Chapter 12

Roles for SUMO Modification during Senescence

Artemisia M. Andreou and Nektarios Tavernarakis*

Abstract

SUMOylation is a reversible post-translational modification, where a small peptide (SUMO) is covalently attached to a target protein and changes its activity, subcellular localization and/or interaction with other macromolecules. SUMOylation substrates are numerous and diverse and modification by SUMO is involved in many biological functions, including the response to stress. The SUMO pathway has recently been implicated in the process of cellular senescence, the irreversible loss of cell replication potential that occurs during aging in vivo and in vitro. SUMO peptides, a SUMO E3 ligase and a SUMO-specific peptidase can induce or hinder the onset of senescence, thus supporting an association of SUMOylation with cell growth arrest and organismal aging. Preliminary results on comparative analysis of proteomics and mRNA levels between young and old human and murine tissues show elevated levels of global protein SUMOylation and a decrease in components of the SUMOylation process with age. Further connections between the SUMO pathway and the aging process remain to be elucidated.

Introduction to the SUMO Modification System

The small ubiquitin-related modifier (SUMO) belongs to a large family of proteins related to ubiquitin (Ub) and the small ubiquitin-like proteins (Ulp). The overall sequence identity with ubiquitin is small (around 18%), but the C-terminus of the protein, which confers most of its activity, is almost super-imposable to the equivalent region of ubiquitin.[1,2] Although SUMO shares similar attachment mechanisms to Ub, its function is completely different and sometimes counteractive to the ubiquitin/proteasome pathway. Conjugation of SUMO can block the sites of attachment for ubiquitin and can thus protect proteins from degradation. Since its discovery just over a decade ago, the list of SUMOylation targets has been growing constantly and is now well into the hundreds. Perhaps a reason why this fairly ubiquitous modification has only recently been identified and studied lies in the reversibility of the process and the fact that, apart from very few exceptions, the amount of any SUMO-modified protein within a cell only makes up a very small percentage of its total amount, thus making detection by various molecular and biochemical methods more challenging.[3]

SUMO Isoforms

SUMO is highly conserved in all eukaryotic cells and in higher organisms it is present in all tissues and developmental stages. It has been shown to be essential for cell viability both at the organism level and in cells in culture. The number of SUMO genes differs between organism families,

*Corresponding Author: Nektarios Tavernarakis, Institute of Molecular Biology and Biotechnology (IMBB), Foundation for Research and Technology Hellas (FORTH), N. Plastira 100, Vassilika Vouton, PO Box 1385, Heraklion GR 70013, Crete, GREECE
Email: tavernarakis@imbb.forth.gr

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with one SUMO species present in yeast, nematodes and fruit flies and four in mammals, termed SUMO-1, SUMO-2, SUMO-3 and SUMO-4. SUMO-4 is the most recently identified isoform, through an 86% similarity to SUMO-2. mRNA transcripts show limited expression compared to the other SUMO genes and are present mainly in kidney, lymph system and spleen.[4] SUMO-1 is 50% identical in sequence to SUMO-2 and -3, while SUMO-2/3 share a 95% identity. This observation translates to functional activity as well; activity of SUMO2/3 is almost indistinct, while SUMO-1 has a dissimilar function. Furthermore, SUMO-1 is rarely found unattached within cells, but there are pools of free SUMO-2/3 available, which can be promptly conjugated to target proteins under specific stress conditions.[5] There is a preference between SUMO-1 and SUMO-2/3 in conjugation to certain proteins, but others can be modified equally well by both SUMO species.

Conjugation of SUMO to Target Proteins

Attachment of SUMO to target proteins occurs via an isopeptide bond between the glycine residue at the C-terminal end of SUMO and the ε-amino group of an internal lysine residue within the substrate. Enzymes analogous to the ubiquitin pathway, but specific for SUMO modification, catalyze the formation of this bond in four steps.[6] The SUMO peptide is initially translated as a precursor, ending with a stretch of sequence at its carboxyl end that follows the active –GG part of the protein. The length of this sequence varies between SUMO species. Proteolytic cleavage of this amino acid sequence converts SUMO to its mature form. SUMO-specific peptidases, for example members of the sentrin-specific protease (SENP) family, catalyse this step. SUMO-activating enzymes, also called E1, activate the mature SUMO in an ATP-dependent reaction. Active SUMO is then transferred onto the E2 SUMO-conjugating enzyme Ubc9 (ubiquitin-like protein SUMO-1 conjugating enzyme 9). Conjugation of SUMO to target proteins occurs through Ubc9 with the aid of an E3 ligase.[7] Substrate specificity for SUMO is conferred by both Ubc9 and various E3 ligases. Ubc9 actually recognizes a consensus motif on the protein substrate and forms the covalent attachment of SUMO to its targets[8] while the SUMO ligases probably interact with other areas of the substrate and provide more specificity (Fig. 1).[6,9]

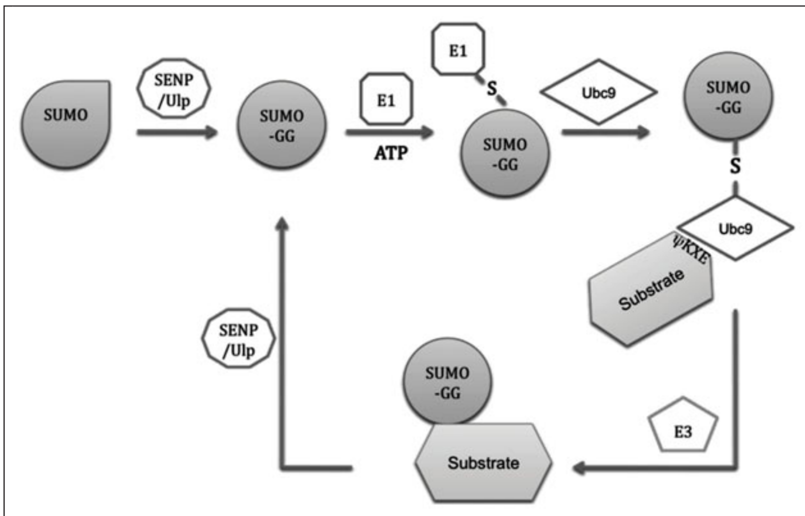

Figure 1. A brief description of the SUMOylation process. Attachment of SUMO to and de-conjugation from target substrate proteins happens in distinct enzymatic steps, similar to those of the Ubiquitin pathway. SUMO-specific enzymes convert SUMO to its mature form, which is then activated and passed on, through subsequent thioester bonds, from the E2-conjugating enzyme Ubc9 to its target protein. SUMO can then be released from the complex via the action of a SUMO isopeptidase of the SENP/Ulp family.

Protein Recognition Sites

A general consensus recognition site for SUMO attachment is ψKXE,[10,11] where ψ is a large hydrophobic amino acid, like leucine, isoleucine or valine; K is the lysine residue at which the attachment takes place; X is any amino acid and E is a glutamic acid. Although this consensus site is conserved, a number of alternatives have been described, where for example a D can be present at the position of the E, or the amino acid before the lysine can be a different one from the three consensus residues. Other sequences may also be involved, since in some cases, proteins have been shown to be SUMOylated that either do not contain the consensus site, use a different motif for SUMO attachment[12] or maintain SUMOylation after the site has been mutated. More extensive SUMO conjugation motifs have also been described; it has been suggested that acidic residues downstream of the core SUMOylation motif have a role in enhancing specificity for substrates.[13]

Links with Other Post-Translational Protein Modifications

Although ubiquitination, acetylation and methylation all take place on lysine residues of their target proteins, it was perhaps more expected (at least initially) to study a possible link between SUMOylation and the Ubiquitin pathway, due to the extensive similarity between the peptides themselves and the enzymes facilitating the two processes. Indeed, IκBα and PCNA can be modified by either SUMO or ubiquitin on the same lysine in their sequence, with each modification resulting in a separate function for the substrate.[14,15]

Besides ubiquitination, other post-translational modifications have been associated with the SUMO modification process. SUMOylation of proteins including GATA1 and heat shock factors HSF1 and HSF4b has been shown to be dependent on their phosphorylation status. A phosphorylation-dependent SUMOylation motif (PDSM) has been described for such proteins.[16] Phosphorylation of this motif results in increased SUMOylation of HSF1 and MEF2, while SUMO attachment to IκBα, p53, c-Fos and c-Jun is negatively regulated by phosphorylation.[17-19] Furthermore, the association of SUMO with histones supports a role in genome organization and stability. Histone deacetylases, including HDAC2 and HDAC6, have been shown to preferentially interact with SUMO-modified substrates.[20,21] It has been suggested that deacetylation of histones by HDAC enzymes may make more lysine (K) residues available for SUMOylation.[7] A SUMOylation switch based on acetylation/deacetylation has been described,[22] and increased SUMOylation of H4 correlates with decreased acetylation of the gene, when Ubc9 is targeted to the promoter region.[23]

De-Conjugation of SUMO from Substrate

SUMO attachment is a reversible and highly transient modification. The same enzymes that facilitate the initial maturation of SUMO molecules also catalyse the cleavage from their substrates.[6] Ulp1 and Ulp2 are SUMO-specific proteases in yeast,[24,25] while six members of the SENP family, SENPs 1-3 and 5-7, have been shown to have this role in human tissues.[9] In contrast to the SUMO-conjugating enzymes, SUMO proteases are not similar to the equivalent enzymes in the ubiquitin pathway, but the homology they share appears closely related to viral proteases.[26] Differences in the sub-cellular localization of the SENP proteins is believed to be dictated by nonconserved N-terminal sequences and provides the specificity for the SUMO-substrate complexes they regulate.[27,28] SENP1 is localized mainly in the nucleus with little, albeit persistent, cytoplasmic presence.[29,30] SENP2 is associated with the nuclear pore,[31] as is Ulp1,[32] SENP3 and SENP5 are nucleolar,[33] while contradictory reports place SENP6 in both the nucleoplasm and the cytosol.[34,35] Since the SUMO targets described to date are present throughout the cell, the differential localization of the SENP proteins is perhaps expected.[36,37] Specificity towards certain conjugates may be achieved through the sub-cellular and sub-nuclear location of each protease.

Physiological Functions of SUMO Modification

SUMO attachment has been implicated in a number of cell processes, such as regulation of transcription, nuclear transport, DNA repair, protein stability, cell cycle and chromatin structure. Although its function is as diverse as its substrates, one generalisation could be that modification

of a protein substrate by SUMO alters its interactions with other protein and DNA molecules. SUMOylation can aid or block protein-protein interactions equally well, depending on the substrate proteins involved. For example, during DNA replication in yeast, PCNA needs to be SUMOylated in order to recruit Srs2 helicase to the site of the replication fork and prevent recombination.[38,39] Reversely, interaction of the CtBP corepressor with PDZ domains is hindered when the former is SUMOylated.[40] The most well studied example of SUMO modification altering the DNA-binding ability of a protein is that of the DNA repair enzyme thymine DNA glycosylase (TDG). After TDG has completed the base excision, it needs SUMO association in order to detach itself from the DNA, as SUMO-TDG has much lower affinity for DNA. Once in the nucleoplasm, the SUMO protein is removed from the conjugate by a specific peptidase, thus allowing TDG to participate in another round of DNA base excision repair.[41,42]

Recently, proteins with active roles in the control of cell survival and proliferation have been identified as substrates for SUMOylation and enzymes partaking in the SUMO modification pathway have been associated with the onset of cellular senescence. It is thus very likely that SUMOylation may actively contribute to phenotypes of growth arrest and cellular aging.

Cellular Senescence

Derived from the Latin *senex*, meaning "old man", "old age" or "advanced in age", cellular senescence was first described in the early 1960s as the process that limits indefinite growth of primary fibroblasts in culture.[43] The term replicative senescence was favoured later to more specifically describe the irreversible loss of cell division potential at this final stage in the lifespan of somatic cells in culture.

Senescence as a Model for Aging

Cellular senescence is considered a major tumor suppressor mechanism, as a process for eliminating the proliferation of damaged or dysfunctional cells.[44,45] Besides its importance in tumour suppression, replicative senescence can occur independently of cancer and is regarded as a model for cellular and organismal aging.[46] This correlation has been supported by various observations and experimental data. Senescent cells have been identified in human and other tissues in vivo and become more abundant as the organism ages. In cultured cells, the time period before the cells exit the proliferating state and become growth-arrested is directly related to the maximum lifespan of the species from which they were obtained. In addition, cells derived from patients with premature aging syndromes enter senescence more rapidly in culture. A recent study that characterized the role of p63 showed that deficiency in this molecule in mice resulted in premature aging and a shortened lifespan.[47] Induction of p63 deficiency in a tissue-specific way lead to extensive cellular senescence and accelerated aging phenotypes, thus presenting a causative association between senescence and—at least premature—aging. In vivo, the presence of elevated numbers of senescent cells significantly limits the regeneration potential of animal tissues and changes intra- and inter-tissue communication through the cells' ability to modify their extracellular environment. Senescent cells secrete biochemical signals that may target them for destruction by the immune system, but these signals can be harmful to their environment, especially as numbers of senescent cells start to accumulate. This subsequent alteration in tissue and organ homeostasis may ultimately lead to organismal aging.[48]

Characteristics of Senescent Cells

Besides the significant suppression of DNA synthesis and cell proliferation, senescence is characterized by certain changes in the cell morphology, metabolism and epigenetic state. Cells usually appear enlarged, flattened and more granular, they show higher levels of cellular autofluorescence and senescence-associated beta-galactosidase activity, while a number of proteins involved in cell cycle arrest are up-regulated, as for instance p21 and p16.[49] These morphological characteristics together with SA-β- gal activity (measured at specific pH levels) are used to distinguish senescent cells.[50] After they have entered senescence, cells in culture can remain alive and metabolically active for long periods of time.[51]

Replicative and Stress-Induced Senescence

The cellular mechanism leading to senescence has been mainly associated with the gradual shortening of telomeres.[52,53] Due to the semi-conservative nature of DNA replication, where the polymerase only adds nucleotides in a 5′ to 3′ direction and requires binding of an RNA primer, the ends of chromosomes become shorter with each round of cell division. Telomerase, the enzyme responsible for maintenance of telomeric ends, is normally absent from most human somatic cells. Consequently, when telomere ends reach a critical length, signals are initiated as the cellular response to DNA damage and activate p53-mediated pathways that lead the cell to senescence or apoptosis. This theory is supported by data showing that expression of telomerase increases the proliferating time period of cells.[54] In addition, in mice—which normally possess longer telomeres and show more extensive somatic expression of telomerase than humans[55]—absence of telomerase results in a premature aging phenotype[56] and seriously compromises the replicative lifespan of stem cells.[57]

However, cell proliferation potential can also be hindered in ways that are independent of telomere shortening. Various types of stress, such as DNA damage, chromatin remodelling, activated oncogenes, oxidative stress and chemotherapeutic agents may impede normal cell proliferation and result in a prematurely arrested state that greatly resembles cellular senescence.[58] The time limit of the replicative state and entry into senescence can be clearly manipulated in cultured cells by optimizing physiological conditions of oxygen levels and the presence of serum, in ways unrelated to telomere length.[59] Stress- induced senescence is acute, rapid and homogeneous, in contrast to replicative senescence occurring normally, where the cells may differ in the time they enter senescence and the rate by which they reach growth arrest. Thus, since the pattern of gene expression between the two states is extensively overlapping, induced senescence may be preferably used in experiments for practical reasons.[60,61]

Pathways Mediating Stress Response

When the stress response pathways are activated within a cell, signalling is usually transduced through the p21/p53 and p16/pRB pathways.[62,63] A number of genes associated with regulation of senescence have been shown to be part of either the p53 or pRB pathways.[64] The proteins involved in these signalling cascades, mainly p53 and pRB, will determine how a cell will respond to the stress factor(s). This response is most commonly balanced between cells entering senescence or undergoing apoptosis, as both mechanisms are used to control unsolicited cell growth.[65]

SUMO and Senescence

A good indication that the SUMOylation pathway may be involved in cellular senescence was the identification of a number of senescence-associated proteins as targets for SUMO conjugation. Since this post-translational modification has been shown to greatly influence protein activity, stability and interaction of substrates with other macromolecules, the active participation of the SUMO pathway in the mechanisms of senescence induction and, subsequently, aging was an appealing thought.

SUMOylation has been associated with responses to various types of cellular stress. Altered interactions of a number of proteins with both SUMO-2/3 and/or SUMO-1 upon exposure to such stresses support this involvement. For example, the expression of SUMO-1 has been shown to increase during hypoxia.[66] On the other hand, oxidative stress, induced by treatment of cells with hydrogen peroxide, results in increased levels of SUMO-2/3- modified p53, while levels of p53/SUMO-1 conjugates appear unaffected.[67] Because of the close and often causative, association between environmental and cellular stress and the onset of senescence, involvement of the SUMO pathway in stress response provides an important, though indirect, link between SUMO, senescence and, very likely, the aging process.

Recently, SUMO species themselves as well as a number of enzymes that participate in SUMO attachment and de-conjugation processes have been associated with senescence. SUMO proteins, a SUMO ligase and a SUMO isopeptidase have been shown to either induce or repress the

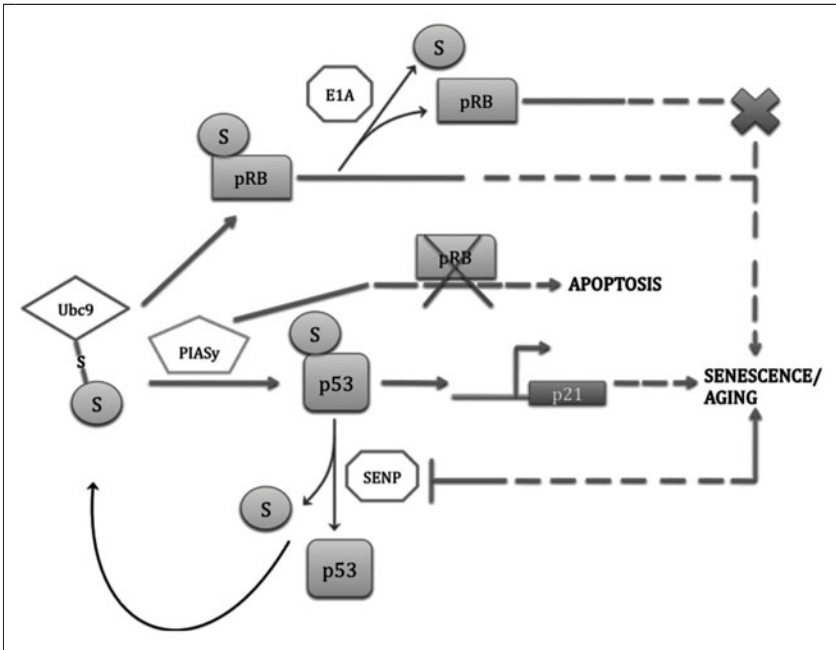

Figure 2. Model of SUMO modification proteins in pathways leading to cellular senescence and aging. The SUMOylation cycle of p53 affects downstream cascades leading the cell to senescence/aging and disturbances at both the SUMO conjugation and de-conjugation steps can inhibit the onset of senescence. SUMOylation of pRB can influence the cell's decision to undergo senescence or apoptosis. The SUMO E3 ligase PIASy and SUMO proteases of the SENP family also appear to have important roles in these pathways.

onset of cellular senescence. Figure 2 presents a model of how these molecules may be involved in senescence-inducing pathways and more details on each of them are described in the text below. In addition, elevated numbers of SUMOylated proteins have been shown to accumulate in senescent cells compared to normal replicating cells,[68] while levels of SUMO isoforms and associated enzymes appear to decrease with age, in a different tissue type.[69]

SUMO Molecules in Senescence

SUMO-1 and SUMO-2/3 species can have different preferences for substrates and thus be involved in different cascades within the cell, even when these belong to the same greater pathway. Recent experiments have shown that over-expression of SUMO-2/3 in cultured cells results in a premature senescence morphology, supported by slow cell growth and early growth arrest, as shown by reporter assays.[67] In contrast, over-expression of SUMO-1 appears not to directly affect the process of cellular senescence.[70] This is perhaps not surprising, considering that SUMO-2/3 is thought to be the isoform(s) mainly and most frequently associated with the response to stress. However, it is interesting that under normal conditions SUMO-1 appears mainly conjugated to target proteins within the cells, while unconjugated pools of SUMO-2/3 species are abundant and available to be used as required.

The major players of the pathways that lead to senescence, p53 and pRB, actively inhibit unsolicited cell growth and this function is regulated by post-translational modifications, including phorpshorylation, acetylation and ubiquitination.[19,71-73] The SUMO modification pathway has also been shown to modulate activity of these proteins, as they are subject to SUMOylation by both SUMO-1 and SUMO-2/3. The transcriptional activity of p53 is positively regulated

by SUMO-1 attachment, as shown by up-regulation of *p21* expression, a p53 target gene.[67] In addition, the repressor activity of pRB on E2F-regulated target genes is controlled by components of the SUMO pathway.[74] Under normal cell conditions, pRB is de-SUMOylated by E1A, a viral oncoprotein; [72] it has been suggested that this may be a strategy used by viruses to suppress cell senescence. Over-expression of SUMO-2/3 surpasses this de-SUMOylation, leaving pRB-SUMO-2/3 conjugates free to stimulate senescence.[67]

Down-regulation of p53 and pRB by RNA interference appears to counteract the senescence phenotype seen in SUMO-2/3 over-expressing cells, suggesting that the effect of SUMO-2/3 modification on senescence occurs via p53- and pRB-mediated pathways.[67] p53-induced up-regulation of p21 is a known pathway for activation of senescence.[75] During SUMO-2/3 over-expression, the transcriptional activity of p53 is significantly enhanced. Levels of p53 protein seem to remain unchanged, while the senescence-associated protein p21 is clearly up-regulated. Since p21 is under the transcriptional control of p53, this increase in p21 protein levels may be due to the altered SUMOylation state of p53, modified by SUMO-2/3.[67]

SUMO-Specific E3 Ligase PIASY and Senescence

Protein inhibitors of activated STAT (PIAS) have been shown to function as E3 SUMO ligases and data from various SUMO conjugates make them one of the largest families of SUMO-specific ligases.[76] During replicative senescence the levels of endogenous PIASy, a member of this protein family, are significantly increased compared to presenescent cells, as do levels of hyper-sumoylated proteins.[74]

This effect is considered specific to PIASy, as no other member of the PIAS protein family appears to have similar activity. In addition, over-expression of PIASy can induce cellular senescence or apoptosis.[74] The entry into either process occurs through the p53 and pRB tumour-suppressor pathways and depends on their state within the cell. Induction of senescence is conferred by the E3 ligase activity of PIASy, which facilitates the SUMOylation of p53 and subsequent activation of p53 target promoter regions, as shown by the increase activation of the *p21* promoter upon PIASy overexpression. Mutation of the PIASy E3 ligase active site abolishes the effect. The onset of senescence through PIASy is counteracted by the E6 oncoprotein, through inhibition of the SUMO ligase activity of PIASy.[74] Interestingly, an extended lifespan is observed in cells that over-express mutant forms of PIASy with an inactive E3 ligase site.

In further support of this process, deletion of PIASy in mouse embryo fibroblasts results in a significant delay of the onset of senescence after appropriate signalling. Even after induction of p53 expression by a pro-senescence signal, for example through oncogenic RAS, p53 target genes *p21* and *MDM2* are not up-regulated in the absence of PIASy. In parallel, PIASy can induce p53-dependent apoptosis during pRB deficiency; interestingly inactivation of pRB by hyper-phosphorylation is not enough to give similar results and the effect of PIASy is not there when pRB is present, even in an (as far as we know) inactive state.[74]

All available data to date support an active contribution of PIASy to the senescence process and perhaps also to aging. The difference in the cellular response to PIASy, depending on the pRB status, suggests a possible role for PIASy as one of the factors influencing the cell's decision to undergo senescence or apoptosis. This may occur through an altered binding affinity between pRB and its cofactors, in a SUMOylation-mediated manner. More specifically, it has been suggested that hypophosphorylated pRB enlists its corepressors together with components of the SUMO pathway to the site of genes promoting proliferation. A number of these cofactors could be themselves targets of SUMOylation and these interactions could stabilize the pRB repressor complex. Also, as it has been shown that SUMO attachment increases affinity between protein partners,[77] the presence of SUMO-modified pRB repressor group on DNA could provide a high affinity site for the recruitment of proteins involved in chromatin remodelling and reorganization.[68] This process could ultimately lead to the silencing of genes involved, also facilitated by the activity of histones, which are substrates for SUMOylation and have major roles in transcriptional repression in their modified state.[23,78]

SUMO Proteases (SENP Family) and Senescence

Senescence may be induced either by increased SUMOylation of common target conjugates of the SUMO proteases or by an increase in total levels of SUMOylated proteins.[79] Repression of a number of SUMO proteases, of the SENP family, has been shown to result in a senescence-like phenotype. SUMO proteases may thus be required for the proliferation of normal human cells and have important roles in age-related phenotypes.

Cells that undergo the induced senescence caused by Senp protein repression display all key morphological characteristics and activity (as measured by SA-β-gal activity) associated with a senescent state. In human firbroblasts, SUMO-containing PML bodies that accumulate in the nucleus after many cell passages and during normal replicative senescence are also seen to increase in number upon repression of SUMO proteases Senp1, Senp2 and Senp7. Repression of Senp1 in particular and Senp7 perhaps to a lesser extend, provokes premature senescence through the p53 signalling pathway.[79] Inactivation of the p53 pathway limits the induction of senescence caused by Senp1 repression. This data points to a role of Senp1 in maintaining a balance in the cell after exposure to stress and perhaps preventing premature senescence.

SUMO and Maintenance of Telomere Length

Functional telomeres are required for cells to maintain their replication potential. In addition to the gradual shortening of telomeres after certain numbers of cell division, mutated or depleted proteins that protect telomere ends may also result in telomere dysfunction.[80,81]

In yeast, deficiencies in homologues of SUMO and E3 ligases of the PIAS family have been shown to provoke a significant increase in telomere length.[82,83] These results advocate a role for SUMO in maintaining telomere length and suggest that the SUMO pathway may be a negative modulator of this process. SUMO modification of factors associated with telomeres through DNA damage response pathways further supports an important role for SUMO in telomere maintenance and consequently tumour suppression, cellular senescence and normal aging.[68]

Changes in Global Protein SUMOylation during Aging

Recent experiments have shown that the amount of SUMOylated proteins in rodent spleen tissue increases with age and this increase is not subject to limitation by dietary restriction, as is the case for global protein ubiquitination.[84] Furthermore, mRNA levels of components of the SUMO pathway *sumo-1*, *ubc-9* and *senp1* show significant decrease in aged murine brain tissues, as compared to young ones and the effect is mimicked upon inflammation stimuli in astrocytes.[69] These results suggest a role for protein SUMOylation in aging tissues that is most likely tissue-specific at least in mammals and perhaps leads to altered protein function that is clearly distinct from that of ubiquitin. It would be very interesting to include further tissue and cell types in similar studies, in order to confirm a more general effect of aging on protein SUMOylation.

Conclusion

Damaged, oxidised or mislocalized proteins that would be properly dealt with in healthy proliferating cells, may accumulate in aging cells due to changes in the activities of the SUMOylation and ubiquitination pathways and this may have an important role in the onset of senescence and age-related disease.[79] In regard to the SUMO modification pathway, elevated SUMOylation of certain target proteins can cause premature cellular senescence,[67,74] the E3 SUMO ligase PIASy has recently been associated with the induction of senescence,[74] while the SUMO isopeptidase Senp1 appears to obstruct it.[79]

Targets for SUMOylation have been identified in almost every cell and part of the cell and the SUMO pathway is constantly being linked to more cellular processes. The physiological function of protein modification by SUMO ranges greatly and includes pathways from DNA repair and transcription to protein-protein interactions and subcellular localization. Besides the activity of SUMO substrates, integrity of these molecules has been shown to be controlled by SUMOylation in a number of occasions. For instance, stability and DNA binding of the stem cell transcription factor Oct4 increases upon SUMOylation,[85] as does stability of Pax8,[86] Ku70[87] and Apa-1, the

latter being associated with senescence of human fibroblasts.[88] Moreover, HIF1α steady state is regulated by Senp1, in an example of SUMOylation acting synergistically with the Ubiquitin pathway to promote protein degradation.[89] Similarly, the process of Specificity Protein 1 (Sp1) turnover is dependent on its SUMOylation, which increases interaction with proteasome subunits and targets Sp1 for proteolysis.[90]

So, the SUMO pathway affects the levels, stability and half-life of proteins by protecting them from Ubiquitin through occupation of lysine residues in their sequence, or by leading them to proteasome-mediated degradation. Although in the area of cell senescence and tissue aging SUMO has been predominantly associated with the DNA damage response and maintenance of telomere integrity, it is not absurd to imagine, or even expect, that SUMOylation, either as a whole or through its individual components (or both), may also have an active role in regulating protein synthesis and degradation during these processes. Proteins that are important in pathways leading to cellular senescence and organismal aging have already been linked to SUMOylation, as have enzymes facilitating the modification process, but a direct link between SUMO and protein turnover during aging needs to be elucidated. Results from ongoing and future experiments in this area remain to be seen, but since the rates and balance of protein synthesis and degradation are crucial during aging, it seems likely that SUMO will be shown to have an important role in these processes.

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