

## PML nuclear bodies and apoptosis

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**Promyelocytic leukaemia nuclear bodies (PML NBs) are structured protein complexes associated with the nuclear matrix. PML constitutes the scaffold component of NBs and recruits onto these domains a striking variety of proteins, many of which are involved in apoptosis control. Several reports have directly implicated PML in apoptosis and senescence, but the mechanisms by which these are conveyed are still largely unsettled. Recruitment of partner proteins onto NBs is regulated by PML sumolation, a specific post-translational modification also found in many NB-associated proteins. Among these, several are implicated in transcription repression or activation, like the transcriptional repressor Daxx or the transcriptional activator P53. Whether NBs constitute platforms where active sites of enzymatic modifications are carried out, as suggested for P53, sites of intranuclear protein sequestration, as proposed for Daxx or organelles specialized in catabolism, is still debated. A variety of stress-related signalling pathways dramatically modulate the formation of PML NBs, which may provide a clue as to their physiological function.**

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### Nuclear bodies (NBs), SUMO and promyelocytic leukaemia (PML)

Cellular biology has revealed that the nucleus is not homogeneous as, even in the absence of inner nuclear membranes, nuclear subdomains can be defined both for the genome and for nuclear proteins (Spector, 2001). Among these domains, several NBs have been identified as spheres of various sizes by either immunofluorescence or ultrastructural analysis (Roth, 1995). PML-NBs are nuclear subdomains that recruit and locally accumulate an amazing number of proteins, many of which are key regulators of various processes. PML is present both in the nucleoplasm and in NBs, which are nuclear matrix associated (Stuurman *et al.*, 1992). The PML protein exists as seven major isoforms generated by alternative splicing, which all contain the RBCC/TRIM motifs, but differ in the C-terminal regions (Jensen *et al.*, 2001).

Such diversity of the C-terminal regions could be an important mechanism for generating diverse PML-binding interfaces for a variety of factors. PML was shown to traffic between the nucleus and the cytoplasm and two PML isoforms, which do not contain the nuclear localization sequence, were recently identified (Stuurman *et al.*, 1997; Reymond *et al.*, 2001). In addition, a specific PML isoform with a nuclear export signal has also been found (Henderson and Eleftheriou, 2000).

These domains have fascinated many biologists despite the absence of known associated functions, because an astonishing number of completely unrelated studies came across PML NBs. Hence, these domains are the prototype of orphan nuclear organelles in search for a role. Not surprisingly, an array of functions (transcription regulation, DNA repair, apoptosis, DNA replication and RNA transport) have been assigned to these domains, each based on one's favourite partner protein. These have been covered in a number of recent reviews (Negorev and Maul, 2001; Borden, 2002; Salomoni and Pandolfi, 2002), but it is fair to state that confusion prevails. Several key observations should not be forgotten when thinking about PML bodies. First, PML is the organizer of these domains: in the absence of PML expression, PML NBs do not exist and all proteins normally targeted to these domains adopt a diffuse localization or concentrate onto distinct speckles. Second, for most, if not all, NB-associated proteins, only a small subfraction of the protein is actually concentrated on these domains. Yet, this relative accumulation is easily detected by fluorescence. Note that great care should be taken when interpreting colocalization data obtained in cotransfected cells, as some recruitment onto NBs of proteins that have never been seen as residents in these domains may be observed in this setting (Guiochon-Mantel *et al.*, 1995; Borden, 2002). It remains to be determined if two proteins that colocalize in the bodies similarly form nucleoplasmic complexes. Finally, the formation of the most common subset of PML NBs (mature PML bodies) is tightly regulated by a protein-tagging mechanism, sumolation (Ishov *et al.*, 1999; Zhong *et al.*, 2000a; Lallemand-Breitenbach *et al.*, 2001).

The link between PML NBs and SUMO came from the observation that many cellular or viral sumolated proteins were targeted to these domains (Seeler and Dejean, 2001). Sumolation was first proposed to target PML toward NBs, behaving as an NB-targeting signal

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(Muller *et al.*, 1998). This was suggested by the observation that As<sub>2</sub>O<sub>3</sub> simultaneously increased PML sumolation and NB size by recruiting PML from the nucleoplasm to the NBs (Zhu *et al.*, 1997; Muller *et al.*, 1998). Nevertheless, localization of other NB-associated proteins was not affected by the mutation of their SUMO target lysines (Sternsdorf *et al.*, 1999), and in the case of PML, the formation of primary NBs and nuclear matrix targeting was shown to occur independent of any sumolation (Lallemand-Breitenbach *et al.*, 2001). The functional significance of the presence of so many sumolated proteins onto NBs remains to be understood; while sumolation is clearly not an NB-targeting signal, it might be a consequence of the NB location (Eskiw and Bazett-Jones, 2002).

Many *in vivo* and *in vitro* data have directly implicated PML overexpression in growth suppression, apoptosis and replicative senescence (Mu *et al.*, 1994; Quignon *et al.*, 1998; Pearson and Pelicci, 2001; Salomoni and Pandolfi, 2002), but the direct demonstration for a physiological role of PML in apoptosis control came from the phenotypic analysis of PML<sup>-/-</sup> mice (Wang *et al.*, 1998a, b). Cells derived from PML<sup>-/-</sup> mice presented defects in apoptosis induced by Fas, TNF, interferons and ceramides. Apoptosis induction was reduced, but not abrogated, implying a role for PML as a modulator, rather than as an essential trigger. Intriguingly, despite the number of abnormalities described in PML<sup>-/-</sup> cells, PML<sup>-/-</sup> mice do quite well (Wang *et al.*, 1998a, b) and no gene homologous to PML has been found in *Drosophila melanogaster* nor in *Xenopus laevis*. Yet, PML<sup>-/-</sup> mice are more sensitive to cancer-promoting drugs and conversely more resistant to  $\gamma$ -irradiation, due to defects in the apoptosis process. Finally, expression studies have shown that in normal human tissues, PML expression is restricted to some myeloid and endothelial cells (Flenghi *et al.*, 1995; Koken *et al.*, 1995). However, PML expression pops up in response to a number of stresses (Koken *et al.*, 1995; Terris *et al.*, 1995). All of these observations, which suggest a role of PML – and hence PML bodies – in stress responses, should be kept in mind when thinking about PML bodies.

Several models have been put forward to assign a function to PML bodies. All these models have to take into account the number and striking variety of partner proteins, as well as the unessential nature of the PML gene and NBs. PML bodies were proposed to be: (i) active sites for some enzymatic modifications of partner proteins, in particular sumolation, but also ubiquitination or acetylation (Everett, 2000); (ii) sites of transient accumulation of sequestered proteins, in particular transcription factors, coactivators or corepressors such as Daxx (Li *et al.*, 2000a; Lehembre *et al.*, 2001); (iii) sites of degradation of proteins misfolded or tagged for degradation (Anton *et al.*, 1999; Lallemand-Breitenbach *et al.*, 2001; Lafarga *et al.*, 2002). It is also possible that some functions of PML are independent of its ability to form nuclear bodies, as proposed by a recent study (Bischof *et al.*, 2002).

If the formation of the structure is linked to function, then external factors that influence NBs are likely to provide insights into their function. In that respect, PML localization and sumolation are regulated by phosphorylation, heat shock and exposure to proteasome inhibitors or arsenic (Muller *et al.*, 1998; Lallemand-Breitenbach *et al.*, 2001; Negorev and Maul, 2001; Pokrovskaja *et al.*, 2001; Zhu *et al.*, 2002). The latter observation is particularly interesting, because arsenic trioxide induces clinical remissions in acute promyelocytic leukaemia (Zhu *et al.*, 1997, 2002), a disease in which PML is fused to RARA (de Thé *et al.*, 1990, 1991; Warrell *et al.*, 1993). Arsenic triggers a rapid PML or PML/RARA sumolation, followed by proteasome-dependent catabolism (Zhu *et al.*, 1997; Muller *et al.*, 1998; Lallemand-Breitenbach *et al.*, 2001). PML nuclear matrix targeting, the first step of NB formation, is dependent on dephosphorylations (Muller *et al.*, 1998; Lallemand-Breitenbach *et al.*, 2001), whereas the second step – NB maturation with recruitment of partner proteins – is dependent on PML sumolation (Ishov *et al.*, 1999; Zhong *et al.*, 2000a). After mitosis, PML aggregates in the cytoplasm without any NB-associated proteins (Koken *et al.*, 1995), reflecting PML phosphorylation and desumolation (Everett *et al.*, 1999). In contrast to As<sub>2</sub>O<sub>3</sub>, which induces recruitment of partner proteins through a induction of PML sumolation, cellular stresses (including heat shock) induces desumolation and release of partner proteins from PML NBs (Maul *et al.*, 1995).

### PML and apoptosis: a connection via P53?

Among the NB-associated proteins, many are involved in cell death and could be implicated in both PML-triggered apoptosis and modulation of apoptosis/senescence by endogenous PML. The principal focus of recent studies has been the P53 protein (Ferbeyre *et al.*, 2000; Fogal *et al.*, 2000; Guo *et al.*, 2000; Pearson *et al.*, 2000). P53 is a key regulator of cell cycle arrest, premature senescence and apoptosis, whose function is controlled by a variety of post-translational modifications. P53 plays a central role in premature senescence induced by oncogene expression. In response to the expression of activated Ras, P53 induces growth arrest in mouse primary fibroblasts in a PML-dependent manner (Pearson *et al.*, 2000). In this pathway, PML seems to be required for post-translational modifications of P53, in particular acetylation, which enhances P53 activity (Pearson *et al.*, 2000). Upon PML overexpression, P53 and the acetyltransferase CBP were shown to be recruited onto NBs, leading to an increase of P53 acetylation, enhancement of P53 activity and, depending on the stimuli and cell types, premature senescence or apoptosis. In particular, the presence of PML was proposed to favour the expression of senescence-associated targets such as p21. Surprisingly, P53 can be recruited to NBs by overexpression of all PML isoforms, even though only PML IV has been shown to

interact with the DNA-binding domain of P53 and to trigger senescence (Fogal *et al.*, 2000; Guo *et al.*, 2000; Bischof *et al.*, 2002). Yet, a recent report (Mallette *et al.*, 2004) suggests that engagement of the RL pathway may be more important than the P53 pathway during PML-Triggered genes cancer.

In response to different stimuli, P53 is stabilized through a phosphorylation-induced inhibition of its degradation mediated by the E3-ubiquitin ligase HDM2 and inhibited by the ubiquitin-protease HAUSP (Li *et al.*, 2002). Stabilization allows P53 to activate the transcription of its target genes. A number of other modifications such as acetylation by CBP or deacetylation by hSIR2 (Langley *et al.*, 2002) or sumolation by PIAS (Megidish *et al.*, 2002; Schmidt and Muller, 2002) modulate the intrinsic transactivating properties of P53. The p14ARF tumour suppressor binds MDM2, impeding its association with P53 or promoting HDM2 sumolation (Xirodimas *et al.*, 2002). Strikingly, all of these key proteins (p14, HAUSP, CBP, hSir2, PIAS and HDM2) that regulate the post-translational modifications of P53 have been found to accumulate on PML NBs, at least in some settings (reviewed in Hofmann and Will, 2003). These observations raise the possibility that PML NBs form a scaffold, which concentrates P53 molecules for efficient post-translational modifications.

A fraction of HDM2 was also found to be associated with PML NBs, especially after the inhibition of nuclear export (Lain *et al.*, 1999). Recently, HDM2 was shown to interact directly with PML (Wei *et al.*, 2003) and PML IV to protect P53 from degradation by HDM2 (Louria-Hayon *et al.*, 2003). HDM2 overexpression was shown to promote independently PML nuclear exclusion and to inhibit the ability of PML to activate P53. Furthermore, DNA damage (UV), inhibition of proteasome activity or As<sub>2</sub>O<sub>3</sub> treatment were also shown to induce PML/HDM2 colocalization on NBs in a P53-independent manner (Kurki *et al.*, 2003). UV-irradiation caused rapid rearrangement of PML NBs and promoted PML/P53 and PML/HDM2 complex formation, coinciding with P53 stabilization. Altogether, these data suggest that PML could stabilize P53 in response to cellular stress through a specific interaction with HDM2. Accordingly, PML was shown to enhance transactivation by P53 (Zhu *et al.*, 2003). Finally, in addition to its nucleolar distribution, p14ARF overexpression was shown to induce nuclear inclusion formation containing P53, HDM2, PML and proteasome (Kashuba *et al.*, 2003). This could suggest an alternative mode of regulation by targeting p14ARF/HDM2 complex for proteasome degradation.

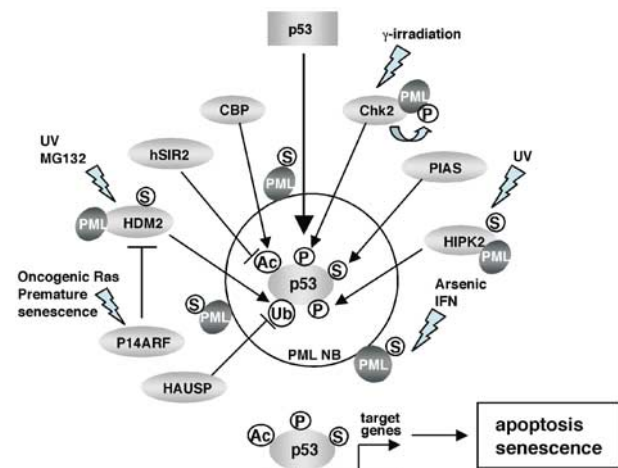
### Would all P53 modifiers be NB-associated?

Surprisingly, a set of kinases implicated in the regulation of P53 activity were also shown to localize onto NBs. HIPK2 is a UV-activated serine/threonine kinase that phosphorylates P53 on serine 46 and partially colocalizes with P53 on PML NBs (D’Orazi *et al.*, 2002;

Hofmann *et al.*, 2002). HIPK2 cooperates with P53 to induce growth arrest and UV-induced apoptosis. Association of HIPK2 with PML NBs is independent of P53. Conversely, PML was shown to be required for HIPK2-mediated P53 phosphorylation and for the antiproliferative function of HIPK2 (Moller *et al.*, 2003). Localization of HIPK2 to speckles depends on its sumolation (Kim *et al.*, 2002). HIPK2 harbours a peptide motif that allows its interaction with SUMO-1 (SIM) (Minty *et al.*, 2000; Engelhardt *et al.*, 2003). Direct interactions between HIPK2 and PMLIV have been reported, promoting HIPK2 targeting onto PML NBs and blocking sumolation of PML. Altogether, these observations point to a tight relation between HIPK2 and PML that have a significant effect on P53 function, although the molecular details require further analyses.

The DNA-damage checkpoint kinase Chk2 induces P53 phosphorylation on serine 20 upon  $\gamma$ -irradiation. This phosphorylation blocks the P53/HDM2 interaction, leads to P53 accumulation and apoptosis. Chk2 interacts with PML and colocalizes on NBs. PML enhances P53 S20 phosphorylation by recruiting Chk2 and P53 onto PML NBs upon  $\gamma$ -irradiation (Yang *et al.*, 2002). Yet, Chk2 also mediates  $\gamma$ -irradiation-induced apoptosis in a P53-independent manner, through an ATM-Chk2-PML pathway (Yang *et al.*, 2002). Indeed, upon  $\gamma$ -irradiation, Chk2 induces the phosphorylation of PML on serine 117 and the latter is required for  $\gamma$ -irradiation-induced apoptosis, but not for FAS or TNF-induced apoptosis. Thus, Chk2 acts through two different pathways both requiring PML, one in which PML prolongs P53 phosphorylation on S20, and the other in which Chk2 phosphorylates PML, triggering apoptosis by an unknown, P53-independent mechanism.

In conclusion, PML NBs are encountered when studying most protein complexes that control P53 stability or function (Figure 1). The variety of P53



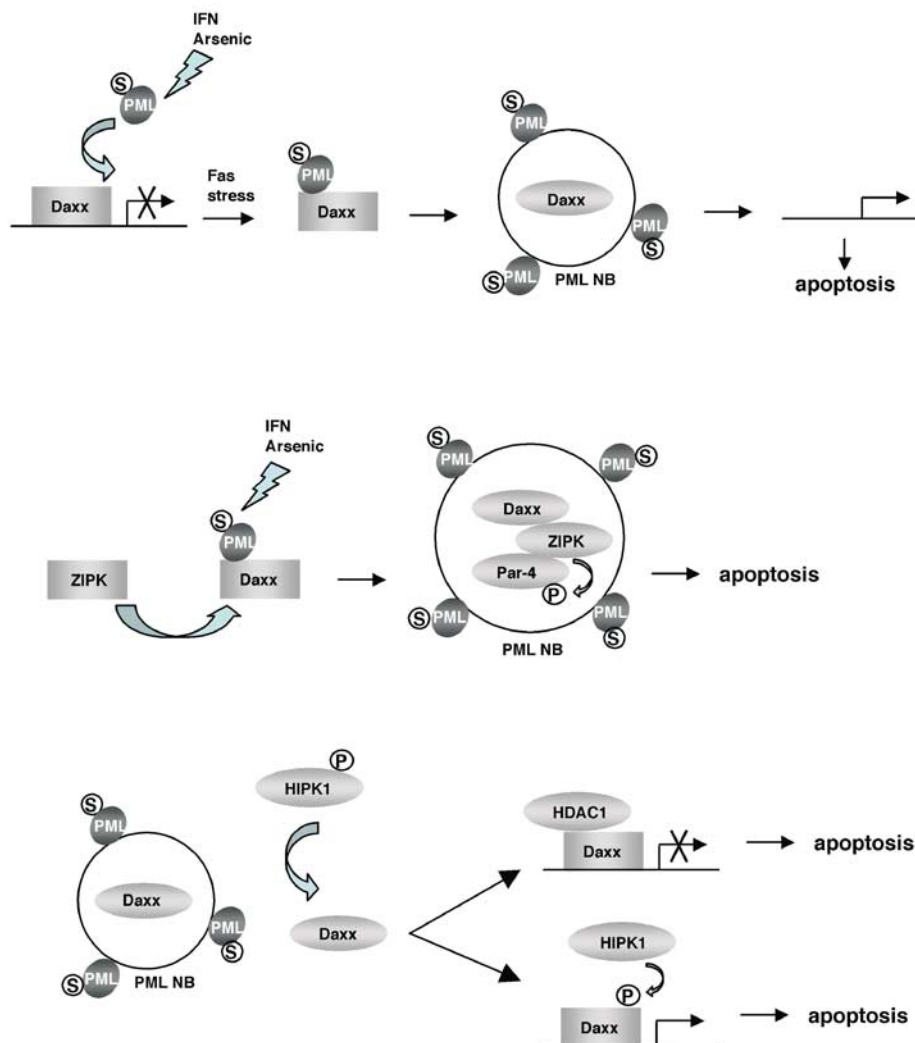
**Figure 1** NBs as active sites for P53 post-translational modifications. The different partner proteins implicated in the control of P53 post-translational modifications and activity that relate to PML NBs are shown, together with the stress signals that induce their localization on NBs. S: SUMO; P: phosphorylation; Ac: acetylation; Ub: ubiquitination

regulators with which PML was also proposed to interact is troublesome and clearly deserves additional studies. Moreover, PML may trigger apoptosis in P53-null cells. It is quite intriguing that some of these mechanisms of P53-independent apoptosis are controlled by proteins such as Chk2, which also modulate P53 function (Yang *et al.*, 2002).

#### *Daxx, another proapoptotic partner of PML bodies*

First implicated as a modulator of Fas-induced apoptosis, Daxx is a multifunctional protein that participates in different apoptotic pathways. Daxx acts as a transcription corepressor of Pax3 or Ets-1, but was recently described as a coactivator of Pax5, depending on cell types (Torii *et al.*, 1999; Li *et al.*, 2000a,b; Lehembre *et al.*, 2001; Emelyanov *et al.*, 2002). Daxx localizes on NBs, but also on chromatin or centromeres

(Ishov *et al.*, 1999). The PML-interacting C-terminal part of Daxx is required for NB localization and for the enhancement of FAS-induced apoptosis (Torii *et al.*, 1999). Moreover, Daxx is upregulated during splenocyte activation-induced cell death (Zhong *et al.*, 2000b). Daxx may also be sumoylated, but this modification does not appear to be required for PML NBs targeting (Jang *et al.*, 2002). Daxx is a potent repressor and its sequestration on NBs, away from its active sites in the chromatin, could be a very efficient way to regulate transcription in response to signals that regulate NB formation (Figure 2). Surprisingly, it was also shown that Daxx exerts antiapoptotic functions, since *Daxx*<sup>-/-</sup> mice presented defaults in embryogenesis due to massive apoptosis (Michaelson *et al.*, 1999). In addition, siRNA-mediated downregulation of Daxx also showed an antiapoptotic function of Daxx, suggesting that this effect is not restricted to embryogenesis (Michaelson



**Figure 2** Models for Daxx-controlled apoptosis. Top: sequestration/derepression model. PML recruits Daxx onto NBs, liberating target promoters from the repressive effects of Daxx. This pathway is activated by interferons (that induce PML expression) and arsenic trioxide (that triggers PML sumoylation, recruiting Daxx onto NBs). Middle: activation model. ZIPK/Daxx and Par-4 are recruited onto NBs where phosphorylation of Par-4 triggers cell death. Bottom: HIPK1 relocalizes Daxx from NBs to chromatin, where it represses transcription through interactions with HDAC1 or diminishes its repressive activity through phosphorylation by HIPK1

and Leder, 2003). Daxx was shown to be relocated from PML NBs to the nucleoplasm by the HIPK1 kinase, which also modulates Daxx's repressive activity by phosphorylation (Ecsedy *et al.*, 2003). Another Daxx-interacting protein, the ZIP kinase (ZIPK), was found to be associated with PML NBs (Kawai *et al.*, 2003). ZIPK is a proapoptotic protein kinase that phosphorylates Daxx and the Par-4 proapoptotic protein. ZIPK recruitment on PML NBs is increased by  $\gamma$ -IFN/As<sub>2</sub>O<sub>3</sub> treatment and Daxx, ZIPK and Par-4 all appear to be required for  $\gamma$ -IFN/As<sub>2</sub>O<sub>3</sub>-induced apoptosis (Figure 2). While it is clear that Daxx makes important contributions to apoptosis regulation and has the ability to modulate transcription through its repressor domain, many mechanistic aspects of this regulation are still unclear.

### Apoptosis and PML NBs in real life

Schematically, the data reviewed above may reflect two distinct situations. In some experiments, a PML-dependent, arsenic-enhanced, change in the localization of interacting proteins triggers apoptosis (Quignon *et al.*, 1998; Puccetti *et al.*, 2003). In other experimental systems, such as oncogene-triggered senescence, quantitative changes were observed when comparing PML<sup>+/+</sup> and PML<sup>-/-</sup> cells (Pearson *et al.*, 2000). Yet, there are only few examples of major changes when comparing these two types of cells with physiological end points.

The first model raises immediate concerns about overexpression artefacts. To address its relevance to real life, one could focus on the physiological factors that control the formation of PML NBs. Transcription of the *PML* gene is tightly regulated by interferons (Stadler *et al.*, 1995). Strikingly, many NB-associated proteins, Sp100, ISG20, P53 and Daxx, are similarly interferon

target genes (Shimoda *et al.*, 2002; reviewed in, Regad and Chelbi-Alix, 2001). Hence, several groups have looked for modulation of death pathways regulated by PML NBs through analyses of cells treated with interferons (that induces PML expression) and arsenic (that triggers PML sumolation and thus recruits partner proteins onto NBs). In such a sequestration model for NB function, NB-associated apoptotic pathways should be triggered or enhanced by this combination, which was indeed found (Quignon *et al.*, 1998; Torii *et al.*, 1999; Lehembre *et al.*, 2001; Kawai *et al.*, 2003). Moreover, recent data have directly linked PML expression to arsenic sensitivity (Puccetti *et al.*, 2003), as originally proposed (Quignon *et al.*, 1998).

The second situation, best exemplified by the P53/PML connection, is clearly more difficult to understand at present. Too many, apparently unconnected, pathways have been found and there is a striking contrast between strong biochemical links between PML and actors of the P53 pathway and modest effects *in vivo* when comparing normal fibroblasts to those deprived of endogenous PML. Yet, this may reflect the fact that PML NBs are of key importance for adaptive responses and that we have not yet analysed the appropriate situation or stress in which PML is critical.

Altogether, the wealth of information on PML NBs and apoptosis has not allowed a clear picture to emerge, probably because too much information has relied on localization studies and overexpression. Possibly, the molecular mechanisms controlling apoptosis induction and tuning of senescence are distinct. Yet, it is more than likely that PML and PML NBs connect to both.

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