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PML links aberrant cytokine signaling and oncogenic stress to cellular senescence

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1. ABSTRACT

Senescence is a tumor suppressor mechanism triggered by oncogenic stimuli and characterized by a permanent cell cycle arrest mediated by tumor suppressors such as p53, Rb and PML. PML itself is critical for the formation of nuclear bodies (PML bodies) that accumulate in senescent cells rendering them suitable markers for the senescence phenotype. The mechanism of PML-induction during senescence is complex and includes increased PML gene transcription by p53 or transcription factors of the interferon/Jak/Stat pathway. In turn, PML engages both p53 and Rb, although the precise molecular processes are unknown. PML interacts with the DNA-binding domain of p53 facilitating p53 modifications. PML can also interact with Rb and may play a role in Rb-dependent gene silencing during senescence. Recent studies suggest an additional connection between PML and the senescence program. Senescence involves a constitutive activation of the DNA damage response. Intriguingly, proteins that signal DNA damage or help repairing it localize to PML bodies, suggesting that PML may play a role in the DNA damage response during senescence. We think that the discovery of factors acting upstream or downstream PML may help to understand how cells bypass senescence on their way to tumorigenesis. More importantly the PML pathway may eventually lead to novel anti-cancer therapies.

2. INTRODUCTION

The process of cellular senescence is established in multiple cell types in response to stressors that can potentially transform a normal cell into a cancer cell. Senescence can be induced in primary cell cultures by expressing oncogenes or treating the cells with agents that cause DNA damage such as reactive oxygen species or hydroxyurea (1, 2). The process was originally observed after serial passage of normal cells in culture (3). This procedure leads to erosion of telomeres, mainly because normal human somatic cells do not express the enzyme telomerase, which synthesizes telomeric sequences (4). These pioneering experiments in the tissue culture environment have been recently validated *in vivo* with the discovery that senescence limits oncogenic activity in mice and that senescent cells accumulate in benign tumors both in humans and mice (5-7).

The hallmark of senescence, independently of the inducer, is a permanent cell cycle arrest that is resistant to growth factors and other signals that induce cell proliferation (8, 9). It has been proposed that senescence prevents cancer in the early stages of its development (1, 10). In agreement with this model, genes required for senescence are often found mutated in human cancers (10). Genetic studies have established that the tumor suppressors

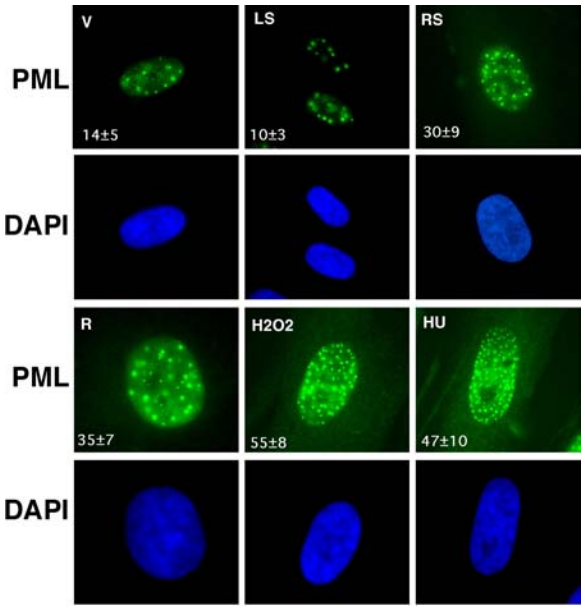

Figure 1. Accumulation of PML bodies in senescent cells independently of the methods of induction. All panels show representative cells of IMR90 fibroblasts (ATCC) grown in DMEM, fixed and stained with anti-PML antibody PG-M3 and Alexa-conjugated anti-mouse secondary antibody. V are control growing cells, LS are cells G0 arrested (48 hours in medium containing 0.1% serum), RS are cells in replicative senescence (they were passed up to 55 population doublings), R denotes ras-induced senescence (cells were infected with a retroviral vector expressing RasV12 as described in (13)), H_2O_2 denote senescence induced by hydrogen peroxide (100 μM for three days) and HU is cells treated with 5 mM hydroxyurea for three days. Senescent was confirmed by staining for senescence-associated β-galactosidase (not shown).

p53 and Rb are the major regulators of the senescence program (10, 11). In mouse cells and in some human cells, inactivation of one of these pathways is sufficient to prevent senescence in response to oncogenes (11, 12). On the other hand, many normal human cells can enter senescence when either p53 or Rb are disabled (11, 13), suggesting that these tumor suppressors independently control a final senescence pathway yet to be discovered.

The search for senescence genes is a very active area of research because these genes are candidates for tumor suppressors. In general, three strategies have been applied to link particular genes to senescence. First, groups working on candidate tumor suppressor genes can use RNA interference or cells from knockout mice to test whether a given gene is required for the senescence process induced by oncogenes or serial passage. Second, several groups have used microarrays to search for genes highly expressed in senescent cells. More recently, the use of libraries of small RNAs that trigger RNA interference has permitted a more effective way to search for genes required for senescence.

PML was originally demonstrated to play a role in oncogene-induced senescence by two independent groups. The laboratories of Pelicci and Pandolfi developed a PML knockout mouse model to understand the tumor suppressor activities of PML (14). Initially, this group reported that PML was required for the induction of the CDK inhibitor p21 and the antiproliferative activity of retinoic acid (14). Later, they found that fibroblasts obtained from these mice were resistant to senescence in response to oncogenic *ras* (15). The laboratory of Lowe, who originally discovered Ras-induced senescence (11), found PML transcriptional up-regulation using gene expression profiles of human fibroblasts expressing RasV12. They demonstrated that the oncoprotein E1A that inhibits Ras-induced senescence in humans cells also prevented the induction of PML in response to oncogenic *ras* (13). Both groups demonstrated that PML was sufficient (i) to induce p53, (ii) prevent the phosphorylation of Rb, and therefore its inactivation, and (iii) induce cellular senescence both in mouse and human primary cells (13, 15). Intriguingly, the PML primary transcript is spliced into multiple isoforms (16). Among the isoforms tested, only PML IV was able to mediate senescence (17). However, PML IV is not sufficient to induce senescence in $pml^{-/-}$ MEFs suggesting that a combination of PML isoforms is required to mediate PML functions in senescence (17).

PML is known to be critical for the formation of discrete protein assemblages in the nucleus known as PML bodies (sometimes also referred to as PML nuclear bodies - PML-NBs, PML nuclear domains – PML-NDs, PML oncogenic dots – PODs, ND10 or Kr-bodies) (18, 19). These bodies accumulate in senescent cells independently of the inducer (Figure 1) suggesting that they can be used as convenient markers of cellular senescence. Interestingly, accumulation of PML was observed in the skin of mice that aged prematurely due to a deficiency in p63 (20). The general tumor suppressor role of senescence initially contrasted with the fact that the association between PML and human cancers was limited to acute promyelocytic leukemia, a rare cancer of blood cells. However, the levels of PML are dramatically reduced in multiple human cancers (21-23). Therefore, linking PML to the senescence program suggests a general and important role for PML in tumor suppression.

3. REGULATION OF PML EXPRESSION

The accumulation of PML in senescent cells is due, at least in part, to the transcriptional induction the PML gene (13). Therefore the regulation of PML gene expression should reflect mechanistic aspects of the senescence process. PML is known to be regulated by the interferon pathway via the STAT transcription factors (24, 25). Interferon also regulates many other components of the PML bodies, suggesting that in conjunction they mediate the antiviral activities of this cytokine (26-29). At least one of these proteins, Sp100 (covered by H. Will in this issue), also accumulates in senescent cells (13). The induction of interferon-target genes during senescence suggested that the interferon pathway may also regulate senescence. In

agreement with this idea, treatment of primary human cells with β-interferon leads to the induction of p53, PML and senescence (30). Also, constitutive STAT5 (ca-STAT5) signaling can activate PML expression and induce senescence (31, 32). STAT5 is activated by many cytokines and hormones and could mediate PML induction in cells exposed to them. These experiments are in agreement with the idea that PML connects cytokine stimulation with the senescence program. However, key questions remain to be answered. For example, in addition to interferon, which other cytokines induce PML and senescence? Can these cytokines act synergistically? How much time of cytokine-exposure is needed to induce the process?

The PML promoter also contains p53 response elements that confer p53-responsiveness during Ras-induced senescence or during the DNA damage response (33). This fact suggests that PML may act downstream of p53 to mediate senescence, perhaps by activating Rb and other growth inhibitory pathways. A critical question that remains to be investigated is whether p53 can cooperate with cytokine stimulated transcription factors (i.e. STATs) on the PML promoter. PML expression is also regulated by β-catenin. However, the mechanism of activation of PML gene expression is independent of the β-catenin-activated TCF transcription factor. Since a fragment of the PML promoter that does not contain any known transcription factor binding sites still conferred responsiveness to β-catenin, it was suggested that β-catenin may operate directly on the basal transcription machinery on the PML promoter (34).

In principle, two other processes may influence PML levels during senescence. First, PML is a sumoylated protein and sumoylation controls the formation of PML bodies (19, 35, 36) (see also review by W. Miller in this issue). The E3 Sumo ligases that control PML sumoylation are not well known but RanBP2 (Nup358), an E3 Sumo ligase of the nuclear pores, is required for PML sumoylation (37). The sumoylation of PML is also controlled by Sumo proteases (38) whose role in senescence remains to be investigated (39). Intriguingly, the sumo protease SENP1 is highly expressed in some patients with prostate cancer and transgenic mice expressing this protein develop prostatic intraepithelial neoplasia (40). Androgens can suppress PML expression in prostate cancer (41) and they also induce the expression of SENP1 (42). Second, PML is degraded via the proteasome, a process originally discovered in cells treated with arsenic trioxide (43). Sumoylation at lysine 160 of PML was required for this degradation process. The recruitment of the proteasome to PML bodies was shown to be dependent on sumoylation at this site, explaining the link between sumoylation and degradation (43). The degradation of PML is also controlled by phosphorylation via casein kinase 2 at serine 517 (44). Inhibition of this process increases the tumor suppressor properties of PML (44), providing further rationale for developing anti-casein kinase 2 therapies for cancer (45, 46).

4. PML ACTIVATES THE P53 TUMOR SUPPRESSOR PATHWAY

The activation of the p53 pathway by PML was initially discovered in the context of Ras-induced senescence (13, 15). These studies suggested that PML stimulated p53 activity by recruiting p53 into PML bodies, inducing specific p53 modifications. Pearson and colleagues reported that PML stimulated the acetylation of p53 at lysine 382, a modification catalyzed by the acetyl transferases CBP which localize to PML bodies (15). Ferbeyre and colleagues observed that PML induced the phosphorylation of p53 at serine 15, a modification that is usually catalyzed by the DNA damage responsive kinases ATM and ATR (13). Proteins that inhibit senescence can reverse these modifications. The NAD dependent deacetylase SIRT1 inhibits PML-induced senescence, localizes to PML bodies and deacetylates p53 at lysine 382 (47). The adenovirus oncoprotein E1A can inhibit senescence in response to oncogenic *ras* or PML. E1A affects the ability of PML to form PML bodies and inhibit p53 phosphorylation in cells expressing oncogenic *ras* (13).

PML physically interacts with p53 and may act as a coactivator of p53 stimulating p53-dependent apoptosis (48). This would imply a function of PML outside the PML bodies. This idea remains controversial because a mutant of PML that cannot be sumoylated and therefore is defective in PML bodies-formation, can bind p53 but cannot enhance its activity (49). It has been reported that PML bodies are in close contact with sites of transcription (50), suggesting that the coactivator functions can be assigned to the whole macromolecular complex. In agreement, tethering reporter constructs to the PML bodies can affect transcription (51). The site of interaction between p53 and PML was mapped to the DNA binding domain of p53 (48, 49). Therefore, p53 may not bind simultaneously to PML and DNA. Intriguingly, among the PML isoforms, PML IV binds p53 more efficiently than PML I or PML-RARα. The latter is a fusion protein found in acute promyelocytic leukemia (APL; covered by D. Grimwade in this issue). In agreement, only PML IV relocalizes p53 into PML bodies when co-transfected with p53 (49). Of note, in normal fibroblasts infected with different PML isoforms, Bishof *et al* reported that PML I, PML II, PML III, PML IV and PML V all recruited endogenous p53 into PML bodies (17). Since only PML IV induces senescence a conclusion from this experiment is that recruitment of p53 into PML bodies is not a sufficient condition to activate senescence. To complicate the picture, PML IV requires the other PML isoforms to induce senescence because as mentioned before *pml* $^{-/-}$ MEFs did not senesce after enforced expression of PML IV (17).

A plausible model bringing together all the data is that p53 recycles between promoters and PML bodies undergoing cycles of reversible posttranslational modifications (Figure 2). Only, a particular combination of PML isoforms, perhaps with a predominance of PML IV would allow this recycle and/or modifications. Recycling of transcription factors at responsive promoters have been already described for four transcription factors regulating

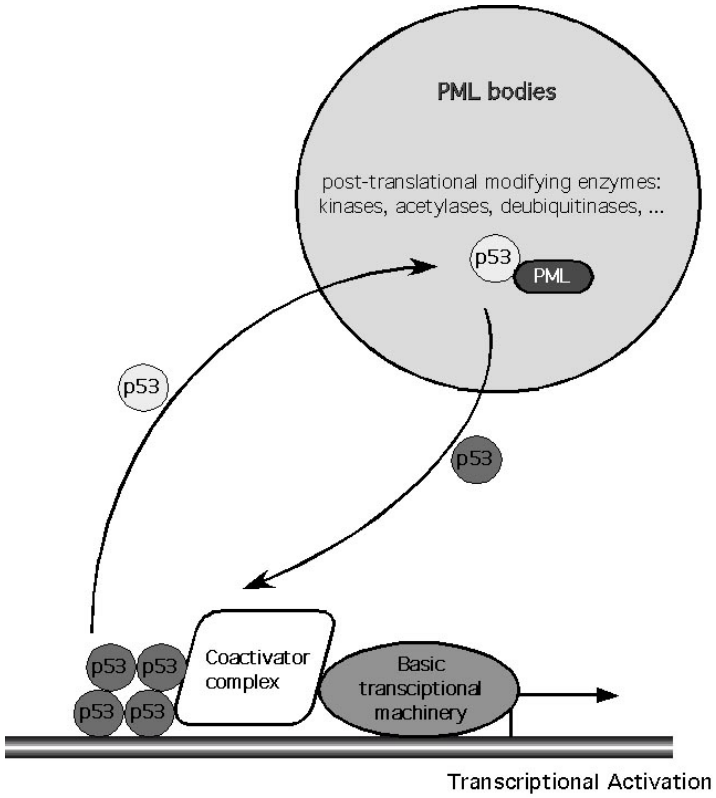

Figure 2. Model of p53 recycling between promoters and PML bodies. Schematic model of p53 recycling between promoters of target genes and PML bodies where p53 modifications can be added or removed in reversible cycles (different shades of gray illustrate a different state of modification).

the mouse insulin 2 receptor (52) as well as for the steroid receptor family of transcription factors especially the estrogen receptor (53, 54) and the glucocorticoid receptor (55). In the latter case, proteasome activity was required for cycling at the promoter (55, 56) but it is not known whether this proteasomal activity is associated to PML bodies. In addition, several coactivators have been reported associated to PML bodies (57-59). Intriguingly, the localization of one of them, SRC-1, changed from the PML bodies to an interlacing filamentous structure upon stimulation of the androgen receptor (59). Collectively, these studies suggest that the elusive role of PML on transcription in general and on p53 in particular may involve a dynamic component difficult to investigate with current technologies.

PML may also activate p53 by binding Mdm2 (60), an E3 ligase that catalyzes the ubiquitination and degradation of p53. The site of interaction between PML and Mdm2 involves amino acids common to several PML isoforms. Also, non-sumoylated PML was found to interact better with Mdm2 (60). Conversely, Mdm2 can relocalize PML from the nucleus to the cytoplasm in transfected cells and in doing so it was able to inhibit stimulation of transcription by a GAL4-CBP fusion protein (60). These studies indicate novel pathways by which Mdm2 could inhibit p53 functions. Moreover, PML was unable to activate a p53 fusion protein lacking its PML binding domain suggesting that the interaction of PML with Mdm2 is not sufficient to activate p53 (61). Trimeric complexes between PML, p53 and Mdm2 were detected in unstressed cells. Upon DNA damage, it was shown that these complexes segregated into PML-Mdm2 and PML-p53 complexes (62). It will be interesting to study whether sumoylation of PML controls the generation of these distinct complexes. Together, these studies suggest that PML can antagonize Mdm2 activity but its ability to stimulate p53 relies primarily on the formation of a p53-PML complex, which is more efficiently formed by PML IV.

A different regulatory pathway was reported by the group of Pandolfi, who observed that PML could recruit Mdm2 into the nucleolus leading to stabilization and activation of p53 (63). This translocation of PML and Mdm2 to the nucleolus was found to be dependent on PML phosphorylation by ATR and interaction of PML with the nucleolar protein L11 (63). In addition, the effects of PML on Mdm2 were ARF independent. ARF, is another regulator of p53 and senescence that can also mediate nucleolar sequestration of Mdm2 (64, 65), This does not mean that PML has no influence on the ARF/p53 pathway. In fact, PML can form a complex with β-catenin that activates transcription of the ARF promoter (34). Finally, Borden and colleagues (see their contribution in this issue) proposed that PML controls the nucleo-cytoplasmic transport of several growth-promoting mRNAs, including

Mdm2 (66). The roles of these Mdm2 inhibitory pathways in PML-induced senescence remain to be investigated.

Independently of the variety of proposed mechanisms, the studies cited above clearly indicate that PML activates p53. Since p53 can induce the expression of PML, these two tumor suppressors are linked in a positive feed-back mechanism that may reinforce the effector functions of p53 and/or PML. On the other hand, there is evidence indicating that PML can have powerful antiproliferative effects in the absence of p53 (34, 67) suggesting that other pathways must be considered in the overall actions of PML especially during senescence.

5. PML AND THE RB PATHWAY

Although the initial studies in mouse fibroblasts concluded that PML regulated senescence via p53, our studies in human cells revealed that PML was able to induce senescence in cells where the p53 pathway was disabled by the papillomavirus oncoprotein E6 or the dominant negative p53 allele p53H175R (68). On the other hand, cells expressing the oncoprotein E7 that inhibit all proteins of the Rb family were resistant to PML-induced senescence. These observations are of difficult interpretation due to the large number of targets reported for E7, including members of the p53 pathway (69). Nevertheless, it is remarkable that PML can trigger senescence in the presence of E6 or dominant negative p53. Similar observations were made for Ras-induced senescence (11) and STAT5-induced senescence (32). Even though E6 and dominant negative p53 may not be able to inhibit 100% of p53 activity as in knockout animals, a plausible model to explain the results is that PML and oncogenes can engage an Rb-dependent senescence program that does not require normal p53. Hence, several groups have investigated links between PML and the Rb pathway.

As observed for p53, Rb was also found to localize to PML bodies during senescence (68). PML and Rb can form a complex that requires the pocket region of Rb and the B boxes and the C-terminal region of PML (70). This complex was also found in erythroid cells, where the inhibition of PML and Rb-expression inhibited erythroid development (71). So far, the functional meaning of the interaction and colocalization of PML and Rb are not clear. There is, however, a meaningful but indirect link between PML and Rb in the regulation of heterochromatin formation during senescence.

The Lowe group reported that senescent cells contain heterochromatin foci (SAHF, for senescence associated heterochromatin foci) associated with E2F target genes, known to be required to progress through the cell cycle. Rb was found to be essential for the formation of SAHF during Ras-induced senescence (72). SAHF may lock E2F target promoters into an inactive conformation because over-expression of E2F1 using adenoviral vectors could not reactivate an endogenous E2F target in senescent cells (72). SAHF do not colocalize with PML bodies but a surprising series of experiments by the Adams' group revealed an intriguing connection between them. The heterochromatin protein HP1 and the histone variant macro H2A/H2B are critical components of SAHF. HP1 transiently localizes to PML bodies before going to SAHF (73). Moreover, the histone chaperone, HIRA, that helps to place macroH2A/H2B into SAHF, also transits through the PML bodies (73). These translocation events to the PML bodies were observed for Ras-induced senescence, replicative senescence (driven by short telomeres) and enforced expression of $p16^{INK4a}$ (74). Intriguingly, they occur before the cell cycle arrest or the appearance of senescence markers such as the senescence-associated β-galactosidase and the SAHF (73, 74). These experiments may suggest that the PML bodies modify or allow the assembly of factors critical for the Rb-dependent process of SAHF formation.

Furthermore, indirect links are also found between PML and the Rb pathway via regulation of Myc and cyclin D. First, PML is able to enhance the repressor functions of the Myc antagonist Mad (75, 76). Second, PML regulates Myc protein stability, perhaps by its ability to interact with Myc, recruiting it into PML bodies together with the proteasome (29, 77, 78). Actually, a recent study investigating events occurring during ca-STAT5-induced senescence, equivalent to an aberrant cytokine signaling, demonstrated the induction of PML and PML bodies along with the down-regulation of Myc protein (32). The importance of Myc regulation during ca-STAT5-induced senescence was further established by the observation that expression of Myc bypassed the senescence phenotype in cells where p53 was also inactivated (32). Finally, PML can also block the expression of cyclin D1 because it prevents the transport of its mRNA to the cytoplasm (79). Both Myc and cyclin D1 stimulate Rb-phosphorylation mediated by the CDK4/6-cyclin D complex.

6. P53 AND RB INDEPENDENT PATHWAYS

Of further importance, it is interesting to consider the observation that although PML cannot induce senescence in cells with disabled Rb and p53 (68) it is still capable of slowing their growth and inhibiting tumor formation (80). This activity must thus be carried out by PML with other cellular factors independently of p53 and Rb. Some particularly interesting candidates are transcription factors, since they can influence whole cellular programs through transcriptional regulation. Some of them have been reported to be affected by PML whether it is through direct interactions, such as Sp1 (81) and c-Jun (82), or indirectly as it is the case of NF-kappaB (83). Their individual function could contribute to PML-induced cell growth inhibition.

Another potential mechanisms by which PML can regulate cell growth and senescence was suggested by the findings that senescent cells accumulate large PML bodies that initially contain nucleolar components (84). Only, PML IV and the abundant PML I were found able to translocate to the nucleolus but PML I was the critical isoform for this process (84). The association of PML to the nucleolus was originally reported in cells treated with

Table 1. DNA damage response proteins reported to colocalize to PML bodies

Protein	Function	References
ATM	Kinase, cell cycle checkpoint	91
ATR	Apical Kinase, cell cycle checkpoint	92
BLM	RecQ DNA helicase	91, 93, 94
BRCA1	Maintenance of genomic stability	91
Chk2	Effector kinase, activates p53	95, 96
MRE11	Exonuclease, Double strand break complex with RAD50/NBN	88, 97, 98
NBN NBS1, p95	Double strand break repair complex with MRE11/RAD50	97, 98
P53	Transcription factor, inhibits recombination	13, 15, 88
RAD50	Double strand break repair complex with MRE11/NBN	91, 98
RAD51	Homologous recombination and repair	93
RAD9	Exonuclease, cell cycle arrest and DNA damage repair	91
RECQL4	RecQ DNA helicase	99
RPA	ssDNA binding protein	92, 93
Top3α	Topoisomerase III alpha	100
TopBP1	DNA damage response protein which interacts with Topoisomerase II beta	91
WRN	RecQ helicase	101, 102

proteasome inhibitors (85). Intriguingly, senescence is characterized by reduced activity of the proteasome (86) that could trigger translocation of PML into the nucleolus. The precise mechanisms by which PML may affect nucleolar functions and whether these PML activities are actually required for senescence remain to be investigated.

On the other hand, expression of p53 (33, 87) or Rb (76) increases the formation of PML bodies and conversely human fibroblasts expressing both E6 and E7 are defective in the formation of PML bodies (68). These observations suggest that p53 and Rb are somehow required for the formation of PML bodies. As a consequence the failure of PML to regulate senescence in the absence of functional p53 and Rb could be due to a defect in formation of PML bodies. An important consequence of these observations is that treatments that induce PML body formation, bypassing the need for p53 and Rb, may possibly inhibit the proliferation of malignant cells where the p53 and the Rb pathways are disabled. Therefore, more work is needed on the p53 and Rb independent antiproliferative activities of PML. In fact, p53 and Rb pathways are disabled in most advanced human cancers. PML may help to discover a novel strategy to eliminate these tumors.

7. PML AND THE DNA DAMAGE RESPONSE

Finally, another mechanism through which PML may be involved in the establishment of senescence, besides its relations to p53 and Rb, is via its interactions with the DNA damage signaling pathway. Indeed, several proteins that play a role in DNA damage response have been reported to localize to PML bodies. These include DNA sensing proteins such as ATM, ATR and p53, helicases, topoisomerase, as well as repair proteins involved in both double strand break and homologous recombination (Table 1). The number and size of PML bodies are generally increased upon DNA damaging treatments leading to the relocalization, trafficking and/or concurrent modification of multiple proteins such as those mentioned in Table 1. Carbone and colleagues proposed that PML bodies are actually sensors of DNA damage induced by radiation contributing to the recognition of the damaged sites and/or their processing (88). Moreover, Dellaire and colleagues demonstrated that the increase in PML bodies is an intrinsic part of cellular response to DNA damage (89).

Interestingly, the DNA damage response pathway and DNA damage foci formation have recently been demonstrated to be an important aspect of senescence (12, 31, 90). It is thus conceivable that PML body interactions with DNA damage proteins do contribute to the DNA damage response observed in senescence and to the proper establishment of this permanent cell cycle arrest.

8. PERSPECTIVES

Senescence is though to contribute to cancer prevention at the cellular level. PML is one of the proteins increased in β-interferon- and oncogene-induced senescence, and is able to induce the process as well when over-expressed. It can interact with both p53 and Rb, two main signaling pathways important in senescence. Likewise, PML bodies have been reported to play a role in recruiting DNA damage response and repair proteins, which might also be part of the DNA damage response recently observed in senescence. Tumorigenesis will occur when this DNA damage response is inactivated, avoiding senescence or perhaps reverting the process. Blocking PML expression early in the carcinogenesis process may contribute to senescence bypass allowing cell growth in the presence of oncogenic signals that induce DNA damage. A challenge for future research will thus be to elucidate the mechanisms by which PML functions and expression are inactivated during tumorigenesis.

9. ACKNOLEDGMENTS

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Abbreviations: ca-STAT5: constitutive STAT5; SAHF: senescence associated heterochromatin foci.

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