SENP1: A perspective from immune cells to disease (Review)

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Abstract. Small ubiquitin-like modifier (SUMO) is a ubiquitin-like protein that modifies target proteins across various eukaryotic subcellular structures. This process, known as SUMOylation, has been established as an essential regulatory mechanism that affects both the activity and positioning of proteins, maintaining cellular homeostasis. SUMOylation and deSUMOylation are reversible post-translational modification processes mediated by SUMO proteins and SUMO/sentrin-specific proteases (SENPs). The human SENP family comprises six members, each characterized by unique cellular localization and substrate specificity. The present review primarily summarizes the role and mechanisms of SENP1 in the development and maturation of immune cells, including lymphocytes, macrophages and erythrocytes, as well as its involvement in tumor cell invasion, metastasis, angiogenesis and resistance to pharmacological therapies. In addition, the introduction of SENP1 inhibitors as a therapeutic approach for cancer treatment is explored. Overall, the present study aimed to offer theoretical insights into cancer therapy strategies that target SENP1.

Contents

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1. Introduction

Small ubiquitin-like modifier (SUMO)ylation represents a significant post-translational modification (PTM) facilitated by a limited number of specialized enzymes while exerting dynamic regulation over a vast array of target proteins. SUMOs can be conjugated to these target proteins either as single monomers or as various forms of polymeric structures (1). The human genome encodes five distinct SUMO proteins, namely SUMO1, SUMO2, SUMO3, SUMO4 and SUMO5 (2). Among these, SUMO1, SUMO2 and SUMO3 constitute the major variants exhibiting distinct substrate specificity profiles in PTM processes. For example, Ran GTPase activating protein 1 is a canonical substrate for SUMO1, whereas topoisomerase II is primarily modified by SUMO2/3 (3,4). SUMO molecules are highly evolutionarily conserved and widely found in protozoa, metazoa, plants and fungi (4). SUMO is coupled as a monomer to lysine residues on substrate proteins, leading to mono-SUMOylation or multi-SUMOylation when multiple lysines are modified, and SUMOylation often targets functionally related protein groups (5). Current evidence has suggested that an enzymatic cascade mediates SUMOylation through four distinct stages: Substrate maturation, E1 activation, E2 conjugation and E3 ligation. Initially, SUMO-specific proteases (SENPs) cleave pro-SUMO proteins through C-terminal truncation, releasing the conserved di-glycine motif essential for functional activation of mature SUMO molecules. Following maturation, SUMO binds the catalytic cysteine of the E1 enzyme, triggering enzyme activation and the establishment of a SUMO-E1 complex. The SUMO protein is then transferred to the E2 conjugating enzyme. Ultimately, the E3 ligase facilitates the transfer of SUMO from E2 to the substrate lysine, catalyzing isopeptide bond formation via a conserved catalytic triad (6,7). The outcomes of SUMOylation encompass alterations in subcellular localization, modification

of protein activity or enhanced protein stability. Furthermore, SUMO can interact with ubiquitin to facilitate the degradation of proteins through SUMO-targeted ubiquitin ligases (8). SUMOylation represents a dynamic and reversible mechanism (Fig. 1). DeSUMOylation, the enzymatic removal of SUMO modifications from target proteins, is catalyzed by a family of cysteine proteases called SENPs.

The SENP enzymatic family comprises cysteine-dependent proteases with conserved catalytic domains. Variations in the N-terminal sequences of SENP isoforms result in variations in both their molecular size and functional properties. Notably, the C-terminal catalytic core in SENPs, critical to deSUMOylation, spans 250 amino acids and mediates substrate binding, stabilizes the transition state and mediates product release (9). Mammalian systems express six distinct SENPs, categorized into three evolutionarily conserved phylogenetic subgroups: SENP1/2, SENP3/5 and SENP6/7 (8). The SENP1 gene is situated at chromosomal locus 12q13, and the SENP1 protein exhibits both cytoplasmic and nuclear distribution, and may be shuttled between the N-terminal nuclear localization signal and the nuclear export sequence near the C-terminal (10,11). SENP2 is localized to nuclear pore complexes, whereas SENP3/5 exhibit nucleolar enrichment. By contrast, SENP6/7 primarily demonstrate predominant nucleoplasmic distribution (2). Among SENPs, SENP1 is the most prevalent SUMO-specific peptidase that preferentially deSUMOylates SUMO1 conjugates over SUMO2/3 (10,12). During mitosis, both SENP1 and SENP2 localize to the centromere and their dysregulation leads to chromosome segregation errors (13). Despite their significant structural homology and shared role in the deSUMOylation of substrate proteins modified by SUMO1-3, SENP1 and SENP2 exhibit distinct biological roles and are not interchangeable (14).

Mitochondrial protein acetylation is a highly prevalent and essential regulatory mechanism of mitochondrial proteins, which is mainly governed by the deacetylase sirtuin 3 (Sirt3). SENP1 promotes Sirt3 deacetylation by mediating its deSUMOylation. SENP1 deficiency leads to hyper-SUMOylation of Sirt3 and hyper-acetylation of mitochondrial proteins, which accelerates aerobic glycolysis and other metabolic reprogramming, thereby promoting the occurrence of malignant tumors (15,16). The present review discusses the immunoregulatory functions of SENP1 and its role in various diseases, offering potential insights for disease treatment.

2. SENP1 in immune regulation

The innate immune response serves as the initial barrier against pathogens, comprising various physical, chemical and cellular mechanisms of defense (17-19). Current evidence has suggested that SENP1 is essential for regulating multiple functions within immune cells, encompassing their development, differentiation and polarization. Furthermore, SENP1 is crucial for initiating transcriptional programs associated with the innate immune response, as well as for the development of B and T lymphocytes (17). Research has indicated that the SENP1-Sirt3 signaling pathway facilitates the recruitment of T cells into tumor microenvironments. Notably, elevated SENP1 expression has been reported to be associated with increased tumor-infiltrating lymphocytes, suggesting its role in augmenting immune-mediated tumor suppression (17,18). Dai *et al* (19) demonstrated that SENP1 could specifically hydrolyze the poly-SUMO chains on mitochondrial antiviral proteins, and antagonize the recruitment and activation of the transcription factor interferon (IFN) regulatory factor (IRF)3, thus preventing the synthesis of type 1 IFN and suppressing the innate antiviral immune response.

SENP1 and lymphocyte development. SENP1 is indispensable for the early developmental phases of T- and B-lymphocyte maturation. Signal transducer and activator of transcription (STAT)5, a key regulator of lymphocyte development, undergoes both acetylation and SUMOylation modifications at lysine residue 696, and SUMOylation of STAT5 has been shown to block its acetylation. In the absence of SENP1, an accumulation of SUMO2-modified STAT5 is observed within early lymphoid precursors; this accumulation hinders the acetylation process of STAT5 and disrupts its downstream signaling pathways, ultimately causing notable impairments in lymphocyte development (20).

SENP1 and memory T cells. Upon antigen stimulation, T cells undergo differentiation into effector cells and subsequently form memory cells. Within the diverse group of effector cells, specific subpopulations, including memory precursor effector cells, progress to develop into long-lived memory T cells. By contrast, other subsets, notably short-lived effector cells, are terminally differentiated and undergo apoptosis following the resolution of antigenic stimulation (21). Mitochondrial fusion enhances the mitochondrial electron transport chain and promotes fatty acid oxidation (FAO) within memory T cells, thereby contributing to their increased viability and functionality. OPA1 orchestrates the fusion of mitochondrial membranes and the structural dynamics of cristae through its proteolytic processing and lipid-binding domains. Its cleavage is modulated by the activity of the mitochondrial inner membrane protein YME1L1. SENP1 facilitates activation of the Sirt3 deacetylase within the mitochondria of T cells via deSUMOylation. This activation leads to the deacetylation of YME1L1 and subsequently inhibits the OPA1 cleavage process, thereby promoting mitochondrial fusion and cristae remodeling in T cells and enhancing mitochondrial oxidative phosphorylation, ultimately contributing to the longevity of T cells and their maturation into memory T cells (18,22-24).

SENP1 and regulatory T (Treg) cells. Treg cells, a specialized subset of T cells, serve a crucial role in modulating cellular immunosuppression throughout the immune response. Foxp3, a forkhead box family transcription factor, governs the differentiation, maintenance and suppressive functions of Treg cells through epigenetic modulation (25). As a member of the IRF family, IRF4 expression is elevated in activated lymphocytes, facilitating immune responses (26,27). IRF4 functions as a co-factor of Foxp3 and is essential for Treg cells to control the T helper 2 cell response. It has been reported that SENP1 deSUMOylates IRF4 and reduces IRF4 accumulation, resulting in lower Foxp3 levels in Treg cells and inhibiting Treg differentiation (28).

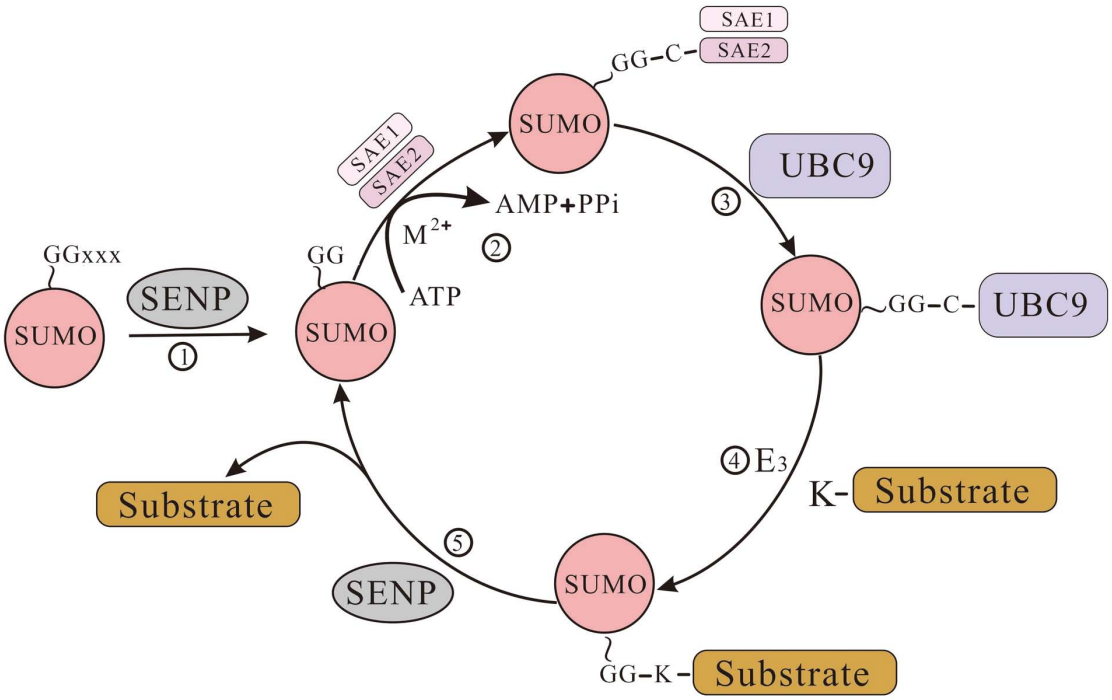

Figure 1. Model of SUMOylation. SUMO precursors are processed by SENPs to generate SUMO-GG. This form is subsequently activated by the SUMO E1 enzyme complex, composed of SAE1 and SAE2. Subsequently, SUMO is conveyed to the conjugating enzyme (UBC9, E2), resulting in the formation of an additional thioester complex. Finally, the attachment of SUMO to the K residue found in target proteins is facilitated by the action of a SUMO E3 K. K, lysine; SENP, SUMO/sentrin-specific protease; SUMO, small ubiquitin-like modifier.

SENP1 and germinal center (GC) B cells. The proliferation of B cells that express high-affinity and class-switched B-cell receptors within the GC represents an essential process for the development of a strong humoral immune response (29). Following antigen exposure, activated B cells migrate into the GC, where they undergo proliferation, and subsequently differentiate into plasma B cells and memory B cells. Furthermore, B cells within the GC increase the diversity of their immunoglobulin genes through somatic hypermutation and class-switch recombination, processes that promote the production of high-affinity antibodies and enable class switching (30). SENP1 mediates the deSUMOylation of paired box protein 5 (PAX5) at K257, which contributes to the increased stability of PAX5 and subsequently elevates the expression of activation-induced cytidine deaminase within GC B cells. The absence of SENP1 in GC B cells leads to a compromised antigen-specific B cell response, characterized by a reduction in the populations of antibody-secreting B cells, plasma B cells and memory B cells, alongside a reduction in overall antibody synthesis (31,32).

SENP1 and plasma cells. B lymphocyte-induced maturation protein-1 (Blimp-1), encoded by the *Prdm1* gene, functions as a DNA-binding and transcriptional repressor. This protein serves an essential role in facilitating the terminal differentiation of B cells (33,34). The transcription factor PAX5 can inhibit plasma cell differentiation (35). C-Myc has a crucial role at critical junctures in cellular growth, facilitating proliferation while inhibiting terminal differentiation. Its suppression is an integral aspect of the Blimp-1 pathway associated with the terminal differentiation of B cells (36). Blimp-1 directly inhibits PAX5 and Myc (36), thereby interfering with the expression of genes required for B-cell identity and proliferation, and ultimately inducing plasma cell differentiation (37). Blimp-1 is subject to SUMOylation and degradation shortly after synthesis. Notably, SENP1 protects Blimp-1 from proteasomal degradation by deSUMOylation (37).

$CD19^{+}CD1d^{hi}CD5^{+}$ B regulatory (Breg) cells exert their immunomodulatory functions primarily through the secretion of IL-10 and are specifically categorized as B10 cells. The transcription factor Blimp-1 serves a crucial dual role in regulating IL-10 transcription within these B10 cells. Under steady-state conditions, Blimp-1 directly inhibits IL-10 transcription; however, upon stimulation of B10 cells, phosphorylated STAT3 collaborates with Blimp-1 to promote the transcription of IL-10. Collectively, these findings underscore the notable role of Blimp-1 in governing the production, differentiation and IL-10 secretion of Breg cells (38). Given its role in deSUMOylating Blimp-1, SENP1 is involved in the regulation of Breg cell generation and function through this mechanism.

SENP1 and macrophages. Macrophages, derived from bone marrow precursors, are vital components of the innate immune system; they possess the ability to phagocytize pathogens and initiate a series of responses that ultimately result in the elimination of these microorganisms (39). As a master regulator, IRF8 coordinates the developmental pathways of monocytes, macrophages and dendritic cells. It is also essential for the manifestation of inherent anti-microbial functions, including the capture, processing and presentation of antigens to lymphocytes. Furthermore, upon recognition of IFN-γ, IFN-β or lipopolysaccharide (LPS), IRF8 drives the transcriptional programs necessary for immune cell activation (40). IRF8

facilitates IFN-γ-mediated macrophage development while simultaneously modulating the production of key cytokines, including TNF-α and IL-12p40 (41,42). Another study has revealed that the activity of IRF8 is inhibited upon binding of lysine 310 to SUMO2/3 in resting macrophages, and SENP1 can reduce both monomeric and polymeric SUMO3 from binding to IRF8, leading to a decrease in the levels of SUMOylated IRF8. This activates IRF8, thereby enhancing the expression of target genes such as IL-12p40, promoting macrophage activation and innate immune response (43).

M1 polarization. Macrophages exhibit the capacity to undergo polarization into distinct phenotypes, specifically classically activated M1-like and alternatively activated M2-like phenotypes, depending on the nature of external stimuli. The initiation of M1 polarization occurs in response to LPS, IFN or TNF. M1-like macrophages exhibit a pro-inflammatory phenotype through the release of cytokines such as TNF-α and IL-1β, coupled with elevated reactive oxygen species (ROS) and nitric oxide production, which synergistically amplify T helper 1 cell responses (44). The polarization of M2 macrophages is induced by IL-4 or IL-13, and this phenotype serves a notable role in the immune response to parasitic helminths, as well as in processes such as tissue remodeling, wound healing and the advancement of tumors (45,46). Macrophage polarization is regulated by various key signaling pathways, including STATs, NF-κB and PPAR (47,48).

Current evidence has suggested that STAT1 is stimulated by IFN-γ during the activation of M1-like macrophages. Conversely, as a key downstream effector of cytokine or growth factor receptors, STAT3 consistently promotes the expression of genes linked to the M2-like macrophage phenotype (IL-10, TGF-β1, MRC1) to counteract STAT1-induced inflammation (49). The activation of STAT1 and STAT3 is subject to reciprocal regulation, and any disturbances in their balanced expression or phosphorylation status can shift cytokine or growth factor signaling pathways from promoting cell proliferation to inducing apoptosis, or from facilitating inflammation to enhancing anti-inflammatory responses (50). SENP1 influences the fate of macrophages by regulating the balance of STAT1:STAT3 activation. SENP1 increases the functionality of protein tyrosine phosphatase 1B through its deSUMOylation, which subsequently leads to the dephosphorylation of the activated form of STAT3. The resulting STAT3 inhibition further maintains the activated state of STAT1 and ultimately promotes macrophage M1 polarization (49).

The NF-κB transcription factor is essential for modulating the behavior of tumor-associated macrophages within the tumor microenvironment. NF-κB can directly regulate the transition of macrophages to the M1 phenotype when stimulated by Toll-like receptor ligands, IL-1β and TNF-α, among others. Kruppel-like factor 4 (KLF4) serve a crucial role in a number of biological processes, including macrophage polarization (51). KLF4 works synergistically with STAT6 to activate an M2 genetic program while simultaneously suppressing M1-associated targets. This process occurs through the sequestration of coactivators essential for the activation of NF-κB (52). SENP1 disrupts the interaction between KLF4 and p300/CPB-associated factor (PCAF) by reducing KLF4 SUMOylation. Accordingly, PCAF binds to NF-κB and enhances its transcriptional activity, resulting in an antitumorigenic macrophage phenotype with enhanced M1-like polarization capacity (53,54).

M2 polarization. The SENP1-Sirt3 signaling pathway mediates mitochondrial glutamine catabolism, thereby driving α-ketoglutarate (αKG) production essential for macrophage metabolic reprogramming. The SUMOylated protein Sirt3 in mitochondria is activated by deSUMOylation of SENP1 (15). Sirt3 subsequently deacetylates mitochondrial glutamate dehydrogenase 1, thereby enhancing its hydrolytic activity to promote αKG production in macrophages. αKG acts as a co-stimulator factor for Jumonji domain-containing protein D3 (Jmjd3); Jmjd3 is an H3K27 demethylase that controls M2 activation through epigenetic regulation. αKG promotes H3K27 demethylation to enhance M2 activation and control metabolic reprogramming in M2 macrophages by regulation of Jmjd3 (55,56). In addition, the accumulation of αKG leads to the upregulation of genes associated with M2 polarization, such as Arg1, Retnlα and Chil3, as well as the production of IL-10, ultimately promoting M2 macrophage polarization (57).

Macrophage death. Nuclear receptor 4A1 (NR4A1), also known as Nur77, TR3 or NGF-IB, belongs to the steroid nuclear hormone receptor superfamily, specifically classified within the NR4A subfamily (58,59). NR4A is an immediate early gene that responds rapidly to various stimuli, including growth factors and stressors, and can be activated in diverse cell types and tissues (60). Notably, NR4A1 expression is associated with macrophage death (61). NR4A1 undergoes RNF4-mediated polyubiquitination, a SUMO-dependent process that triggers its degradation by the proteasome. Notably, SENP1 significantly antagonizes both ubiquitination and subsequent proteasomal degradation of NR4A1 through deSUMOylation, thereby promoting macrophage death (62).

SENP1 and microglia. Microglia, which function as macrophages within the central nervous system, represent a crucial cellular component of the active immune defense mechanism in this region. Their activation is prompted by the increased expression of ROS and receptors for pro-inflammatory cytokines, which occurs following either cerebral injury or immune challenge. Activated microglia secrete a range of inflammatory mediators, including IL-1β, IL-12, TNF-α and inducible nitric oxide synthase (63,64). The release of these cytokines can, in turn, stimulate further activation of microglia, resulting in a detrimental inflammatory cascade; a sustained chronic inflammatory state can lead to neuronal damage (63,64).

Current evidence has suggested that NF-κB represents a central transcriptional regulator in the induction of pro-inflammatory gene expression (65). IκB proteins, which act as inhibitors of NF-κB, include IκBα, IκBβ and IκBε (65). In the resting state, IκBα binds to NF-κB heterodimers (p65/p50) in the cytoplasm, preventing their nuclear translocation. IκBα can be phosphorylated by inhibitor of κB kinase (IKK), and the phosphorylation of IκBα leads to its degradation, which promotes NF-κB phosphorylation and entry into the nucleus, thus facilitating NF-κB-dependent transcription of inflammatory genes, resulting in an inflammatory response (66).

NF-κB essential modulator (NEMO) constitutes a vital component of the cytoplasmic IKK complex (67). SENP1 inhibits IKK by deSUMOylation of NEMO lysine 277/309 and maintains the levels of IκBα, ultimately inhibiting NF-κB activation and the inflammatory response (68). Microglia can be polarized into M1 and M2 phenotypes. The M1 phenotype is primarily present in areas experiencing neuroinflammation and facilitates the release of pro-inflammatory mediators. By contrast, through the upregulation of anti-inflammatory mediators, M2-polarized macrophages facilitate wound healing and tissue remodeling (69,70). Furthermore, it has been reported that target of Myb 1 (TOM1) accelerates migration and phagocytosis of M2-type microglia (71). SUMOylated TOM1 is also degraded in a proteasome-dependent manner, and SENP1 enhances M2-type microglia migration and inhibits neuronal apoptosis through deSUMOylation of TOM1 (72).

SENP1 and erythropoiesis. Besides their essential role as oxygen transporters in vertebrates, erythrocytes contribute to regulation of the immune response. The role played by erythrocytes in immunomodulation has been summarized in a previous review by Papadopoulos *et al* (73). During erythroid differentiation, erythropoietin (EPO) is indispensable for both the proliferation of progenitor cells and their sustained survival. Besides, hypoxia-inducible factor-1 (HIF1α) serves as a key transcriptional regulator in the hypoxic modulation of EPO expression (74). Cheng *et al* (75) reported that the degradation of SUMOylated HIF1α occurs through a proteasome-dependent pathway. The enzyme SENP1 facilitates the deSUMOylation of HIF1α, enabling it to evade degradation under hypoxic conditions, which subsequently regulates the production of EPO (75). GATA binding protein 1 (GATA1), an important member of the GATA transcription factor family, is essential for normal erythropoiesis (76). The accumulation of SUMOylated GATA1 in SENP1-deficient fetal livers leads to a marked reduction in GATA1 transcriptional activity and downregulation of its target genes. By contrast, SENP1 can deSUMOylate GATA1, promoting GATA1 DNA binding activity and GATA1-dependent EPO receptor expression, and finally promote erythropoiesis (76).

Based on the aforementioned findings, the regulatory roles of SENP1 in immune cell development, differentiation and function have been summarized in Fig. 2.

3. SENP1 and infection

In sepsis, SENP1 stabilizes the protein level of specificity protein 3 through its deSUMOylation, which then interacts with NF-κB, promoting NF-κB transcriptional activation and subsequently exacerbating LPS-induced macrophage inflammation. Consistently, downregulation of SENP1 expression via small interfering RNA or inhibitors significantly reduces LPS-induced cellular inflammation (77,78). It has also been shown that infection of host macrophages by *Leishmania donovani* results in upregulation of the SUMOylation pathway genes and downregulation of the deSUMOylation gene *SENP1*. Furthermore, the upregulation of ROS, nitric oxide and proinflammatory cytokines suggests that SUMOylation modulates protective immune responses, thereby promoting parasite survival. SENP1 knockdown in infected macrophages results in decreased levels of IL-10, IL-12p40 and TNF-α, alongside upregulated lysosome-associated membrane protein 1 expression, which ultimately promote the fusion of autophagosomal lysosomes (79). *Leishmania donovani* infection modulates the host SUMOylation process to facilitate its survival and growth in macrophages (79).

4. SENP1 and tissue damage

Oxidative stress is a notable contributor to ischemia-reperfusion (IR) injury and mitochondria serve a critical role as the central regulators of cellular oxidative stress (80). Mitochondrial SENP1 maintains mitochondrial homeostasis and attenuates cerebral IR injury by mediating deSUMOylation of Sirt3. Enhanced deSUMOylation of Sirt3 promotes its deacetylation, which reduces the acetylation level of mitochondrial superoxide dismutase 2, decreases mitochondrial ROS and subsequently restores the level of mitochondrial ATP. This process reverses mitochondrial morphology and alleviates cell apoptosis, thereby mitigating oxidative damage induced by IR injury, a mechanism involving the activation of the AMPK signal transduction pathway (81,82).

SENP1 also has an important role in the pathogenesis of hyperoxia-induced lung injury. SENP1 inhibits Sirt1 deacetylase activity and promotes cell apoptosis via Sirt1. Accordingly, silencing SENP1 can reduce hyperoxia-induced apoptosis (83). Furthermore, alterations in lung mesenchymal cells triggered by the senescence of alveolar epithelial cells (AECs) are crucial for initiating the development of pulmonary fibrosis. TGF-β1 is a key mediator in cellular senescence and lung fibrosis processes, primarily by diminishing the population of AECs and impairing their repair capabilities (84,85). A recent investigation revealed that SENP1 is overexpressed in senescent AECs (86). The deSUMOylation process mediated by SENP1 enhances the activity of crucial downstream proteins, specifically SMAD4 and Ras, within the TGF-β1 signaling pathway (86). Notably, SENP1 may prevent lung resident mesenchymal stem cells (LR-mSCs) from differentiating into myofibroblasts; therefore, therapeutic intervention targeting SENP1 could restore the reparative function of LR-mSCs, representing a potential therapeutic strategy for lung fibrosis (87).

The SENP1-mediated process of deSUMOylation serves a crucial role in the mitochondrial reorganization of endothelial cells under conditions of hypoxic pulmonary hypertension (88). Short-term hypoxia induces SENP1 translocation into endothelial cell mitochondria, where it regulates the deSUMOylation of mitochondrial fission protein mitochondrial fission 1 (FIS1). This action facilitates the assembly of FIS1 with the fusion protein mitofusin 2 (MFN2) and the mitochondrial gatekeeper voltage-dependent anion channel 1 while maintaining MFN2 membrane tethering activity by enhancing its oligomerization. Consequently, SENP1 inhibits mitochondrial fission and preserves the functionality of lung endothelial cells as well as the stability of vascular homeostasis. By contrast, chronic hypoxia reduces mitochondrial SENP1 levels, leading to excessive FIS1 SUMOylation. This contributes to mitochondrial dysfunction and metabolic reprogramming of lung endothelial cells, thereby inducing their phenotypic transformation and promoting pulmonary vascular remodeling (88).

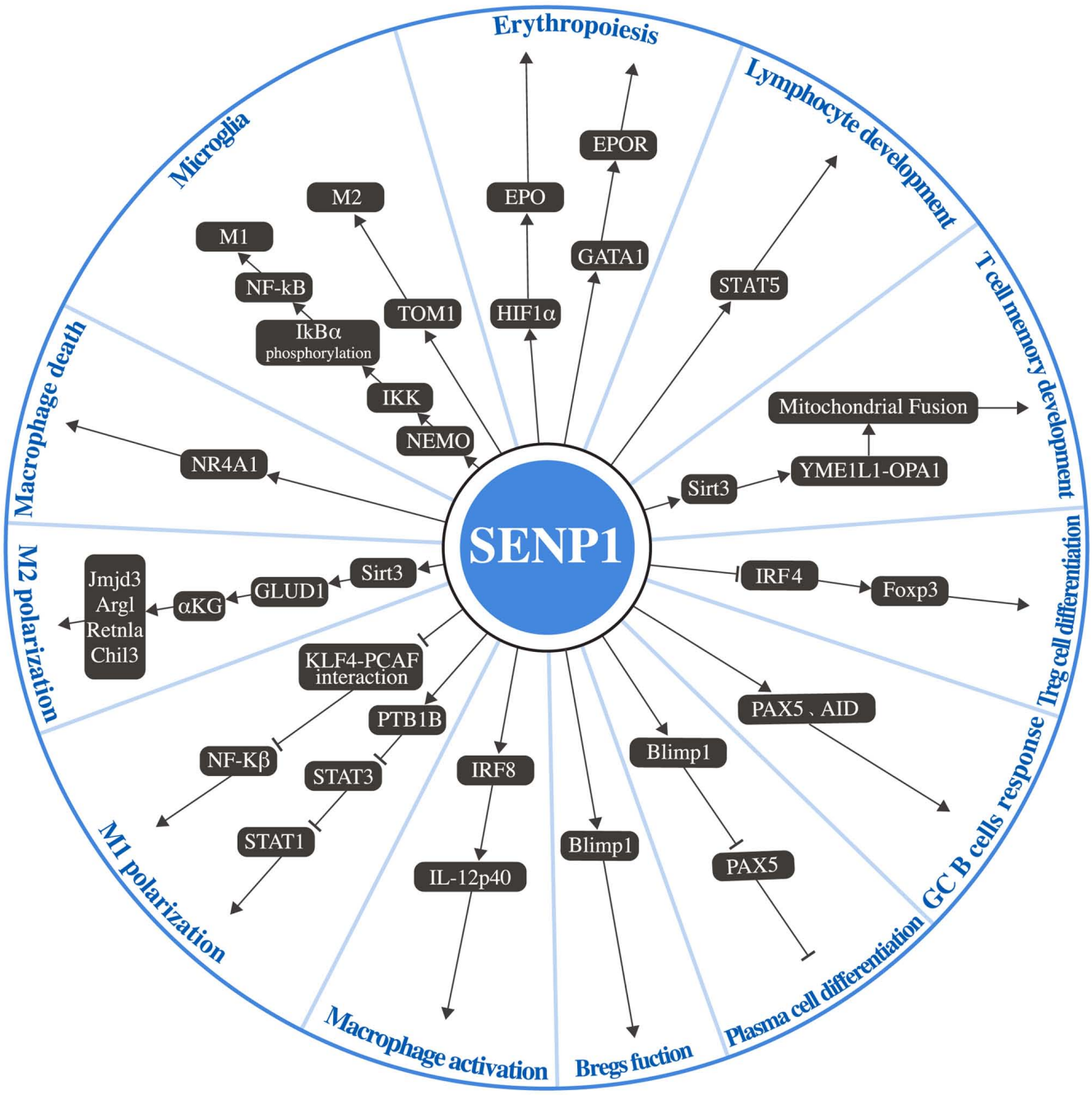

Figure 2. Signaling pathways of SENP1 in immune cells. AID, activation-induced cytidine deaminase; Blimp, B lymphocyte-induced maturation protein; EPO, erythropoietin; Foxp, forkhead box protein; GATA, GATA binding protein; GLUD, glutamate dehydrogenase; HIF, hypoxia-inducible factor; IKK, inhibitor of κB kinase; IRF, interferon regulatory factor; Jmjd, Jumonji domain-containing protein D; KLF4, Kruppel-like factor; NEMO, NF-κB essential modulator; NR4A, nuclear receptor 4A; PAX, paired box protein; PCAF, p300/CBP-associated factor; PTB1B, protein tyrosine phosphatase-1B; SENP, small ubiquitin-like modifier/sentrin-specific protease; SIRT, sirtuin; STAT, signal transducer and activator of transcription; TOM, target of Myb; αKG, α-ketoglutarate.

SENP1 has also been implicated in cardiovascular diseases, as well as various other medical conditions. TEA domain transcription factor 1 (TEAD1) has been identified as a contributor to the development of cardiovascular diseases. Notably, its expression is markedly increased *in vivo* during pressure overload-induced cardiac hypertrophy. SUMOylation of TEAD1 may regulate oxidative stress responses by modulating the nuclear related factor 2 (NRF2)-heme oxygenase 1 (Hmox1) pathway. NRF2 and its downstream effector Hmox1 serve a role in protecting against myocardial hypertrophy, IR injury and various other forms of myocardial damage. SENP1 has a pivotal role in enhancing cardiomyocyte hypertrophy both *in vitro* and in murine models of cardiac hypertrophy, primarily through the deSUMOylation of TEAD1 at lysine residue 173 (89). However, it has been reported that SENP1 can inhibit STAT3 activation by directly interacting with Janus kinase 2 (JAK2) and STAT3 in cardiomyocytes, thereby conferring benefits in cardiac injury caused by chronic stress overload 90).

5. SENP1 and tumors

SENP1-mediated homeostatic imbalance in the deSUMOylation of target proteins is closely associated with tumor development (91-95). While SENP1 is commonly upregulated in cancer, its downregulation has also been observed in some specific types of cancer (96). Elevated SENP1 expression, which demonstrates a strong association with adverse clinical outcomes, holds promise as a prognostic biomarker (97). The present review summarizes the influence of SENP1 on tumor biological behavior (Table I), indicating that targeting SENP1 could offer novel therapeutic approaches for cancer treatment.

SENP1 and transcription factors. STAT5 can reportedly directly or indirectly modulate several metabolism-associated mechanisms within cancer cells, specifically by facilitating aerobic glycolysis via the upregulation of MYC and HIFs. Overactivation of STAT5 has been shown to induce immunosuppression and tumor invasion (98). STAT5 SUMOylation inhibits its lysine acetylation, while SENP1 promotes the activation of STAT5 via deSUMOylation (20). An increasing body of evidence has suggested that SENP1 knockdown inhibits the JAK-STAT5 pathway and tumor growth (99-101).

Epithelial-mesenchymal transition (EMT) refers to a biological process that enables epithelial cells to acquire enhanced migratory and invasive capabilities, particularly in the context of oncology. TGF-β can reportedly trigger the nuclear relocation of the SMAD2/3/4 complex (102); throughout cancer progression, the growth inhibitory effects mediated by TGF-β/SMADs signaling are frequently diminished due to the loss and subsequent inactivation of SMAD proteins (103). In the advanced stages of cancer, TGF-β promotes EMT in tumor cells via both SMAD-dependent and SMAD-independent pathways, which activate EMT-associated transcription factors (104). SUMOylation at lysine residues lysines 113 and 159 of SMAD4 stabilizes the SMAD4 protein and enhances its transcriptional function (105). Notably, SENP1 might reduce SMAD4 levels to promote EMT via deSUMOylation of SMAD4 (106).

Aberrant activation of the AKT signal pathway has been identified as a key feature of tumor progression (107). Histone deacetylase 2 (HDAC2) exhibits pro-tumorigenic properties in various malignancies (108). HDAC2 has also been shown to transcriptionally activate the epidermal growth factor receptor (EGFR) and enhance the AKT signaling pathway (109,110). Moreover, SUMO-modified HDAC2 interferes with its transcriptional activity (109,110). SENP1 can reportedly deSUMOylate HDAC2, which consequently enhances EGFR transcription and activates the AKT pathway (111).

Tumor hypoxia initiates a cascade of adaptive mechanisms that lead to a more aggressive tumor phenotype, processes predominantly governed by the HIF transcription factor family. Among these, HIF1α serves as a crucial regulator in the context of hypoxia-driven tumor metastasis by facilitating EMT through the direct upregulation of TWIST (112). SENP1, which is significantly upregulated in breast cancer, is essential for preserving the stability of HIF1α and HIF2α by facilitating their deSUMOylation. This mechanism enhances the expression of HIF1α-associated target genes, including those related to stem cells (such as Nanog, Oct4 and CD24), as well as MMP2, MMP9 and stanniocalcin-1. Consequently, this upregulation not only promotes invasion but also facilitates metastasis in cancer cells (113-115).

GATA1, a member of the GATA transcription factor family, facilitates the proliferation, migration and invasion of colorectal cancer cells by activating the AKT signaling pathway (116). The deSUMOylation of GATA1 at lysine 137 by SENP1 enables GATA1 to attach to the promoter and enhance the transcription of CNS5, which subsequently suppresses the ubiquitination of zinc finger E-box-binding homeobox 1, leading to EMT, and thereby facilitating breast cancer invasion and metastasis (117).

SENP1 and translation. Eukaryotic initiation factor 3 (eIF3i), a component of the eIF3 complex, is considered a proto-oncogene typically upregulated in cancer, which promotes tumorigenesis by facilitating the integration of growth signals with mRNA translation and protein synthesis (118,119). SENP1 facilitates the removal of SUMO groups from eIF3i at the K298 position, thereby preventing its ubiquitination and subsequent proteasomal degradation. This mechanism leads to the activation of the Wnt/β-catenin signaling pathway, which serves a role in promoting tumor progression (120).

The RING-type E3 ubiquitin ligase RNF146 serves a crucial role in PARylation-dependent ubiquitination, an event closely linked to the Wnt/β-catenin signaling pathway (121). Axin functions as a suppressor of the Wnt/β-catenin signaling pathway by assembling the 'β-catenin destruction complex', thereby facilitating the breakdown of β-catenin (122,123). The SUMOylation of RNF146 facilitates its translocation from the cytoplasm to the nucleus, where it interacts with Axin. This interaction leads to the ubiquitination and subsequent degradation of Axin, thereby activating β-catenin signaling and contributing to cancer progression. SENP1 catalyzes the deSUMOylation of RNF146 to promote its nuclear export, inhibit its binding to Axin, suppressing β-catenin signaling and ultimately inhibiting cancer progression (124).

SENP1 and myeloid-derived suppressor cells (MDSCs). MDSCs constitute a heterogeneous group of primarily immature myeloid cells that emerge in pathological contexts. These cells are characterized by a state of pathological activation and possess notable immunosuppressive capabilities (125), thereby promoting tumor angiogenesis, tumor cell invasion and pre-metastatic niche formation (125,126). STAT3 serves as a crucial positive regulator in the proliferation and functionality of MDSCs. CD45 functions as a specific phosphatase for STAT3. The enzyme SENP1 possesses the ability to remove SUMOylation from CD45, thereby preserving its phosphatase activity. In MDSCs, SENP1 is downregulated, leading to high CD45 SUMOylation, resulting in continuous activation of STAT3, which promotes the differentiation, development and function of MDSCs, thereby driving tumorigenesis (127).

SENP1 and angiogenesis. Angiogenesis is crucial for tumor growth and metastasis. Vascular endothelial growth factor (VEGF), a primary mediator of tumor angiogenesis, is notably influenced by hypoxia-induced signaling through HIF1α (128). Unmodified HIF1α evades ubiquitin/protease-dependent degradation and promotes VEGF transcription and tumor

Table I. Functions of SENP1 in cancer.

Cancer type	Expression of SENP1	Targeting molecules	Function	(Refs.)
Breast cancer	Pregulation	GATA1, p21, p27, MMP9, HIF-1α, α-catenin, c-Myc	Promotes invasion, metastasis and proliferation	(113,117,164-167)
Prostate cancer	Upregulation	HIF1α, hexokinase 2, SMAD4	Promotes proliferation, metastasis and EMT	(92,106,168)
Liver cancer	Upregulation	HIF1α, RNF146, Zeb1, AnxA6, β-catenin, eIF3I, UBE2T	Promotes proliferation, migration, invasion, stemness and EMT	(95,114,120, 150,169-171)
Colorectal cancer	Upregulation	ELOC, RNF168, c-Myc	Promotes proliferation, invasion, stemness and anti-apoptotic activity	(145,172)
Nasopharyngeal carcinoma	Upregulation	STAT1	Promotes proliferation and invasion	(173)
Leukemia	Upregulation	XBP1, HDAC2, PTBP1, SIRT3	Promotes proliferation, autophagy and drug resistance, and anti-apoptotic activity	(111,154, 174,175)
Multiple myeloma	Upregulation	SRC-3	Promotes proliferation and drug resistance, and anti-apoptotic activity	(176)
Mantle cell lymphoma	Upregulation	JAK-STAT5, SOCS2	Promotes proliferation and anti-apoptotic activity	(100)
Head and neck squamous cell carcinoma	Upregulation	ACSL4	Inhibits ferroptosis	(141)
Renal cell carcinoma	Upregulation	NF-κB, HIF2α	Promotes proliferation, metastasis and invasion	(115,177)
Glioblastoma	Upregulation	METTL3, HIF1α, β-catenin	Promotes self-renewal and tumor remodeling	(178,179)
Neuroblastoma	Upregulation	CDH1, MMP9, MMP2	Promotes migration and invasion	(180)
Esophageal squamous carcinoma	Upregulation	Sirt6	Promotes proliferation and migration	(181)
NPM-ALK$^+$ T-cell lymphoma	Downregulation	NPM-ALK	Suppresses proliferation and colony formation	(182)
Lung cancer	Downregulation	Slug	Suppresses metastasis	(183)

ACSL, acyl-CoA synthetase long-chain; ALK, anaplastic lymphoma kinase; Anx, annexin; CDH, cadherin; eIF3I, eukaryotic initiation factor 3; ELOC, elongin C; GATA, GATA binding protein; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; JAK, Janus kinase; METTL, methyltransferase-like; NPM, nucleophosmin; PTBP, polypyrimidine tract binding protein; RNF, RING finger protein; SENP, small ubiquitin-like modifier/sentrin-specific protease; SIRT, sirtuin; SOCS, suppressor of cytokine signaling 2; SRC, steroid receptor coactivator; STAT, signal transducer and activator of transcription; UBE2T, ubiquitin conjugating enzyme E2 T; XBP, X-box binding protein; Zeb, zinc finger E-box binding homeobox.

angiogenesis. Conversely, SUMOylated HIF1α facilitates its interaction with the ubiquitin ligase von Hippel-Lindau protein, which subsequently results in the ubiquitination and degradation of HIF1α (75). SENP1 induces VEGF transcription by improving the stability of HIF1α through deSUMOylation (129).

The NOTCH1 signaling pathway serves as a negative regulator of angiogenesis by inhibiting VEGF receptor (VEGFR) expression and diminishing the angiogenic potential of endothelial cells (130). Proteolytic enzymes act on SUMO-modified NOTCH1 within the membrane, resulting in cleavage that releases its intracellular domain. The latter translocates into the nucleus to bind co-activators and drive the expression of specific target genes. Conversely, SENP1 attenuates NOTCH1 signaling by deSUMOylation of NOTCH1 in endothelial cells, thus enhancing VEGF/VEGFR signaling, and ultimately promoting angiogenesis (131).

Fibroblast growth factor (FGF)2 facilitates angiogenesis through the activation of signaling pathways associated with FGF receptor 1 (FGFR1) in endothelial cells (132). SUMOylation and deSUMOylation processes are pivotal in modulating the competitive recruitment of the adaptor

protein FRS2α by FGFR1 and VEGFR2, thereby facilitating the formation of receptor complexes necessary for effective downstream signaling that adapts to the angiogenic milieu. Specifically, the SUMOylation of FGFR1 enhances the association of FRS2α with VEGFR2, rather than FGFR1, leading to a pronounced activation of VEGFR2 signaling in endothelial cells, which is crucial for developmental angiogenesis. Furthermore, FGFR1 SUMOylation, regulated by SENP1, serves as an inherent regulatory mechanism governing FGFR1 activation, thus maintaining a delicate equilibrium between FGF2/FGFR1 and VEGFA/VEGFR2 signaling pathways, essential for the angiogenic potential of endothelial cells in response to angiogenic stimuli (133).

MSCs promote angiogenesis through paracrine action (134). SENP1 is involved in MSC differentiation and angiogenesis through deSUMOylation of myocardin-related transcription factor A (MRTF-A). In MSCs, SUMOylation of MRTF-A is localized in the cytoplasm. SENP1 facilitates the deSUMOylation of MRTF-A, leading to its translocation into the nucleus. In conjunction with P300 and SRF at the CArG box, this process results in the activation of the angiogenic factor CCN1, thereby initiating the angiogenesis pathway (135).

SENP1 and ferroptosis. Ferroptosis represents a controlled mechanism of cellular death that results from the accumulation of iron-dependent ROS in lipids. Several molecules implicated in the process of ferroptosis, including SLC7A11/xCT, GPX4 and acyl-CoA synthetase long-chain family member 4 (ACSL4), have emerged as promising targets for therapeutic interventions in cancer (136,137). Lysine-specific demethylase 4A (KDM4A) is a JmjC domain-containing histone demethylase that catalyzes the demethylation of histone 3 lysine 9 (H3K9me3/2) and histone 3 lysine 36 (138). SLC7A11, a key protein involved in ferroptosis, is regulated by KDM4A-mediated suppression of H3K9me3 in its promoter region. SUMOylation of KDM4A at K471 suppresses H3K9me3 levels and upregulates SLC7A11 to resist ferroptosis in cervical cancer cells. In this context, SENP1 promotes ferroptosis by deSUMOylation of KDM4A (139,140). However, in head and neck squamous cell carcinoma cells, SENP1 exerts an inhibitory effect on ferroptosis by deSUMOylating ACSL4. This mechanism leads to a reduction in iron ion concentrations and malondialdehyde levels associated with lipid peroxidation, while simultaneously enhancing glutathione levels (141). In diffuse large B cell lymphoma (DLBCL), the silencing of SENP1 enhances ferroptosis by reducing the levels of SLC7A11 and GPX4, while simultaneously increasing ACSL4 expression (142).

SENP1 and chemotherapy resistance. SENP1 influences the responsiveness of cancer cells to chemotherapy and radiotherapy by serving a role in DNA damage repair, apoptosis, cell cycle regulation and tumor angiogenesis (143,144). Ubiquitin-specific protease 51 (USP51) promotes chemoresistance in colorectal cancer by establishing a positive feedback loop with HIF1α. SENP1 mediates the deSUMOylation of elongin C, which promotes USP51-mediated deubiquitylation and stabilization of HIF1α, and leads to chemoresistance in colorectal cancer (145). Li *et al* (146) demonstrated that SENP1 can directly interact with and deSUMOylate JAK2, resulting in its accumulation in the cytoplasm, where JAK2 is activated, leading to drug resistance in ovarian cancer cells.

RING finger protein 168 (RNF168) is a crucial protein involved in recruiting repair proteins to damaged chromosomes. It is recognized as a novel chromatin-associated ubiquitin ligase, possessing the capacity to interact with ubiquitin (147). In response to DNA damage, RNF168 catalyzes the monoubiquitination of histones specifically on lysine 13-15 (148). This modification facilitates the recruitment of various repair proteins, including 53BP1, which is essential for the repair of double-strand breaks in DNA (148). However, SUMOylated RNF168 blocks the recruitment to the damaged site, thereby decreasing the efficiency of DNA repair. Conversely, the deSUMOylation of RNF168 lysine 210 by SENP1 facilitates damage repair, protecting genomic integrity and inducing chemotherapy resistance (97).

Substantial evidence has suggested that Wnt signaling is involved in cancer chemotherapy resistance, as reviewed by Mohammed *et al* (149). Activation of the Wnt/β-catenin pathway via SENP1-mediated β-catenin deSUMOylation is associated with heightened chemotherapy resistance in hepatocellular carcinoma (150). The induction of FAO represents a key metabolic adaptation that drives acquired drug resistance in malignancies (151,152). Sirt3-mediated deacetylation of long-chain acyl dehydrogenase and the activity of multiple enzymes are essential for fatty acid β-oxidation processes (153). In this context, SENP1 has been shown to deSUMOylate Sirt3, thereby preventing its degradation and facilitating FAO (154).

Dynamically regulated SUMOylated MORC family CW-type zinc finger 2 (MORC2) serves a crucial role in chromatin remodeling and DNA repair mechanisms in response to DNA damage, thereby contributing to the development of chemoresistance in breast cancer. SENP1 may reverse MORC2-driven chemoresistance by interfering with MORC2 SUMOylation (155). The key roles of SENP1 across different biological contexts are summarized in Table II.

6. Conclusion and future perspectives

In conclusion, the dual role of SENP1 in regulating immune responses and tumor development highlights its potential as a therapeutic target. Although SENP1 serves a crucial role in diverse biological processes, numerous aspects of its function remain controversial and incompletely understood. Some studies suggest it promotes tumor progression, while others indicate potential suppressive effects in specific contexts. For example, in prostate cancer, SENP1 promotes tumor progression by deSUMOylating HIF1α, thereby promoting tumor progression (92). By contrast, in hepatocellular carcinoma, SENP1 catalyzes the deSUMOylation of RNF146, facilitating its nuclear export and preventing its interaction with Axin, which in turn inhibits β-catenin signaling and ultimately suppresses cancer progression (124). These findings highlight the distinct mechanisms by which SENP1 may function in different types of cancer. Furthermore, the complexity of its interactions with other signaling pathways, and the necessity to clarify its functions and regulatory mechanisms across various tissues and cell types present notable research challenges. For instance, in the cardiovascular system, SENP1 has a role in

Table II. Key roles of SENP1 across different biological contexts.

Biological context	Target/substrate of SENP1	Mechanism of action	Biological or pathological outcome	(Refs.)
Immune regulation	STAT5	deSUMOylation	Promotes the development of lymphocytes	(2)
	Sirt3	deSUMOylation	Promotes T-cell survival, memory T-cell differentiation and M2 polarization	(15,18,22-24)
	IRF4	deSUMOylation	Inhibits Treg cell differentiation	(28)
	PAX5, AID	deSUMOylation	Promotes GC B cell response	(31,32)
	Blimp-1	deSUMOylation	Promotes plasma cell differentiation and regulates Breg generation and function	(37,38)
	IRF8	deSUMOylation	Promotes macrophage activation and innate immune response	(43)
	PTP1B, KLF4-PCAF	deSUMOylation	Promotes M1 polarization	(49,53,54)
	NR4A	deSUMOylation	Promotes macrophage death	(62)
	NEMO	deSUMOylation	Promotes microglia polarizing into M1 phenotypes	(68)
	TOM1	deSUMOylation	Promotes microglia polarizing into M2 phenotypes	(72)
	HIF1α, GATA1	deSUMOylation	Regulates erythropoiesis	(75,76)
Infection	Sp3	deSUMOylation	Promotes LPS-induced cellular inflammation	(77,78)
Tissue damage	Sirt3	deSUMOylation	Reduces oxidative damage induced by IR injury	(81,82)
	Sirt1	deSUMOylation	Promotes apoptosis induced by hyperoxia	(83)
	TGF-β1	deSUMOylation	Promotes cellular senescence and lung fibrosis	(86)
	TEAD1	deSUMOylation	Enhances cardiomyocyte hypertrophy	(89)
	JAK2 STAT3	Interacts with JAK2/STAT3, and inhibits STAT3 activation	Regulates cardiac function	(90)
Cancer	SMAD4, GATA1	deSUMOylation	Promotes EMT	(106,117)
	HDAC2	deSUMOylation	Enhances EGFR transcription and activates the AKT pathway	(111)
	HIF1α, HIF2α	deSUMOylation	Promotes the invasion and metastasis of cancer cells	(113-115)
	eIF3i	deSUMOylation	Activates the Wnt/β-catenin signaling pathway and promotes tumor progression	(120)
	RNF146, CD45	deSUMOylation	Inhibits the progression of tumors	(124,127)
	HIF1α, NOTCH1, FGF2, MRTF-A	deSUMOylation	Regulates angiogenesis within tumors	(129,131, 133,135)
	KDM4A	deSUMOylation	Promotes ferroptosis	(139,140)
	ACSL4	deSUMOylation	Inhibits ferroptosis and promotes tumor progression	(141)
Therapeutic target	ELOC, JAK2, RNF168, β-catenin, SIRT3	deSUMOylation	Promotes chemotherapy resistance in tumors	(97,145,146, 150,154)
	MORC2	deSUMOylation	Inhibits tumor chemotherapy resistance	(155)

ACSL, acyl-coA synthetase long chain; AID, activation-induced cytidine deaminase; Blimp, B lymphocyte-induced maturation protein; eIF3i, eukaryotic initiation factor; ELOC, elongin C; FGF, fibroblast growth factor; GATA, GATA binding protein; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; IRF, interferon regulatory factor; JAK, Janus kinase; KDM4A, lysine-specific demethylase 4A; KLF4, Kruppel-like factor; MORC2, MORC family CW-type zinc finger 2; MRTF-A, myocardin-related transcription factor; NEMO, NF-κB essential modulator; NR4A, nuclear receptor 4A; PAX, paired box protein; PCAF, p300/CBP-associated factor; PTP1B, protein tyrosine phosphatase-1B; RNF, RING finger protein; SENP, small ubiquitin-like modifier/sentrin-specific protease; Sirt, sirtuin; Sp, specificity protein; STAT, signal transducer and activator of transcription; TEAD, TEA domain transcription factor; TOM, target of Myb.

myocardial IR injury, yet the precise mechanisms and specific targets are still unclear (14). In DLBCL, SENP1 is associated with ferroptosis, but the underlying molecular mechanisms have not been fully elucidated (142). Future research should address these controversies and knowledge gaps to enhance the understanding of SENP1, aiming to improve the diagnosis and treatment of related diseases.

Given the promising therapeutic implications of SENP1 in oncology and a range of other medical conditions, there is a growing interest among researchers in the identification and creation of SENP1 inhibitors. A variety of synthetic proteins, peptides, small molecule entities and naturally occurring compounds have been designed and analyzed for their efficacy as inhibitors of SENP1 (91,156). Natural products utilized in the development of anticancer agents possess distinctive benefits, including elevated selectivity, robust efficacy and minimal adverse effects (157). Yoshioka *et al* (158) confirmed that vialinin A and thelephantin G are effective SENP1 inhibitors. Gallic acid, bethanidine (BW467C60), momordin Ic, triptolide, biflavones, flavonoids and streptomycin represent other promising candidate SENP1 inhibitors (159). A dual SENP1 and SENP2 inhibitor, ZHAWOC8697, has also been shown to inhibit proSUMO protein maturation (160). Ursolic acid and the compound UAMMC9 directly bind to the catalytic site of SENP1, notably inhibiting SENP1 activity at the nM level, and overcoming platinum resistance in ovarian cancer (143). Pomolic acid and tormentic acid, which have also undergone *in vivo* animal studies, are promising SENP1 inhibitors for addressing platinum resistance in ovarian cancer (161). Recent advancements include the synthesis of a greater number of SENP1 inhibitors, particularly pyridone indole derivatives and 1-[4-(N-benzylamino)phenyl]-3-phenylurea derivatives. Specific inhibitors demonstrate significant anticancer efficacy and favorable pharmacokinetic properties, exhibiting suitable inhibitory activity against SENP1 *in vitro*. This advancement presents novel opportunities for the clinical management of associated diseases (162,163). However, challenges persist in inhibitor selection. First, the structural similarity among SENP family members can lead to off-target effects. Second, the broad range of physiological functions of SENP1 makes it challenging to inhibit its oncogenic activity without disrupting normal functions. Besides, the development of SENP1 inhibitors is currently in the preclinical stage, necessitating further research before clinical application. Further breakthroughs and applications of SENP1 in disease research are anticipated, which may provide more therapeutic strategies for treating human diseases.

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Authors' contributions

XF and GY wrote the main manuscript text and prepared figures, and both contributed equally to this work and share first authorship. QY supervised the study and reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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