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Review

The Role of Sirtuin 2 in Chemotherapeutic Resistance

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Abstract

The lack of effective chemotherapy agents and the development of multi-drug resistance in advanced cancers are major encountered issues during treatment phase. The resistance of cancer cells against chemotherapeutic agents may occur as a result of different mechanisms. The identification of molecular pathways involved in drug resistance will yield the occurrence of alternative therapeutic strategies. Sirtuin 2 is one of the NAD-dependent deacetylases. It is involved in carcinogenesis to fulfill oncogenic and tumor-suppressing functions. Therefore, Sirtuin 2 modulation becomes a promising approach in cancer treatments. A better understanding of Sirtuin 2 related pathways is required to provide guidance to alternative cancer treatments. There are several studies about the effects of Sirtuin 2 on various types of cancers in recent years. Within the scope of this review, it is aimed to present the molecular pathways of Sirtuin 2 and its association with chemotherapeutic resistance.

Keywords: Drug resistance, neoplasms, Sirtuin 2

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The chemotherapy treatment applied to several advanced cancers fails due to drug resistance.[1] The identification of molecular pathways will contribute to the development of alternative therapeutic strategies for cancer. Recent studies have reported the roles of Sirtuin 2 (SIRT2) in cancer pathogenesis. Thus, that makes SIRT2 modulation a possible alternative approach to cancer treatment.[2] There are seven Sirtuin family proteins in mammals, SIRT1 to SIRT7.[3] SIRT2 is a NAD-dependent deacetylase that is involved in various cellular processes including cell proliferation, cell death, cell migration and microtubule dynamics.[4, 5] The physiological roles of SIRT2 differ according to cell types. SIRT2 has been reported to be both oncogenic and tumor suppressive. SIRT2 is usually found in the cytoplasm.[3] However, it is known that the distribution of SIRT changes across intracellular compartments.[6] The present article reviews the impact of SIRT2 on molecular pathways and drug resistance.

1. SIRT2 Pathway Associated Molecules

SIRT2 possesses an important role in tumorigenesis considering both tumor-promoting and tumor-suppressing functions.[3] The identified deacetylation substrates of SIRT2 are histones, α-tubulin, p300, nuclear factor kappa B (NFκB), phosphoenolpyruvate carboxykinase 1 (PEPCK1), lactate dehydrogenase 1 (LDH1) and forkhead box O3 (FOXO3).[7] Some of the molecules increased by SIRT2 inhibition are hypoxia inducible factor 1 subunit alpha (HIF1α), vascular endothelial growth factor (VEGF) and heme oxygenase-1 (HO-1).[8] SIRT2 downregulates FOXM1 expression in colon cancer via transforming growth factor-beta (TGFβ) mitogen-activated protein kinase (RAF-MEK-ERK) signaling pathway.[9] The Kruppel-like factor 4 (KLF4) has activator or inhibitor effects on carcinogenesis similar to SIRT2. The reduced SIRT2 induc-

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es KLF4 expression and inhibits myeloma cell proliferation and migration.[5] In another multiple myeloma study, SIRT2 knockdown inactivated RAS/ERK signaling and cell proliferation.[10] Aldo-keto reductase family 1 member C1 (AKR1C1) is one of the promoting factors in malignancy. SIRT2 suppresses AKR1C1 activity in nonsmall cell lung cancer.[11] SIRT2/cMYC pathway inhibits apoptosis in cholangiocarcinoma through metabolic regulation.[12] Chaperone Hsp70 is another substrate of SIRT2 pathway. Silencing SIRT2 triggers apoptosis and mitophagy in breast cancer cell line.[13] SIRT2 suppression also leads to activation of p53-p21 pathway and spindle assembly checkpoint in mitosis through P300/CBP-associated factor (PCAF).[14] Molecular mechanisms of SIRT2 in tumorigenesis are not fully elucidated yet due to its complex and unpredicted response.[7]

2. Chemosensitivity by SIRT Inhibition

SIRT2 inhibition attenuate growth of specific cancer cells.[15] The inhibition of SIRT2 can enhance the cytotoxicity of Lapatinib and it can be investigated further as a novel strategy for overcoming Lapatinib resistance in nasopharyngeal cancers.[1] In another study, SIRT2 inhibitor improved the antitumor effect of paxitaksel in breast cancer cell lines.[16] It also enhance sorafenib's effects in hepatocellular carcinoma cell lines.[17] SIRT2 inhibitors have antitumor and proapoptotic activity in nonsmall cell lung cancers.[18, 19] Melanoma is one of the cancers that show high resistance to chemotherapeutics. There are several studies about Sirtuin involvement in drug-resistant melanomas. It is reported that SIRT2 inhibition increases cisplatin sensitivity and reduces downstream molecules of epidermal growth factor receptor (EGFR) pathway in melanoma. ERK 1/2 is one of the downstream signaling molecules of EGFR pathway.[20] SIRT2 is involved in multidrug-resistant acute myeloid leukemia through extracellular signal-regulated kinase (ERK) 1/2 signaling pathway.[21] Loss of SIRT2 enhanced chemotherapy sensitivity in acute myeloid leukemia.[22] High SIRT2 expression was detected in castration-resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC). SIRT2 promotes cell proliferation, migration, invasion while reducing apoptosis via ERK 1/2 pathway.[23] Cell death triggered by dysregulated mitosis is a term that stands for a mitotic catastrophe. SIRT2 deacetylates the structural maintenance of chromosomes protein 1 (SMC1A) and mitosis. Inhibition of SIRT2 or increasing SMC1A acetylation causes abnormal chromosome segregation and promotes mitotic catastrophe in cancer cells. Mitotic catastrophe enhances cancer vulnerability to chemotherapy.[24]

3. Chemosensitivity by SIRT Expression

Contrary to SIRT2 inhibition, there are studies in the literature that states the effects of high SIRT2 levels on drug sensitivity in specific cancer groups. In ovarian cancer, overexpression of SIRT2 enhanced cisplatin sensitivity.[25] The upregulation of SIRT2 increased cell viability in cisplatin/paclitaxel-treated endometrial cancer cells and activated MEK/ERK signaling pathway.[26] Mitogen-activated protein kinase phosphatase-1 (MKP-1) in cancer cells leads to multidrug resistance against chemotherapeutic agents via decrement in drug-induced JNK activation. The suppression of SIRT2 in the renal tubular epithelial cell inhibited cisplatin treatment sensitivity based on the MKP-1 expression.[27]

Conclusion

SIRT2 plays oncogenic or tumor-suppressor roles in different cells. In recent years, researches on the effects of SIRT2 suppression were mostly towards the chemosensitivity. ERK pathway takes part in both chemoresistant and chemosensitive SIRT2 impacts. Based on the results of corresponding studies, it can be inferred to the possible existence of additional substrates belonging the another pathway. The identification of SIRT2 molecular pathways will help to develop alternative therapeutic strategies in cancer. Further studies should investigate SIRT2 in detail to understand molecular mechanisms for different cancer models.

Disclosures

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Conflict of Interest: None declared.

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