Role of sirtuins in esophageal cancer: Current status and future prospects

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Abstract

Esophageal cancer (EC) is a malignant cancer that still has a poor prognosis, although its prognosis has been improving with the development of multidisciplinary treatment modalities such as surgery, chemotherapy and radiotherapy. Therefore, identifying specific molecular markers that can be served as biomarkers for the prognosis and treatment response of EC is highly desirable to aid in the personalization and improvement of the precision of medical treatment. Sirtuins are a family of nicotinamide adenine dinucleotide (NAD+)−dependent proteins consisting of seven members (SIRT1-7). These proteins have been reported to be involved in the regulation of a variety of biological functions including apoptosis, metabolism, stress response, senescence, differentiation and cell cycle progression. Given the variety of functions of sirtuins, they are speculated to be associated in some manner with cancer progression. However, while the role of sirtuins in cancer progression has been investigated over the past few years, their precise role remains difficult to characterize, as they have both cancer-promoting and cancer-suppressing properties, depending on the type of cancer. These conflicting characteristics make research into the nature of sirtuins all the more fascinating. However, the role of sirtuins in EC remains unclear due to the limited number of reports concerning sirtuins in EC. We herein review the current findings and future prospects of sirtuins in EC.

Key Words: Esophageal cancer; Sirtuin; Esophageal squamous cell carcinoma; Esophageal adenocarcinoma; Biomarker; Treatment

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Core Tip: Although there have been several reports on the function of sirtuins in cancer progression, the biological roles and clinical implications of sirtuins in esophageal cancer (EC) remain controversial. This is the first review to focus on sirtuins in the field of EC. In this review, we will briefly summarize the role of sirtuins in cancer and discuss the current findings and future prospects of sirtuins in EC.

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INTRODUCTION

Esophageal cancer (EC) is the seventh leading cause of morbidity and the sixth leading cause of mortality worldwide[1], and the prognosis of advanced EC patients is extremely poor[2]. Therefore, identifying specific molecular markers that can be used as prognostic markers or therapeutic targets for EC is highly desirable to aid in the personalization and improvement of the precision of medical treatment, which can prevent side effects and extra expenses, thereby leading to a more effective multidisciplinary treatment.

Sirtuins are a highly conserved family of proteins that exist in a wide range of prokaryotic and eukaryotic organisms, and their functional activity is dependent on the cofactor nicotinamide adenine dinucleotide (NAD+)[3]. The mammalian sirtuin family is a homolog of the yeast silent information regulator 2 (Sir2) protein and consists of seven members: SIRT1-7. Sirtuins are distinguished by their subcellular localization: SIRT1, SIRT6 and SIRT7 are mainly found in the nucleus; SIRT3, SIRT4 and SIRT5 are mainly located in the mitochondria; and SIRT2 is mainly found in the cytoplasm. Furthermore, the SIRT family proteins have conserved domains in their core catalytic activities, with SIRT1, SIRT2 and SIRT3 designated as class I; SIRT4 designated as class II; SIRT5 designated as class III; and SIRT6 and SIRT7 designated as class IV (Figure 1)[4]. Sirtuins are involved in the regulation of various biological functions, such as apoptosis, metabolism, stress response, aging, differentiation and cell cycle progression[5]. However, while the role of sirtuins in cancer progression has been investigated over the past few years, their precise role remains difficult to characterize, as they have both cancer-promoting and cancer-suppressing properties, depending on the type of cancer[6]. These conflicting characteristics make research into the nature of sirtuins all the more fascinating.

In EC, the clinical impact of sirtuins remains unclear due to the limited number of reports concerning sirtuins in EC. Therefore, this is the first review to focus on sirtuins in the field of EC. In this review, we will briefly summarize the role of sirtuins in cancer and discuss the current findings and future prospects of sirtuins in EC.

LITERATURE SEARCH

PubMed was searched to identify studies on sirtuins and cancer from inception until January 2022. The following search terms were applied: “Sirtuin” or “Silent mating type information regulation 2 homolog” or “SIRT” and “carcinoma” or “cancer”. The reference lists of all related articles were screened for other potentially relevant studies.

SIRT1

The role of SIRT1 in cancer progression is contradictory. This is because SIRT1 can both promote and inhibit tumorigenesis (Table 1 and Figure 2)[7].

Several mechanisms that are responsible for the tumor-promoting nature of SIRT1 have been uncovered as follows: (1) SIRT1 contributes to cell proliferation by epigenetically suppressing the expression and activity of many tumor suppressor genes and proteins with DNA damage repair functions such as protein 53 (p53)[8], forkhead class O transcription factor (FOXO) family members[9], E2F transcription factor 1 (E2F1)[10], protein 73 (p73)[11], retinoblastoma protein (Rb)[12], Ku70[13], secreted Frizzled-related protein 1(SFRP1), SFRP2, GATA4, GATA5 and mutL homolog 1 (MLH1)[14]; (2) SIRT1 acts as a regulator of apoptosis by deacetylating key apoptosis-related proteins and cell signaling molecules such as p53, nuclear factor kappa B subunit 1 (NF-kB), FOXO3, Ku70, protein kinase B (AKT), mitogen-activated protein kinase (MAPK), and nuclear factor erythroid 2-related factor 2 (NRF2), in response to DNA damage and oxidative stress[6]; and (3) SIRT1 induces epithelial-
Table 1 Roles of sirtuins in cancer control

| Role    | Effect                                      | Involved pathway or mechanism                                                                 |
|---------|---------------------------------------------|-------------------------------------------------------------------------------------------------|
| SIRT1   | Promotor                                   | Promote proliferation                                                                          | p53, FOXO family member, E2F1, p73, Rb, Ku70, SFRP1, SFRP2, GATA4, GATA5, MLH1                  |
|         |                                             | Inhibit apoptosis                                                                              | p53, NF-κB, FOXO3, Ku70, AKT, MAPK, NRF2                                                       |
|         |                                             | Induce EMT, promote migration and metastasis                                                   | ZEB1                                                                                            |
|         | Suppressor                                  | Inhibit tumor formation and proliferation                                                     | β-catenin                                                                                       |
|         |                                             | Induce apoptosis                                                                              | survivin                                                                                        |
|         |                                             | Inhibit EMT                                                                                   | SMAD4, TGF-β signaling on MMP7                                                                 |
| SIRT2   | Promotor                                   | Promote proliferation                                                                          | Mediating immune evasion, altering the alkaline environment                                      |
|         |                                             | Inhibit apoptosis                                                                              | cMYC                                                                                            |
|         |                                             | Promote invasion and migration                                                                | Stimulating mitochondrial metabolism, mediating EMT                                            |
|         | Suppressor                                  | Inhibit proliferation                                                                          | Inhibiting fibroblast activity and tumor angiogenesis                                          |
|         |                                             | Inhibit invasion and migration                                                                 | MMP9, E-cadherin                                                                                |
| SIRT3   | Promotor                                   | Inhibit apoptosis and promote proliferation                                                   | p53, SHMT2, IDH2                                                                               |
|         |                                             | Promote invasion and metastasis                                                              | Reprogramming fatty acid metabolism                                                            |
|         | Suppressor                                  | Induce cell arrest and apoptosis                                                               | Bcl-2, p53, HIF1a, PDC, SOD2, G0T2                                                              |
|         |                                             | Inhibit EMT and migration                                                                      | FOXO3A, Wnt / β-catenin pathway                                                                |
|         |                                             | Inhibit tumorigenesis                                                                          | PDH                                                                                             |
| SIRT4   | Promotor                                   | Promote proliferation                                                                          | PTEN                                                                                            |
|         |                                             | Inhibit glutamine metabolism and proliferation                                               | mTORC1 pathway                                                                                  |
|         | Suppressor                                  | Inhibit EMT, invasion and migration                                                            | E-cadherin                                                                                      |
|         |                                             | Induce G1 cell cycle arrest                                                                    | Cyclin D, cyclin E                                                                             |
| SIRT5   | Promotor                                   | Promote proliferation                                                                          | GLUD1, SHMT2, NRF2, PKM2, SUN2                                                                 |
|         |                                             | Inhibit mitochondrial apoptosis                                                                | Cyt c                                                                                            |
|         |                                             | Promote autophagy                                                                             | AMPK–mTOR pathway                                                                               |
|         |                                             | Promote invasion and migration                                                                | E2F1                                                                                            |
|         |                                             | Promote resistance to chemotherapy                                                            | SDHA                                                                                             |
|         | Suppressor                                  | Inhibit carcinoma development                                                                  | ACCOX1                                                                                          |
|         |                                             | Inhibit proliferation                                                                          | SOD1                                                                                             |
|         |                                             | Represent protective mechanism for tumor cells                                                 | Inhibiting ammonia-induced autophagy                                                            |
| SIRT6   | Promotor                                   | Promote proliferation and inhibit apoptosis                                                   | ERK1/2 pathway, AKT                                                                            |
|         |                                             | Promote invasion and migration                                                                | ERK1/2/MMP9 signaling                                                                           |
|         |                                             | Contribute to cancer development and progression                                              | Regulating autophagy                                                                            |
|         | Suppressor                                  | Inhibit proliferation                                                                          | PCBP2, ERK1/2                                                                                   |
|         |                                             | Inhibit Warburg effect                                                                        | HIF-1α                                                                                           |
|         |                                             | Induce apoptosis                                                                              | NF-κB, Bax, survivin                                                                            |
Inhibit proliferation, invasion and migration

PKM2

Promote proliferation

ERK1/2, H3K18ac

Inhibit apoptosis

miR34a, NF-κB family subunits, mTOR/IGF2 pathway

Promote invasion

Vimentin, fibronectin, E-cadherin, β-catenin

Inhibit proliferation and invasion

SMAD4

Inhibit EMT

TGF-β signaling

ACOX1: Acyl-CoA oxidase 1; AKT: Protein kinase B; Bax: BCL2 associated X; β-catenin: Catenin beta; Cyt c: Cytochrome C; E2F1: E2F transcription factor 1; E-cadherin: Cadherin 1; ERK1/2: Extracellular signal-regulated kinases 1/2; FOXO: Forkhead class O transcription factor; GLUD1: Glutamate dehydrogenase 1; GOT2: Glutamic-oxaloacetic transaminase 2; H3K18ac: Histone H3 lysine 18 acetylation; HIF1α: Hypoxia inducible factor 1 subunit alpha; IDH2: Isocitrate dehydrogenase 2; IGF2: Insulin like growth factor 2; MAPK: Mitogen-activated protein kinase; MLH1: MutL homolog 1; MMP7: Matrix metalloproteinase 7; MMP9: Matrix metalloproteinase 9; mTOR: Mammalian target of rapamycin; mTORC1: Mammalian target of rapamycin complex 1; NF-κB: Nuclear factor kappa B; NFKB: Nuclear factor erythroid 2-related factor 2; p53: Protein 53; p73: Protein 73; PCBP2: Poly(rC) binding protein 2; PDH: Pyruvate dehydrogenase; PKM2: Pyruvate kinase M2; PTEN: Phosphatase and tensin homolog; Rb: Retinoblastoma protein; SDHA: Succinate dehydrogenase complex flavoprotein subunit A; SFRP: Secreted Frizzled-related protein; SHMT2: Serine hydroxymethyl transferase 2; SIRT: Sirtuin; SMAD4: SMAD family member 4; SOD1: Superoxide dismutase 1; SOD2: Superoxide dismutase 2; SUN2: Sad1 and UNC84 domain containing 2; TGF-β: Transforming growth factor beta; ZEB1: Zinc finger E-box binding homeobox 1.

Figure 1 Schematic representation of the subcellular localization of sirtuins. Catalyst domains reflecting sirtuin classes are shown in purple (Class I), green (Class II), blue (Class III) and red (Class IV). SIRT: Sirtuin.

mesenchymal transition (EMT) and promotes cell migration and metastasis by cooperating with EMT transcription factors such as zinc finger E-box binding homeobox 1 (ZEB1) in prostate cancer[15]. It has also been reported that the high expression of SIRT1 is associated with an advanced stage and poor prognosis in certain types of cancer such as gastric cancer[16], lung adenocarcinoma[17] and colorectal cancer[18].

However, SIRT1 has also been reported to function as a tumor suppressor through the following mechanisms: (1) SIRT1 inhibits tumor formation and proliferation by deacetylating catenin beta (β-catenin) in colon cancer[19]; (2) SIRT1 induces apoptosis in breast cancer 1 (BRCA1)-related breast cancer by suppressing survivin, an inhibitor of apoptosis[20]; and (3) SIRT1 suppresses EMT in cancer by deacetylating SMAD family member 4 (SMAD4) and inhibiting the effect of transforming growth factor beta (TGF-β) signaling on matrix metalloproteinase 7 (MMP7), a target gene of SMAD4[21].
In EC, SIRT1 has been reported as a tumor-promoting factor (Table 2). Suppression of SIRT1 inhibits cell proliferation, cell migration and EMT in esophageal squamous cell carcinoma (ESCC) cell lines[22, 23]. SIRT1 has been suggested to be useful as a biomarker in EC as follows: (1) It has been reported that SIRT1 expression is associated with a poor prognosis in both ESCC and esophageal adenocarcinoma (EAC)[23-28]; (2) SIRT1 has also been demonstrated to be related to chemotherapy and chemoradiotherapy resistance in several ESCC studies[29-32]; and (3) SIRT1 has been described to be a useful biomarker for high-grade dysplasia and cancer of Barrett’s esophagus[33]. Furthermore, we conducted a meta-analysis of these articles and demonstrated that a high expression of SIRT1 was correlated with a poor overall survival (OS), deeper tumors and a more advanced TNM stage in patients with ESCC[34]. In addition, recent studies have reported the potential utility of SIRT1 as a therapeutic target in EC. Liu et al[35] reported that rapamycin suppressed cell viability, migration, invasion and the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways in EC by negatively regulating SIRT1. Jiang et al[36] reported that sirtinol inhibited cell viability in EAC in a dose-dependent manner, affected proliferation in the long term and potentially suppressed resistant and recurrent tumors under hypoxic conditions. Taken together, these reports suggest that SIRT1 inhibition may play an important role in the therapeutic field of EC.

SIRT2

Similar to SIRT1, SIRT2 has been reported to have both tumor-promoting and tumor-suppressing effects depending on the cancer type (Table 1 and Figure 2). SIRT2 has been reported to promote cell proliferation in hepatocellular carcinoma (HCC), pancreatic cancer and neuroblastoma[37, 38]. SIRT2 also promotes cell growth by interacting with the tumor microenvironment, such as mediating immune evasion and altering the alkaline environment[39]. In cholangiocarcinoma, SIRT2 inhibits apoptosis via the peroxidation reaction through metabolic reprogramming by activating cMYC[40]. In addition, SIRT2 promotes invasion and migration in HCC by stimulating mitochondrial metabolism and mediating EMT[41, 42].


**Table 2 Roles of sirtuins in esophageal cancer**

| Type   | Role     | Effect                                                                                                                                                                                                 | Ref.   |
|--------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| SIRT1  | ESCC     | Suppression of SIRT1 inhibits cell proliferation, cell migration, and EMT in ESCC cell line. SIRT1 expression is associated with poor prognosis. SIRT1 enhances chemotherapy and chemoradiotherapy resistance. Rapamycin suppresses cell viability, migration, invasion by negatively regulating SIRT1. | [22, 23] |
|        | EAC      | SIRT1 is associated with poor overall survival. SIRT1 is a useful biomarker for high-grade dysplasia and cancer of Barrett's esophagus. Sirtinol, SIRT1 inhibitor, inhibits cell viability, affects proliferation in the long term, and potentially suppresses resistant and recurrent tumors under hypoxic conditions. | [26] |
|        | ESCC     | Rapamycin suppresses cell viability, migration, invasion by negatively regulating SIRT1. | [35] |
|        | EAC      | SIRT1 is associated with poor overall survival. | [28] |
|        | EAC      | SIRT1 expression is associated with poor prognosis. | [23-27, 34] |
| SIRT2  | ESCC     | SIRT2 expression was associated with tumor invasion, lymph node metastasis, advanced clinical stage, poor progression-free survival, and overall survival. | [47] |
|        | EAC      | Dysregulation of SIRT2 is associated with poor prognosis. | [48, 49] |
| SIRT3  | ESCC     | Serum SIRT3 levels are higher in ESCC patients compared to those in the control subjects. SIRT3 induces the proliferation inhibition and apoptosis. High SIRT3 expression is associated with poor survival outcome. | [63] |
|        | EAC      | No report. | [64] |
|        | EAC      | No report. | [65, 66] |
| SIRT4  | ESCC     | Low SIRT4 expression is associated with a high distant recurrence rate and poor prognosis, and in vitro, knockdown of SIRT4 promotes cell proliferation and migration. | [76] |
|        | EAC      | No report. | [77] |
| SIRT5  | ESCC     | No report. | |
| SIRT6  | ESCC     | SIRT 6 is overexpressed in ESCC tissues and that it also promotes cell proliferation and induces the expression of Bcl2, an important anti-apoptotic factor, and autophagy in ESCC cells. | [102] |
|        | EAC      | No report. | |
| SIRT7  | ESCC     | No report. | |
|        | EAC      | No report. | |

EAC: Esophageal adenocarcinoma; EMT: Epithelial-mesenchymal transition; ESCC: Esophageal squamous cell carcinoma; SIRT: Sirtuin.

Conversely, SIRT2 has been reported as a tumor suppressor that inhibits the growth of tumor cells through interaction with the tumor microenvironment, such as by inhibiting fibroblast activity and tumor angiogenesis[39]. In addition, the increased expression of matrix metalloproteinase 9 (MMP9) and decreased expression of cadherin 1 (E-cadherin) were shown to promote cell migration and invasion in SIRT2-deficient mouse embryonic fibroblasts[43]. In addition, a low expression of SIRT2 is reportedly associated with a poor prognosis in prostate cancer[44], cervical cancer[45] and colorectal cancer[46].

In EC, Yan et al[47] reported that SIRT2 expression was associated with tumor invasion, lymph node metastasis, advanced clinical stage, a poor progression-free survival and the OS in ESCC patients (Table 2). In contrast, SIRT2 has been reported to be a tumor suppressor in EAC. Ong et al[48] revealed that dysregulation of SIRT2 significantly increased the hazard ratio of death. Peters et al[49] also demonstrated that the dysregulation of SIRT2 was significantly associated with a poor prognosis in esophageal and junctional adenocarcinoma.

**SIRT3**

Whether SIRT3, a major mitochondrial deacetylase, functions as a tumor promoter or suppressor remains controversial (Table 1 and Figure 2).
SIRT3 regulates deacetylation to a variety of substrates, including p53, serine hydroxymethyltransferase 2 (SHMT2) and isocitrate dehydrogenase 2 (IDH2), preventing apoptosis and promoting cell proliferation[50-52]. In addition, Li et al[53] showed that SIRT3 promotes infiltration and metastasis of cervical cancer cells by reprogramming fatty acid metabolism.

In contrast, many studies have suggested the role of SIRT3 as a tumor suppressor. It has been reported that SIRT3 induces tumor-suppressing effects such as cell arrest and apoptosis by controlling Bcl-2, p53, hypoxia inducible factor 1 subunit alpha (HIF1α), pyruvate dehydrogenase complex (PDC), superoxide dismutase 2 (SOD2) and glutamic-oxaloacetic transaminase 2 (GOT2)[54-59]. Regarding metastasis, Li et al[60] revealed that SIRT3 promoted FOXO3A expression by weakening the Wnt/β-catenin pathway thereby inhibiting EMT and prostate cancer cell migration. Furthermore, Ozden et al[61] reported that activation of pyruvate dehydrogenase (PDH) by SIRT3 increased oxidative phosphorylation and reactive oxygen species production and reduced glycolysis which contributed to reduced tumorigenesis in cancer cells.

The relationship between SIRT3 expression and the clinical prognosis reportedly differs depending on the type of cancer and no clear consensus has yet been reached[62].

Regarding EC, several reports showed SIRT3 as a tumor promoter in ESCC (Table 2). Cobanoglu et al[63] reported that serum SIRT3 Levels were significantly higher in ESCC patients than in the control subjects. Yang et al[64] showed that downregulation of SIRT3 induced the proliferation inhibition and apoptosis in ESCC cells. In addition, two articles demonstrated that a high SIRT3 expression was significantly associated with a poor survival outcome[65,66]. There have been no reports yet on the relationship between EAC and SIRT3.

**SIRT4**

SIRT4 has been reported primarily as a tumor suppressor (Table 1 and Figure 2). Wang et al[67] revealed that SIRT4 was downregulated in 30 cancers according to an analysis using data from The Cancer Genome Atlas (TCGA) database. SIRT4 is an important component of the DNA damage response pathway that inhibits glutamine metabolism, arrests the cell cycle and suppresses tumors. When SIRT4 is deficient, glutamine-dependent proliferation and stress-induced genomic instability increase resulting in a tumorigenic phenotype[68]. Csihi et al[69] also reported that the mammalian target of rapamycin complex 1 (mTORC1) pathway inhibited SIRT4 and stimulated glutamine metabolism and cell proliferation. In addition, SIRT4 has been reported to enhance E-cadherin and inhibit EMT, thereby decreasing migration and the invasion ability in gastric and colorectal cancer cells[70,71]. Furthermore, Hu et al[72] showed that overexpression of SIRT4 induced G1 cell cycle arrest through the inhibition of the phosphorylated extracellular signal-regulated kinases cyclin D and cyclin E. In addition, several studies have revealed that a low SIRT4 expression was significantly correlated with a poor prognosis in patients with various cancers[73].

In contrast, a small number of studies have reported the function of SIRT4 as a tumor-promoting factor (Table 1). Jeong et al[74] demonstrated that the overexpression of SIRT4 protected cancer cells from DNA damage or endoplasmic reticulum stress, and conversely, the loss of SIRT4 sensitized cells after drug treatment. Furthermore, when cells are starved of nutrients, SIRT4 cooperates with insulin-degrading enzymes to degrade phosphatase and tensin homolog (PTEN), a tumor-suppressing factor, and promote the survival of cancer cells[75].

In EC, SIRT4 has been reported as a tumor suppressor (Table 2). Cui et al[76] revealed that SIRT4 was negatively regulated by miR-424-5p, and overexpression of SIRT4 strongly rescued the promoting effect of miR-424-5p on ESCC cell proliferation and migration capacity. In addition, Nakahara et al[77] reported that a low SIRT4 expression was significantly associated with a high distant recurrence rate and poor prognosis, and *in vitro*, knockdown of SIRT4 promoted glutamine dehydrogenase activity and stimulated cell proliferation and migration.

**SIRT5**

As with other sirtuins, the role of SIRT5 in cancer is highly controversial with some reports emphasizing the cancer-promoting function of SIRT5. (Table 1 and Figure 2). SIRT5 functionally activates glutamate dehydrogenase 1 (GLUD1), an important regulator of intracellular glutaminolysis, and is involved in cell proliferation[78]. In addition, Yang reported that SIRT5 mediated the desuccinylation of SHMT2 and enhanced its activity, which in turn promotes serine metabolism in tumor cells thereby promoting cancer cell growth[79]. Furthermore, studies have shown that SIRT3 promotes cell proliferation by targeting NRF2, pyruvate kinase M2 (PKM2), and Sad1 and UNC84 domain containing 2 (SUN2)[80-82]. Regarding apoptosis, SIRT5 has been reported to deacetylate cytochrome C (Cyt c) and induce mitochondrial apoptosis[83]. Gu et al[84] demonstrated that SIRT5 enhances autophagy and exerts tumor-promoting functions in gastric cancer cells. Moreover, SIRT5 promotes cancer cell invasion and migration by targeting E2F1[85]. Du et al[86] revealed that SIRT5 demalonylated and inactivated...
SIRT6

SIRT6, like other sirtuins, functions as a double-edged sword in cancer (Table 1 and Figure 2). SIRT6 inhibits tumor growth by targeting poly(rC) binding protein 2 (PCBP2) and extracellular signal-regulated kinases 1/2 (ERK1/2)[91,92]. SIRT6 represses HIF-1α and regulates the expression of multiple glycolytic genes[93]. This indicates that SIRT6 plays a role in tumor suppression by inhibiting the Warburg effect. In addition, SIRT6 induces apoptosis in cancer cells by acting on NF-xB, BCL2 associated X (Bax) and survivin[94,95]. Bhardwaj et al[96] found that SIRT6 inhibited the oncosgenic activity of PKM2, which has a non-metabolic nuclear carcinogenic function, resulting in a reduced cell proliferation, migration ability and invasiveness. One meta-analysis revealed that a high SIRT6 expression was associated with a longer OS in gastrointestinal cancers and a favorable TNM stage[97].

However, the role of SIRT6 as a tumor-promoting factor has also been reported. SIRT6 enhances HCC cell proliferation and inhibits apoptosis through the regulation of the ERK1/2 pathway[98]. In addition, Zhou et al[99] revealed that SIRT6 inhibited the acetylation of AKT and promoted its activation thereby preventing apoptosis and inducing cell proliferation. Bai et al[100] reported that the overexpression of SIRT6 in non-small-cell lung cancer cell lines promoted migration and invasion via ERK1/2/MMP9 signaling. SIRT6 has also been reported to positively regulate autophagy in melanoma cells and to exhibit tumor-promoting effects[101].

In EC, SIRT6 has been reported as a tumor-promoting factor (Table 2). Huang et al[102] demonstrated that SIRT6 was markedly overexpressed in ESCC tissues and that it also promoted cell proliferation and induced the expression of Bcl2, an important anti-apoptotic factor and autophagy in ESCC cells.

SIRT7

Like other sirtuins, SIRT7 has also been reported to have both tumor-promoting and tumor-suppressing roles (Table 1 and Figure 2). SIRT7 promotes cell proliferation by regulating ERK1/2 and histone H3 Lysine 18 acetylation (H3K18ac)[103,104]. In addition, SIRT7 induces apoptosis via miR34a, NF-xB family subunits and the mTOR/insulin like growth factor 2 (IGF2) pathway[105-107]. SIRT7 also influences the metastasis of cancer cells. Yu et al[103] showed that cells overexpressing SIRT7 had elevated levels of vimentin and fibronectin, which are markers of mesenchymal lineage, and decreased levels of E-cadherin and β-catenin, which are markers of epithelial lineage indicating enhanced invasion of colon cancer cells.

The role of SIRT7 as a tumor suppressor has been reported to include inhibition of growth and metastasis. Li et al[108] demonstrated that SIRT7 inhibited cell proliferation and invasion by deacetylating SMAD4 in oral squamous cell carcinoma. In addition, Tang et al[109] also revealed that loss of SIRT7 activated TGF-β signaling and promoted EMT.

Reports concerning the relationship between the SIRT7 expression and the prognosis are conflicting, with some citing a good prognosis while the others describe a poor prognosis[110].

In EC, there are no reports investigating the role of SIRT7, and whether it acts as a tumor-promoting factor or a tumor-suppressing factor remains unclear.

FUTURE PERSPECTIVES

As mentioned above, sirtuins have been investigated in a variety of cancer types and play a dichotomous role depending on the situation. This trend is also true in the field of EC. SIRT1, SIRT2, SIRT3 and SIRT6 have been reported as tumor-promoting factors in ESCC, along with SIRT1 in EAC,
while SIRT4 and SIRT2 have been reported as tumor suppressors in ESCC and EAC, respectively. SIRT5 and SIRT7 are interesting targets of study since their roles in both ESCC and EAC have not yet been reported.

One of the future points to be explored concerning sirtuins in EC is expected to be their utility as biomarkers. In most previous studies, the degree of sirtuin expression was assessed by immunohistochemistry. However, the cut-off values for sirtuin expression differed among studies, and this heterogeneity in assessment methods may have led to conflicting results among cancer types. Therefore, more accurate and less-invasive evaluations are anticipated in the future. Serum SIRT3 Levels have been reported to be a potentially useful biomarker, not only in EC[63] but also in lung cancer[111], suggesting that serum sirtuin levels merit exploration as a minimally invasive biomarker. Furthermore, in recent years, a wide variety of public databases, such as TCGA, have been used for analyses[67]. This is expected to make it possible to obtain more comprehensive and standardizable information in the future.

Since sirtuin enzymes play an important role in the regulation of various cellular events, there is strong interest in pursuing sirtuins as therapeutic targets. Although many reports related to the development of sirtuin inhibitors/activators have been found in electronic searches, only a very limited number of small-molecule compounds, such as reveratrol and Ex-527, have been subjected to clinical trials[112]. In the field of EC, the effects of the SIRT1 inhibitors rapamycin and sirtinol have been reported in vitro and in vivo[35,36]. However, SIRT1, like other sirtuins, has been suggested to promote or inhibit cancer in a context-dependent manner so many comprehensive studies are needed to determine its clinical application. Although not yet presented, other sirtuin-targeted agents still have great therapeutic potential and advances in this area will contribute to the development of EC treatment.

In recent years, the breakthrough of immunotherapy has been considered an important topic in EC[113]. The involvement of sirtuins in immunity has been widely studied since the early discovery that SIRT1 regulates NF-κB, a transcription factor known to control inflammation and immune cell proliferation[114]. There have been no reports on the role of sirtuins in immunotherapy of esophageal cancer, although some reports have appeared in other cancer types. Zhang et al[115] showed that pharmacological inhibition of SIRT2 increased natural killer cell infiltration into the tumor and suppressed tumor growth in allograft melanoma. Furthermore, Xiang et al[116] demonstrated that SIRT7 suppressed myocyte enhancer factor 2D acetylation and programmed death ligand 1 expression and promoted HCC cell proliferation. Thus, the role of sirtuins in anti-tumor immunity in EC is an issue that deserves further attention and research.

CONCLUSION

In summary, sirtuins may be a key target for EC treatment in the future. However, much research is still needed to determine the clinical application as many aspects remain unresolved. We hope that this review will contribute to the development of this field.

FOOTNOTES

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