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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.

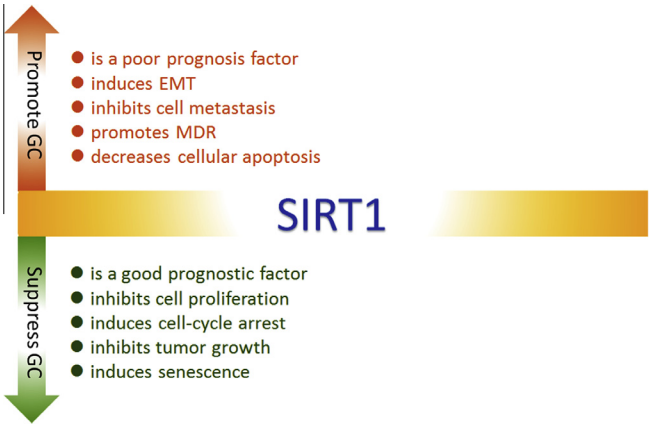

Fig. 1. SIRT1 can be be a tumor promoter or a tumor suppressor in GC. SIRT1 is a tumor promoter in GC and a poor prognosis indicator. It induces EMT, inhibits cell metastasis, promotes MDR, and decreases cellular apoptosis of GC cells. SIRT1 can also inhibit GC by repressing cell proliferation and tumor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

in GC cells was found to inhibit metastasis, decrease anoikis resistance and induce epithelial-mesenchymal transition (EMT) by inhibiting SIRT1 [13].

In GC, multidrug resistance (MDR) remains a challenge for effective therapeutic intervention. For example, activating transcription factor 4 (ATF4) promoted GC MDR by up-regulating the expression of SIRT1. In contrast, inhibition of SIRT1 expression using small interfering RNAs (siRNA) or a specific inhibitor (EX-527) restored the efficacy of therapeutic strategies by reversing the GC MDR phenotype promoted by ATF4 [14]. Together, these results suggest that changes in the level of expression of SIRT1 correlate with the progression and effective treatment of GC.

Using an animal model, Li et al. [15] found that in GC the expression levels of iNampt, SIRT1 and c-myc proteins were significantly higher in obese mice than in the lean mice. In addition, they found that upregulated expression of the pro-survival Nampt/SIRT1/c-myc positive feedback loop enhanced murine fore stomach carcinoma cell migration, proliferation and cell cycle progression while decreasing cellular apoptosis [15]. Therefore, based on the evidence obtained from the animal models SIRT1 is involved in the progression of GC. In addition, SIRT1 is important for the effective treatment of GC, which varies depending on the tumor stage, tumor microenvironment, activated signaling pathways and cellular stress levels among others.

2.4. SIRT1 has a dual role in GC

SIRT1 can function as a tumor promoter and a tumor suppressor. It contributes to cancer cell death inhibiting tumor growth. On the other hand, SIRT1 can also upregulate oncogenic signaling pathways and create a microenvironment favorable for cancer cell growth and survival. Brooks and Gu [81] considered this mainly because of the presence or absence of functional p53. while Song and Surh [82] considered this dual role of SIRT1 in cancer may be determined by its subcellular localization. Therefore, more work is needed to clarify the switching mechanism of the two-edged sword of SIRT1.

3. Autophagy in GC

Autophagy is an intracellular degradation process to break down cytoplasmic cargo (superfluous or damaged organelles, misfolded or long-lived proteins or invading microorganisms) at the lysosome. This process yields substrates for energy generation and biosynthesis [18]. Autophagy can be upregulated as a cell-survival mechanism or lead to cell death [17] during the development and treatment of GC, depending on the tumor stage and cellular context [20,83,84] (Fig. 2). Therefore, autophagy can be a double-edged sword in GC biology.

3.1. Autophagy can suppress GC

Recent studies have reported that the induction of autophagy is important for the suppression of GC under certain cellular stress conditions such as inactivation or mutation of related genes [22,24,85,86], *Helicobacter* pylori (HP) infection [87] or exposure to chemotherapy [88–90].

Beclin-1 is a marker and regulator of autophagy. High levels of beclin-1 expression have been reported to be a predictive factor of a favorable prognosis in GC [91–96], which suggests that autophagy might have a role in suppressing the progression of GC. Autophagy can also prevent the occurrence of GC. For example, in the case of infection by HP, upregulation of IFN-γ serves to eradicate the bacterial infection and autoimmune disease and also acts as a tumor suppressor in GC by inducing autophagy. Tu et al. [97] reported that in the course of an HP infection IFN-γ lead to increased expression of beclin-1 which in turn served to induce autophagy, suppress gastric progenitor cell expansion and reduce epithelial cell apoptosis. Furthermore, there are reports in the literature that limited exposure to vacuolating cytotoxin A (VacA), which is secreted by HP, induced autophagy in human gastric epithelial cells, limiting toxin-induced cellular damage and protecting them from carcinogenesis [87,98,99]. In contrast, prolonged exposure to VacA could disrupt autophagy by preventing maturation of the autolysosome and contribute to inflammation and carcinogenesis in human gastric epithelial cells and primary gastric cells from mice [87,100]. Yahiro et al. [101] reported that VacA regulates toxin-induced autophagy in gastric epithelial cells by binding to the low-density lipoprotein receptor-related protein-1 (LRP1), which functions as the receptor of VacA. Interestingly, VacA-induced autophagy can also suppress GC through the degradation of cytotoxin-associated gene A (CagA) protein, a type IV secretion effector of HP that is closely associated with the development of GC [21]. Together, the evidence in the literature to date supports the notion that autophagy plays an important role in preventing the occurrence of GC in the advent of a HP infection.

The occurrence of GC also correlates with the inactivation or inhibition of tumor suppressor genes which induce autophagy.

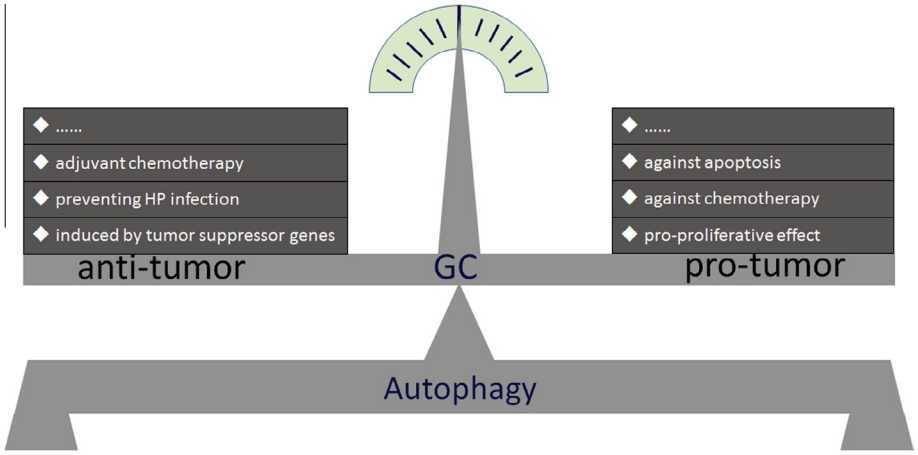

Fig. 2. Autophagy has both pro-, and anti-tumor effects during the development and therapy of GC. It can be induced by tumor suppressor genes, prevents HP infection, and enhance the efficacy of adjuvant chemotherapy in GC. In parallel, it can promote GC by protecting cells against chemotherapy and apoptosis and upregulating the proliferation of cells.

For example, klotho is a tumor suppressor gene that is epigenetically inactivated in GC. Upon restoration of klotho expression, cell proliferation is inhibited and apoptosis and autophagy are stimulated by the downregulation of insulin-like growth factor-1 (IGF-1)/insulin receptor substrate 1 (IRS-1)/phos-phoinositide 3-kinase (PI3K)/Akt/mTOR signaling pathways which regulate both the apoptosis and autophagy pathways [22]. Moreover, inhibitors of autophagy were found to block the activity of klotho on cell viability, apoptosis induction and cell cycle arrest [22]. Therefore, klotho has a tumor suppressor activity through its effects on autophagy. Protocadherin 17 (PCDH17) is another tumor suppressor gene that is frequently silenced by methylation in GC cell lines, but not in the normal gastric mucosa. Upon restoration of PCDH17 expression, GC cell growth was inhibited in vitro and in vivo through the upregulation of apoptosis and autophagic cell death [24]. Lastly, ultraviolet (UV) radiation resistance-associated gene (UVRAG) is an autophagy-related gene that can induce autophagy through its association with beclin-1. A frameshift mutation in UVRAG was found to significantly reduce autophagy and increase tumorigenicity in cancer cells [85]. Kim et al. [86] reported the occurrence of frameshift mutations of the UVRAG gene in GC and the subsequent decrease in autophagic cell death as well as the inhibition of PCDH17. Together, these results suggest that autophagy acts as a tumor suppressor and exerts its anti-proliferative activity partly by inducing autophagic cell death.

Inducing autophagy could enhance the efficacy of adjuvant chemotherapy. In the case of GC, recent studies have shown that some of the anticancer drugs used in the clinic exert their anti-tumor effect mainly by inducing autophagy. Matrine, evodiamine (an alkaloid isolated from evodia rutaecarpa) and E Platinum (a newly synthesized derivative of oxaliplatin), were reported to have a wide range of pharmacological effects including antitumor activity both in vitro and in vivo. However, the molecular mechanisms mediating their antitumor activity remain undefined. In GC cells, matrine, evodiamine and E Platinum were found to significantly inhibit the proliferation of two gastric cancer cell lines, SGC-7901 and BGC-823, induce cell cycle arrest and activate autophagy which partially contributed to cell death [88–90]. Therefore, autophagy is an active process mediating the antitumor effects of matrine, evodiamine and E Platinum and can act as a tumor suppressor.

Autophagy is regulated by several cell cascades such as ATGs, mitogen-activated kinase, death-associated protein kinase, beclin-1, and class I phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathways [102]. Other factors besides tumor suppressor genes and anticancer drugs can also inhibit GC by inducing autophagy through the activation of molecular and cell signaling pathways. For example, Sun et al. [23] reported that expression of the adenovirus vector-mediated XIAP-associated factor 1 (adeno-XAF1) induced autophagy through the up-regulation of beclin-1 expression and the inhibition of the Akt/p70S6K signaling pathway in GC cells and xenograft tumors. As a result, tumor growth was inhibited. Similarly, inhibition of the class I PI3K/AKT and its downstream target mTOR has been shown to contribute to autophagy [103,104]. Additionally, there is evidence in the literature that LY294002 (an inhibitor of class I PI3K) inhibited the viability of SGC7901 cells by up-regulating autophagy through the activation of the p53 pathway [105]. Therefore, inhibitors of the class I PI3K/AKT/mTOR signaling pathway have emerged as an important and attractive therapeutic target for GC therapy because of their potential to upregulate autophagy. Interestingly, there is accumulating evidence that tetracycline and its derivatives (doxycycline and minocycline), which have broad antimicrobial activity, also have anti-cancer properties. Tang et al. [106] reported that tetracycline inhibited GC cell proliferation and induced autophagy by activating the adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling pathway which then suppressed its downstream targets mTOR and p70S6K. Therefore, the upregulation of autophagy contributed to the antitumor effects of tetracycline.

Together, the evidence in the literature so far supports the notion that autophagy acts as a tumor-suppressor by mediating type II PCD in GC cells.

3.2. Autophagy can promote GC

Although there is extensive evidence in the literature that autophagy suppresses GC, there are also some studies reporting that autophagy can promote GC.

Even though there is ample clinical evidence supporting that a high level of expression of beclin-1 correlates with a favorable prognosis in GC, Ahn et al. [107] reported that beclin-1 is expressed in 83% of gastric carcinomas, indicating that elevated levels of expression of beclin-1 might play a role in gastric tumorigenesis also. Supporting this hypothesis, Yoshioka et al. [108] documented a high level of expression of the microtubule-associated protein I light chain 3 (LC3; the mammalian homologue of yeast ATG8), a protein involved in autophagosome formation, in 58% of GC, suggesting that LC3 expression was advantageous to cancer development especially during the early stages of carcinogenesis. Beclin-1 and LC3 are two important markers and regulators of autophagy. Together, these studies suggest that authophagy might contribute to carcinogenesis under some conditions.

Inhibiting autophagy can sometimes enhance the efficacy of chemotherapy. For example, quercetin [26] (a dietary antioxidant present in fruits and vegetables), beta-elemene [25], resveratrol [29] and matrine [28] exhibit both apoptosis and autophagy-promoting activities in GC cells. However, inhibiting autophagy could enhance the antitumor effects of these drugs in the treatment of GC, suggesting that autophagy plays a protective role against GC cells from death.

Oxaliplatin is a well-studied chemotherapeutic drug, which can lead to the survival of HCC cells by activating autophagy [109]. In GC MGC803 cells, oxaliplatin can induce protective autophagy, which partially blocks apoptosis in these cells [27]. Similarly, cisplatin, another chemotherapy drug used in the treatment of GC, induced authophagy and apoptosis in the human GC cell line SGC7901. In contrast, the use of chloroquine to inhibit autophagy lead to enhanced apoptosis [33]. Therefore, autophagy can protect GC cells against cell death induced by cisplatin or oxaliplatin.

There is evidence to support the administration of proteasome inhibitors in the treatment of GC. For example, the proteasome inhibitor MG-132 has been shown to inhibit cell proliferation and induce autophagy [32]. Knockdown of Vps34 (Class III phosphatidylinositol-3 kinase) or ATG5/7 in turn can inhibit autophagy and therefore enhance the antiproliferative effect of MG-132 in GC cells by promoting cell cycle arrest [32].

3.3. The switching mechanism of the two-edged sword of autophagy in GC

Autophagy plays an important role in maintaining the cell homeostasis but it can also function as a cell-survival mechanism when the cells are under stress conditions, for example during nutrient deprivation. Inducing autophagy under this conditions will result in cell death, which is known as autophagic cell death or type II PCD [17]. The exact role of autophagy in cancer is still undefined. Rouschop and Wouters [110] suggested that autophagy suppresses tumor growth during the early stages of tumorigenesis but promotes tumor cell survival during cancer progression. Therefore, autophagy seemed to be beneficial for cancer prevention. However, a recent study reported that induction of autophagy

in tumor cells contributed to resistance to various anti-cancer therapies [111]. Moreover, cancer cells may survive by inducing autophagy when subjected to stress such as during nutrient deprivation [112]. Therefore, autophagy plays a distinct role in the occurrence and development of GC but the switching mechanism of the two-edged sword of autophagy in GC remains undefined.

4. SIRT1 is a deacetylase protein that mediates autophagy

SIRT1 is a deacetylase protein whose expression is regulated by cellular stress (starvation, glucose deprivation, and calorie deprivation), protein factors (AROS, SUMO, NAD+/NADH, HuR, DBC1, HIC1, Dif1 and so on), SIRT1 agonists (resveratrol, SRT1720) or SIRT1 inhibitors (tenovins, EX-527 and sirtinol). SIRT1 can target proteins in the nucleus and the cytosol which are involved in regulating cancer cell proliferation, DNA damage repair, gene transcription, survival and autophagy such as histones [113], p53 [114,115], FoxO1 [116], β-catenin [117,118], Ku70 [119], NF-κB [45], survivin [120], PTEN [121], E2F1 [43], ATG5, ATG7, and ATG8 [122] as shown in Fig. 3. There are reports that glucose deprivation can increase the AMP/ATP ratio which then phosphorylates the AMP-activated Protein Kinase (AMPK) and activates it [123]. The activated AMPK can regulate autophagy by either phosphorylating ULK1 which then activates the PI3K complex [123] or inhibiting mTOR which inhibits the phosphorylation of the ULK1 complex [123].

Activation of AMPK can also upregulate SIRT1 in a NAD-dependent manner [124] (Fig. 4). Interestingly, SIRT1-mediated autophagy plays a role in proliferation, metabolism, and resistance to cellular stress [34–39]. For example, resveratrol was found to protect human umbilical endothelial vein cells (HUVECs) from oxidative damage caused by the oxidized low-density lipoprotein (ox-LDL) by upregulating SIRT1-dependent autophagy via the AMPK/SIRT1 pathway [125]. These results were confirmed using an inhibitor of autophagy (3-methyladenine; 3-MA) and SIRT1 (EX527) [125]. Resveratrol can also attenuate endothelial inflammation by inducing autophagy, which in part was mediated through the activation of the cAMP-PRKA-AMPK-SIRT1 signaling pathway [126]. In HCC cells, inhibition of SIRT1 was found to impair cell proliferation and rapamycin-induced autophagy [127]. Similarly, SIRT1 was found to be required for the induction of autophagy in human colorectal (HCT 116) or cervical (HeLa) cancer cells growing under nutrient deprivation or caloric restriction conditions, while knockdown of SIRT1 expression prevented the induction of autophagy by resveratrol or by caloric restriction in human cancer cells [34].

Together, the evidence to date suggests that SIRT1 can be directly or indirectly involved in the induction of autophagy under conditions of nutrient depletion or cellular stress (for example endoplasmic reticulum stress and oxidative stress) [34].

4.1. SIRT1 regulates autophagy through the deacetylation of ATGs

SIRT1 plays an active role in autophagy through the deacetylation of ATGs, such as ATGs5, 7 and 8 (Fig. 4). Lee et al. [35] reported that transient overexpression of SIRT1 induced basal rates of autophagy in the absence of nutrient deprivation. In contrast, autophagy is not fully activated in SIRT1$^{-/-}$ mouse embryonic fibroblasts growing under starvation conditions. In this way, SIRT1$^{-/-}$ mice were found to be similar to ATG5$^{-/-}$ mice which are unable to activate autophagy under starvation conditions [35]. They also demonstrated the molecular mechanisms mediating autophagy in the presence of SIRT1. SIRT1 initially forms a complex with ATGs5, 7 and 8 which are the essential components of the autophagy and mediates their deacetylation in an NAD-dependent fashion promoting autophagy [35]. Based on these studies, we considered that acetylation or deacetylation was an important post-translational modification regulating the induction of autophagy.

Activation of SIRT1 can induce autophagy and has a protective role in neurons against neurodegenerative disorders by regulating mitochondrial homeostasis. For example, Jeong et al. [36] reported that overexpression of SIRT1 in neurons prevented the accumulation of the prion protein (PrP; 106-126) and neurotoxicity by inducing autophagy. Correspondingly, downregulation of SIRT1 or ATG5 expression using siRNAs blocked the effect of a SIRT1 activator and inhibited PrP(106-126)-induced mitochondrial dysfunction and neurotoxicity [36].

Fluoride has also been reported to activate SIRT1 phosphorylation and to initiate autophagy by increasing the expression of

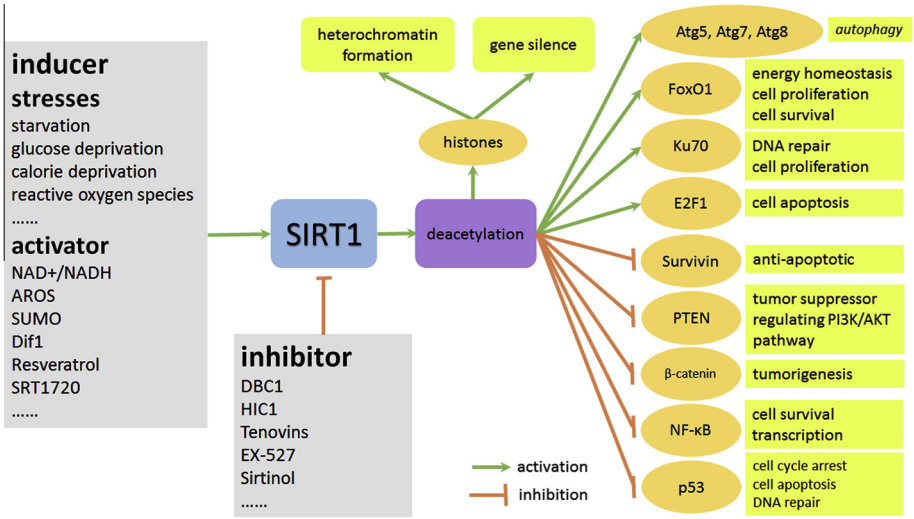

Fig. 3. The SIRT1 pathway. The deacetylase SIRT1 can be induced or inhibited by cellular stress (starvation, glucose deprivation, and calorie deprivation), protein factors (AROS, SUMO, NAD+/NADH, HuR, DBC1, HIC1, Dif1) and some SIRT1 agonists (resveratrol, SRT1720) or inhibitors (tenovins, EX-527, sirtinol). SIRT1 is an NAD$^+$-dependent deacetylase which targets histones and many non-histone proteins. As a result, cellular metabolism is altered. *Abbreviations:* AROS, active regulator of SIRT1; SUMO1, small ubiquitin-like modifier; DBC1, deleted in breast cancer 1; HIC1, hypermethylated in cancer 1; FoxO1, forkhead box, subgroup O1; NF-κB, nuclear factor kappa B; PTEN, phosphatase and tensin homolog deleted on chromosome ten; ATG, autophagy-related gene.

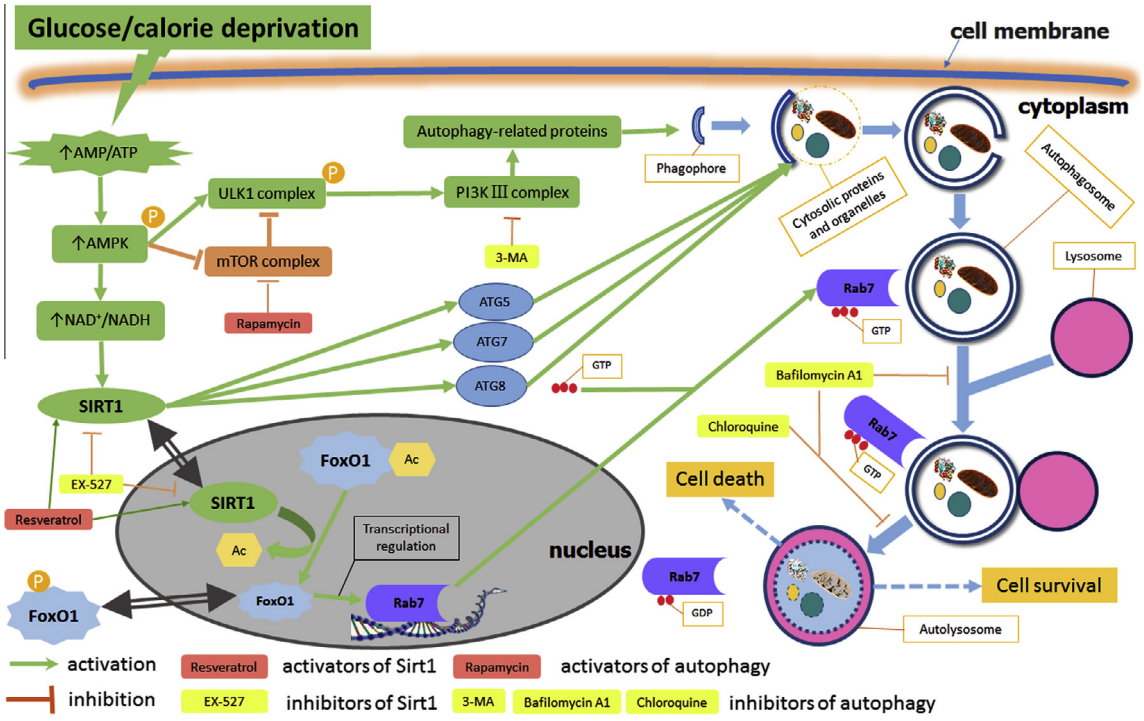

Fig. 4. SIRT1 regulates autophagy. Glucose/calorie deprivation can induce autophagy through the activation of AMPK by phosphorylation, which induces autophagy through the activation of the ULKI complex or the inhibition of the mTOR complex to activate class III PI3K complex which then activates the "Autophagy-related proteins" (ATGs 3, 4, 5, 7, 8(LC3), 10, 12, 16) to induce autophagy. On the other hand, AMPK can also activate Sirt1 in a NAD^+-dependent manner, which then regulates autophagy through deacetylation of ATG5, ATG7, ATG8 or increasing deacetylation, activation and nuclear translocation of FoxO1. Then, FoxO1 can upregulates Rab7, a small GTP binding protein that mediates autophagosome-lysosome fusion, and thereby enhances autophagic flux, resulting in cell death or survival. EX-527 and resveratrol are inhibitor and agonist of SIRT1, respectively. Rapamycin can induce autophagy by inhibit mTOR. 3-MA, bafilomycin A1 and chloroquine are all inhibitors of autophagy by inhibiting the PI3K III complex and the fusion with the lysosome, respectively.

ATGs5, 7 and 8 at the mRNA and protein levels. As a result, ameloblasts cells are protected from the fluoride-induced endoplasmic reticulum stress and enamel formation is not interrupted [39]. In these cells, resveratrol was found to increase autophagy and decrease fluoride cytotoxicity through the SIRT1/ATGs5, 7, 8/autophagy pathway both in vivo and in vitro [39].

4.2. The SIRT1-FoxO1-Rab7 axis mediates autophagy

SIRT1 can also induce autophagy by mediating the deacetylation of FoxO1 under starvation conditions. Specifically, SIRT1 can induce an increase in autophagic flux and upregulate the expression of Rab7, a small GTP-binding protein that mediates late autophagosome–lysosome fusion [38]. Here we describe the evidence to date on the role of the SIRT1-FoxO1-Rab7 axis in autophagy (Fig. 4).

In one study, Hariharan et al. [38,128] showed that SIRT1 expression is upregulated under glucose-deprivation conditions. As a result, autophagy is stimulated through the deacetylation of FoxO1, which leads to the nuclear translocation and activation of the protein in cardiac myocytes. FoxO1 was also shown to increase the expression of Rab7, an essential factor for the fusion of autophagosomes and lysosomes [128–130], which completes the process of autophagy [129]. In these cells, over-expression of Rab7 stimulated autophagy, while knockdown of Rab7 or FoxO1 or mutation of FoxO1 inhibited autophagy under glucose starvation conditions. Together, the results of this study conclusively demonstrated glucose deprivation could induce autophagy via the SIRT1-FoxO1-Rab7 axis (Fig. 4).

Autophagic dysfunction has also been reported in diabetes mellitus [131]. Unexpectedly, resveratrol exhibits a protective effect on diabetic cardiomyopathy in mice through its SIRT1-dependent regulation of autophagic flux [131]. Extended exposure to resveratrol was found to improve oxidative injury in the heart of the diabetic mouse heart by upregulating autophagy, promoting SIRT1 activity and increasing Rab7 expression. In contrast, inhibition of autophagy didn't influence the activity of SIRT1 or the expression levels of Rab7 [131]. In parallel, resveratrol was found to reverse the effects of oxidative stress in H9C2 cells and enhance FoxO1 DNA binding at the Rab7 promoter region in a SIRT1-dependent fashion [131]. Together, these results highlight the role of the SIRT1-FoxO1-Rab7 axis in the upregulation of autophagy by resveratrol.

4.3. SIRT1 regulates autophagy through the deacetylation of other mediators

SIRT1 has been reported to associate with other regulators of autophagy [35,132] such as H4K16ac [37,40], FoxO3 [41], E2F1 [42,43], p73 [133], PPAR-γ co-activator 1α (PGC1α; also known as PPARGC1A) [134], S6K [44], NF-κB [45], p53 [46] and TSC2 [47].

Resveratrol has been shown to inhibit prostate cancer cell proliferation by inducing autophagy in a SIRT1 dependent manner, while downregulation of SIRT1 significantly attenuated resveratrol induced autophagy by inhibiting the phosphorylation and activation of p70-S6 Kinase 1 (S6K1) and the eukaryotic initiation factor 4E binding protein 1 (4E-BP1), two substrates of mTORC1. Therefore, SIRT1 plays an important role in resveratrol-induced autophagy in prostate cancer cells by activating S6K [44]. Specifically, SIRT1 can bind to the mTOR inhibitor TSC2 which represses autophagy [47]. SIRT1 can also inhibit inflammation by up-regulating autophagy. For example, in THP-1 cells inactivation of SIRT1 induced inflammation by activating NF-kB which

impaired autophagy via nutrient-sensing pathways such as the mTOR and AMPK pathways [135].

5. Conclusion

GC remains a serious health burden worldwide and the molecular mechanisms mediating its development remain unclear. SIRT1 and autophagy have a dual role in the development of GC. SIRT1 has been shown to be required for autophagy induction through the deacetylation of ATGs and mediators of autophagy. The evidence to date suggests that SIRT1 can play a dual role in autophagy in GC-suppression or promotion. The SIRT1-FoxO1-Rab7-autophagy pathway has a potential protective role in GC and might lead to novel strategies for therapeutic intervention in the treatment of GC.

Conflicts of interest

The authors declare no conflict of interest.

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