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Review

SIRT1 is a regulator of autophagy: Implications in gastric cancer progression and treatment

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ABSTRACT

Silent mating type information regulation 1 (SIRT1) is implicated in tumorigenesis through its effect on autophagy. In gastric cancer (GC), SIRT1 is a marker for prognosis and is involved in cell invasion, proliferation, epithelial-mesenchymal transition (EMT) and drug resistance. Autophagy can function as a cell-survival mechanism or lead to cell death during the genesis and treatment of GC. This functionality is determined by factors including the stage of the tumor, cellular context and stress levels. Interestingly, SIRT1 can regulate autophagy through the deacetylation of autophagy-related genes (ATGs) and mediators of autophagy. Taken together, these findings support the need for continued research efforts to understand the mechanisms mediating the development of gastric cancer and unveil new strategies to eradicate this disease.

1. Introduction

Both silent mating type information regulation 1 (SIRT1) and autophagy have dual effects (cell survival or death) in gastric cancer (GC) progression and treatment under different conditions. Sirtuin proteins (silent mating type information regulators; SIRTs) were first isolated in yeast. There are 7 members in the SIRT family (SIRT1-SIRT7) and they are class III histone deacetylases (HDACs) with different functions, structure, and intracellular distribution [1]. SIRT1 is the most studied family member. It deacetylates histones and many non-histone targets and mediates tumor development, energy homeostasis, autophagy, DNA damage repair, life-span extension, neurodegeneration, age-related disorders, obesity, heart disease and inflammation among others [2–10]. Expression of SIRT1 is a prognosis indicator for many cancers including GC [11,12]. Several studies have reported that SIRT1 plays a role in invasion, proliferation, epithelial-mesenchymal transition or chemoresistance in GC cells [13–16] and is therefore instrumental for GC progression and an important target for treatment.

Autophagy is an important regulator of cell physiology and abnormalities in this process can lead to disease such as GC. This intracellular degradation process transports cytoplasmic cargo to the lysosome for degradation and can be of three types: macroautophagy, microautophagy and chaperone-mediated autophagy. Here, we focus on macroautophagy, hereafter referred to as autophagy. Autophagy is necessary for cell homeostasis. Prolonged or heightened induction of autophagy however can result in autophagic cell death or type II programmed cell death (PCD), while moderate induction of autophagy is key for cell survival [17]. There is growing evidence that autophagy can have an effect on the efficacy of chemotherapy or immunotherapy of tumor cells [18–20]. However, the molecular mechanisms mediating this effect are not completely understood. Interestingly, recent studies report that autophagy induced after irradiation, anticancer drugs or other agents could function as a tumor suppressor [21–24] or promote tumor growth [25–33] in GC cells. Therefore, autophagy plays a

Abbreviations: GC, gastric cancer; SIRT1, silent mating type information regulation 1; HDACs, histone deacetylases; PCD, programmed cell death; TSC2, tuberous sclerosis complex 2; ATGs, autophagy-related genes; EMT, epithelial-mesenchymal transition; MDR, multidrug resistance

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role in the genesis of GC and may be a key target for therapeutic intervention.

Interestingly, SIRT1-mediated autophagy is important for cell proliferation, metabolism, and resistance to stress [34–39]. SIRT1 can mediate autophagy through the deacetylation of a number of transcription factors, including histone H4 (at lysine residue 16; H4K16ac) [37,40], FoxO1 [40], FoxO3 [41], E2F1 [42,43], S6K [44], NF-κB [45], p53 [46], tuberous sclerosis complex 2 (TSC2) [47]. Following deacetylation, the transcription factors then activate autophagy-related genes and can also induce autophagy by deacetylating ATGs5, 7 and 8 under nutrient deprivation conditions [35]. Here, we review the role of SIRT1 in the induction and regulation of autophagy and describe its importance in GC progression and treatment.

2. SIRT1 in GC

SIRT1 has been reported to play a role in energy homeostasis, autophagy, DNA damage repair, and life-span extension in a variety of diseases [4–6,8]. However, its role in the development of cancers such as GC remains undefined [12,48,49]. The expression of SIRT1 in cancer cells such as clear cell renal cell carcinoma (CRCC) [50], breast cancer [51,52], gastro esophageal junction (GEJ) cancer [53], colorectal adenocarcinoma [54,55], hepatocellular carcinoma (HCC) [56], GC [12,48,49,57], soft tissue sarcomas [58], non-small cell lung cancer (NSCLC) [59,60], pancreatic ductal adenocarcinoma (PDAC) [61] has been documented in the literature. Here, we summarize the expression of SIRT1 in cancer and the function of SIRT1 in GC.

2.1. Expression of SIRT1 in established tumors

The level of expression of SIRT1 varies with the tumor type, the tumor microenvironment and cellular stress. There are several studies reporting an elevated expression level of SIRT1 in CRCC [50], breast cancer [52,62], GEJ cancer [53], colorectal adenocarcinoma [54,63], HCC [56,64–67], GC [12,48], soft tissue sarcomas [58,68], NSCLC [59,69], PDAC [61], prostate cancer [70], ovarian and cervical cancers [71], medulloblastoma [72], and lymphoma [73]. A downregulated expression of SIRT1 has only been reported for colorectal cancer [74,75] and GC [49]. In all cases, SIRT1 served as a good prognosis indicator for disease progression (see Table 1). The histological studies on the level of expression of SIRT1 in different cancers do not establish whether this protein is acting as a tumor promoter or tumor suppressor in tumorigenesis. Further studies are needed to define the specific role of SIRT1 in cancer.

2.2. SIRT1 acts as a tumor suppressor in GC

Even though the exact role of SIRT1 in GC remains undefined, several studies have suggested that SIRT1 is a good prognostic factor in GC and that SIRT1 can inhibit tumor growth in these tissues (Fig. 1).

SIRT1 is considered a good prognostic factor in GC because its expression is negatively correlated with tumor TNM stage, lymphatic invasion and positively correlated with improved survival [57]. Therefore, SIRT1 may act as a tumor suppressor in GC. In addition, SIRT1 can inhibit GC cells in vitro and in vivo in a nude mouse xenograft model. Specifically, overexpression of SIRT1 was found to inhibit cell proliferation and tumor development through the downregulation of NF-kB activity and inhibition of cyclin D1 signaling [49]. Resveratrol, an agonist of SIRT1, was found to cause cellular senescence in a SIRT1-dependent manner both in vivo and in vitro [16]. Together, these studies suggest that SIRT1 can suppress the development of human GC.

Table 1
Expression of SIRT1 and its prognostic significance in cancer.

Tumor types	Expression	Prognosis	Ref.
CRCC	High	Poor	[50]
Breast cancer	High	Poor	[52,62]
GEJ cancer	High	Poor	[53]
Colorectal adenocarcinoma	High	Poor	[54,63]
HCC	High	Poor	[56,64–67]
GC	High	Poor	[12,48]
GC	High	Good	[57]
Soft-tissue sarcomas	High	Poor	[58,68]
NSCLC	High	Poor	[59,69]
PDAC	High	Poor	[61]
Colorectal cancer	High	Good	[76]
Colorectal cancer	Low	Good	[74,75]
GC	Low	Good	[49]
Melanoma	High	n	[77]
HNSCC	High	Good	[78]
Prostate cancer	High	Poor	[70]
Thyroid cancer	High	n	[79]
Ovarian and cervical cancers	High	Poor	[71]
Medulloblastoma	High	Poor	[72]
Lymphoma	High	Poor	[73]
AML	High	n	[80]

CRCC: clear cell renal cell carcinoma; GEJ: gastroesophageal junction cancer; HCC: hepatocellular carcinoma; GC: gastric cancer; NSCLC: non-small cell lung cancers; PDAC: pancreatic ductal adenocarcinoma; HNSCC: head and neck squamous cell carcinoma; AML: acute myelogenous leukemia. High: high expression of SIRT1 in exact cancer; low: low expression of SIRT1 in exact cancer; n: no prognostic significance for SIRT1 has been reported; poor: poor prognostic factor; good: good prognostic factor; Ref.: reference.

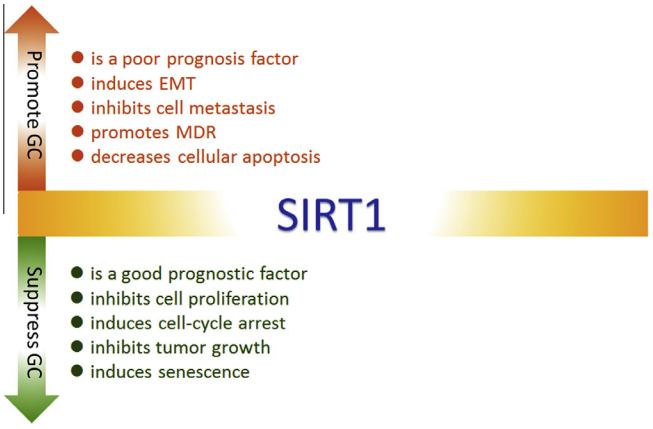

Fig. 1. SIRT1 can be be a tumor promoter or a tumor suppressor in GC. SIRT1 is a tumor promoter in GC and a poor prognosis indicator. It induces EMT, inhibits cell metastasis, promotes MDR, and decreases cellular apoptosis of GC cells. SIRT1 can also inhibit GC by repressing cell proliferation and tumor growth or inducing a G1-phase cell-cycle arrest and senescence.

2.3. SIRT1 acts as a promoter in GC

Recent studies have reported a role for SIRT1 promoting GC growth (Fig. 1). Specifically, Cha et al. [12,48] showed that nuclear expression of SIRT1 was detected in 73% (130 of 177) of GC patients. In addition, SIRT1 expression correlated with tumor stage, lymph node metastasis and tumor invasion. No correlation was observed with p53 expression or decreased or relapse-free survival. Therefore, SIRT1 may function as a tumor promoter in GC.

Increasing evidence suggests that microRNAs (miRNAs) regulate tumorigenesis and metastasis through the post-transcriptional regulation of gene expression. For example, miR-204 is significantly downregulated in GC when SIRT1 mRNA levels are upregulated, which indicates that SIRT1 is a target of miR-204 in GC [13]. Correspondingly, overexpression of miR-204