SIRT1 and tumor resistance

Yuewen Qi

Department of Pathogenic biology, Qingdao University Medical College, Qingdao, Shandong Province, 266071, China

qiyuewen316@163.com

Abstract

SIRT1 is a NAD+ (nicotinamide adenine dinucleotide) dependent histone deacetylase. Growing evidences suggestes that SIRT1 plays the part of metabolic sensor in regulating the level of acetylation in cell proliferation and other aspects of tumor development. The expression of SIRT1 is related to multiple pathways of resistance. In this review, we have summarizes the recent progress of SIRT1, and provides the overview of the correlation with cancer drug resistance by targeting SIRT1.

Keywords

SIRT1, Drug resistance.

1. Introduction

SIRT1 is a member of the sirtuin family that belongs to class III histone deacetylase, which is highly homology with Sir2(silencing information regulator 2) [1, 2]. In normal cells, sirt1 is associated with the aging process of human cells. Recent studies have showed that SIRT1 participate in regulating the tumor pathway through its modification of substrate deacylation [3]. SIRT1 also plays an important role in cell cycle control, gene stability, mitochondrial function protection, inflammatory response, and resistance to oxidative stress [4]. In drug resistance, SIRT1 can also regulate the inhibitory pathway of tumor , such as p53, E2F1 and FOXO.

2. Structure and biological function of SIRT1

SIRT1 is located in the nucleus and regulated by a special end area of C. The SIRT1 coding gene with a length of 33000bp is located at chromosome 10q22.1, and the encoded protein is 120000. The catalytic core is composed of 277 amino acid residues, which contains two subdomains, a larger Rossmann fold NAD binding domain and a area that is structure of the NAD+ module and the Zn2+ module generates [5].

SIRT1 is known as the "longevity gene". It is a metabolic sensor that modify the aging process by deacetylation to histone and partly non-histone in normal cells. Studies have shown that SIRT1 regulates the expression of genes involved in skeletal muscle energy metabolism by acting on AMPK [6]. SIRT1 regulates the energy metabolism through liver, pancreas and other organs. And promoting the formation of glucose to stimulates the secretion of insulin, then regulates the liver gluconeogenesis [7, 8]. In the promotion of apoptosis, SIRT1 regulates cell apoptosis with different mechanisms. A wealth of data has shown that SIRT1 reduces apoptosis through mediated by FOXO family members [9, 10].

3. Effects of SIRT1 in tumors

3.1 Promotion factor

SIRT1 is heterogeneous and participates in the formation and development of tumors. Accumulating evidence indicates that SIRT1 is highly expressed in some tumor cells, such as breast cancer, ovarian cancer, prostate cancer and acute myeloid leukemia [11]. Previously, a induced SIRT1 level has been shown to related to clinicopathological features of cancer in Gastric and colorectal cancer [12]. These results reveal SIRT1 is a promoting factor.

3.2 Inhibitory factor

At this point, SIRT1 might have tumor suppressor functions, the inhibition appears to be a good approach to overcome cancer. In colon cancer, Endogenous SIRT1 limits cell proliferation and inhibits tumor formation. Similarly, SIRT1 inhibits the transcription of RelA/ P65 protein, thereby deacetylating the RelA/ P65 subunit of NF- Kβ and promoting TNF-α induced sensitive cell apoptosis. Mice studies support that Knockdown of SIRT1 increased the rate of tumor growth, whereas overexpression of SIRT1 reduced the formation of transplanted tumors. In addition, SIRT1 can also induce apoptosis of breast cancer by reducing the expression of survivin [13]. Together, SIRT1 acts as a tumor suppressor in these tissues [14].

4. Relation of SIRT1 with drug resistance

Recent years, more and more evidence have demonstrated that SIRT1 plays a key role in cancer resistance. The mechanisms of drug resistance by SIRT1 ,include 1) SIRT1 changes the permeability of tumor cells to drugs. Drug penetration is the key to cancer treatment, SIRT1 can reduce the intake of intracellular drugs, increase the efflux and activation of cell detoxification system and so on. The literature reports that SIRT1 positively regulates the expression of the nuclear receptor Liver X (LXR), thereby increasing the expression of target ABCA1 gene. Activation of SIRT1 deacetylation of FOXO1, increasing the expression of ABC transporters, P-glycoproteins and MDR1. Thus, SIRT1 increase the drug efflux and reduce the intracellular drug intake, leading to drug resistance [15, 16]. 2) SIRT1 promotes tumor cell proliferation and resistance to apoptosis. Deacetylation of SIRT1 reduces apoptosis, thereby increasing tolerance and reducing sensitivity to DNA damage by inhibiting E2F1 activity. 3) SIRT1 enhance the ability of DNA damage repair in tumor cells. Sirt1 enhances DNA damage repair pathways, including non homologous end joining repair, homologous recombination repair, nucleotide excision repair, and base excision repair. SIRT1 regulates these pathways by deacetylation of Ku70, Nijmegen fracture syndrome protein, and Werner syndrome protein [17]. Thus, activation of SIRT1 promotes DNA repair and cell survival at fracture sites. 4) SIRT1 promotes acquired resistance through genetic mutations such as liver cancer, colon cancer, ovarian cancer, and other cancers [18, 19]. By controlling apoptosis and senescence, mutant cells can eliminate the efficacy of targeted drugs and promote tumor formation. 5) SIRT1 promotes tumor cells to acquire stem cell properties. Overexpression of the ABC transporter causes tumor stem cells to have multiple resistance mechanisms. Previous studies have shown that the level of SIRT1 in CML stem cells is significantly higher than that in differentiated cancer cells [20]. 6) SIRT1 change the tumor microenvironment. The rapid growth of tumors and hypoxia can limit the transport of anti-cancer drugs and promote the non autonomous effects of cells. SIRT1 is involved in the regulation of angiogenesis and the balance of anti angiogenic molecules that modulate angiogenesis [21].

4.1 SIRT1 and cervical cancer resistance

More and more studies show that activated SIRT1 plays an inhibitory role in the process of resistance to cervical cancer cells. It was found that inhibition of SIRT1 could promote cell proliferation and accelerate the growth of HCT116 cell allograft xenografts in the absence of growth factors, whereas overexpression of SIRT1 inhibited tumor formation [22]. The inhibition of SIRT1 can also reduce the drug resistance and promote apoptosis [23]. Other studies have shown that catecholamines can activate beta 2-AR and induce the SIRT1 to deacetylate the p53, and thus induce apoptosis, thereby reducing the resistance of cervical cancer cells to drugs [24].

4.2 SIRT1 and gastric cancer resistance

SIRT1 was thought to be a unique nucleoprotein originally. However, it can be observed in part or temporary cytoplasmic localization. Recent reports indicate that the cytoplasmic localization of SIRT1 seems to be sensitive to the cell apoptosis which was mediated by oxidative stress [25]. The results indicate that the expression of DBC1 was positively correlated with the expression of SIRT1. DBC1 and SIRT1 advanced clinical pathology and expression of gastric cancer, and adverse prognostic factors in patients with gastric cancer significant correlation. P53 protein is a key regulator

of cell cycle progression and apoptosis. During the tumor progression, upregulation of SIRT1 allows cells to bypass apoptosis and survive DNA damage, through metabolizes deacetylation and inactivation of p53 [26].

4.3 SIRT1 and breast cancer resistance

In breast cancer, SIRT1 stabilization is contribute to the oncogenic potential of estrogen receptor alpha (ER-α), but SIRT1 activity is also associated with deacetylation and inactivation of ER-α. The physical interaction between ER-α and SIRT1 have been demonstrated. ER-α increases the transcription of SIRT1 through combines its promoters. SIRT1 induced by ER-α is sufficient to activate antioxidants and inactivate tumor suppressor genes survival genes in breast cancer cells, such as catalase and glutathione peroxidase. In addition, SIRT1 inactivation eliminates estrogen ER-α induced cell growth and triggers apoptosis. These results suggest that SIRT1 is essential for estrogen induced breast cancer growth [27].

4.4 SIRT1 and chronic myeloid leukemia resistance

Chronic myeloid leukemia (CML) is the most common malignant myeloproliferative disease in chronic leukemia in China. It is a malignant tumor that affects blood and bone marrow. In hematopoietic cells, BCR-ABL and KRAS oncogenes activate the expression of SIRT1 gene[28]. Li et al. showed that acts as a stress-dependent NAD-dependent deacetylase, SIRT1 is expressed in chronic myeloid leukemia and normal stem cells CD34 +, CD38- [29][30]. The inhibition of SIRT1 can selectively reduce survival and the sensitivity of leukemic stem cell (LSC) proliferation to tyrosine kinase inhibitor (TKI) therapy.[31] In vivo, Tenovin-6 treatment reduces the number of CML LSCs, while reduces the LSC implantation in secondary receptors, and prolongs survival after treatment. These observations suggest that SIRT1 plays an important role in maintaining CML LSC and its resistance to TKI therapy, SIRT1 inhibition may represent a potential strategy to enhance the elimination of CML LSC who is treated with TKI [32][33].

SIRT1 is not only closely related to the drug resistance of these tumors, but also plays an important role in promoting the resistance to chemotherapy and radiation tolerance in many kinds of tumors, such as liver cancer and prostate cancer. SIRT1 plays an important role in the treatment of resistance in the maintenance of CML LSC and the inhibitor of tyrosine kinase (TKI). Whatmore, SIRT1 inhibition may enhance the elimination for LSC in TKI treated patients with CML [34, 35].

5. Conclusion

To sum up, SIRT1 plays an important regulatory role in metabolism, aging, tumor formation and resistance to drugs. As the biggest obstacle to cure tumor, drug resistance of tumor urgently needs to be studied and solved. Further study of the relationship between SIRT1 and tumor resistance will hopefully provide a new therapeutic target for tumor resistance.

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