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The role of SUMOylation in ageing and senescent decline

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ABSTRACT

Posttranslational protein modifications are playing crucial roles in essential cellular mechanisms. SUMOylation is a reversible posttranslational modification of specific target proteins by the attachment of a small ubiquitin-like protein. Although the mechanism of conjugation of SUMO to proteins is analogous to ubiquitination, it requires its own, specific set of enzymes. The consequences of SUMOylation are widely variable, depending on the physiological state of the cell and the attached SUMO isoform. Accumulating recent findings have revealed a prominent role of SUMOylation in molecular pathways that govern senescence and ageing. Here, we review the link between SUMO attachment events and cellular processes that influence senescence and ageing, including promyelocytic leukaemia (PML) nuclear body and telomere function, autophagy, reactive oxygen species (ROS) homeostasis and growth factor signalling.

Contents

1. Introduction

Cells respond to external or internal stimuli in large part by altering protein functions through posttranslational protein modifications. The reversible character of most such modifications renders them ideal regulatory events in most physiological contexts. SUMOylation, the attachment of small ubiquitin-like modifier (SUMO) to a target protein, is one of the most recently characterized posttranslational modifications, discovered only 20 years ago (Matunis et al., 1996). Since then its role has been shown in diverse cellular processes, including DNA damage response, protein-protein interactions, protein degradation, mitochondrial dynamics, development and cellular senescence among others. SUMOylation is mediated by a conserved molecular mechanism from yeast to mammals, and it is analogous to ubiquitination (Wilkinson and Henley 2010; Flotho and Melchior 2013). The main enzymes responsible for SUMOylation of a target protein are: E1 activating enzymes, E2 conjugating enzyme (UBC9 is the sole enzyme for this purpose up to date), E3 SUMO ligases and SENP SUMO proteases (Fig. 1). Protein SUMOylation requires a consensus SUMOylation motif in the target protein: ψKXD/E, where ψ is a large hydrophobic amino acid, K is the target lysine, X is any amino acid and D/E is aspartate or glutamate (Hay 2001; Rodriguez et al., 2001). The attachment of SUMO can change the subcellular

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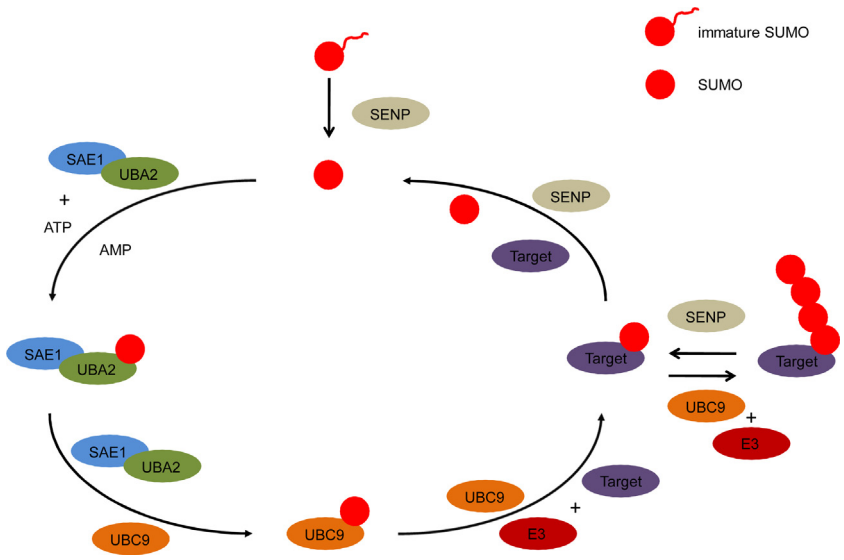

Fig. 1. SUMOylation pathway. SUMO is synthesized as an immature protein. A C-terminal cleavage by a SUMO protease (SENP) is needed for its maturation. The E1 enzyme, a heterodimer consisting of SAE1 and UBA2, activates SUMO through an ATP dependent reaction, and transfers it to the E2 enzyme, UBC9. UBC9, together with the E3 ligase will attach SUMO to the target protein. A protein can be mono- or polySUMOylated. The process is reversible: a SENP will cleave SUMO from the target protein.

localization (cytoplasmic vs nuclear), the activity or the interacting partners of a protein. Invertebrates harbour only one gene encoding SUMO, while mammals have 4 SUMO proteins. SUMO-1 is largely conjugated to its target proteins under normal conditions and only a very small steady-state pool of free SUMO-1 proteins is maintained within cells, whereas SUMO-2/3 becomes attached to targets under stress conditions (Saitoh and Hinchey 2000). While SUMO-1 and SUMO-2/3 are expressed ubiquitously, SUMO-4 shows tissue specificity (Bohren et al., 2004; Wei et al., 2008).

The processes of ageing and senescent decline are influenced by several independent pathways and mechanisms, with extensive crosstalk coordinating their progression (Dolivo et al., 2016). In this article, we review emerging findings implicating SUMOylation in the regulation of nuclear PML body function, telomere maintenance, autophagy, reactive oxygen species (ROS) homeostasis and growth factor signalling.

2. SUMO and nuclear PML body function in senescence

Promyelocytic leukaemia nuclear bodies (PML NBs) have 3 major components: PML, SUMO and UBC9 (the sole SUMO E2 enzyme); PML bodies are highly dynamic, non-membrane bound structures within the nucleus, that regulate transcription, antiviral response, DNA repair, apoptosis, senescence and tumour suppression (Lallemand-Breitenbach et al., 2010). The recruited partner proteins depend on the nature of stress experienced by the cell and on the protein SUMOylation. Contrary to initial observations suggesting that SUMOylation is needed for the nucleation of PML NBs (Weger et al., 2003; Takahashi et al., 2005), recent evidence demonstrates that this process is stress responsive and could take place in the absence of SUMOylation (Sahin et al., 2014b). A novel study supports this hypothesis: inhibition of PML SUMOylation by CACUL1/CAC1 does not change the number of PML bodies in the nucleus, but the size (Fukuda et al., 2016). PML NBs also provide the ideal environment for protein group SUMOylation. This type of SUMOylation targets functional, in some cases already assembled protein groups where several members of the group possess SUMOylation sites or SUMO interacting motifs (SIMs) through which they strengthen their interaction (Jentsch and Psakhye 2013).

Senescent cells exhibit all or some of the following extreme phenotypes: flat, vacuolated morphology, increase in β-galactosidase activity, senescence-associated heterochromatic foci (SAHF) enriched in H3K9 methylation, high protein levels of p53 and p21 and cell cycle arrest in the G1 phase (Munoz-Espin and Serrano 2014). Interestingly, repression of Senp1 (a SUMO-specific protease) – a condition, where the amount of SUMOylated proteins in the cell is elevated – induces a senescent phenotype in human fibroblasts with the same characteristics as replicative senescence (Yates et al., 2008). This provides an indication for the crucial role of SUMOylation in the onset of senescence. However, the findings of Yates and colleagues have recently been challenged: SENP1 knockout in mouse MEFs delayed cellular senescence. This effect is through the accumulation of SUMOylated Bmi1 on the promoter of p19, which leads to its transcriptional repression (Xia et al., 2016). The authors explain the difference between the two studies with 2 major alterations: the model system (one being human, and the other mouse) and the type of lesion utilized in the two studies (shRNA vs. gene deletion). Further research in this area is needed to clarify this phenomenon, since it could be that the explanation lies in the balance of SUMOylated state, and discrepancy from the ideal case could cause both early-onset and delayed senescence.

The main regulator of cellular senescence, p53, can be modified by SUMO-1 (Gostissa et al., 1999; Rodriguez et al., 1999) and SUMO-2/3 (Li et al., 2006) on the same lysine residue (K386). While SUMO-1 is attached to p53 under normal conditions, SUMO-2/3 conjugate to p53 under oxidative stress conditions, in a tissue specific manner. SUMOylation of p53 takes place in PML NBs. Modification of p53 by SUMO-1 requires the interaction of PML IV with ARF (ADP-ribosylation factor) and leads to the stabilization of p53 and to the induction of senescence (Ivanschitz et al., 2015). However the attachment of SUMO-2/3 to p53 is mediated by a complex composed of MDM2, ARF and L11, and elicits a change in the transcriptional activity of p53 (Stindt et al., 2011). This differential regulation paradigm exemplifies how SUMOylation can achieve substrate and isoform specificity even with a significantly smaller number of enzymes compared to ubiquitination.

A new study raises the possibility of a fifth SUMO protein in primate genomes. Liang and colleagues describe SUMO5 transcripts in specific tissues, like blood cells, testis, spleen and lung, where it is needed for the growth of PML NBs. Furthermore, PML NBs

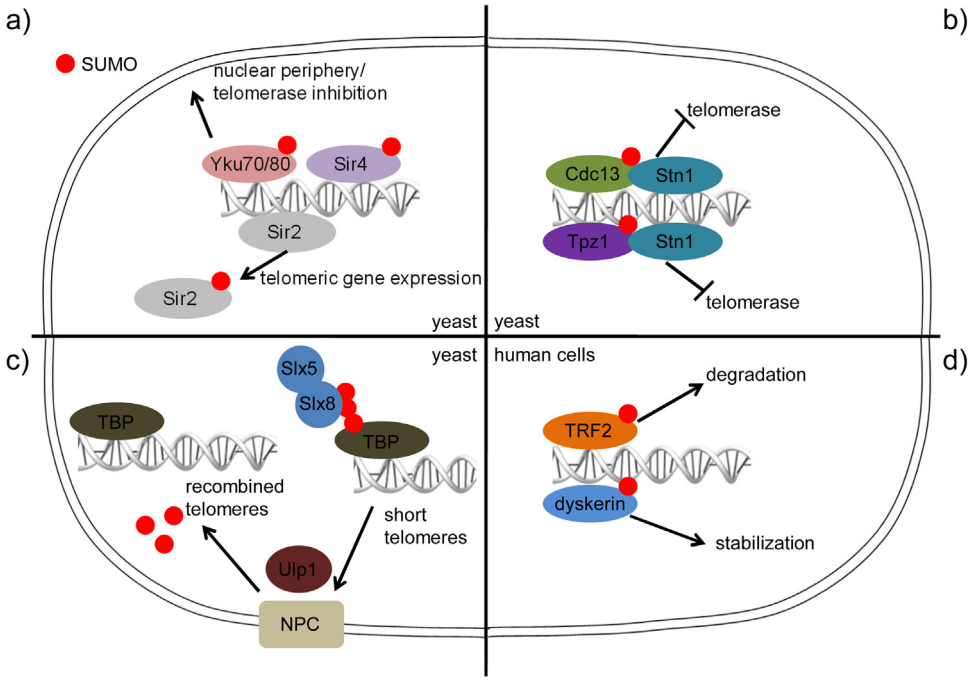

Fig. 2. SUMOylation at telomeres. a) In yeast, SUMO conjugation to telomere proteins Yku70/80 and Sir4 triggers the translocation of telomeres to the nuclear periphery and the inhibiton of telomerase. However, Sir2 SUMOylation allows the expression of genes at telomeric sequences by dissociating from the DNA. b) The yeast Stn1 telomere protein can form a complex with SUMOylated Cdc13 or Tpz1; both protein complexes block the activity of telomerase. c) In the case of significantly shortened yeast telomeres, SUMO accumulates at telomere binding proteins (TBP) and initiates the binding of Slx5-8 complex, leading to the translocation of telomeres to the nuclear pore complex (NPC). Here, a SUMO protease (Ulp1) cleaves the SUMO from TBPs and the telomeres can undergo recombination to preserve their length. d) In human cells SUMOylation of TRF2 leads to its degradation which is essential to maintain the proper levels of this telomere binding protein. SUMO modification of dyskerin is critical for its stabilization and failure in this process leads to premature ageing syndromes.

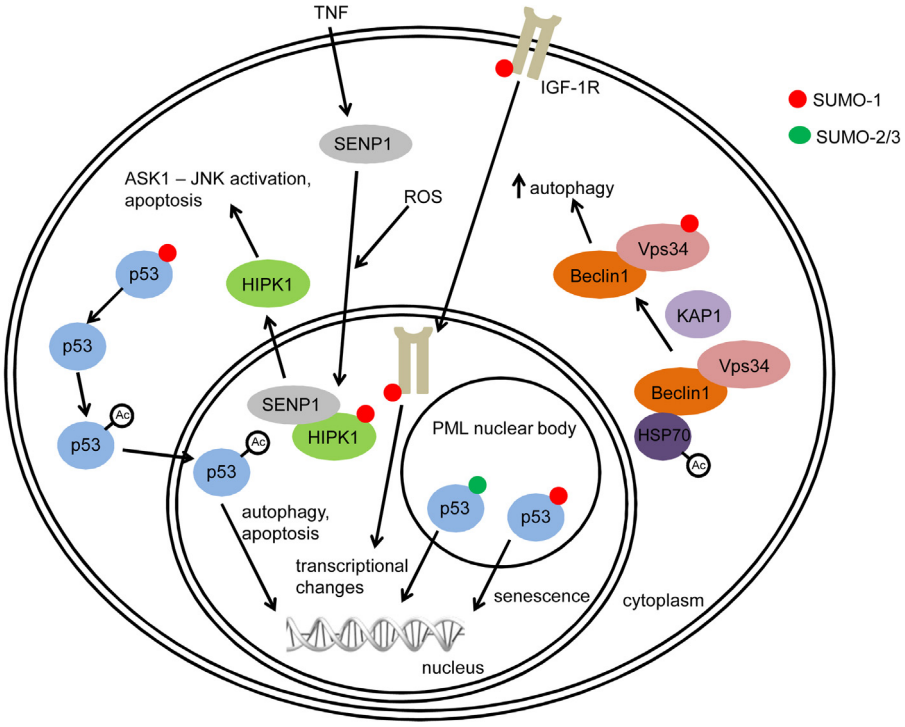

Fig. 3. SUMOylation induced senescence. SUMOylation can mediate cellular senescence through different mechanisms. SUMOylation of p53 in the nucleus activates transcription of senescence-related genes. However, SUMOylation of p53 in the cytoplasm triggers its acetylation, nuclear translocation, and the activation of autophagy and apoptosis genes. The nuclear translocation of SUMOylated IGF-1R causes transcriptional changes and cancerous transformation of cells. ROS-induced SENP1 translocation to the nucleus leads to the deSUMOylation and nuclear exit of HIPK1, activating apoptosis through ASK1-JNK pathway.

Table 1
Key proteins that modulate cellular senescence upon SUMOylation.

Name	Function	Reference
p53	Main transcription factor regulating cellular senescence. It can be SUMOylated by SUMO-1 or SUMO-2/3.	(Gostissa et al., 1999; Rodriguez et al., 1999; Li et al., 2006; Stindt et al., 2011; Ivanschitz et al., 2015)
SIRT1	Protein deacetylase, when SUMOylated promotes survival of normal and cancer cells.	(Yang et al., 2007; Campagna et al., 2011; Han et al., 2016)
Bmi1	Polycomb complex protein, its SUMOylation causes reduced expression of p19 and delayed cellular senescence.	(Xia et al., 2016)
Yku70/80	Telomeric complex in yeast, promotes the interaction of telomeres with nuclear envelope upon SUMOylation.	(Ferreira et al., 2011)
Sir4	Telomere binding complex component, its SUMOylation leads to the binding of telomeres to the nuclear envelope.	(Ferreira et al., 2011)
Sir2	Protein deacetylase, upon SUMOylation it dissociates from telomeres, activating telomeric gene expression.	(Pasupala et al., 2012; Hannan et al., 2015)
Cdc13	Telomere binding protein, when SUMOylated interacts with Stn1 and inactivates telomerase.	(Hang et al., 2011)
Tpz1	Telomere binding protein, in its SUMOylated form blocks telomerase activation in a complex with Stn1.	(Garg et al., 2014; Miyagawa et al., 2014)
TRF2	Telomere binding protein, it dissociates from telomeres when SUMOylated and becomes degraded.	(Her et al., 2015; Churikov et al., 2016)
Dyskerin	Telomere binding protein, impairment in its SUMOylation causes unstable and fragile telomeres.	(Brault et al., 2013)
Vps34	Phosphatidyl-inositol 3 kinase, key component of autophagy, its SUMOylation leads to increased autophagy.	(Yang et al., 2013)
IGF-1R	Insulin-like growth factor 1 receptor, it translocates to the nucleus upon SUMOylation and causes changes in the transcription of the cell	(Sehat et al., 2010; Deng et al., 2011)
HIPK1	Homeodomain-interacting protein kinase 1, its SUMOylated form resides in the nucleus.	(Li et al., 2008)
HIPK2	Homeodomain-interacting protein kinase 2, its SUMOylation – acetylation switch controls the survival threshold under oxidative stress	(de la Vega et al., 2012)
NOX2	NADPH oxidase 2, under stress it undergoes SUMOylation which blocks its activity.	(Kim et al., 2011)
Prdx6	Peroxiredoxin 6, it plays a cytoprotective role in the cell which is inhibited when SUMOylated.	(Chhunchha et al., 2014)

dissociate upon replacement of SUMO5 by SUMO-2/3 (Liang et al., 2016). However, it should be noted that the study does not show an endogenous expression of the protein, and so it is still possible that this is only a pseudogene. The potential emergence of a new SUMO isoform in primates remains a curious event, and calls for additional research to establish its function and real expression. These further studies should determine if it plays an isoform-specific role in the cell, or it merely ensures the process of SUMOylation, even in the absence of other SUMO isoforms. Both scenarios could explain the observed tissue specific expression: in the first case a new, tissue-specific role has been acquired for SUMOylation, while the second would suggest that unperturbed SUMOylation is critical and needed for survival in specific tissues.

The recruitment of some proteins to PML NBs stabilizes its structure through non-covalent interaction between SUMO and SUMO interacting motif (SIM)(Sahin et al., 2014a). SIRT1 is SUMOylated and interacts with PML NBs via its SIM (Yang et al., 2007). This interaction stabilizes PML NBs, giving a modified function to SIRT1 which is independent of deacetylation (Campagna et al., 2011). The histone deacetylase HDAC4 acts as an E3 ligase and it is responsible for the SUMOylation of SIRT1, generating a pro-survival signal both in ageing and cancer cells (Han et al., 2016).

3. SUMO and telomere integrity

Telomeric DNA length is a critical determinant of cellular senescence (Blackburn and Gall 1978). Telomeres are nucleoprotein complexes which form at the end of chromosomes and serve a protective function against degradation, end-to-end fusions and irregular recombination (de Lange 2005). SUMOylation of several telomeric proteins results in the inhibition of telomerase, the enzyme responsible for the elongation of telomeric DNA that is mostly active in stem and cancer cells. In yeast, when telomeres are long, telomerase accumulation is inhibited once telomeres are anchored to the nuclear envelope. Siz2 is a SUMO E3 ligase which SUMOylates the telomere proteins Yku70/80 and Sir4 triggering the association of the telomere with the nuclear periphery (Ferreira et al., 2011) (Fig. 2a). Another target protein of yeast Siz2 is Sir2. When Sir2 becomes SUMOylated, it dissociates from telomeres which results in the derepression of genes at telomeric loci (Pasupala et al., 2012; Hannan et al., 2015)(Fig. 2a). Cdc13 can also be subject of SUMOylation. In its modified form, Cdc13 interacts with Stn1 and initiates inhibition of yeast telomerase (Hang et al., 2011)(Fig. 2b). Stn1 forms a complex with SUMOylated Tpz1 as well, which blocks telomerase activation (Garg et al., 2014; Miyagawa et al., 2014)(Fig. 2b). In the case of significantly shortened yeast telomeres, SUMO modified telomere-bound proteins recruit the SUMO-targeted ubiquitin ligase complex Slx5-Slx8. This interaction triggers the transfer of telomeres to the nuclear pore complex where the SUMOylated proteins are removed and possibly recycled. Under these circumstances telomeres undergo type II recombination, maintaining their length (Churikov et al., 2016)(Fig. 2c). In human cells, TRF2 protects telomeres by preservation of their proper structural organization. Appropriate levels of TRF2 are achieved through SUMOylation dependent degradation (Fig. 2d). PIAS1 (a SUMO E3 ligase) is responsible for the SUMOylation of TRF2 which then dissociates from the telomere and is recognized by RNF4, a SUMO-targeted ubiquitin ligase (STUbL). Ubiquitination by RNF4 leads to subsequent degradation of TRF2, regulating TRF2 protein amount in the cell (Her et al., 2015). While SUMO modification of TRF2 induces its degradation, SUMOylation of human dyskerin, another protein in the telomerase complex, is crucial for stability (Fig. 2d). Upon disruption of dyskerin SUMOylation, telomerase activity becomes impaired. Consequently, telomeres are shortened, resulting in the premature ageing syndrome, dyskeratosis congenita. Even though, dyskerin is

a target for both SUMO-1 and SUMO-2/3, they are not interchangeable (Brault et al., 2013). These studies highlight the importance of SUMOylation in the maintenance of telomere integrity.

4. SUMO and autophagy

It is well established that the process of autophagy plays a central role in the progress of senescent decline and the associated pathologies (Rubinsztein et al., 2011; Ntsapi and Loos, 2016). One of the many regulators of autophagy is p53, a target of SUMOylation in the nucleus and also in the cytoplasm. Consequences of p53 SUMOylation in the nucleus has been discussed earlier. In the cytoplasm, SUMOylation is followed by acetylation and translocation to the nucleus, where, through transcription of relevant genes, p53 modulates autophagy and apoptosis (Naidu et al., 2012) (Fig. 3). A crucial protein complex regulating autophagy comprises of Beclin-1 and Vps34. Under stress conditions, acetylated Hsp70 binds to the Beclin-1-Vps34 complex and subsequently recruits a SUMO E3 ligase, KAP1/TRIM28. KAP1 SUMOylates Vps34 and this modification increases Beclin-1-bound Vps34 activity in human breast cancer MCF7 cells (Yang et al., 2013) (Fig. 3). Overexpression of UBC9 in mouse cardiomyocytes leads to a general increase in SUMOylation levels and a raise in autophagic flux. Moreover, upon UBC9 overexpression in a cardiac proteotoxicity model, it upregulates autophagy and protects the heart against proteotoxic pathology (Gupta et al., 2016). While boosting autophagy by SUMOylation can be beneficial in heart, in the nervous system it can precipitate accumulation of amyloid-β protein, the main culprit implicated in Alzheimer disease (Cho et al., 2015). In agreement with these findings, another study also showed that elevated levels of SUMO1 impair synaptic transmission, significantly reducing dendritic spine density and causing memory loss (Matsuzaki et al., 2015). Taken together, these observations indicate that the balance of SUMOylation status is important in the regulation of autophagy, with both positive and negative effects on the cell physiology and survival, depending on the tissue type.

5. SUMO and ROS homeostasis

The first link between SUMOylation and ROS was established in 2008 when a study reported that the TNF-induced nuclear translocation of SENP1 is ROS dependent. In the nucleus SENP1 deSUMOylates HIPK1, which leads to its exit to the cytoplasm where it activates ASK1-JNK signalling and subsequently cell apoptosis (Li et al., 2008) (Fig. 3). ROS dependent JNK activation also requires reduction of PIAS1 activity. Overexpression of PIAS1 causes hyper SUMOylation of target proteins, including c-Jun, and inhibits JNK signalling. Knockdown of PIAS1 alters the transcriptional response to oxidative stress signals as demonstrated by expression profiling studies. Taken together, these findings indicate that PIAS1 is a determinant of JNK activity, connecting ROS signalling with SUMOylation and driving oxidative cell death (Leitao et al., 2011). SUMOylation of HIPK2 (a proapoptotic kinase) under low concentrations of ROS recruits HDAC3, blocking HIPK2 acetylation and ensuring the survival of the cell. However, elevation of ROS levels results in a switch between SUMOylation and acetylation of HIPK2, changing the threshold of the cell for oxidative stress and promoting survival under unfavourable conditions (de la Vega et al., 2012). SUMO1 is not only responsive to ROS but also plays a role in the generation of ROS. Upon heat shock, SUMO1 is attached to NADPH oxidase 2 and blocks its activity, thus inhibiting ROS production and protecting the cell from oxidative stress-induced death (Kim et al., 2011). ROS also modulates the activity of the SUMOylation pathway E1 and E2 enzymes by creating a disulfide bond between their catalytic cysteines and temporarily inactivating them. When this transient enzyme inhibition cannot occur, cells are not capable of responding properly to DNA damage and become more sensitive to ROS (Stankovic-Valentin et al., 2016). In lens epithelial cells (LECs) which are experiencing oxidative stress or ageing, the level of SUMO1 conjugated proteins is increased significantly. One target of this aberrant SUMOylation is Peroxiredoxin 6 (Prdx6), which has a cytoprotective role. SUMOylation of Prdx6, triggered by ROS, causes inactivation by decreasing its protein levels and transcription through the Prdx6 transcriptional activator, Sp1. As a result, these cells become vulnerable to oxidative stress, but the process is reversible with overexpression of Prdx6 or the SUMO protease Senp1 (Chhunchha et al., 2014). These studies suggest that the detrimental consequences of ROS are mediated at least in part by deregulation of the SUMOylation pathway.

6. SUMO and growth factor signalling

Senescent cells have the risk to become cancer cells, by reprogramming their metabolism, re-entering to the cell cycle and making use of pro-survival signals to sustain themselves. The IGF-1 signalling pathway regulates cell survival, proliferation and growth via the function of the cognate tyrosine kinase receptor (Zha and Lackner 2010). Interestingly, IGF-1R can translocate to the nucleus upon SUMOylation, where it associates with enhancer elements in the genome, causing transcriptional activation (Fig. 3). The nuclear function of IGF-1R is independent from its kinase-driven signalling function, since this function remains unaffected by blocking SUMOylation (Sehat et al., 2010). In the MCF7 breast cancer cell line, elevation of Ubc9 levels causes extreme nuclear accumulation of IGF-1R. This results in deregulation of gene expression and probably takes part in the process of cancerous transformation (Deng et al., 2011). In acute myeloid leukaemia, SUMOylation of IGF-1R enhances cell proliferation rates. Elimination of SUMOylation sites or reduction of Ubc9 levels results in suppression of cell proliferation, demonstrating an important role of SUMOylation in cancer cell lines (Zhang et al., 2015). Given that many cancer therapies target the IGF-1 pathway, it is crucial to better understand how SUMOylation impinges on this signalling cascade and what type of modifications influence it. Thus, modulation of SUMOylation may become a potential mode of therapeutic intervention in specific cancer types.

7. Concluding remarks

The importance of SUMOylation has been established in many essential cellular processes. Ongoing studies are well-poised to provide decisive insights on the exact molecular mechanisms regulating SUMO attachment to proteins and the mechanisms mediating the after effects of such modifications. The ratio between SUMOylated and deSUMOylated state is emerging as the key modulatory factor. The main protein SUMOylation targets implicated in cellular senescence are shown in Fig. 3 and Table 1. These proteins and the relevant pathways mediating their SUMOylation are potential therapeutic intervention sites in various associated disorders (Sireesh et al., 2014; Huang et al., 2015; Licciardello and Kubicek 2016). Thus, further characterization of the relevant mechanisms and consequences of protein SUMOylation is an important priority.

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