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Review Article

ROLE OF SIRT1 IN CANCER: A REVIEW

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ABSTRACT

The sirtuin family has emerged as important regulators of diverse physiological and pathological events, including life-span extension, neurodegeneration, age-related disorders, obesity, heart disease, inflammation, and cancer. SIRT1 can deacetylate histones and a number of nonhistone substrates, which are involved in multiple signaling pathways. Numerous studies have suggested that SIRT1 could act as either a tumor suppressor or tumor promoter depending on its targets in specific signaling pathways or in specific cancers. SIRT1 has been considered as a tumor promoter because of its increased expression in some types of cancers and its role in inactivating proteins that are involved in tumor suppression and DNA damage repair. However, recent studies demonstrated that SIRT1 levels are reduced in some other types of cancers, and that SIRT1 deficiency results in genetic instability and tumorigenesis, while overexpression of SIRT1 attenuates cancer formation in mice heterozygous for tumor suppressor p53 or APC. Here, I review these recent findings and discuss the possibility that activation of SIRT1 both extends lifespan and inhibits cancer formation.

Key words: SIRT1, Tumor Suppressor, Tumor promoter, DNA damage repair

INTRODUCTION

Epigenetic modifications of protein, histone, and chromatin play an important role in regulating gene expression, cancer formation, and lifespan. In budding yeast, Sir2 is a NAD+-dependent histone deacetylase that plays a role in chromatin silencing, longevity and genomic stability**.** Sirtuin are proteins that possess either mono-ADP-ribosyltransferase, or deacylase activity, including deacetylase, desuccinylase, demalonylase, demyristoylase and depalmitoylase activity[1]. They have drawn emerging attention due to their diverse roles in various physiological and pathological events, including life-span extension, neurodegeneration, age-related disorders, obesity, heart disease, inflammation, and cancer[2, 3]. In mammals, there are 7 members of sirtuin from SIRT1-SIRT7 in the sirtuin family, which belong to class III histone deacetylases (HDACs) and show different functions, structure, and localization[4]. SIRT1, a member of the NADþ-dependent [5]class III histone deacetylases known as the Sirtuins, has been shown to play a role in not only cancer, but also a number of other physiological processes and health conditions, including metabolic disease, inflammation, neurodegeneration, and cardiovascular disease[6].And it is the most extensively studied sirtuin member[7].Sirt1can deacetylate histones and a number of non-histone substrates that contribute to cellular regulation (reaction to stressors, longevity)[8].

Role of SIRT1 in Cancer:

The role of SIRT1 in cancers has been extensively studied in the past decade. However, controversy regarding cancer and sirtuins exists and is still under debate since it could act as either a tumor suppressor or tumor promoter depending on the cellular context or its targets in specific signaling pathways or specific cancers.SIRT1-mediated deacetylation suppresses the functions of several tumor suppressors including p53, p73, and HIC1, it has been suggested that SIRT1 has a promoting function in tumor development and progression[9-12]. In contrast, SIRT1 may have a suppressive activity in tumor cell growth by suppressing NF-κB[13, 14], transcription factor playing a central role in the regulation of the innate and adaptive immune responses and carcinogenesis, the dysregulation of which leads to the onset of tumorigenesis and tumor malignancy[15]. In addition to the above 2 pathways, this SIRT1 substrates also involved in energy homeostasis[16], hypoxia response[17],the PI3K/AKT pathway[18] the transforming growth factor-β (TGF-β) signaling pathway[19], the Wnt signaling pathway[20], and the DNA damage repair pathway[21] in cancer cells.

SIRT1 as Tumor Suppressor:

p53 is one of the most important the tumor suppressor gene during the cell cycle and is regarded as the guardian of the genome[22] . p53 is a well-known substrate of SIRT1 as well as other substrates with diverse functions involved in multiple signaling pathways[9, 10, 23].Furthermore, SIRT1 was shown to deacetylate and affect the activity of both members of the PGC1-alpha/ERR-alpha complex, which are essential metabolic regulatory transcription factors[24, 25]. SIRT1 is found to target p53 for deacetylation and to

attenuate p53-mediated transcriptional activity[9, 10]. Overexpression of wild-type SIRT1 remove p53 acetylation, but overexpression of catalytically inactive SIRT1 failed to do so, suggesting that SIRT1 regulation of p53 transcriptional activity depends on its deacetylase activity[9]. SIRT1 deacetylase activity is according to NAD dependent it inhibits the SIRT1 by NAM (nicotinamide) which then enhance the p53 acetylation[10]. Moreover, SIRT1 can exert a second layer of regulation on p53 activity by deacetylating p300, which is a histone acetyltransferase of p53[26]. Since the acetylation of p300 promotes its binding to p53 and inhibition of SIRT1 would lead to the elevation of p300-mediated p53 activation and its target on gene transcription[27]. Then this Activated p53 function on the cell cycle arrest, apoptosis, and DNA repair. The SIRT1 has been found to reduce p53-mediated apoptosis[10] and negatively regulate p53-induced cellular senescence[28]as well.

The nonspecific and specific inhibitors of SIRT1 are the nicotinamide inhibitor, the 2-hydroxynaphthaldehyde derivative sirtinol, the coumarin derivative splitomicin, the splitomicin derivative HR73 and cambinol, the tenovins , and the indole derivative EX527[29]. The inhibition of SIRT1 activity leads elevated p53 acetylation and transactivation which results in enhanced apoptosis and cytostasis. And activation of p53 has dual functions. On one hand, activated p53 contributes to tumor cell death whereas on the other hand, it induces cancer cell cycle arrest, and this could accumulate further mutations and compromise the killing effect of the therapy[30],.

Several studies have provided convincing evidence that SIRT1 serves as a tumor suppressor. Firestein*et al* demonstrated that overexpression of SIRT1 in study on mice decrease the colon cancer formation instead of increase[31]. They demonstrated that reduction in tumor development is caused by the ability of SIRT1 to deacetylatecatenin and promote cytoplasmic localization of the nuclear-localized oncogenic form of catenin.Their further analysis also showed that the over-expression of SIRT1 also greatly reduces cellproliferation in a human colon cancer cell line whosegrowth is driven by active catenin[31].

In the similar way Wang *et al.[32]*found that SIRT1 expression is muchlower in the BRCA1-associated breast cancer thanBRCA1-wildtype breast cancer in human . The BRCA1 binds to the *SIRT1* promoterand positively regulates *SIRT1* gene expressionat both the mRNA and protein level, and that BRCA1deficiency causes reduced SIRT1 levels, which may beresponsible for the malignant transformation ofBRCA1 mutant cells. Consistently, restoration ofSIRT1 levels in BRCA1 mutant cancer cells inhibitedproliferation of these cells in vitro and tumor formationin vivo when the cells were implanted into nudemice. In addition, resveratrol, which activates SIRT1deacetylase activity, induced apoptosis in thesecells and inhibited tumor formation[32, 33]. These datasuggest that SIRT1 not only acts as a tumor suppressorin the context of BRCA1 deficiency, but also that aSIRT1 activator, such as resveratrol. So, it could serve as anexcellent strategy for targeted therapy forBRCA1-associated breast cancer in future study.

Interestingly, SIRT1 interacts with hypermethylated in cancer 1 (HIC1), a tumor suppressor and transcriptional repressor that is epigenetically inactivated but not mutated in human cancers47 to form a transcriptional repression complex, which directly binds the SIRT1 promoter and represses SIRT1's tran-

scription. Depletion of HIC1 expression results in an upregulated SIRT1 level, which deacetylates p53 and attenuates p53 function, thus allowing cells to bypass apoptosis, survive DNA damage, and promote tumorigenesis. Inhibition of SIRT1 expression in HIC1 cells abolishes the resistance to apoptosis. Since the HIC1 promoter is hypermethylated and epigenetically silenced by age, the resultant upregulation of SIRT1 may promote the survival of aging cells and increase cancer risk in mammals[11].

FOXO proteins are phylogenetically conserved and regulate key physiological functions, including cell proliferation, cell differentiation, and survival, and their dysregulation is associated with tumorigenesis. While the molecular mechanisms for such an effect remain to be studied, SIRT1-mediated deacetylation of FOXO proteins can either activate or inhibit their transcriptional activity. For example, SIRT1-mediated activation of FOXO3a induces cell cycle arrest and oxidative stress resistance but inhibits FOXO3a-induced cell death[16].

Subsequent studies indicate that SIRT1 regulates a variety of cellular processes through deacetylating FOXO family transcription factors including FOXO3a, FOXO1, and FOXO4[34, 35].. Recently, Wang *et al*.[36] reported that deacetylation of FOXO3 by SIRT1 leads to Skp2-mediated FOXO3 ubiquitination and degradation, implying that SIRT1 regulates the transcriptional activities of FOXO family proteins through multiple mechanisms. During the acute nutrient withdrawal , both SIRT1 and FOXO3a will be expressed,52 but knockdown of FOXO3a inhibits the starvation-induced SIRT1 expression[37]. Which is repressed by p53.52 In contrast, p53 interacts with FOXO3a under starvation conditions and stimulates SIRT1 transcription through two p53 binding sites in the SIRT1 promoter. p53 is required for starvation-induced FOXO3a to stimulate SIRT1 expression since SIRT1 expression was not induced in starved p53-deficient mice. Thus, SIRT1, p53, and FOXO3a, these three proteins implicated in aging, constitute a nutrient-sensing pathway in mammalian cells[37]. Since cancer is an age-related disease, these studies may provide a clue to understand the complex role of SIRT1 in certain kinds of tumors.

Oberoerffer et al.[38] had also perform the study to investigate the role of SIRT1 in tumorigenesis, they crossed the transgenic strain carryingoverexpression of SIRT1 with *p53+/-* mice and found that SIRT1 overexpression in *p53+/-* mice led to a decreasedincidence of thymic lymphoma and increasedsurvival following exposure to □-irradiation. A similareffect was also observed in *p53+/-* mice that weretreated with resveratrol, which activates SIRT1.These data provide strong evidence that SIRT1 servesas a tumor suppressor through its role in Damaged DNA Response(DDR) and DNA-double strand breaks(DSB) repair that are essential for maintaining genomeintegrity. Because SIRT1 overexpression also suppressesthe age-related transcriptional changes, itsuggests that activation of SIRT1 might both extendlifespan and reduce cancer risk

SIRT1 and its role in DNA Repair:

SIRT1 also functions as the repair of DNA during the cell growth cycle that are being damage due to

different environments and processes. The recent investigations reported that SIRT1 plays an important role in DNA damage repair and in maintaining genome integrity. In study of mice, Wang *et al*. found that *Sirt1* embryos die at middle gestation stages, displaying increased acetylation of H3K9 and H4K16, reduced chromosome condensation, impaired heterochromatin formation, and abnormal mitosis[39]. SIRT1 cells displayed chromosome aneuploidy and structural aberrations, conceivably originated from the continuous division of abnormal mitosis. SIRT1 deficiency also causes reduced ability to repair DNA-double strand breaks (DSBs), radiation sensitivity, and impaired DDRs characterized by diminished γH2AX, BRCA1, RAD51 and NBS1 foci formation upon γ-irradiation. Thus, SIRT1 may play a role in recruiting these proteins to DNA damage sites. Western blot analysis detected reduced level ofγH2AX, but not that of BRCA1, RAD51 and NBS1 upon DNA damage in SIRT1 mutant cells comparedwith wild type cells. To assess whether the reduced γH2AX levels/foci formation is a direct consequenceof SIRT1 loss, the researchers transfected SIRT1-deficient cells with a SIRT1 expression vector, and the data indicated that the SIRT1-reconstituted *Sirt1* cells contained relatively equal numbers of γH2AX foci compared with wild type controls upon γ-irradiation[39]. . Using mouse embryonic stem cells, Oberdoerffer*et al[38] also* demonstrated that SIRT1 binds to highly repetitive DNA and contributes to the silencing of major satellite repeats [42]. In response to oxidative DNA damage, SIRT1 dissociates from its original loci and relocalizes to DSBs to promote repair and maintain genome integrity. Their data indicated that the efficient recruitment of SIRT1 to DSBs requires DNA damage signaling through ATM and H2AX. Without SIRT1, recruitment of RAD51 and NBS1 to DSBs was delayed and strongly reduced, thus highlighting a key role of SIRT1 in the DNA damage repair process. These observations suggest that γH2AX plays an important role in mediating functions of SIRT1 in DNA damage foci formation and DNA damage repair.

SIRT1 as Cancer Promoter:

The role of SIRT1 in cancer still remains controversial regarding it is only the cancer suppressor or itself promote the cancer as tumorogenesis. Many studies have suggested SIRT1 as tumor suppressor as well as promoter function[40].

Di Sante[41] et al. presented this controversy that the role of SIRT1 as tumor suppressor in prostate cancer. They used a Sirt1 mouse model and fibroblasts to demonstrate a protective role of SIRT1 against the induction of prostate intraepithelial neoplasia, increased cellular proliferation, and accompanied mitophagy but it was found that they inhibit reactive oxygen species production and induces superoxide dismutase 2 activity, and the expression of the tumor suppressor TP63 increases with the loss of SIRT1. More recently, it was shown that inhibition of SIRT1 by a specific inhibitor causes p53 hyperacetylation and increases p53-dependent transcriptional activity[42]. In addition, overexpression of SIRT1 epigenetically represses expression and/or activity of many tumor suppressor genes, and proteins withDNA damage repair functions. This includes forkhead class O transcription factor (FOXO) family members (FOXO1, FOXO3a and FOXO4)[34], p73[12], RB[43], SFRP1, SFRP2, GATA4, GATA5, CDH1, MLH1[44], Ku70 [45] and others.

Consistent with these data, a number of studies showed that depletion of SIRT1 by siRNA reduces drug resistance and/or induces growth arrest of cancer cells in vitro. In the same way expression SIRT1 are also subjected to regulation by several tumor suppressors. Hypermethylated in cancer-1 (HIC1) encodes a transcriptional repressor with zinc finger motifs and a N-terminal BTB/POZ domain that cooperates with p53 to suppress age-dependent development of cancer in mice[46]. HIC1 and SIRT1 form a transcriptional repression complex, which directly binds to *SIRT1* promoter and represses *SIRT1* transcription. In both normal and cancer cells, inactivation of HIC1 results in upregulated SIRT1 expression, which deacetylates and inactivates p53, allowing cells to bypass apoptosis and survive DNA damage[11].

During the repair of DNA damage is accomplished, subsequent decreased p53 can lead to decreased HIC1 and increased SIRT1 expression for keeping p53 in an inactive state. However, during the course of aging, the *HIC1* promoter undergoes hypermethylationprocess. There will be upregulation of SIRT1 in aging cells due to epigenetic silencing of*HIC1* might be like a double-edged sword that both promotessurvival of aging cells as well as increases in risk of promotion of cancer in mammals[11] . The study by Zhao et al.[47] suggested that that DBC1 (deleted in breast cancer-1), which wasinitially cloned from a region (8p21) homozygouslydeleted in breast cancer, forms a stable complex withSIRT1 and inhibits SIRT1 activity, leading to increasedlevels of p53 acetylation and upregulation ofp53-mediated function. Consistently, knockdown ofDBC1 by RNA interference (RNAi) promotedSIRT1-mediated deacetylation of p53 and inhibitedp53-mediated apoptosis induced by genotoxic stress.These effects were reversed in cells by concomitantRNAi-mediated knockdown of endogenous SIRT1, So, thissuggest that increased in SIRT1 expression and its activity may increase the risk of cancer in mammals by inhibiting p53 and potentiallyother tumor suppressor genes.

CONCLUSION

The controversy over whether SIRT1 serves as a tumor promoter or a tumor suppressor has not been completely solved and the discussion will likely continue. One of the major concerns that SIRT1 activation may increase cancer risk comes from the observation that SIRT1 deacetylates and inactivates p53, and other tumor suppressors. However, it is also known that p53 positively regulates SIRT1 transcription and loss of p53 impairs SIRT1 induction. Thus, through a negative feedback loop, p53 inactivation can, in theory, reduce expression level of SIRT1, thereby increasing p53 activity. Similar negative feedback loops are also found in FOXO3a , FOXL2 and E2F1, which act as tumor suppressors under certain circumstances. Thus, like p53, the activities of these proteins are not easily inactivated by SIRT1 due to this negative feedback mechanism. Despite the lack of in vivo evidence that activation of SIRT1 may increase cancer risk, however, it remains possible that SIRT1 plays dual functions in different tissue contexts depending on the spatial and temporal distribution and abundance of different SIRT1 downstream targets and factors that regulate SIRT1. Further studies are needed to provide a conclusive answer.

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