



Targeting *SEN1* as a Novel Cancer Therapeutic Strategy

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Abstract

SEN1 (SUMO1-Specific Protease 1), a Sentrin/SUMO-specific protease, plays an important role in SUMO family members maturation and target proteins deSUMOylation. Aberrant expression and regulation of *SEN1* has been found in various cancers. Furthermore, dysregulation of *SEN1* is significantly associated with cancer biological behaviors. This review focuses on the role of *SEN1* in cancer proliferation, apoptosis, invasion, migration, metabolism and immune, providing theoretical basis for cancer diagnosis, treatment and prognosis.

Keywords: SUMO specific protease 1; deSUMOylation; Cancer progression

Introduction

The SUMO-specific protease family is a cysteine protease involved in cancer progression [1]. Among the six members (*SEN1*, *SEN2*, *SEN3*, *SEN5*, *SEN6*, and *SEN7*), *SEN1* is a 73 kDa protein which can shuttle between the nucleus and cytoplasm [2]. The human *SEN1* gene locates on chromosome 12 at 12q13.11 and regulates the processing and maturation of SUMO and deSUMOylation of target proteins [3]. SUMOylation is a dynamic and reversible Post-Translational Modification (PTM), which involved in multiple biological processes, including cell division, DNA replication/repair, signal transduction, and cellular metabolism [4]. Aberrant expression of *SEN1* has been found in various cancers. The changes in the homeostasis of target protein SUMOylation mediated by *SEN1* are closely related to cancer progression. In this review, we systematically elucidate the expression and function of *SEN1* in various cancers, providing new insight for cancer diagnosis, treatment and prognosis.

SEN1 in cancer proliferation and apoptosis

Cancer cells have unlimited proliferation and resistance to apoptosis ability. *SEN1* promotes tumor proliferation through positively modulating c-Myc and PIN1 stability in breast cancer while knockdown of *SEN1* drastically induces cell cycle arrest [5]. Furthermore, *SEN1* deletion decreases triple negative breast cancer cell proliferative ability through blocking cell cycle [6]. Several studies demonstrated that *SEN1*-mediated deSUMOylation of HIF-1 α could upregulate HIF-1 α stability and transcriptional activity, as well as downstream target genes expression, thus enhancing the proliferation and resistance to apoptosis of cancer cells. For example, *SEN1* promotes liver cancer cells growth through HIF-1 α mediated stemness-related genes including Oct 3/4, Nanog, Notch1 and BMI-1 expression increase [7]. In Wilms tumor, *SEN1* upregulates Cyclin E1 level by deSUMOylating HIF-1 α , which promotes the survival and cell cycle progression [8]. Furthermore, *SEN1* down-regulates the expression of apoptotic protein BAX while up-regulates the expression of anti-apoptotic protein Bcl2, thereby suppressing the apoptosis procession of osteosarcoma cells under hypoxia [9]. In glioma, knockdown *SEN1* decreases the expression of Cyclin D1 and suppresses proliferation. Moreover, apoptosis analysis shows that *SEN1* deletion drastically induces apoptosis [10]. Mechanistically, *SEN1* suppresses astrogloma cells apoptosis through NF- κ B/AKT signaling pathway [11]. In lung cancer cells, *SEN1* is upregulated and silencing *SEN1* suppresses cancer proliferation, while promotes its apoptosis [12]. The carcinogenic effect of *SEN1* is not only reflected in solid tumors, but also in hematological tumors. In Multiple myeloma, *SEN1* deficiency can down regulate the phosphorylation of p65 and I κ B α through which block NF- κ B signal, and thus triggering tumor cells apoptosis and reducing their proliferation [13]. Furthermore, *SEN1* knockdown also inhibits cell proliferation while promote cell apoptosis in Mantle Cell Lymphoma (MCL) [14]. In summary, *SEN1* promotes proliferation while suppresses apoptosis in several cancer progression.

SEN1 in cancer invasion and migration

Invasion and migration are key features in tumor progression, which causes poor prognosis and death of cancer patients. To explore the specific mechanism of *SEN1* in cancer invasion and

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Table 1: The role of *SENPI* in various cancers.

Cancer	Biological function	Target	Reference
Breast cancer	Promotes proliferation, invasion, metastasis and epithelial mesenchymal transition	c-Myc; PIN1; GATA1; HIF-1 α	[5,24,38]
Liver cancer	Promotes proliferation, invasion, metastasis and epithelial mesenchymal transition	HIF-1 α ; ZEB1	[7,23]
Wilms tumor	Promotes proliferation and poor prognosis	Cyclin E1	[8]
Osteosarcoma	Promotes proliferation, invasion, epithelial mesenchymal transition and inhibits apoptosis. Acts as a prognostic biomarker	HIF-1 α	[9,35]
Glioma	Promotes proliferation and suppresses apoptosis	Cyclin D1; NF- κ B/Akt	[10,11]
Multiple myeloma	Promotes proliferation and suppresses apoptosis	P65; I κ B α	[13]
Mantle cell lymphoma	Promotes proliferation and suppresses apoptosis	JAK/STAT5; SOC2	[14]
Prostate cancer	Promotes glycolysis, proliferation, invasion, metastasis and epithelial mesenchymal transition	SMAD4; HK2	[22,27]
Renal clear cell carcinoma	Promotes proliferation and glycolysis	HIF-1 α	[28]
Ovarian cancer	Contributes to platinum resistance, poor prognosis, and tumor progression	JAK2; HIF-1 α	[32,33]
Colorectal cancer	Promotes proliferation, invasion, migration, Irinotecan resistance, and suppresses apoptosis	HIF-1 α ; c-Myc	[34,40]

migration will help to restrict tumor progression. As we all know that the local invasion and distant metastasis are closely associated with tumor angiogenesis and Epithelial Mesenchymal Transition EMT, we will discuss the specific role of *SENPI* in angiogenesis and EMT.

Continuous angiogenesis is one of the top ten markers of malignant tumor [15]. Tumor angiogenesis not only provides nutrients and oxygen for the growth of cancer cells, but also provides an approach to spread and migrate [16]. Vascular Endothelial Growth Factor (VEGF) and NOTCH signaling pathway play important roles in angiogenesis. *SENPI* has been reported to contribute to the expression and secretion of VEGF under hypoxia. The deletion of *SENPI* enhances the SUMOylation of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), which impairs its signaling pathway and reduces pathological angiogenesis of endothelial cells [17]. In addition, *SENPI* can suppress NOTCH over activation, which facilitates germination of new blood vessels [18].

The biological process that loss epithelial cells feature while gain mesenchymal cells features is called Epithelial Mesenchymal Transformation (EMT) [19]. EMT progression in cancer cells represents as the decrease of epithelial markers E-cadherin while the increase of stromal markers including N-cadherin and vimentin [20]. It is essential for the formation of EMT that SAMD complex transcripts and activates mesenchymal genes in Transforming Growth Factor β (TGF β) pathway [21]. *SENPI* upregulates SMAD4 at post-translational level through deSUMOylation, thus decreasing E-cadherin expression while inducing EMT, ultimately promoting invasion and migration in prostate cancer cells [22]. In liver cancer, *SENPI* knockdown upregulates E-cadherin expression and down regulates fibronectin and N-cadherin expression through deSUMOylating ZEB1 [23]. Mechanistically, *SENPI* mediates the deSUMOylation of GATA1 to enhance the binding of GATA1 to CSN5 promoter, which transactivates CSN5 and subsequently regulates the stability of ZEB1, thereby promoting invasion and migration of triple-negative cells [24]. Hypoxia promotes tumor invasion and metastasis through EMT and chen et al. [25] found that *SENPI* played a promoting role in hypoxia induced EMT [25]. Furthermore, *SENPI*-HIF-1 α axis has a similar effect on EMT in osteosarcoma [9]. In conclusion, *SENPI* promotes tumor invasion and migration through regulating angiogenesis and EMT signaling pathway.

***SENPI* in tumor metabolism**

Cancer growth depends on the glycolytic pathway largely to maintain enough energy production. It has been shown that *SENPI* is a crucial molecule in Warburg effect [26]. Another study found that *SENPI* regulated metabolism in prostate cancer. Human Hexokinase 2 (HK2) is an important regulator in cell glycolysis. *SENPI*-mediated deSUMOylation promotes HK2 binding with mitochondria through which increases glucose consumption and lactic acid production, ultimately resulting in tumor growth [27]. The positive correlation between *SENPI* and glycolysis level was also observed in renal clear cell carcinoma. *SENPI* stabilizes HIF-1 α through deSUMOylation, which increases the expression of key glycolysis enzymes and glycolysis flux, ultimately resulting in cancer progression [28].

***SENPI* in tumor immune**

Recently, tumor immunotherapy has been the new hope for cancer treatment. Researchers found that *SENPI* is essential for early lymphocyte development. *SENPI* deficiency suppresses the activation of STAT5 and subsequent signal transduction, which leads to severe defects in the early development of T cell and B cell [29]. He et al. found that glucose limitation in immune microenvironment could activate *SENPI*-SIRT3 axis through AMPK, resulting in T cell memory development and anti-tumor immunity [30]. Furthermore, *SENPI* expresses differently in the myeloid cell subsets of tumors. The deletion of *SENPI* in Myeloid-Derived Suppressor Cells (MDSC) inhibits STAT3 dephosphorylation by enhancing the SUMOylation of CD45, which leads to the expansion of MDSC and the increase of immunosuppression, causing tumor progression eventually [31]. In summary, these findings confirm the important regulatory significance of *SENPI* in anti-tumor immunity. However, immune regulation is a complex process that needs to be further explored.

***SENPI* in cancer chemotherapy tolerance and prognosis**

Currently, drug resistance is a major problem that limits the efficacy of tumor therapy and affects prognosis. *SENPI* is recognized as a potential target for overcoming platinum resistance in various cancer progressions. High level of *SENPI* causes JAK2 accumulation in cytoplasm through the deSUMOylation of JAK2, which promotes JAK2/STAT3 signaling pathway, resulting in poor survival rate of ovarian cancer patients with platinum therapy [32]. Furthermore, research confirmed the desensitization of *SENPI* in platinum therapy of ovarian cancer [33]. Targeting *SENPI* is expected to be an important strategy to resist irinotecan resistance and improve

prognosis in colorectal cancer cells [34]. In Wilms tumor, patients with high *SENPI* expression have significantly lower Overall Survival (OS) and Disease-Free Survival (DFS) than those with low *SENPI* expression [8] (Table 1). The upregulation of *SENPI*-HK2 axis is closely associated with short progression-free survival and poor prognosis with docetaxel treatment in prostate cancer patients [27]. Therefore, targeting *SENPI* might contribute to improve the therapeutic effect and prognosis of cancer [34-40].

Conclusion and Future Perspectives

The aberrant expression of *SENPI* in tumors and its crucial role in tumorigenesis indicate that *SENPI* may be a new therapeutic target for cancer treatment. Clinically, the level of *SENPI* in patient plasma exosomes with osteosarcoma may serve as a prognostic biomarker, which indicates that early detection of *SENPI* is expected to improve the poor prognosis of cancer patient. Recently, several studies have found that microRNA can inhibit tumor growth, invasion and metastasis by targeting *SENPI* in colorectal cancer, renal cell carcinoma and prostate cancer. Moreover, the development of *SENPI* inhibitors, such as Streptonigrin and Momordin Ic, may help slow down tumor progression. These findings suggest that directly targeting *SENPI* might be a beneficial antitumor therapy. At present, a large number of researches have shown that *SENPI* promote progression of cancer cells. However, *SENPI* has different biological effects in tumor immunity which needs to be further illuminated. In summary, *SENPI* is involved in cancer proliferation, apoptosis, invasion, migration, metabolism, immune, chemotherapy tolerance and prognosis which are closely related to cancer initiation, development and progression. The study of *SENPI* specific regulatory process in cancer will provide a novel effective approach for cancer treatment.

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