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The impact of dysregulation SUMOylation on prostate cancer

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Abstract
Prostate cancer (PCa) remains one of the most common malignancies in men, with its development and progression being governed by complex molecular pathways. SUMOylation, a post-translational modification (PTM) that involves the covalent attachment of small ubiquitin-like modifier (SUMO) proteins to target substrates, has emerged as a critical regulator of various cellular processes such as transcription, DNA repair, cell cycle progression, and apoptosis. Emerging evidence reveals that abnormal SUMOylation may contribute to PCa pathogenesis, and notably, SUMO-associated enzymes are commonly dysregulated in PCa. This review explores the mechanisms by which SUMOylation is implicated in the regulation of key pathways, and summary aberrant expression of SUMO-related enzymes or SUMOylation sites mutations of substrtes in PCa, as well as the therapeutic implications of targeting the SUMO-related enzymes in PCa treatment.

Keywords SUMOylation, Prostate cancer, Tumorigenesis, Cancer therapy

Introduction

Prostate cancer (PCa) is a common malignancy of the male reproductive system and ranks as the second leading cause of cancer-related mortality among men [1]. Androgen deprivation therapy (ADT) is the standard treatment for localized and advanced PCa, aiming to reduce androgen levels and inhibit tumor growth [2]. However, most patients eventually develop into castration-resistant PCa (CRPC) within 2 to 3 years, even after initial ADT and additional therapies [3]. Despite the availability of chemotherapy and second-generation androgen receptor (AR) pathway inhibitors (ARPI), such as enzalutamide and abiraterone, the prognosis for CRPC remains poor, with rapid disease progression and low 5-year survival rates [4–6]. These challenges underscore the urgent need to better understand the molecular mechanisms driving PCa progression and resistance to therapy to identify novel therapeutic strategies for more effective management of the disease.

One of the key regulatory processes involved in cancer biology is SUMOylation, a reversible PTM in which a SUMO protein is covalently attached to a lysine residue on a target protein [7, 8]. Unlike ubiquitination, which generally leads to proteasomal degradation, SUMOylation primarily functions to modulate the activity, localization, and interactions of proteins without inducing their degradation [7, 8]. This modification plays a crucial role in a wide variety of cellular processes, including transcription, DNA repair, stress responses, and protein-protein interactions, all of which are vital for

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maintaining cellular function and responding to environmental changes [7, 8].

SUMOylation process involves three key enzymatic steps: activation, binding, and ligation [9] (Fig. 1). Initially, SUMO is activated by the E1 enzyme complex, comprising SAE1 and SAE2, which forms a thioester bond with SUMO [9, 10]. The activated SUMO is then transferred to the E2 enzyme, UBC9, which catalyzes the direct conjugation of SUMO to the target protein [9, 10]. While E3 ligases can enhance the efficiency of this conjugation, UBC9 alone is also capable of mediating SUMOylation [7, 10]. The conjugation typically occurs at the consensus motif ψKx[E/D], where ψ represents a hydrophobic residue, x denotes any amino acid, K stands for lysine, and E/D represents glutamic or aspartic acid [10]. Alternatively, a reversed motif [E/D]xK may also be recognized by SUMO [10]. SUMOylation is dynamically regulated by SUMO-specific proteases (SENPs), which reverse the modification (deSUMOylation) and help maintain cellular homeostasis [10].

The human SUMO family consists of several isoforms (SUMO1–5), with SUMO1, SUMO2, and SUMO3 being the most extensively studied [8]. SUMO2 and SUMO3 share high sequence homology, which makes them difficult to distinguish by antibodies, and are often collectively referred to as SUMO2/3 [11]. Notably, SUMO2 and SUMO3 can form poly-SUMO chains, whereas SUMO1 lacks internal lysine residues and cannot form such chains [12]. Moreover, SUMO2/3 expression levels in cancer cells are usually higher than SUMO1 expression levels [13]. Although the functions of SUMO1, SUMO2, and SUMO3 are well characterized, the roles of SUMO4 and SUMO5 remain less understood, indicating a need for further investigation into the potential contributions of these isoforms to cellular regulation [7, 10].

The dysregulation of SUMOylation has been implicated in the pathogenesis of various diseases, including cancer

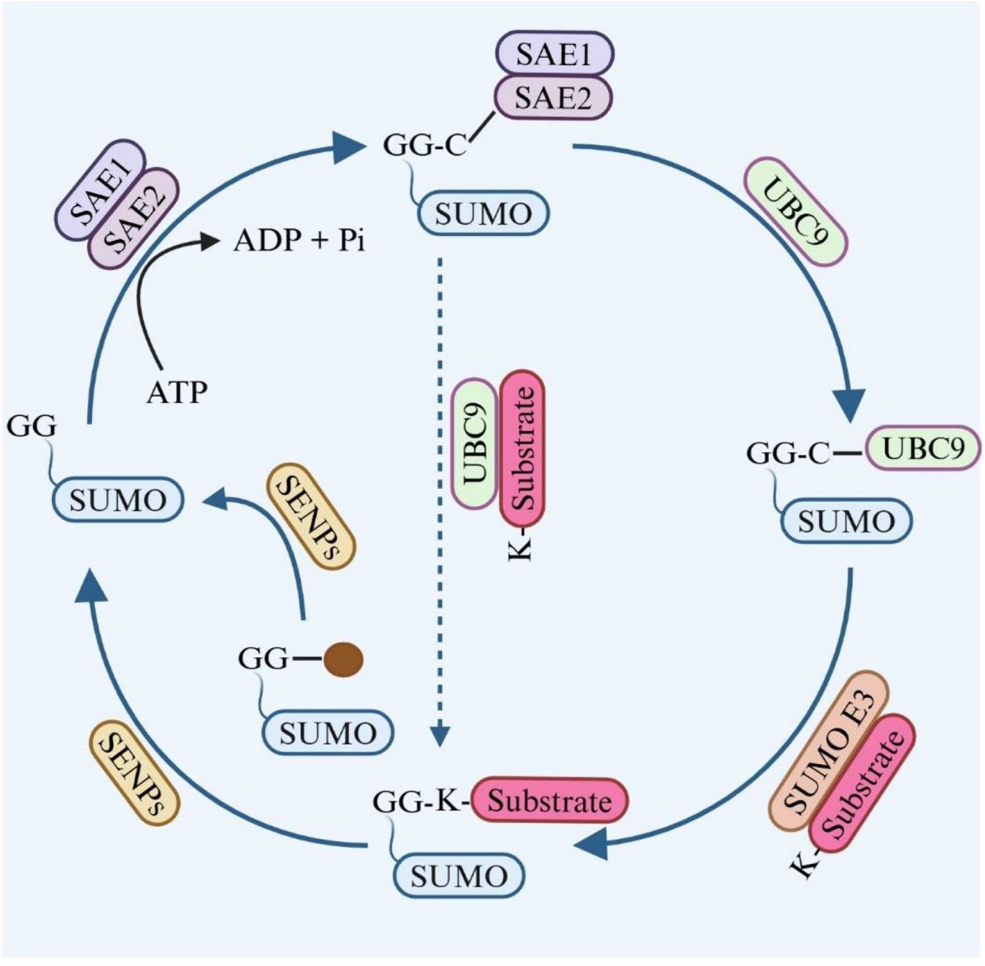

Fig. 1 SUMOylation modification process. The inactive precursor SUMO exposes the C-terminal glycine under the action of SENPs. In each conjugation cycle, E1 activates the enzyme SAE1/SAE2 by linking it to the C-terminal glycine residue of SUMO in an ATP dependent manner. Then, with the assistance of UBC9, SUMO was connected to the target protein. This step requires SUMO E3 enzyme; However, this is not necessary. Finally, SENPs promote the de SUMOylation of substrate proteins to ensure the stability of the intracellular SUMO cycle

[7]. In the context of PCa, alterations in the SUMOylation process have been shown to impact tumor progression, metastasis, and the response to treatment. SUMOylation can regulate key signaling pathways involved in tumor development, such as AR, PI3K/AKT (phosphoinositide 3-kinase/serine/threonine protein kinase AKT), p53 signaling pathways [14]. Changes in SUMOylation affect the activity of these signaling pathways, potentially contributing to the development of CRPC and resistance to therapy. Moreover, SUMOylation can influence other critical processes, such as cell proliferation, metabolic reprogramming and epithelial mesenchymal transition (EMT), which are essential for tumor survival and metastasis.

This review aims to explore the role of SUMOylation in PCa, with a particular focus on its dysregulation and the resulting effects on tumorigenesis, and comprehensive understanding of these molecular mechanisms is crucial for identifying new therapeutic targets and improving the management of PCa.

Dysregulation of SUMO-related enzymes in PCa

Accumulating evidence indicates that dysregulation of SUMO-related enzymes plays a pivotal role in the initiation and progression of PCa. Alterations in the expression or activity of SUMO-related enzymes can disrupt several key cellular processes, including the AR signaling pathway, EMT, and antitumor immunity. These disruptions facilitate tumorigenesis, underscoring the importance of SUMOylation in the development of PCa (Table 1).

SUMO E2 conjugating enzyme

UBC9, the sole SUMO E2 conjugating enzyme, is integral to the SUMOylation pathway and has been implicated in the progression of PCa [9, 10]. UBC9 is often overexpressed at the protein level in early PCa tissues, but its expression is reduced in metastatic PCa, indicating its involvement in disease progression [15]. On the one hand, UBC9 can inhibit the transcriptional activity of AR by promoting SUMOylation at K386 and K520 sites [16]. On the other hand, Poukka et al. demonstrated that UBC9 can act as an AR cofactor independent of its ability to catalyze SUMO-1 coupling, enhancing its transcriptional activity and promoting PCa progression [17]. In addition to its role in AR signaling, UBC9 has been shown to SUMOylate various substrates that contribute to PCa progression [18–23]. For example, Jang et al. reported that UBC9 facilitates SUMO2/3 modification of Flot1 (Flotillin-1) at K51 and K195 sites, promoting its nuclear localization [19]. In addition, UBC9 is highly expressed in tumor associated macrophages (TAMs) and regulates anti-tumor immunity by promoting SUMOylation modification of STAT4 (signal transducer and activator of transcription 4) at the K350 site [18]. These findings collectively underscore the central role of

Table 1 The dysregulation of SUMO-related enzymes in PCa

Enzyme		Physiological evidence (animal models)	Pathological evidence (human specimens)	Biochemical evidence (substrates)	Biological functions	Refs
UBC9		Deletion of Ubc9 in macrophages (LyzM-Cre + Ubc9fl/fl) mouse	Overexpression in early PCa tissues, underexpression in metastatic PCa.	STAT4, Flot-1, Pontin, LATS1	Regulation of anti-tumor immunity, promotion of tumor progression and invasion	[18, 19, 20, 21, 22, 23]
SP-RING domain family proteins	PIAS1	Subcutaneous tumor model (injected PIAS1 knockdown cells)	Overexpression	AR, AKT, LATS1, VIM	Promotion of tumor progression, resistance to doxostat	[22, 28, 31, 78]
	PIAS2	N/A	N/A	AR, AKT, LATS1	Promotion of tumor progression	[21, 28, 31]
	PIAS3	N/A	Overexpression	AKT, STAT3, STAT5, AR	Inducing apoptosis in PCa and inhibiting PCa invasion and metastasis	[32, 126]
	PIAS4	N/A	N/A	AR	Inhibit the transcriptional activity of AR	[34]
SIM-containing proteins	RanBP2	N/A	N/A	p53	Promote PCa cell proliferation and cell survival	[44]
	ZNF451	N/A	N/A	AR	Promote the transcriptional activity of AR	[45]
	Pc2	N/A	N/A	WWOX	Suppression of tumorigenesis	[20]
SENP1		SENP1-transgene (SENP1-Tg) mouse, Subcutaneous tumor model (injected SENP1 knockdown cells)	Overexpression	PTEN, AR, HK2, HP1α, FOXA1, TBL1 TBLR1. CSR1	Promotion of tumor progression	[49]
SENP2		N/A	N/A	ERK5	Inhibit nuclear input of ERK	[91]
SENP3		Subcutaneous tumor model (injected SENP3 knockdown cells)	Overexpression	SIX1	Promotion of tumor progression and invasion	[47]

UBC9 in the regulation of protein function and its potential as a therapeutic target in PCa.

SUMO E3 ligases in PCa

Although UBC9 is capable of catalyzing SUMOylation independently, the involvement of SUMO E3 ligases significantly enhances the specificity and efficiency of this modification. SUMO E3 ligases are responsible for facilitating the transfer of SUMO to substrates, thereby amplifying the SUMOylation process. Several family members with SUMO E3 ligase activity have been identified, including the SP-RING domain family, the tripartite motif (TRIM) superfamily, noncanonical ligases, ligase-like factors, and additional SUMO E3 ligases, all of which contribute to the regulation of SUMOylation by promoting substrate recognition and SUMO conjugation.

The SP-RING domain family proteins

The SP-RING domain family, including PIAS (Protein Inhibitor of Activated STAT) proteins, plays a crucial role in SUMOylation. These proteins, particularly PIAS1, PIAS2 (PIASx, including PIASx α and PIASx β), PIAS3, and PIAS4 (PIASy), interact with UBC9 through their RING domain to facilitate the SUMOylation of substrate proteins [24].

PIAS1 is frequently overexpressed in PCa, and its expression correlates with poor prognosis, making it a potential prognostic marker [25, 26]. Moreover, PIAS1 is associated with doxostat resistance in PCa cells [26]. Meanwhile, PIAS1 is known to influence stability, subcellular localization, and transcriptional activity of AR in PCa cells. As an AR co-regulator, PIAS1 promotes cell growth by selectively activating AR target genes, independent of its SUMO ligase activity [27, 28]. In addition, PIAS1 can promote AR SUMOylation, which partially inhibits the transcriptional activity of AR but also suppresses the degradation of AR [28–30]. Meanwhile, AR ChIP Seq experiments showed that PIAS1 is one of the downstream target genes induced by AR-mediated transcription [28].

Furthermore, PIAS1 has been shown to activate the PI3K/AKT signaling pathway via the SUMOylation of AKT, further contributing to cancer progression [31]. In addition, PIAS1 regulates the tumor suppressor protein p21 (CIP1/WAF1) and the Large Tumor Suppressor 1 (LATS1) in PCa [22, 25]. PIAS1-mediated SUMOylation of LATS1 at K829 has been shown to activate LATS1 and inhibit PCa progression [22]. However, mutations at the K830 site of LATS1, commonly found in human metastatic PCa, may impair this tumor-suppressive effect [22].

PIAS3, another member of the PIAS family, plays a more complex role in PCa. Although PIAS3 is overexpressed in PCa and inhibits PCa cell proliferation by upregulating p53 and p21 to induce apoptosis, it may also enhance AR transcriptional activity, like PIAS1 [32–35]. On the contrary, the roles of PIAS2 and PIAS4 in PCa are still unclear. PIAS2 may exert anti-tumor effects by promoting SUMOylation of AR, PTEN (phosphatase and tensin homolog), and LATS1, while PIAS4 may inhibit AR transcriptional activity through its N-terminal LXXLL motif, probably exhibiting a tumor-suppressive effect on PCa [22, 34, 36].

Additionally, the PIAS-like protein hZimp10 has been identified as a transcriptional coactivator for p53 [37], SMAD3 [38], and AR [39]. In PCa, unlike other AR SUMO E3 enzymes, hZimp10 promotes the SUMOylation of AR at K386 and K520 sites, enhancing its transcriptional activity [39]. However, further research is needed to understand the broader role of hZimp10 in PCa and other cancers.

Other SUMO E3 enzyme families

The TRIM family of proteins, characterized by a RING domain and B-box domains, also includes several SUMO E3 ligases. For examples, TRIM11 and TRIM19 exhibit both tumor-promoting and tumor-suppressing roles through SUMOylation of substrate proteins in PCa [40, 41]. TRIM19 could induce SUMOylation of p53, enhancing its transcriptional activity and promoting tumor suppression [42]. In contrast, TRIM11 inhibits apoptosis by promoting the SUMOylation of MCL1, an anti-apoptotic protein, thus inhibiting its ubiquitination and degradation [43].

Other SIM-containing proteins, such as RanBP2, polycomb2 (PC2), and ZNF451, have also been identified as having SUMO E3 ligase activity. They bind to the UBC9-SUMO complex through the SIM, thereby promoting SUMO binding to substrates. RanBP2 promotes the proliferation and survival of PCa cells by mediating the SUMOylation of p53, which facilitates p53's nuclear export and subsequent degradation [44]. ZNF451, a zinc finger protein, interacts with AR in a SUMO-enhanced manner, and depletion of ZNF451 in PCa cell lines suppresses AR target gene expression, suggesting a potential regulatory role in AR-mediated tumorigenesis [45]. Conversely, Choi et al. found that Pc2-mediated SUMOylation of WWOX reduced PCa cell proliferation and xenograft tumorigenesis [20].

SUMO proteases

The SENP family, particularly SENP1, SENP3 and SENP7, plays a critical role in reversing deSUMOylation by cleaving SUMO from target proteins. Both SENP1 and SENP3 are highly expressed in PCa tissues, suggesting their involvement in tumor progression [46, 47]. Downregulation of SENP1 has been shown to inhibit PCa cell growth, making it a promising therapeutic target [46]. Moreover, SENP1 expression is directly correlated with

the androgen or IL-6 stimulation status of PCa cells [48]. Similarly, transgenic mice overexpressing SENP1 are more prone to prostate intraepithelial neoplasia, indicating that SENP1 is a carcinogenic factor for PCa [48]. SENP1 and SENP3 promote PCa cell proliferation and metastasis by deSUMOylation from various substrates [47, 49–52]. On the other hand, SENP7 is associated with cellular aging in PCa, mitigating cellular senescence and promoting tumor progression by inhibiting the SUMOylation of HP1α [53]. Additionally, SPOP, a ubiquitinated E3 ligase with significant mutations in PCa, promotes the ubiquitination-mediated degradation of SENP7, thereby fostering cellular aging [53]. Interestingly, another study suggests that SPOP may also undergo SUMOylation at multiple sites [54]. The SUMOylation of SPOP may affect the functionality of SPOP and deserves further investigation.

The impact of sumoylation disorders in PCa tumorigenesis

The PCa tumorigenesis is a complex, multi-step process involving genetic, epigenetic, and molecular changes that disrupt the normal regulatory mechanisms of prostate epithelial cells. Recent studies have highlighted that SUMOylation plays a crucial role in this process, particularly in key carcinogenic events such as epigenetic reprogramming, tumor invasion and metastasis, cell proliferation and evasion of apoptosis, metabolic reprogramming and immune escape.

SUMOylation in epigenetic reprogramming

Epigenetic-reprogramming refers to the modification of cellular epigenetic landscapes that alters gene expression without changes to the underlying DNA sequence [55]. This process plays a crucial role in the initiation and progression of PCa. Notably, SUMOylation is a key regulatory mechanism that influences epigenetic reprogramming in PCa, particularly in modulating the expression of AR (Fig. 2).

AR is modified by SUMOylation at specific lysine residues, primarily at K386 and K520 [16, 29]. Key enzymes involved in this modification include UBC9, PIAS1, PIASxα (PIAS2α) and HDAC4, which facilitate SUMO1 conjugation to AR [29, 56]. Notably, mutations at the SUMOylation sites (K386/520R) in AR not only enhances its transcriptional activity, but also accelerates its protein degradation [29]. Moreover, SUMOylation not only inhibits AR activity, but also regulates the interaction between AR and chromatin and receptor target gene selection [28]. Meanwhile, in CRPC, the G524D mutation, located near the SUMOylation site, partially disrupts SUMOylation of AR, leading to an increase in AR transcriptional activity [57]. Interestingly, Sharma et al. found that hZimp10 can increase the transcriptional activity of AR by mediating AR SUMOylation [39].

Moreover, PIAS1 enhances AR SUMOylation at K386 form a SUMO3-modified AR-PIAS1 complex that translocates from the nucleus, thus recruiting MDM2 to ubiquitinate and degrade AR, contributing to the regulation of AR turnover and stability [58].

Under normal conditions, AR predominantly undergoes SUMO1 modification, but during cellular stress, SUMO2/3 modifications increase [59]. The SUMO2/3 modification leads to AR's dissociation from chromatin and relocation to the nuclear matrix, which helps protect AR from protein toxicity [59]. Interestingly, in PCa, SUMO2/3 levels are often elevated compared to SUMO1, and they exert different effects on AR in various PCa cell lines [59]. In primary prostate epithelial cells, SUMO2/3 does not affect the transcriptional activity of AR [60]. However, in LNCaP and DU145 cells, SUMO2/3 enhances AR transcriptional activity [60], suggesting that unknown factors in PCa convert SUMO2/3 from a negative regulator to a positive one, thereby amplifying AR-driven transcription and driving cancer progression. SUMO2/3 also stimulates PCa cell proliferation independently of AR SUMOylation, representing a mechanism distinct from the SUMO1-mediated inhibition of AR [61].

AR transcriptional activity is regulated not only by AR itself but also by a variety of cofactors that bind to AR and chromatin, influencing gene expression [62]. Dysregulation of these cofactors can alter AR's transcriptional function. SUMOylation of AR itself has been shown to inhibit its transcriptional activity while also disrupting its binding to certain cofactors. Lin et al. demonstrated that SUMOylated AR associates with DAXX, which further represses AR's transcriptional activity [63]. Additionally, SUMOylation of AR cofactors can regulate AR-mediated gene expression. FOXA1, a key transcription factor that facilitates chromatin remodeling for AR binding, is a critical driver of PCa pathogenesis [23]. In PCa cells, SUMO2/3 modification of FOXA1 at specific lysine residues (K6, K267, and K389) negatively regulates its interaction with AR and AR-dependent gene transcription [23]. Histone deacetylase 1 (HDAC1), an AR co-repressor, is similarly modified by SUMO1 at K444 and K476 sites [64]. The mutation at the SUMOylation site of HDAC1 significantly reduces the ability of HDAC1 to inhibit AR mediated transcription [65]. P68 (DDX5), a member of the DEAD-box RNA helicase family, acts as a transcriptional coactivator of the AR and is frequently overexpressed in PCa [66]. SUMOylation of P68 occurs primarily at the K53 lysine residue, where it is modified by SUMO2/3, though the modification by SUMO1 is less pronounced [67]. In vitro study has demonstrated that PIAS1 can enhance the SUMOylation of P68, which in

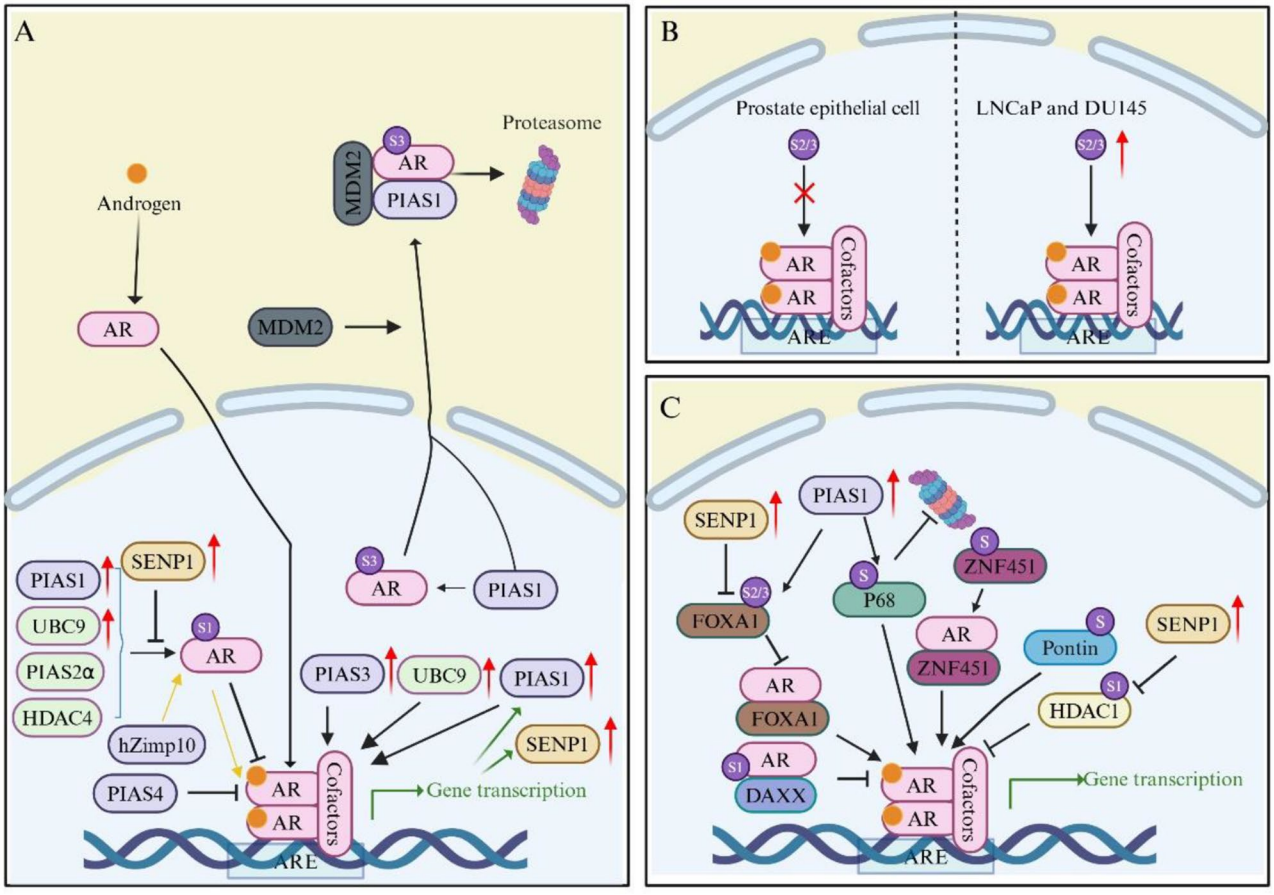

Fig. 2 SUMOylation regulates the transcriptional activity of AR. In PCa cells, UBC9, PIAS1, PIAS3, SUMO2/3, and SENP1 are typically upregulated (marked by red arrows). (**A**) Androgen binding causes AR to form dimers and transfer to the nucleus. Then, with the assistance of cofactors, AR exerts its transcriptional activity. On the one hand, PIAS1, UBC9, PIAS2α, and HDAC4 inhibit the transcriptional activity of AR by promoting SUMO1 modification, but hZimp10 promotes its transcriptional activity. SENP1 can reverse the SUMOylation of AR. Meanwhile, PIAS1, PIAS3, and UBC9 can directly promote the transcriptional activity of AR, while PIAS4 inhibits the transcriptional activity of AR. It is interesting that PIAS1 and SENP1 are target genes for AR. On the other hand, PIAS1 promotes the SUMO3 modification of AR to dissociate AR dimers, leading to the export of AR to the cytoplasm. Then, MDM2 recruits and degrades AR proteins. (**B**) In PCa, SUMO2/3 levels are usually higher than SUMO1 levels. In primary prostate epithelial cells, SUMO2/3 does not affect the transcriptional activity of AR. However, in PCa LNCaP and DU145 cells, SUMO2/3 enhances AR transcriptional activity. (**C**) SUMOylation regulates the binding of AR to co factors. SUMOylated AR is more likely to bind to DAXX, further inhibiting the transcriptional activity of AR. The SUMOylation of ZNF451, p68, and Pontin promotes the transcriptional activity of AR; The SUMOylation of FOXA1 and HDAC1 inhibits the transcriptional activity of AR. At the same time, SENP1 reverse the SUMOylation of FOXA1 and HDAC1, while PIAS1 promotes the SUMOylation of p68 and FOXA1

turn stabilizes the P68 protein [68]. This SUMOylation-dependent stabilization of P68 is thought to contribute to the progression of PCa [67]. Furthermore, SUMOylation of ZNF451 enhances its interaction with AR, and depletion of ZNF451 impairs AR transcriptional activity in PCa cells [45].

The regulation of *AR* gene expression also relies on chromatin remodeling complexes, including pontin that facilitates the interaction between AR and DNA. SUMOylation of pontin, specifically at the K225 site, enhances the transcription of AR target genes, thereby promoting PCa cell proliferation and growth [21]. The ongoing study of SUMOylation in these processes provides valuable insights into the molecular mechanisms underlying AR signaling in PCa and offers potential therapeutic targets to overcome treatment resistance.

Given SUMOylation's induced suppressive role on AR transcription, much research has focused on SENP1, that removes SUMO1 from AR [69]. After androgen stimulation and AR translocation to the nucleus, SENP1 rapidly removes the SUMOylation of AR, thereby enhancing its transcriptional activity [69]. SENP1 also plays positive feedback induced by AR-mediated transcription [70]. Moreover, knocking down SENP1 reduces androgen driven LNCaP cell growth [70]. Beyond AR, SENP1 also targets other AR-related transcription factors and co-regulators. For example, SENP1 induces deSUMOylation of FOXA1, enabling FOXA1 to interact with AR and enhances AR's binding to chromatin [23]. SENP1

also deSUMOylates HDAC1, thereby potentiating AR-dependent gene expression [65]. Additionally, SENP1 is involved in the response to environmental factors, such as cadmium exposure, which upregulates SENP1 expression and reduces AR SUMOylation [71], further boosting AR transcriptional activity and promotes PCa cell proliferation, particularly in the context of environmental carcinogens and androgen mimicry.

Integrating these findings provides a deeper understanding of the molecular mechanisms of epigenetic reprogramming mediated by SUMOylation in AR signaling, offering new opportunities for the development of effective treatment strategies for both early and advanced stages of PCa.

SUMOylation in tumor invasion and metastasis

EMT is a crucial cellular process involved in cancer metastasis and invasion, where epithelial cells lose their adhesive properties and acquire mesenchymal traits, thus gaining migratory and invasive abilities [72]. Snail and other key transcription factors are key regulatory factors of EMT, and their abnormal expression in tumor tissues is closely related to the metastasis and recurrence of various cancers, including PCa [72].

Recent studies have elucidated the role of SUMOylation in regulating EMT in PCa (Fig. 3). For instance, Jang et al. demonstrated that SUMO2/3 modification of Flot1 at K51 and K195, mediated by UBC9, promotes its nuclear translocation [19]. In the nucleus, Flot1 interacts with Snail and inhibits its ubiquitination and degradation in a SUMOylation-dependent manner, thereby stabilizing Snail and enhancing EMT and PCa metastasis [19]. Furthermore, TGF-β treatment induces SUMO1 modification of Snail at K234 in PCa cells [73], and SUMOylation site (K234R) mutation inhibits Snail SUMOylation, resulting in reduced invasive potential of PCa cells [73]. SLUG, like Snail, is another EMT-inducing factor that promotes cancer metastasis by downregulating E-cadherin [74]. In PCa cells, p14 (ARF) stabilizes SLUG by promoting its SUMO1 modification at K192, thereby enhancing EMT [75]. ASC-J9 (AR degradation enhancer) promotes SUMOylation of STAT3 at the K679 site, inhibits STAT3 phosphorylation, and thus suppresses EMT-SLUG signaling in PCa cells [76].

Vimentin (VIM), a type III intermediate filament protein involved in cytoskeletal organization and cell motility, is upregulated during EMT, weakening intercellular adhesion and making cells more prone to metastasis [77].

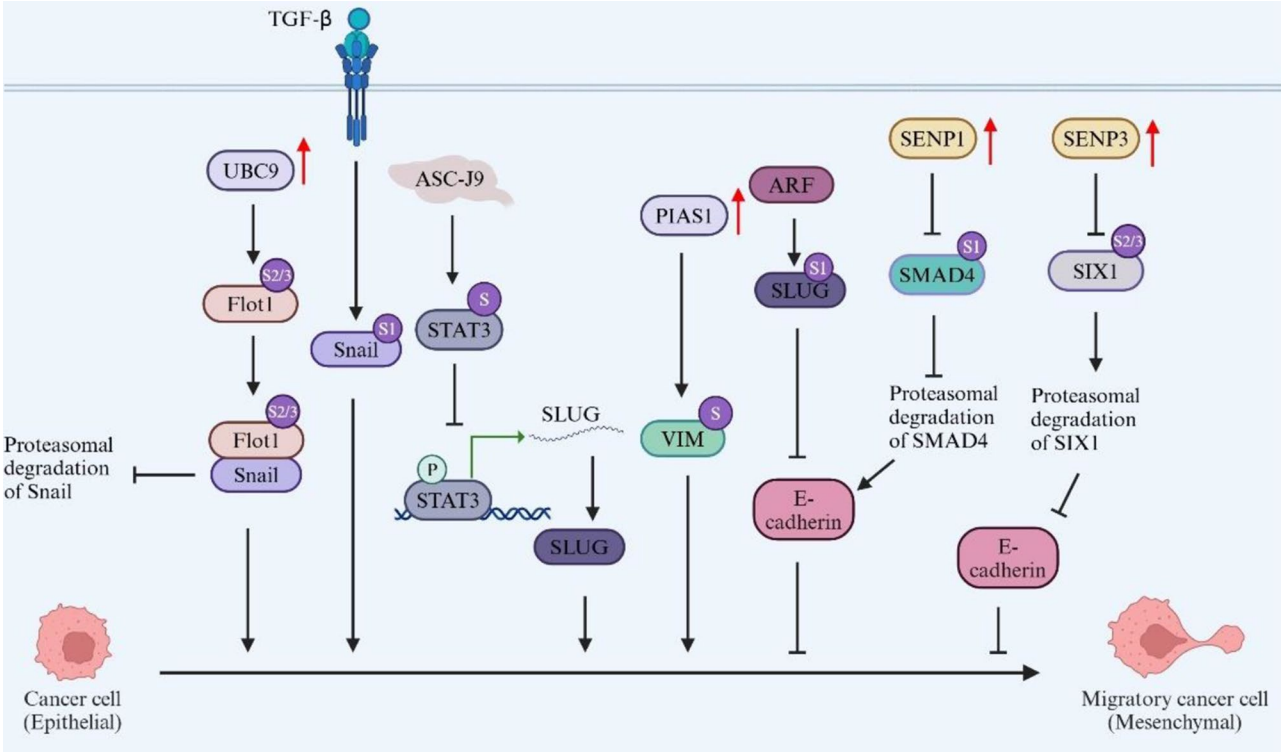

Fig. 3 SUMOylation regulates EMT in PCa. In PCa cells, UBC9, PIAS1, SENP1, and SENP3 are typically upregulated (marked by red arrows). UBC9 mediated SUMO2/3 modification of Flot1 stabilizes Snail and promotes EMT. In addition, TGF - β induced SUMOylation of Snail in PCa cells also promotes EMT. Meanwhile, p14 stabilizes SLUG by promoting SUMOylation, thereby enhancing EMT. In addition, ASC-J9 (AR degradation enhancer) promotes SUMOylation of STAT3, inhibits STAT3 phosphorylation, and suppresses EMT. PIAS1 mediates SUMOylation of VIM, leading to increased invasion of PCa cells. In addition, SENP1 reverses the SUMOylation of SMAD4, thereby reducing the expression of E-cadherin and increasing VIM levels, further promoting EMT in PCa cells. In addition, SENP3 inhibits the degradation of SIX1 by mediating the de-SUMOylation of SIX1, further promoting the migration and invasion of PCa cells

Li et al. showed that PIAS1 mediates the SUMOylation of VIM at K439 and K445 sites, leading to increased invasion of PCa cells [78]. Additionally, Zhang et al. found that the SENP1 mediates deSUMOylation of SMAD4, thereby reducing the expression of E-cadherin and increasing VIM levels, further promoting EMT in PCa cells [79]. In addition, SIX1 signaling transduction is reactivated in multiple cancers including PCa, promoting cell invasion by regulating EMT [80]. Shao et al. found that SENP3 inhibits the degradation of SIX1 by mediating its de-SUMOylation modification, further promoting the migration and invasion of PCa cells [47].

By regulating the stability and activity of transcription factors such as Snail, SLUG, and other EMT-related proteins, SUMOylation enhances the invasive phenotype of PCa cells. Together, these findings underscore the potential of targeting the SUMOylation pathway as a therapeutic strategy to inhibit EMT and combat PCa progression.

SUMOylation in cell proliferation and evasion of apoptosis

The ability to replicate infinitely and evade apoptosis are characteristics of tumor cells [81]. Increasing evidence suggests that SUMOylation plays a crucial role in regulating tumor cell proliferation and evading apoptosis (Fig. 4).

The PI3K/AKT pathway plays an important role in regulating cell proliferation and apoptosis [82]. As we all know, PTEN exerts tumor suppressive effects by dephosphorylating PIP3 and inhibiting the activation of PI3K/AKT pathway [82]. However, *PTEN* deletion is present in about 20% of primary PCa and 50% of advanced PCa [83].

Recent studies have revealed the importance of SUMOylation of PTEN in regulating its stability, activity, and subcellular localization. Huang et al. found that the SUMO1 modification of K266 in the C2 domain of PTEN made PTEN more likely to bind to the cell membrane, thus further opposing the PI3K/AKT pathway by dephosphorylation of PIP3 [84]. In addition, Wang et al. found that the SUMO1 modification of PTEN at K266 site was mediated by PIASxα, and this study also identified two other SUMOylation sites of PTEN (K254 and K289) [36]. Moreover, the SUMO1 modification of PTEN promotes PTEN translocation outside the nucleus, particularly to the plasma membrane in PCa cells [84]. Meanwhile, the SUMO1 modification of PTEN at K254 and K266 was increased after MG132 treatment in PCa

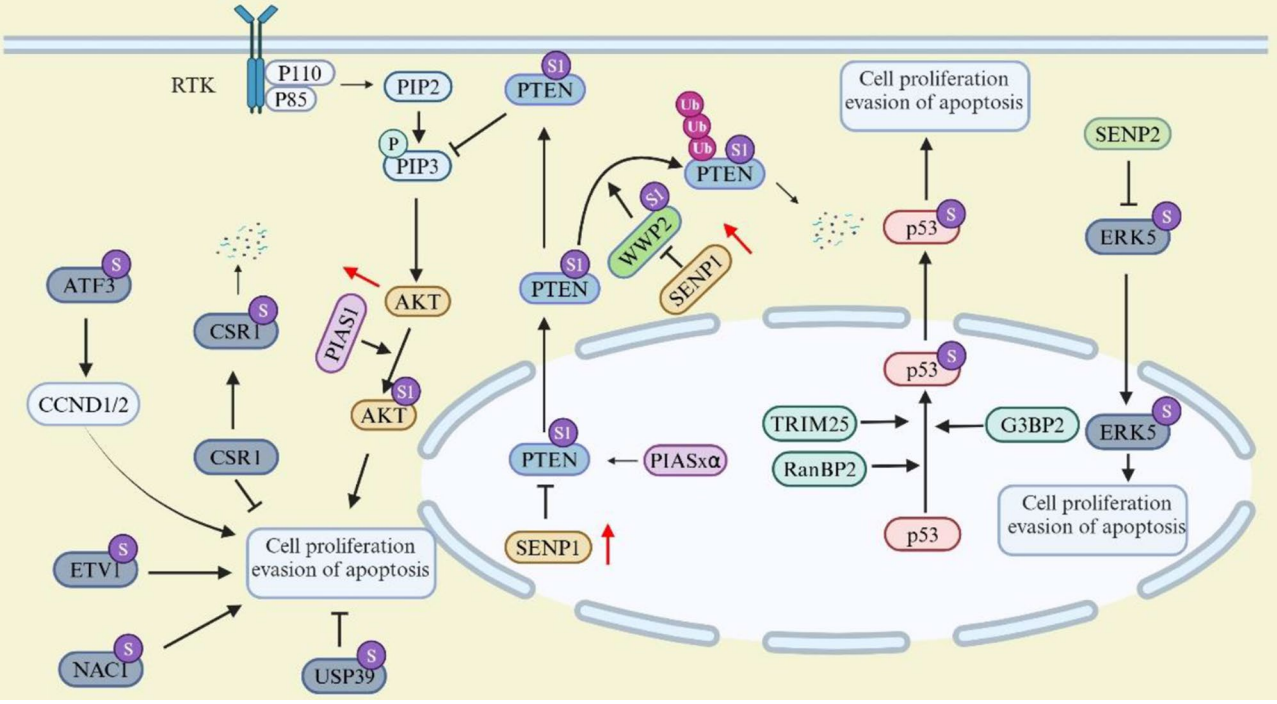

Fig. 4 SUMOylation regulates PCa cell proliferation and evasion of apoptosis. In PCa cells, PIAS1, and SENP1 are typically upregulated (marked by red arrows). The SUMOylation of PTEN helps to inhibit the activation of the PI3K/AKT pathway, but SENP1 can remove the SUMOylation of PTEN, and SUMOylated PTEN is more easily degraded by WWP2 ubiquitination. At the same time, PIAS1 promotes SUMOylation of AKT, upregulates AKT kinase activity, and promotes PCa cell proliferation. In the presence of androgens, RanBP2 promotes SUMOylation and nuclear export of p53 along with TRIM25 and G3BP2, while cytoplasmic p53 promotes proliferation and survival of PCa cells. On the contrary, the SUMOylation of ERK5 promotes nuclear input of ERK5, thereby promoting the proliferation of PCa cells. Meanwhile, the SUMOylation of ETV1, ATF3, and CSR1 also promote the proliferation of PCa cells. The SUMOylation of USP39 inhibits proliferation and metastasis of PCa cells

cells [52]. Additionally, the SUMO1 modification of PTEN increases its susceptibility to ubiquitin-mediated degradation, particularly by WWP2 [52]. Moreover, the unique SIM of WWP2 sets it apart from other E3 ligases of PTEN, such as CHIP and SMURF1 [52]. The SIM motif not only enhances the ubiquitination of SUMO1 modified PTEN, promoting its accelerated degradation, but also provides a key regulation of PTEN stability and modulating PCa progression [52].

PTEN also plays a critical role in maintaining genomic integrity, with its nuclear localization being important for DNA repair processes. In 293T cells, Bassi et al. found that the SUMO2 modification of PTEN at the K254 site promoted its nuclear localization [85]. And when DNA damage was repaired, the nuclear retained SUMOylation PTEN would be phosphorylated by ATM at its T398, and the phosphorylated PTEN would promote DNA damage repair (DDR), but the level of SUMOylation PTEN would gradually decrease, thus exiting the nucleus; after DDR, the level of SUMO2-modified PTEN protein in the nucleus would gradually recover [85]. Nonetheless, under normal circumstances, there is less SUMO2/3 modification of PTEN in PCa cells [52]. However, after starvation treatment, the SUMO2/3 modification of PTEN in PCa cells dramatically increased and promoted cell autophagy [86].

In contrast to PTEN, the PI3K/AKT pathway is often hyperactivated in PCa due to activating mutations in PI3K [82]. Li et al. showed that SUMO1 modification of AKT at K276, mediated by PIAS1, enhances AKT kinase activity, thereby promoting PI3K/AKT signaling [31]. In addition, p53 is a key tumor suppressor transcription factor that plays an important role in regulating cell proliferation and apoptosis [87]. In PCa cells, RanBP2 is closely related to the SUMOylation of p53 and its regulation of stability and function [44]. With the assistance of TRIM25, RanBP2 forms a complex with G3BP2 (GTPase-activating protein-binding protein 2), promoting SUMO1 modification of p53 and causing p53 transfer from the nucleus to the cytoplasm, thereby inhibiting p53 tumor suppressive function in the nucleus [44]. CSR1, a tumor suppressor protein, is often downregulated or absent in PCa. SUMOylation at the K582 site leads to rapid ubiquitination and degradation of CSR1 in PCa cells, thereby promoting PCa cell proliferation [49]. Conversely, SENP1 interacts with CSR1, reversing its SUMOylation and dramatically increasing its protein half-life [49].

The overexpression of NAC1 (Nuclear Accumulation Factor 1) is associated with tumor development, recurrence, and resistance to chemotherapy [88]. NAC1 could be SUMOylated at multiple lysine residues (K167, K318, K368, K483, and K498) [89]. Notably, compared to the wild-type NAC1, the SUMOylation-deficient mutant of NAC1 impairs cell proliferation and tumor growth in both PCa cell lines and animal models, suggesting that SUMOylation of NAC1 is crucial for its role in tumorigenesis [89]. Additionally, ERK5 is highly expressed and promotes both cell differentiation and proliferation [90]. SUMOylation of ERK5 at K6 and K22 sites facilitates its nuclear translocation, a key event for its activity [91]. However, mutation of these SUMOylation sites abolish the nuclear import of ERK5, leading to reduced proliferation of PCa cells [91].

Activating Transcription Factor 3 (ATF3), a member of the ATF/CREB family, is another key player in tumor cell proliferation [92]. SUMOylation of ATF3 at K42 enhances the activity of cyclins CCND1 and CCND2, which are critical regulators of the G1/S transition in the cell cycle [93]. This modification promotes the proliferation of PCa cells, such as PC3 and DU145 [94]. Similarly, the ETS transcription factor 1 (ETV1) is also implicated in PCa development and progression. ETV1 can be modified by SUMO1 at several lysine residues (K89, K228, K257, and K317) [94]. The inhibition of ETV1 SUMOylation in PCa cells suppresses tumor growth, indicating that SUMOylation plays a vital role in ETV1-mediated oncogenesis [94].

In addition, Wen et al. employed amino acid stable isotope labeling (SILAC) quantitative proteomics technology to identify over 900 potential SUMO target proteins in PC3 cells [95]. Among these, USP39, a protein involved in pre-mRNA splicing, was found to be SUMOylated at multiple sites (K6, K16, K29, K51, and K73) [95]. Mutations in these SUMOylation sites of USP39 enhance its proliferative role in PCa cells, highlighting the critical role of SUMOylation in regulating key proteins involved in tumor growth [95].

SUMOylation in metabolic reprogramming and tumor microenvironment

Metabolic reprogramming is a defining characteristic of cancer, wherein tumor cells undergo significant alterations in their energy production pathways compared to normal cells [96]. SUMOylation has been implicated in the regulation of these metabolic changes in cancer cells [97] (Fig. 5). One of the hallmark features of metabolic reprogramming in tumors is the shift towards aerobic glycolysis, commonly referred to as the Warburg effect [96]. Hexokinase (HK), the first rate-limiting enzyme in glycolysis, catalyzes the conversion of glucose to glucose-6-phosphate [98]. Among the five known isoforms of hexokinase, HK2 is predominantly expressed in various tumor types and is considered a promising therapeutic target for cancer treatment [98]. SUMOylation of HK2 at the K315 and K492 sites regulates its interaction with the outer mitochondrial membrane, which is critical for its oncogenic activity [51]. Mutations at these sites of HK2 enhance its binding to mitochondria, leading to increased

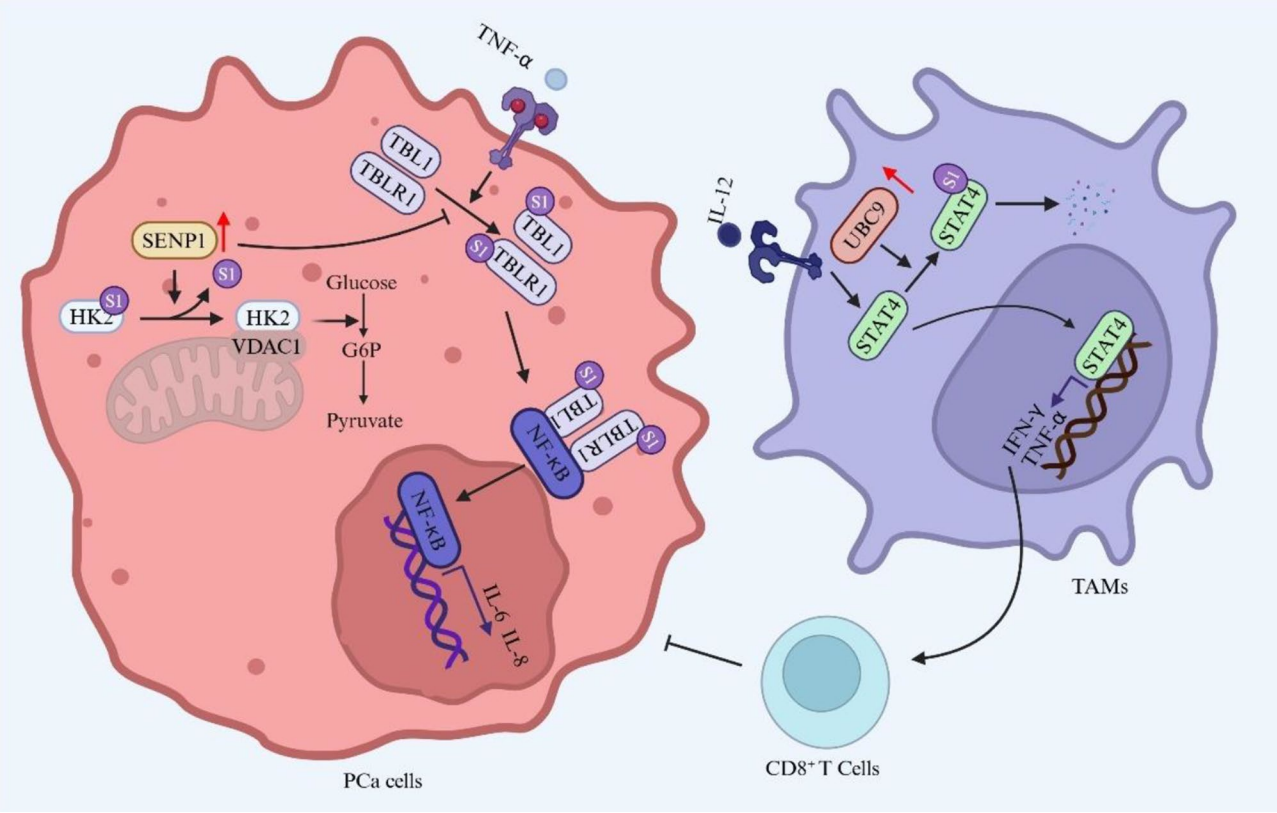

Fig. 5 SUMOylation regulates metabolic reprogramming and tumor microenvironment in PCa cells. In PCa cells, SENP1 is typically upregulated (marked by red arrows). In TAMs, UBC9 is typically upregulated (marked by red arrows). The SUMOylation of HK2 promotes its binding to VDAC1 on the outer membrane of mitochondria, thereby further promoting glycolysis in PCa cells. At the same time, under the action of TNF-α, the SUMOylation of TBL1 and TBLR1 in PCa cells increases, promoting the activation of NF-κB and the production of some inflammatory mediators. Under the action of inflammatory mediator IL-12, STAT4 in TAMs is activated to transfer cytoplasmic nuclei, promoting the activation of CD8 + Tcell by substances such as IFN - γ. However, UBC9 is highly expressed in TAMs, promoting SUMOylation modification of STAT4 and further ubiquitination degradation

glucose consumption and lactate production, driving metabolic reprogramming in PCa cells [51]. Additionally, SENP1 can reverse HK2 SUMOylation, further promoting metabolic changes that favor PCa cell survival [51].

The tumor microenvironment (TME) refers to the complex and dynamic milieu in which tumor cells interact with surrounding stromal cells, extracellular matrix components, blood vessels, and immune cells [99]. Inflammation plays a crucial role in TME and is a defining feature of many cancers [100]. Elevated levels of pro-inflammatory cytokines are often associated with poor prognosis in PCa [81]. The SUMOylation of TBL1 and TBLR1 is positively correlated with inflammatory cytokine levels in PCa cells [101]. Upon TNF-α stimulation, SUMOylation of TBL1 and TBLR1 increases, which in turn activates NF-κB-mediated transcription of cytokine genes [101]. In contrast, SENP1 can reverse the SUMOylation of TBL1 and TBLR1, modulating this inflammatory response [101]. Furthermore, in hepatocellular carcinoma (HCC), SUMO1 mediates the SUMOylation of MANF (midbrain astrocyte-derived neurotrophic factor) and the p65 subunit, interfering with the activation of NF-κB and limiting the release of inflammatory factors such as IL-6, IL-8, and TNF-α [102]. Additionally, the SUMOylation of IκBα at the K21 site prevents its signal-induced degradation, thereby inhibiting NF-κB activation [103]. In contrast, IκBα modified with SUMO2/3 is more susceptible to proteasomal degradation [104], highlighting the complexity of SUMOylation in regulating NF-κB signaling.

TAMs are key players in shaping the immune response within the TME [105]. IL-12 activates STAT4 in TAMs, which in turn promotes CD8 + T cell activation through the production of interferon-gamma (IFN-γ) [18]. In TAMs, UBC9 inhibits the pro-inflammatory activation of ATM by promoting the SUMOylation of STAT4 at the K350 site, thereby suppressing anti-tumor immunity [18]. Therefore, further research on the specific details of SUMOylation can help us better understand how SUMOylation affects tumor metabolic reprogramming and immune response, providing a foundation for the development of new therapeutic strategies and targeted drugs.

Therapeutic implications of targeting sumoylation

The accumulating evidence highlighting the pivotal role of SUMOylation in PCa progression underscores its potential as a therapeutic target [97]. Disrupting key components of the SUMOylation machinery, such as SENPs, UBC9, or E3 ligases, or SUMOylation sites mutations of substrates, potentially destroying normal cellular function. Alternatively, strategically enhancing SUMOylation in certain contexts may inhibit the activity of proteins that drive tumor progression, offering a dual strategy for therapeutic intervention.

SUMO E1, functioning as an activating enzyme in the form of the SAE1/2 dimer, is associated with cancer progression [106]. Upregulation of SAE1 or SAE2 has been linked to the proliferation and metastasis of various tumor types [107–110]. Several natural compounds have been identified as inhibitors of SAE1/2, including ginkgolic acid, anacardic acid, kerriamycin B, and Davidiin [97]. Notably, Davidiin has been shown to inhibit the growth of DU-145 PCa cells [111]. Additionally, small-molecule inhibitors targeting SAE1/2, such as TAK-981, have been developed [112–115]. TAK-981 has demonstrated the ability to enhance myeloma cell sensitivity to lenalidomide and dexamethasone, as well as to promote anti-tumor activity in pancreatic cancer models [116–119]. Although TAK-981 has not yet been tested in specialized clinical trials for PCa, ongoing phase 1/2 studies may indicate its potential for treating cancer (NCT Numbers: NCT04065555, NCT04074330, NCT03648372, NCT04381650, NCT04776018, NCT05976334) (Table 2).

As previously discussed, UBC9, a critical enzyme in the SUMOylation pathway, is overexpressed in PCa, where it promotes the SUMOylation of several key substrates that contribute to tumorigenesis [15, 18–23]. Various small molecule inhibitors of UBC9 have been identified, including GSK145A, 2-D08, Spectomycin B, and Compound 2 [121]. Notably, 2-D08 has shown a promising effect on preclinical models, inhibiting PCa progression in PC3 xenografts and enhancing the anti-tumor effects of TAMs [18]. Meanwhile, the combination of 2-D08 and anti-PD-1 therapy significantly inhibited the progression of PCa [18]. SENP1 also plays a significant role in promoting PCa progression. By deSUMOylation of key proteins such as AR and HK2, SENP1 facilitates the aggressive phenotype of PCa cells. Inhibiting SENP1 has emerged as a potential therapeutic strategy, with several inhibitors identified through both in vitro screening and computational simulations [95, 120]. Triptolide and Momordin Ic have demonstrated efficacy in suppressing the proliferation of PCa cells, highlighting their potential as novel SENP1-targeting agents [121, 122]. Bellail et al. have revealed that CPD1 and its derivative HB007 can promote the ubiquitination and degradation of SUMO1, a key component of the SUMOylation pathway [123]. By targeting SUMO1 degradation, these compounds disrupt the SUMOylation of oncogenic substrates, thereby exerting potent anticancer activity across various tumor cell lines [123].

SUMO E3 ligases play a central role in determining substrate specificity and facilitating the transfer of SUMO from the E2 ligase to the substrate. However, the development of small-molecule inhibitors targeting SUMO E3 ligases remains limited. UNC3866 is a selective inhibitor that binds to the CBX chromodomain of the SUMO E3 ligase CBX4, thereby inhibiting its activity in PC3 prostate cancer cells [124]. In addition, UNC3866

Table 2 Clinical trials of sumoylation inhibitors

NCT Number	Phases	Conditions	Intervention	Enrollment	Sponsor	Start Date	Primary Completion Date	Completion Date
NCT04065555	Early Phase 1	Head and Neck Cancer	TAK-981 and TAK-981 combined with cetuximab or avelumab	12	Presage Biosciences	2020/10/7	2022/6/20	2022/7/20
NCT04074330	Phase 1/2	CD20-Positive Non-Hodgkin Lymphoma	TAK-981 combined with Rituximab	38	Takeda	2019/10/15	2023/4/26	2023/4/26
NCT03648372	Phase 1/2	Advanced solid tumors or cancers in the immune system (lymphomas)	TAK-981	109	Takeda	2018/10/1	2023/11/22	2023/12/14
NCT04381650	Phase 1/2	Advanced or metastatic solid tumors	TAK-981 combined with pembrolizumab	49	Takeda	2020/8/17	2025/11/30	2025/11/30
NCT04776018	Phase 1/2	Relapsed or refractory multiple myeloma (RRMM)	TAK-981 combined with anti-CD38 monoclonal antibodies (mAbs)	27	Takeda	2021/4/20	2023/8/2	2023/11/9
NCT05976334	Phase 1	Advanced or metastatic solid tumors	[14 C] Subasumstat (TAK-981) and Subasumstat	3	Takeda	2023/11/14	2024/6/21	2024/7/16

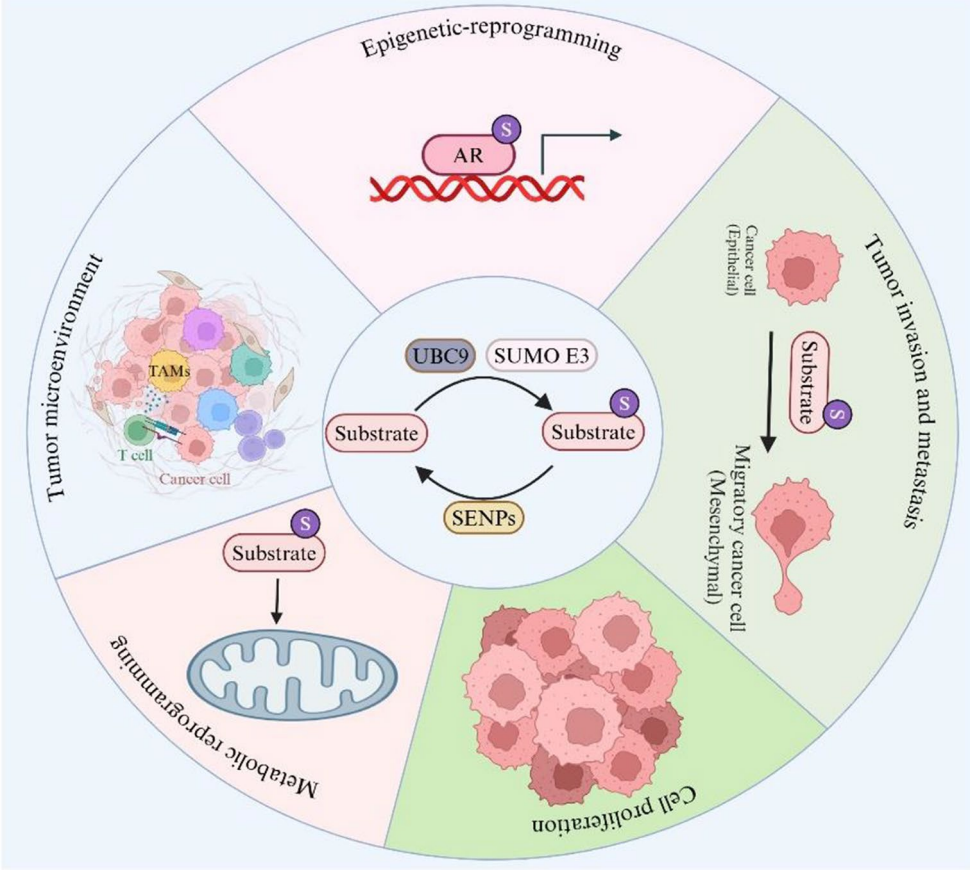

Fig. 6 Summary of the role of SUMOylation in PCa

disrupts the anti-tumor effects of CBX4, contributing to reduced tumor cell proliferation and the suppression of cancer stem cell-like properties [124]. In addition, studies have found that the combination of abiraterone or enzalutamide therapy and PIAS1 depletion is more effective than single drug therapy in multiple PCa cell models, making PIAS1 a promising target protein [28]. So further research on PIAS1 inhibitors can be used to improve the combination therapy for future PCa therapies.

Recent studies have also highlighted the potential of melatonin in modulating SUMOylation. Specifically, melatonin-induced HDAC1 SUMOylation leads to inhibition of AR transcriptional activity, suggesting a novel mechanism for targeting AR signaling in PCa [50]. Additionally, ASC-J9, a compound that enhances AR degradation, has been shown to effectively reduce cell proliferation and invasion in PCa models [76]. Research has found that ASC-J9 can also inhibit the invasion and metastasis of PCa by promoting the SUMOylation of STAT3, thereby suppressing STAT3 phosphorylation [76].

These findings collectively suggest that targeting components of the SUMOylation pathway, whether through inhibition or enhancement of SUMOylation, holds considerable promise as prostate cancer treatment.

Conclusion

In conclusion, the intricate balance between SUMOylation and deSUMOylation plays a pivotal role in the progression of PCa (Fig. 6). SUMOylation functions both as an oncogenic driver and, paradoxically, as a potential tumor suppressor, highlighting the complexity of its regulatory effects in cancer biology. The current limited therapeutic strategies targeting SUMOylation in PCa underscore a significant gap in our understanding, emphasizing the critical need for the development of novel chemical modulators capable of precisely manipulating this pathway.

The emergence of selective SAE inhibitors, such as TAK-981, marks a promising advancement in SUMOylation-targeted therapies, demonstrating efficacy across various malignancies and suggesting potential applicability in PCa, particularly in cases where SUMOylation exacerbates tumor progression. However, targeting SUMO E3 ligases, which regulate the specific transfer of SUMO to substrates, may offer a more refined and precise therapeutic approach. Despite this, such therapies remain largely undeveloped. As our molecular understanding of SUMOylation's role in oncogenic signaling continues to evolve, it opens new avenues for

developing innovative treatment strategies and personalized therapies tailored to the unique molecular profiles of individual tumors.

At present, most research is limited to the cellular level, but due to the complexity of the tumor microenvironment, these studies are difficult to reflect the overall impact of SUMOylation disorder on PCa. At the same time, the rise of genomics and proteomics provides a good way to reveal the overall impact of SUMOylation disorder on PCa tissue. For example, Sun et al. explored the impact of SUMOylation related genes on the prognosis of PCa patients through genomics [126], Launonen et al. deeply revealed the effect of SUMO2/3 modification on AR transcriptional activity through chromatin proteomics [61], and Wen et al. revealed through the SUMO proteome of PC3 cells that SUMOylation of splicing factors is crucial for the development of PCa [96].

Ultimately, investigating SUMOylation in the context of PCa represents a promising frontier in cancer research. By unraveling the complex roles of SUMOylation and its interactions with other cellular processes, we can lay the groundwork for novel therapeutic approaches that aim to improve patient outcomes. Ongoing research in this field is essential to translating these insights into clinical practice, with the potential to reshape the treatment landscape for PCa and offer hope to patients confronting this challenging disease.

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Conceptualization, K.L. and X.J.; methodology, K.L. and H.W.; writing—original draft preparation, K.L. and B.J.; writing—review and editing, X.J. and K.L.; visualization, K. L.; supervision, K.L. All authors read and agreed to the published version of the manuscript.

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Data availability
Not applicable.

Declarations

Institutional review board
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Informed consent
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Conflict of interest
The authors declare no conflicts of interest.

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