Review

Cancer Research

The Role of PIAS SUMO E3-Ligases in Cancer

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Abstract

SUMOylation modifies the interactome, localization, activity, and lifespan of its target proteins. This process regulates several cellular machineries, including transcription, DNA damage repair, cell-cycle progression, and apoptosis. Accordingly, SUMOylation is critical in maintaining cellular homeostasis, and its deregulation leads to the corruption of a plethora of cellular processes that contribute to disease states. Among the proteins involved in SUMOylation, the protein inhibitor of activated STAT (PIAS) E3-ligases were initially described as transcriptional coregulators. Recent findings also indicate that they have a role in regulating protein stability and signaling transduction pathways. PIAS proteins interact with up to 60 cellular partners affecting several cellular processes, most notably immune regulation and DNA repair, but also cellular proliferation and survival. Here, we summarize the current knowledge about their role in tumorigenesis and cancer-related processes. *Cancer Res; 77(7); 1542–7. ©2017 AACR.*

The Process of SUMOylation

SUMOylation is an enzymatic cascade whereby small ubiquitin-like modifier (SUMO) proteins are covalently bound to lysine residues (K) present on target proteins (Fig. 1A). The components of the SUMOylation machinery are highly conserved and ubiquitously expressed throughout the eukaryotic kingdoms. There are several recent publications on this topic: We will review here only the essentials regarding the SUMOylation cascade (1, 2).

SUMOylation targets a wide variety of proteins, including transcription factors, membrane receptors, and enzymes, and it is essential during embryonic development (1, 2). Whole-proteomic analysis showed that approximately 2% of the entire mammalian proteome is SUMOylated (3).

In vertebrates, five SUMO genes exist (SUMO1–5). SUMO1–3 are ubiquitously expressed, whereas SUMO4 and SUMO5 are tissue specific, and their functions are not completely defined yet (2, 4). SUMO modifications can be distinguished in mono-, poly-, and multi-SUMOylation (Fig. 1B; refs. 2, 3).

The PIAS Family: Classification and Physiologic Roles

In striking contrast with the ubiquitination system, where hundreds of distinct E3-ligases mediate the recognition of specific substrates, only the PIAS family and few other SUMO E3-ligases have been described. Thus, it is not completely understood how substrate recognition is achieved in the SUMOylation system (5, 6). The RING domain and the SUMO-interacting motif (SIM) of the SUMO E3-ligases contribute to substrate specificity and facilitate the interaction of UBC9 and SUMO with target proteins (5, 6). However, it seems unlikely that this is the only mechanism mediating the specificity of substrate selection, and future research will likely shed more light on this process.

PIAS orthologs can be found throughout the eukaryotic kingdoms, and mammals have four PIAS genes (Fig. 2A; ref. 7).

PIAS proteins were initially identified as inhibitor of STAT transcription factors (7–9), but it is becoming clear that they regulate a broader range of proteins. For instance, PIAS family members regulate nuclear trafficking, DNA damage repair, NF-κB signaling, several transcription factors, and many nuclear receptors (7, 10–13).

At the organismal level, PIAS members are involved in embryonic development, hematopoiesis, innate and adaptive immune response, spatial learning, and long-term memory (14–17).

Of note, the functions of PIAS proteins are not always strictly associated with their SUMO E3-ligase activity, suggesting that their enzymatic activity might be just one of their functions. For instance, both PIAS1 and PIAS4 regulate LEF-1 and Tp53, regardless of the integrity of the RING domain, which is necessary for their SUMO E3-ligase activity (18, 19).

Regulation of PIAS Proteins in Cancer

Several posttranslational modifications (PTM) modulate the function of PIAS family members; however, their mechanistic underpinnings and functional consequences are still not completely understood.

PIAS1 is phosphorylated by casein kinase 2 (CK2) *in vitro* on three conserved serine residues adjacent to the SIM domain (20). This phosphorylation event is of biological relevance as PIAS1 promotes the interaction between CK2 and PML tumor suppressor (PML), which in turn leads PML to ubiquitin-mediated degradation (21). We will discuss the role of the SUMO-dependent RNF4 ubiquitin E3-ligase in this process, later in this review. Furthermore, CK2 itself undergoes SUMOylation (22). These observations suggest that PIAS1 and CK2 are part of an integrated signaling network dedicated to degradation of PML in cancer cells.

During inflammation, PIAS1 is rapidly phosphorylated on S90 by IKKα, and this modification seems to promote PIAS1 E3-ligase

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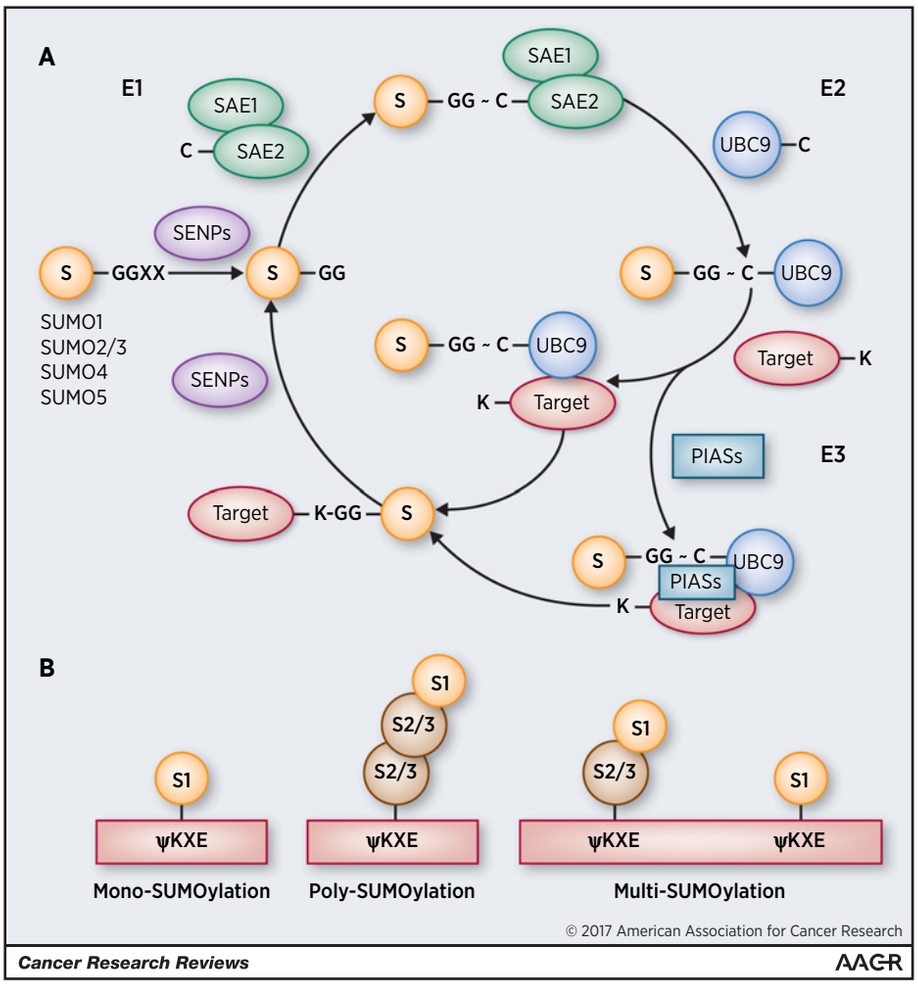

Figure 1.
Mechanism of SUMOylation. **A,** Sentrin-specific proteases (SENP) catalyze the maturation of the SUMO (S) proteins (cleavage of Gly-Gly tail, GG) that are transferred to the final substrate through an enzymatic cascade comprising the heterodimeric SAE1-SAE2 (SUMO-activating enzyme 1 and 2, respectively) E1-ligase and the E2-ligase UBC9. This last enzymatic step is often facilitated by an E3-ligase, which facilitates the transfer of SUMO to target proteins. As SUMOylation is a reversible modification, SENPS accounts also for the de-SUMOylation process. **B,** SUMO2 and SUMO3 (S2/3), can form poly-SUMO chains. SUMO1 (S1), lacking internal lysine residues, is a SUMO chain terminator. The figure depicts a classic ψKXE SUMOylation consensus site, where ψ is a branched aliphatic residue and X is any amino acid. Additional motifs have been identified: NDSM, amino acid–dependent SUMOylation motif; PDSM, phosphorylation-dependent SUMO-motif; pSuM, phosphorylated SUMOylation motif.

activity (23). There is no evidence that these phosphorylation events influence the role of PIAS proteins in cancer. However, as CK2 and NF-κB pathways are often deregulated in cancer, it is likely that downstream phosphorylation of PIAS proteins contribute to tumorigenesis.

The mechanisms that regulate the transcription of PIAS family members are still largely unknown; however, PIAS genes are often overexpressed in cancer (24). This area of research will likely be explored in the near future. Little is known regarding the turnover of PIAS family members, and it will not be discussed here.

SUMO Ligases and Cancer

Several components of the SUMO machinery are highly expressed in cancer, suggesting that SUMOylation is required to initiate or sustain tumorigenesis. For example, SAE1/2 are amplified in breast, prostate, and pancreatic cancers (24). Moreover, SAE1/2 is a *MYC* synthetic lethality in breast cancer cells (25). In this context, SAE1/2 silencing inhibits MYC SUMOylation causing the repression of a subset of MYC target genes, causing a mitotic catastrophe (25). Moreover, elevated levels of SAE1/2 are found in patients with hepatocellular carcinoma, while UBC9 is amplified or overexpressed in breast, prostate, and pancreatic cancer (24).

PIAS1 and PIAS3 have been most often implicated in tumorigenesis: PIAS1 is overexpressed in prostate cancer, where it suppresses p21, leading to an increased proliferation rate (26, 27); PIAS1 overexpression correlates with a poor clinical outcome in multiple myeloma (28); PIAS3 is often overexpressed in colorectal cancer (24). As described in the following sections, PIAS proteins promote tumorigenesis and cancer cell survival through the interaction with several tumor suppressors and oncogenes.

PIAS Family Members and the Regulation of Tp53

The tumor suppressor Tp53 is a master regulator of apoptosis and senescence. Tp53 is often lost or inactivated in many types of cancer (29). *In vitro* assays using both cell-free and cell culture–based assays have shown that all PIAS members physically interact with Tp53 (29). SUMOylation of Tp53 primarily occurs at K386, but in its absence, other lysine residues can be SUMOylated (29). However, the functional consequence of Tp53 SUMOylation has been controversial. For example, it was reported that PIAS4-dependent SUMOylation promotes the transcriptional activity of wild-type Tp53, leading to senescence (29). However, others reported that PIAS4 ligase

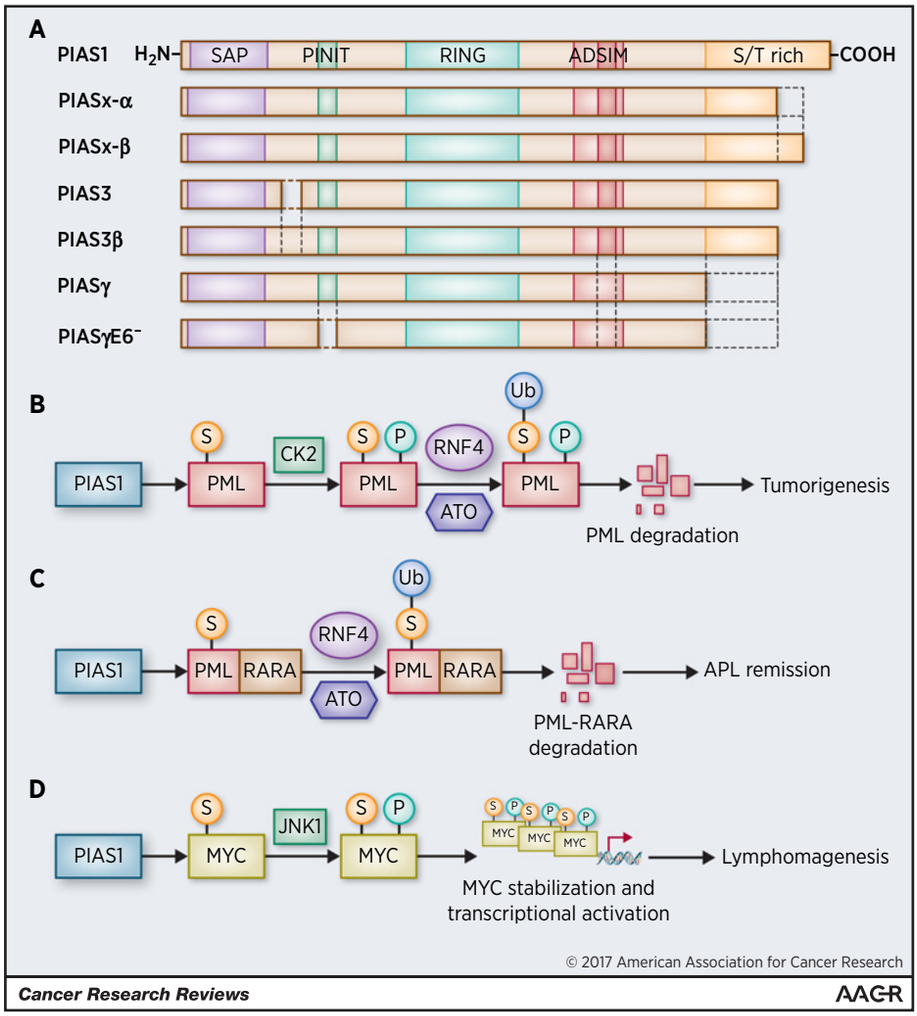

Figure 2.

PIAS proteins structure and significance in cancer. **A,** In mammals, four PIAS genes exist: *PIAS1, PIAS2* (also known as PIASx, with the two splice variants PIASx-α and PIASx-β), *PIAS3* (with the splice variant PIAS3β), and *PIAS4* (also known as PIASy, with the splice variant PIASyE6^{-}). These genes share 40% of homology and domain organization. The N-terminal SAP domain binds to (A+T)-enriched DNA sequences and to transcriptional coregulator through the α-helical LXXLL motif (not shown in the figure). The PINIT domain mediates nuclear localization; the RING finger–like zinc-binding domain is required for the E3-ligase activity. In the C-terminal region, a highly acidic region (AD) and a serine/threonine-rich region (S/T rich) are present. The AD of PIAS1, PIAS2, and PIAS3 also contains a SIM, which can modulate the enzymatic activity of the protein. PIASyE6^{-} is the splice variant of PIAS4 lacking exon 6 (i.e., the PINIT domain). **B,** In lung cancer cells, PIAS1 SUMOylates the tumor suppressor PML, leading to the recruiting of CK2 that, in turn, phosphorylates PML, leading to its proteasomal degradation. ATO facilitates PIAS1-driven SUMOylation of PML and its subsequent ubiquitination by RNF4 ubiquitin E3-ligase that is recruited on SUMO chains. **C,** In APL, PIAS1 SUMOylates PML-RARA. ATO induces PIAS1-dependent PML-RARA hyper-SUMOylation. RNF4 directs the ubiquitin-mediated degradation of hyper-SUMOylated PML-RARA, causing the apoptosis of APL cells. **D,** PIAS1 SUMOylates MYC, recruiting JNK1, which in turn phosphorylates MYC, increasing its stability and transcriptional activity. These events contribute to B-cell lymphomagenesis. S, SUMOylation; P, phosphorylation; Ub, ubiquitination.

promotes the nuclear export of Tp53, counteracting its transcriptional activity (29).

It was also reported that both PIAS1 and PIASx-β SUMOylate Tp53. Also in this case, it is still unclear whether PIAS1 and PIASx-β–dependent SUMOylation either activates or represses Tp53, and whether they exert these functions independently of their E3-ligase activity (29). One possible explanation for such divergent results is that the effects of PIAS proteins on Tp53 are influenced by cellular context, PTMs, or other, yet to be identified, interacting proteins.

Interestingly, also the other Tp53 family members p63 and p73 and the Tp53 ubiquitin ligase MDM2 undergo PIAS-mediated SUMOylation. PIAS1-dependent SUMOylation negatively regulates the transcriptional activity of p73 (29). Moreover, both PIAS1 and PIASx-β SUMOylate the nuclear localization signal of MDM2 at K182, promoting MDM2 nuclear translocation (30).

All together, these data indicate that PIAS proteins are able to modulate the activity and the fate of Tp53 and Tp53-related members, highlighting their relevance in Tp53 regulation.

PIASs and the PI3K/AKT Axis

The serine/threonine kinase AKT plays a pivotal role in the regulation of several physiologic and oncogenic processes (31). AKT is regulated by several PTMs, including PIAS1-dependent SUMOylation on K276. This modification is essential for AKT activation, and mutation of K276 completely abrogates its kinase activity. Moreover, PIAS1 also SUMOylates AKT E17K, which is a common cancer-associated mutation, more efficiently than wild-type AKT. Furthermore, ablation of K276 dramatically decreases the tumorigenic activity of AKT E17K (32). Neither the activation of PI3K nor the ability of AKT to bind to the plasma membrane affects its SUMOylation. Instead, the SUMOylation of AKT is negatively regulated by PML upon nutrient starvation or wortmannin treatment (33).

In contrast, PIASx-α opposes PI3K/AKT signaling by directly SUMOylating the tumor suppressor PTEN, which inhibits PI3K/AKT signaling through its phosphatase activity. The effect of PTEN SUMOylation is a reduction of its ubiquitin–proteasomal degradation (34).

These results suggest that PIAS1 and PIASx-α have an opposite influence on the PI3K signaling axis. Future experiments will elucidate the mechanistic insights by which PIAS1 and PIASx-α control PI3K–AKT signaling pathway.

PIAS1, PML, and PML-RARA

The tumor suppressor PML was one of the first proteins described to be SUMOylated (35, 36). Initially identified as a component of the PML-RARA oncoprotein of t(15;17) of acute promyelocytic leukemia (APL), PML tumor suppressor is frequently lost in human cancer through aberrant ubiquitin–proteasomal degradation triggered by CK2 (37, 38). PIAS1 and PIASx-α are PML SUMO E3-ligases (21). PIAS1-dependent SUMOylation drives PML to ubiquitination and degradation by promoting the recruitment of CK2 to poly-SUMOylated PML (Fig. 2B). Indeed, loss of PIAS1 in the developing embryo or silencing of PIAS1 in non–small cell lung cancer (NSCLC) cell lines leads to upregulation of PML and decreased cell proliferation (16, 21). Even though PIAS1 is not commonly mutated in cancer, it is often amplified in NSCLC cell lines and is overexpressed in NSCLC and several other cancer types (21, 24). Thus, it is notable that PIAS1 and PML protein levels are inversely correlated in human primary NSCLC samples (21). All together, these observations support the conclusion that PIAS1 is oncogenic and that PML is its *bona fide* target.

We expect that the identification of the transcriptional and posttranscriptional mechanisms that mediate PIAS1 overexpression and substrate selection will reveal novel details regarding cancer underpinnings.

SUMOylation plays a dual role in the regulation of PML-RARA. Mono- or oligo-SUMOylation of K160 stabilizes PML-RARA and is essential for leukemogenesis. Arsenic trioxide (ATO) treatment (a major therapeutic agent in APL) induces a conformational change of both PML and PML-RARA that causes their poly-SUMOylation. Subsequently, the RNF4 E3-ubiquitin ligase binds to poly-SUMOylated PML and PML-RARA through its SIMs, directing their ubiquitin-dependent proteasomal degradation (39). Although ATO does not distinguish between PML and its fusion protein, the degradation of PML-RARA causes the death of APL cells and ultimately remission in APL patients (40).

It has been demonstrated that PIAS1 is the PML-RARA SUMO E3-ligase that SUMOylates PML at K160 in basal conditions. Furthermore, PIAS1 mediates the ability of ATO to induce PML-RARA hyper-SUMOylation. Thus, PIAS1 is required for the therapeutic action of ATO (Fig. 2B and C; ref. 21).

These data demonstrate that the nature and the intensity of the stimulus that activates PIAS1 critically influence its biological function. We also speculate that PIAS1 may contribute to other effects of ATO, such as its well-known carcinogenic effects and the induction of oxidative stress responses.

The role of PIASx-α in the regulation of PML has not been characterized yet; however, unpublished data from our laboratory suggest that PIASx-α might be involved in the promotion of replicative senescence (A. Rabellino unpublished data). This observation suggests that PIAS family members have divergent biological roles even when SUMOylating a common substrate. Future investigations are needed to clarify whether this property is due to the SUMOylation of specific lysine acceptors or to the quality or composition of SUMOylated chains conjugated to the substrate.

PIAS1, MYC, and Lymphomagenesis

MYC exerts critical oncogenic activities in a wide variety of human cancers. MYC is strictly regulated by several posttranslational modifications, including phosphorylation and ubiquitination (41). MYC family members are also SUMOylated (42). The observation that the SUMO E1-ligase is required for the viability of MYC-dependent breast cancer cells suggests that SUMOylation is involved in the regulation of MYC-dependent processes (25). However, until recently, it was unknown whether SUMOylation directly regulates MYC.

Recently, PIAS1 has been reported to account for MYC SUMOylation (Fig. 2D; refs. 43, 44). K51/52 are the major MYC SUMOylation sites. SUMOylation not only prolongs MYC half-life preventing its proteasomal degradation, but also positively regulates MYC transcriptional activity. Significantly, we also demonstrated that MYC is SUMOylated in primary B-cell lymphomas (43). Furthermore, PIAS1-mediated SUMOylation is required to maintain the oncogenic activity of MYC in lymphoma cells. Accordingly, we found that PIAS1 and MYC are often coexpressed in human and murine diffuse large B-cell lymphoma (43). This study also suggests that PIAS1 regulates MYC during B-cell maturation and activation *in vitro*. These observations are consistent with the observation that Pias1-null mice have defective differentiation of the lymphoid lineage *in vivo* (15).

We propose that when expressed at physiologic levels, PIAS1 promotes the expansion and differentiation of B cells through the physiologic activation of MYC. Instead, in conditions of upregulation of MYC, as it often occurs in cancer, PIAS1 promotes the supraphysiologic activation of MYC, contributing not only to B-cell lymphomagenesis but also to other cancer types (43).

In this regard, it is noteworthy that PIAS1 is required also for the viability of MYC-dependent breast cancer and of lung cancer cells (and A. Rabellino unpublished results; ref. 43). These findings support the conclusion that PIAS1 is a requirement of other MYC-driven malignances. Consistent with this view, several components of the SUMOylation machinery are upregulated by MYC in mouse and human B-cell lymphomas. Furthermore, inhibition of SUMOylation induces the apoptosis of MYC-dependent lymphoma cells (45).

González-Prieto and colleagues reported that PIAS1 induces MYC degradation in a SUMO-dependent manner (44). Even though this report is consistent with the notion that PIAS1 SUMOylates MYC, it reaches a conclusion that is at odds with ours (43). We reason that this discrepancy could be explained by the fact that the experiments of González-Prieto and colleagues were performed mainly using ectopically expressed genes in U2OS and HeLa cell lines, which could have influenced the outcome of their experiments. Future experiments will undoubtedly further address the role of PIAS1 in the regulation of MYC. For instance, our laboratory is performing experiments with a Pias1 conditional null mouse to dissect the function of PIAS1 on tumorigenesis *in vivo*.

PIAS1, Cell Migration, EMT, and Metastasis

Metastasis requires complex cellular changes, including cytoskeleton remodeling, loss of cell polarity, and of cell adhesion. Focal adhesion kinase (FAK) plays a crucial role in these processes. Indeed, FAK is overexpressed in many kinds of tumors, including breast, pancreas, lung, and colon cancer (46). A crucial step in FAK activation is the autophosphorylation on tyrosine (Y) 397, which is required for the activation of its downstream signaling network. It was shown that PIAS1 SUMOylates FAK promoting Y397 phosphorylation and increasing its kinase activity (46). Moreover, it has been discovered that PIAS1 and FAK are coamplified in a subset of NSCLC. Furthermore, overexpression of PIAS1 leads to FAK activation, while PIAS1 silencing leads to apoptosis and focal adhesion turnover (47).

Epithelial-to-mesenchymal transition (EMT) is an essential developmental process that is a critical factor contributing to metastasis and drug resistance. TGFβ is a key regulator of EMT: TGFβ-induced EMT is often associated to tumor progression in many types of cancers, including breast, prostate, and colorectal cancer (48). TGFβ induces the degradation of PIAS1 during EMT (48). However, it was also reported that PIAS1 negatively regulates EMT by antagonizing the activity of TGFβ in a SUMO-dependent manner (48). The latter set of observations, describing PIAS1 as a metastasis inhibitor, seems in contrast with the reports that PIAS1 promotes the activity of FAK, which is a positive regulator of EMT (46, 47). We reason that the preponderance of evidence supports the conclusion that PIAS1 plays a positive role in EMT and metastasis. However, further studies are needed to solve these inconsistencies.

Conclusions

Recent evidence indicates that SUMOylation is directly involved in the regulation of oncogenic networks and in the promotion of cancer. Accordingly, several SUMO-ligases, including PIAS family members, are often overexpressed in cancer. PIAS proteins are emerging as key positive regulators of several oncogenic networks. At present, PIAS1 is the family member that has been involved more consistently in tumorigenesis through its ability to positively regulate AKT and MYC and negatively regulate PML, Tp53, and PTEN. In addition, PIAS1 is a critical determinant of the therapeutic action of ATO. These activities coordinately regulate several oncogenic networks to cooperate toward tumorigenesis. Several compounds that target SAE1/SAE2 or UBC9 are entering clinical testing. We also reason that PIAS1 could be a worthy therapeutic target (45, 49). We expect that future studies combining cancer genetics, functional studies, and *in vivo* models will continue to increase our understanding of the role of the SUMOylation machinery in cancer and in determining the response to therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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