancer (Fig. 3).

Conclusion

Over the past decade, SIRT1 has been the most investigated gene involved in diverse cellular functions. The link between SIRT1 and both cancer and aging provide new insight into the therapeutic potential of small molecule activators or specific targets of SIRT1 for the prevention and treatment of cancer and aging. Further investigation into the specific mechanism of SIRT1 is required to realize this potential.

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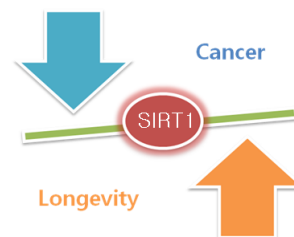


Fig. 3. Optimal balancing of aging and cancer by SIRT1. The control of SIRT1 activity is important for the prevention of aging and cancer. Activators of SIRT1 such as the small chemical activators, AROS, and small ubiquitin-like modifier (SUMO) may provide the basis for the development of anti-aging drugs. SIRT1 inhibitors similar to DBC1 may provide therapeutic agents for the treatment of dysregulated SIRT1 in cancer.

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