Emerging role of sirtuins on tumorigenesis: possible link between aging and cancer

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Aging is the strongest risk factor for cancer development, suggesting that molecular crosstalks between aging and tumorigenesis exist in many cellular pathways. Recently, Sirtuins (Sirt1-7), the mammalian homologues of aging-related sir2α in yeast, have been shown to modulate several major cellular pathways, such as DNA repair, inflammation, metabolism, cell death, and proliferation in response to diverse stresses, and may serve as a possible molecular link between aging and tumorigenesis. In addition, growing evidence suggests that sirtuins are directly implicated in the development of cancer, and they can act as either a tumor suppressor or promoter, depending on the cellular context and tumor types. While the functions of Sirt1 in tumorigenesis have been reported and reviewed in many studies, the connection between sirtuins 2-7 and the development of cancer is less established. Thus, this review will present the recent updates on the emerging roles of Sirt2-7 members in carcinogenesis. [BMB Reports 2013; 46(9): 429-438]

INTRODUCTION

Mounting experimental and clinical results have shown that aging is the single most important risk factor in the development of many diseases, such as cancer, cardiovascular disorders, neurodegenerative diseases, osteoporosis, and metabolic disorders (1, 2). In previous decades, aging research has been extensively focused on understanding the molecular crosstalk between increasing age and the development of diseases. Aging has been observed to have tentative hallmarks such as genomic instability (3, 4), telomere shortening (5), improper epigenetic alterations (6), imbalance of protein homeostasis (7), mitochondrial dysfunctions (8), replicative senescence (9), stem cell exhaustion (10), deregulated inter-cellular and intra-cellular communications (11), and impaired nutrient signaling (12,13). Many of these traits are also observed during carcinogenesis (1-3).

The observation that the frequency of cancer increases with age suggests a mechanical relationship between cancer and aging. Sirtuins, mammalian homologues of Sir2 in yeast that extend lifespan by calorie restriction, include seven members, Sirt1-7. Sirtuins have been studied intensively as potential anti-aging and age-related diseases targets (14-18). In most recent studies, it has been demonstrated that sirtuins have NAD+-dependent histone deacetylase activity (Sirt1, 2, 3, 5, 6, and 7) (17), as well as mono-ADP-Ribosyltransferase (Sirt4 and 6) (17), demalonylase, desuccinylase (Sirt3) (19), and deacetylase (Sirt6) (20) activities. Based on their enzymatic activities, sirtuins have been involved in a variety of cellular pathways such as proliferation, apoptosis, DNA repair, metabolism, and inflammation under basal or stress conditions (17), suggesting that sirtuins can play a pivotal role in cellular homeostasis. Given the fundamental role of sirtuins in age-related homeostasis, mounting evidence over the past decade has shown that sirtuins play an important role in the development of aging-related cancer (21-24) as well. This review will highlight the emerging roles of Sirt2-7 in tumorigenesis.

SIRT2 AND TUMORIGENESIS

Sirt2 and cellular homeostasis

Among the sirtuins present in mammals, Sirt2 is primarily localized in the cytoplasm, but moves to the nucleus in the G2-M phase of the cell cycle (25, 26). One study showed that many vertebrate Sirt2 proteins, including its yeast orthologue Hst2, have putative nuclear export sequences, and can transport from the nucleus to the cytoplasm, although the exact mechanism remains elusive (27). Sirt2 has NAD-dependent histone deacetylase activity, and deacetylates non-histone proteins such as alpha-tubulin (28), Forkhead Box 1 (Foxo1) (29), Forkhead Box 3 (Foxo3) (30), p53 (31), Cadherin 1 (Cdh1) (32), Cell division cycle 20 (Cdc20) (32), and Phosphoenolpyruvate carboxykinase (PEPCK) (33), as well as Histone 3K56 (34) and Histone 4K16 (26), all of which are important for cellular homeostasis. Notably, Sirt2 deacetylates histone proteins to alter the interactions of its substrates with binding partners under a variety of conditions. Sirt2 has been implicated in the
regulation of the mitotic phase of the cell cycle through the deacetylation of Cdh1, Cdc20, or H4K16. The absence of Sirt2 in mouse embryonic fibroblasts demonstrated increased genomic instability, aneuploidy, and mitotic catastrophe (26, 32). In addition, Sirt2 can be phosphorylated by several CDKs during the mitotic phase of the cell cycle (35, 36), which might decrease the activity of Sirt2, leading to increased genomic instability.

In mice, Sirt2 showed increased endogenous expression in brain cells as compared to other tissue types, indicating that Sirt2 may have a developmental function in the brain (37). In fact, Sirt2 has been implicated in physiological brain function and development such as oligodendrocyte differentiation, and neuronal motility, and also appears to promote neurodegeneration, whereas Sirt1 has been shown to be neuroprotective (37). Outeiro et al. showed that Sirt2 inhibitor can rescue the toxicity mediated by alpha-synuclein in Parkinson’s disease (38). Mechanistically, Sirt2 has been known to regulate glucose metabolism by the deacetylation of PEPCK in a cell culture system, but this finding has not yet been validated in a murine model (33). In addition, Sirt2 can regulate adipocyte differentiation by the deacetylation of Foxo1 (29). In response to cellular stress, Sirt2 deacetylates Foxo3a in response to the accumulation of reactive oxygen species and calorie restriction in NIH3T3 cells and white adipocytes or in the kidney in mice, and thus increases the activity of Foxo3a to promote cell death and ultimately decrease the level of reactive oxygen species (30). In the most recent study, Sirt2 was shown to play a pivotal role in programmed necrosis through the deacetylation of Receptor-Interacting Protein 1 (RIP1), and that Sirt2 inhibitor may be useful as a novel therapy in ischemic stroke and myocardial infarction (39).

**Sirt2 in cancer**

During tumorigenesis, Sirt2 functions as both a tumor promoter and suppressor, depending on the cellular context or tumor types. Earlier studies gave insights that Sirt2 might function as a tumor suppressor by maintaining mitotic integrity in a cell culture system (40-43). Consistent with this, it was observed that the expression of Sirt2 was down-regulated in several cancers, such as human gliomas (40, 41), breast cancers (32), head and neck squamous cell carcinoma (HNSCC) (43), and esophageal adenocarcinoma (EAC) (44)., Regions of the Sirt2 gene are also frequently deleted in human gliomas (40).

The overexpression of Sirt2 in human gliomas remarkably increased the cell number of colony formation compared to that of a control vector (41). Sirt2 can block hyperploid cell formation in glioma cells, and thus function as a mitotic checkpoint under mitotic stresses (41). Kim et al. showed that a deficiency of Sirt2 in a murine model caused the development of gender-specific tumorigenesis, with the development of mammary tumors in females, and hepatocellular carcinoma (HCC) in males (32), both of which are aging-related cancers. The loss of Sirt2 increased the levels of mitotic regulators such as the Aurora kinases that drive mitotic catastrophe, which includes centrosome amplification, aneuploidy, and mitotic cell death (32). It was reported that Sirt2 regulates the anaphase-promoting complex (APC/C) activity, which plays a key role in the M to G1 phase transition, through the deacetylation of Cdh1 or Cdc20, and thus maintains genome integrity and suppresses tumorigenesis (32). In addition, the level of Sirt2 was more frequently decreased in human breast tumors and HCC tissues as compared to a wild-type control (32). Serrano et al. also reported that Sirt2 modulates H4K20me1-3 deposits, which are important for cell cycle regulation, through the deacetylation of H4K16Ac, and thus, Sirt2-deficient mice exhibited enhanced genomic instability and were more prone to tumor formation in DMBA/TPA-induced skin tumorigenesis assay, although spontaneous tumors were not observed (26).

Sirt2 functions as a tumor suppressor through the deacetylation of its substrates, such as Foxo1 (29), Foxo3a (30), Cdh1 (32), Cdc20 (32), H3K36 (34), or H4K16 (26), which are all important molecules that maintain cellular homeostasis, ranging from cell cycles, replication, and DNA damage response.

However, there are also some opposing data suggesting that Sirt2 may also have tumor-promoter qualities. The level of Sirt2 expression was increased in certain cancers, including acute myeloid leukemia (45), neuroblastoma cells, or pancreatic cancer cells (46), and the up-regulation of Sirt2 was statistically correlated with advanced tumor stages in HCC (47). In contrast to observations by Kim et al. (32), the knockdown of Sirt2 in HCC cell lines revealed remarkable inhibition of the motility and invasiveness, while the forced expression of Sirt2 enhanced the epithelial-mesenchymal transition (EMT) property (46). Interestingly, Sirt2 inhibited the transcription of developmentally down-regulated protein 4 (NEDD4), an E3 ubiquitin ligase that targets Myc proteins for degradation, through the deacetylation of acetyl histone H4K16 in the promoter region, resulting in the stabilization of N-myc and C-myc proteins, ultimately promoting oncogenic phenotypes in neuroblastoma and pancreatic cancer cells (46). In the most recent study, it was demonstrated that Sirt2, together with HDAC6, can also target K-Ras in many cancers, through the deacetylation of lysine 104 site, and thus dramatically promote the tumorigenesis of cancer cell lines (48).

Like many proteins with vital roles in tumorigenesis, Sirt2 also has been shown to have opposing functions depending on the cellular context during tumorigenesis (26, 32, 47) (Table 1). Future studies are essential for further delineating the mechanisms and functions of Sirt2 in tumorigenesis.

**SIRT3 AND TUMORIGENESIS**

**Function of Sirt3 in mitochondria**

Amongst Sirutins in mammals, Sirt3, Sirt4, and Sirt5 are exclusively localized in the mitochondria. Sirt3 has been shown to have the most active NAD+-dependent histone deacetylase activity among them (49). Mounting data also suggest that
Table 1. In vitro and in vivo experimental evidence demonstrating the roles of sirtuin in cancer

| Tumor suppression | Tumor promotion |
|-------------------|----------------|
| **Sirt2: localized in both cytoplasm and nucleus with activity of deacetylase** | **Sirt2 ↑:** |
| - Gliomas, Breast cancers, HCC, Head and neck squamous cell carcinoma, Esophageal adenocarcinoma | - Acute myeloid leukemia, Neuroblastoma, Pancreatic cancer, HCC. |
| - Phenotypes of Sirt2 KO mice: Liver cancer, Mammary gland tumor | - Phenotypes of Sirt2 KO mice: Liver cancer, Mammary gland tumor |
| - Pathways: Genome stability by modulation of mitotic integrity | - Pathways: Myc signaling |
| - Substrates: Foxo1, Foxo3a, Cdh1, Cdc20, H3K56, H4K16, etc. | - Substrates: H4K16 in promoter of NEDD4, K-Ras |

**Sirt3: localized in mitochondria with activity of deacetylase**

- Breast cancer, HCC, Head and neck squamous cell carcinoma
- Phenotypes of Sirt3 KO mice: Mammary gland tumors
- Pathways: Redox homeostasis, Cell survival
- Substrates: Mr5SOD, Skp2, etc.

**Sirt4: localized in mitochondria with activities of deacetylase and Mono-ADP-Ribosyltransferase**

- Phenotypes of Sirt4 KO mice: Lung cancer
- Pathways: Glutamine metabolism
- Substrate: Glutamine dehydrogenase

**Sirt5: localized in mitochondria with activities of deacetylase, demalonylase, and desuccinylase**

No reported

**Sirt6: localized in nucleus with activities of deacetylase, Mono-ADP-Ribosyltransferase, and deacylase**

- Pancreatic cancer, Colon carcinoma, Liver cancer
- Phenotypes of Sirt6 KO mice: Increased adenoma in Sirt5<sup>−/−</sup>; V-C; APC<sup>min</sup>.
- Pathways: DNA repair, Inflammation, Gene transcription in glycolysis, Myc signaling, ribosomal biogenesis.
- Substrates: H3K9, H3K56
- Binding partners: Hif1α, c-Jun, Myc, Nf-kB

- Sirt6 ↑: Pancreatic cancer cells
- Pathways: Inflammation, Angiogenesis, Resistance against chemotherapeutic agents.
- Substrates: Foxo3a

**Sirt7: localized in nucleolus and nucleus with activity of deacetylase**

No reported

- Sirt7 ↑: Hepatocellular carcinoma (HCC)
- Pathways: Anchorage independent growth, Contact inhibition
- Substrates: H3K18
- Binding partners: Elk4, etc.

many proteins are modified by acetylation in mitochondria, suggesting that the acetylation/deacetylation of proteins is an efficient way to sense physiological signals (50) in mitochondria. Recently, Sirt3 with active deacetylase activity was mainly localized in the mitochondria, whereas Sirt4 and Sirt5 found in mitochondria had much less or no activity as deacetylases (49), suggesting that Sirt3 may be the predominant Sirt-related deacetylase in mitochondria. Sirt3 has been implicated in several metabolism processes, such as ATP homeostasis (51), fatty acid beta oxidation (52), mitochondrial biogenesis (53), and ROS homeostasis (54). For energy homeostasis, Sirt3 targets several components of the Kreb’s cycle and electron transport chain to regulate ATP production, such as NADH Dehydrogenase (Ubiquinone) 1 Alpha Subcomplex, 9 (NDUFA9) (51),
and ATP synthase (55). For ROS homeostasis, Sirt3 regulates the activity of Manganese Superoxide Dismutase (MnSOD) and isocitrate dehydrogenase 2 (IDH2) through deacetylation (54, 56). Sirt3 also deacetylates long-chain acyl CoA dehydrogenase (LCAD) (52), and thus regulates fatty acid β-oxidation. Consistent with these Sirt3 functions, Sirt3-deficient mice were shown to have increased ROS, hepatic steatosis, lower ATP levels, and increased spontaneous tumorigenesis compared to wild-type mice under basal or fasting conditions (51, 52, 54). Furthermore, Sirt3 has been shown to play a prominent role in the beneficial effects of calorie restriction through deacetylating mitochondrial proteins (57).

**Sirt3 and tumorigenesis**

The reprogramming of energy metabolism is one of the hallmarks of cancer, as outlined by Hanahan and Weinberg (2). An increasing amount of evidence has shown that the tumorigenesis is remarkably correlated with abnormal energy metabolism. In many cancer cells, glycolysis is a major source of many biosynthetic intermediates, but several metabolic pathways in mitochondria are also needed to generate anaerobic metabolites. In this regard, Kim et al. showed that mitochondrial-derived Sirt3 knock-out mice have increased spontaneous tumorigenesis in mammary glands, indicating that Sirt3 can function as a tumor suppressor (54). Furthermore, while the knock-down of Sirt3 in cancer cells led to increased tumor size, the overexpression of Sirt3 inhibited cell proliferation and tumor xenografts (54). Several group studies have demonstrated that under stress conditions, Sirt3 regulates ROS homeostasis through deacetylating and activating superoxide dismutase (SOD2), which is a key antioxidant enzyme in mitochondria (58, 59). The reduction of Sirt3 expression led to enhanced production of ROS through diminished activity of SOD2 or increased leakage of electrons in the electron transport chain (ETC), which promoted genomic and mitochondrial DNA instability that initiates or develops tumorigenesis (54). An imbalance of ROS production can promote tumorigenesis through many cellular signaling pathways, and is a common property of many cancers. Another group demonstrated that Sirt3-deficient cells have increased glycolytic metabolism driven by enhanced Hif1α protein stability by an increased endogenous ROS level, and thus, were prone to developing oncogenic phenotypes (60). Sirt3 also can inhibit tumorigenesis by deacetylating and inactivating S-phase kinase-associated protein 2 (Skp2), a subunit of E3 ubiquitin kinase important as an S phase cell cycle checkpoint, and has been shown to be a tumor promoter (61). Consistent with the function of Sirt3 as a tumor suppressor, several human cancers were shown to have reduced expression of Sirt3 compared to wild-type counterparts in human breast cancers, hepatocellular carcinoma, and head and neck squamous cell carcinoma (62). In addition, some human cancer samples were showed the deletion of the Sirt3 gene in the genome (62). Interestingly, unlike Sirt1 and Sirt2, no studies have directly shown that Sirt3 can act as a tumor promoter. Overall, Sirt3 has been shown to act as a tumor suppressor in a variety of cancer cell lines, a knockout murine model, and human cancer samples (Table 1). Future studies are needed to elucidate whether Sirt3 itself or each of the Sirt3 substrates could be novel therapeutic targets for cancer.

**SIRT4 AND TUMORIGENESIS**

An earlier study showed that Sirt4 is the only member of the sirtuin family with no detectable deacetylase activity, but has NAD+-dependent mono-ADP ribosyltransferase activity localized in mitochondria (63). However, a recent study demonstrated that Sirt4 can deacetylate malonyl CoA decarboxylase (MCAD) in skeletal muscle and white adipose tissue (64). Consequently, Sirt4-deficient mice were shown to have increased tolerance of exercise and diet-induced obesity (64). It has been known that Sirt4 regulates the activity of glutamate dehydrogenase (GDH), which promotes the metabolism of glutamate and glutamine to generate ATP, via ADP-ribosylation (63). In fact, Sirt4-deficient mice were shown to have enhanced insulin secretion induced by stimulation with amino acid, suggesting that Sirt4 counteracts the beneficial effects of calorie restriction in the pancreas (63). In addition, Sirt4 can also modulate fatty acid oxidation and mitochondrial gene expression in liver and muscle cells, although the mechanism remains elusive, and in vivo data are absent (65). Sirt4 can protect against cell death under genotoxic stresses together with the mitochondrial NAD salvage pathway and Sirt3 (66), indicating that Sirt4 might be involved in cancer under certain conditions. Recently, direct evidence has implicated Sirt4 in tumorigenesis through the regulation of energy metabolism. Jeong et al. showed that Sirt4 is an essential factor to inhibit mitochondrial glutamine metabolism under genotoxic stresses (67). The loss of Sirt4 enhanced glutamine metabolism under genotoxic stress, and led to genomic instability and oncogenic phenotypes (67). Furthermore, Sirt4-deficient mice were shown to have increased spontaneous lung tumors compared to wild-type mice (67). Future studies should analyze the expression or activity of Sirt4 in a variety of human cancer samples, as well as target glutamine metabolism as a potential anti-cancer strategy (Table 1).

**SIRT5 AND LACK OF TUMORIGENESIS**

Unlike other members of the sirtuin family, Sirt5 has NAD+-dependent deacetylase, deacylase, demalonylase, and desuccinylase activities in mitochondria (68). Nakagawa et al. first reported the role of Sirt5 in regulating the urea cycle through the deacetylation of carbamoyl phosphate synthetase 1 (CPS1), which plays a critical role in the initial order of the urea cycle for ammonia detoxification (69). Loss of Sirt5 in mice causes enhanced ammonia levels in blood under fasting, calorie restriction, or high protein diet compared to that in the wild type (69). Recently, Du et al. also showed a striking result that Sirt5 also possesses the activities of NAD+-dependent de-
Sirt6 in cancer

Given the biological roles of Sirt6 in metabolism, DNA repair, and inflammation, it has been speculated that Sirt6 may be involved in tumorigenesis. In regard to metabolism, Zhong et al. demonstrated that Sirt6 binds Hif1α to localize to the promoter of Hif1α target genes, and regulates multiple glycolytic genes via the deacetylation of H3K9, suggesting that Sirt6 may be involved in tumorigenesis through cancer cell metabolism modulated by Hif1α activity (78). The same group revealed that Sirt6 functions as a tumor suppressor through the repression of Myc and Hif1α transcriptional activity (79). Sirt6-deficient mice or cells were shown to have increased incidence and aggressiveness of cancer (79). Moreover, the expression of Sirt6 was down-regulated in human pancreatic cancer and colon carcinoma compared to normal counterparts (79), indicating that Sirt6 can function as a potential tumor suppressor in mice and humans.

In recent reports by several groups, the biological effects of Sirt6 on the development of liver tumor have been noteworthy. Min et al. reported that Sirt6 can suppress the initiation of liver cancer through repression of survivin via the deacetylation of H3K9 and by reducing NF-kB activity (80). Its expression was also attenuated in human dysplastic liver nodules (80). Consistently, Sirt6-deficient mice showed a severe inflammation phenotype in liver starting at a young age, and developed premature fibrosis. The selective loss of Sirt6 in T cells or myeloid-derived cells can also cause a severe inflammation phenotype, suggesting that chronic inflammation results from Sirt6-deficient immune cells (81). The investigation of SIRT6 expression in normal, cirrhotic livers, and liver cancers via microarray with human liver specimens showed that SIRT6 was remarkably attenuated in cirrhotic livers and cancers compared to that of normal liver, indicating that the down-regulation of SIRT6 is relevant to the development of liver cancer in humans as well (82). In addition, some established HCC biomarkers such as alpha-fetoprotein (AFP), insulin-like growth factor 2 (IGF2), H19, and Glypican-3 were enhanced in Sirt6-deficient hepatocytes, providing persuasive evidence that Sirt6 is a major initiator of liver tumorigenesis (82). Taken all together, Sirt6 functions as a tumor suppressor in mice and humans through the regulation of metabolism, DNA repair, and inflammation (Table 1).

It has been well documented that many proteins with tumor suppressive capacity can also function as a tumor promoter depending on the cellular context or tumor types. One study showed that Sirt6 can enhance cytokine secretion by cancer cells, which results in cancer symptoms and increased angiogenesis, through the regulation of Ca2+ responses or the deacetylation of TNFα in pancreatic cancer cells (83). The overexpression of Sirt6 in breast cancer cell lines also led to enhanced resistance in response to chemotherapeutic agents such as paclitaxel and epirubicin, through the inhibition of Foxo3a activity (84), suggesting that Sirt6 can positively contribute to cancer survival (Table 1). Therefore, in order to use Sirt6 as a target of anti-tumor therapy, future studies should investigate the biological effects and molecular mechanism of Sirt6 in tumorigenesis in the context of individual tumors.

SIRT7 AND TUMORIGENESIS

Compared to other members of the sirtuin family, the bio-
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logical roles of Sirt7 are only beginning to be elucidated. It was first reported that Sirt7, which is localized primarily in the nucleolus and nucleus, has NAD+-dependent histone deacetylase activity and can function as an activator of rDNA transcription. The loss of Sirt7 resulted in the inhibition of cell proliferation and the induction of apoptosis, although targets of Sirt7 remain unknown (85). The deletion of Sirt7 in mice led to a reduction of life span by the development of heart hypertrophy and inflammatory cardiomyopathy (86). Sirt7 deacetylated and hyperactivated p53, leading to increased apoptosis in the myocardium (86). According to previous results, it has been postulated that Sirt7 can function as an oncogene. Barber et al. showed that while the gain of function of Sirt7 triggers the oncogenic capacity of cancer cells such as anchorage-independent growth and the loss of contact inhibition, the loss of Sirt7 function significantly reduced the tumorigenic potential of cancer cells, suggesting Sirt7 has a tumor-promotive function (87). It was demonstrated that Sirt7 can be recruited to promoters of a specific set of genes in part through interaction with the ETS domain containing protein (Elk4), which function as a transcription repressor of several ribosomal protein genes, and represses the transcription of tentative tumor suppressive genes via the deacetylation of H3K18 with specificity (87). Among the target genes of Sirt7, mutations or the inactivation of several ribosomal protein genes have been relevant to cancer progression, whereas molecular mechanisms underlying the links between tumorigenesis and ribosomal proteins remain unclear (87, 88). According to a recent report, the expression of Sirt7 was markedly enhanced in human hepatocellular carcinoma (HCC) compared to normal counterparts, and Sirt7 deletion led to the suppression of cell growth (89), suggesting that Sirt7 can be a potential target in cancer therapy. Taken together, the biological functions of Sirt7 that regulate tumorigenesis are emerging (Table 1), and future studies are needed to uncover the molecular mechanisms of Sirt7 in tumorigenesis.

CONCLUDING REMARKS

The sirtuin family has received significant attention in cancer biology due to its diverse functions in regulating genomic stability, inflammation, metabolism, cell death, and cellular proliferation, which are all hallmarks in tumorigenesis and aging. So far, studies have shown that sirtuin family members have complicated and diverse functions in cancers. Based on its emerging biological and pathological functions, it is increasingly clear that sirtuins may help answer questions regarding the molecular link between aging and the development of cancer. Future work will undoubtedly involve pinpointing the exact molecular mechanism that each sirtuin member plays depending on the tumor context. As the mechanism of sirtuin function is further explored, the question of how aging leads to carcinogenesis will undoubtedly be answered, and possible chemopreventive agents against age-related cancers will be provided.

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