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Mathieu Vernier & Gerardo Ferbeyre

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Mathieu Vernier and Gerardo Ferbeyre*; Université de Montréal; Québec, Canada; *Email: G.Ferbeyre@umontreal.ca; http://dx.doi.org/10.4161/cc.28090

Cellular senescence is a program that prevents malignant transformation in part by avoiding cell cycle progression.[1] The senescent cell cycle arrest is controlled by the retinoblastoma protein (RB), which negatively regulates the activity of the E2F transcription factors, leading to repression of proliferation genes.[2] This event is common to senescence and quiescence, a dormant state from which cells can re-enter proliferation in response to an external signal. Thus, another layer of regulation is necessary to make the distinction between a transient and a permanent growth arrest. E2F target genes can undergo an RB-dependent heterochromatinisation process.[3] More precisely, RB interacts, via a LXCXE motif, with proteins involved in chromatin remodeling, and a mutant RB lacking the LXCXE interaction domain is defective for heterochromatinization, stable repression of E2F target genes, and maintenance of senescence.[4] RB cooperates with the promyelocytic leukemia protein (PML) during the establishment of senescence.[5] PML is the main constituent of spherical nuclear structures known as PML bodies, in which RB/E2F complexes, along with E2F target gene promoters, can relocalize in an RB-dependent manner during senescence.[5] Also, several proteins involved in heterochromatinisation have been shown to transiently localize to PML bodies prior to their integration into regions of heterochromatin embedding E2F target genes in senescence.[6] Finally, $PML^{-/-}$ mouse fibroblasts fail to senesce in response to oncogene expression, demonstrating the importance of PML in the regulation of the process. Thus RB and PML are important players in the regulation of senescence and interact together to repress genes essential for proliferation.[5]

In this issue, Talluri and Dick report that the interaction between RB and PML is dependent on the LXCXE binding motif of RB, and that this interaction is critical for chromatin reorganization on promoters of cell cycle genes, leading to their stable repression and a permanent cell cycle arrest. To do so, they took advantage of an elegant mouse model carrying a mutant form of RB lacking the LXCXE interaction domain (called $RB1^{\Delta L}$). $RB1^{\Delta L/\Delta L}$ MEFs were infected with vectors expressing the oncogene RASV12 or PML to induce senescence. In this context, the authors observed a normal induction of early senescent events, such as an increase of β-galactosidase activity, DNA damage, and an increase in the number of PML bodies. However, the repression of E2F target genes was less efficient than in wild-type MEFs, explaining why these cells can incorporate BrdU and resume proliferation when challenged with ectopic E2F expression. Of interest, the recruitment of PML to the promoters of E2F-target genes and the marker of constitutive heterochromatin H3K9me3 were also absent in E2F target promoters in $RB1^{\Delta L/\Delta L}$ MEFs. Mechanistically, Talluri and Dick found that PML and RB only interact in the context of senescence. They also observed high molecular forms of PML in interaction with RB, suggesting that sumoylation of PML might be required.

The study of Talluri and Dick sheds new light into the complexity of the senescence tumor suppressor response. Their work suggests that what we call senescence is not a single cellular state, and at least 2 types can be defined. They defined incomplete senescence (type I) as the process occurring in $RB1^{\Delta L/\Delta L}$MEFs in response to oncogenes. These cells arrest their proliferation, are SA-β-Gal-positive, and display signs of DNA damage and an increase in the number of PML bodies. However, their cell cycle arrest is not stable, and they can resume cell proliferation. On the other hand, complete senescence (type II) is essentially a permanent process due, at least in part, to the formation of heterochromatin at E2F target genes, which requires the interaction between PML and RB via its LXCXE binding motif as defined by Talluri and Dick. Of note, Vernier et al. discovered abundant PML bodies in benign prostatic hyperplasia (BPH), which are benign prostate tumors that do not progress to cancer. In contrast, prostatic intraepithelial neoplasia (PIN), which are premalignant lesions with the potential to progress into prostate cancer, do not have PML bodies.[5] These 2 lesions may represent clinical examples of complete and incomplete senescence.

References

1. Kuilman T, et al. Genes Dev 2010; 24:2463-79; PMID:21078816; http://dx.doi.org/10.1101/gad.1971610
2. Dick FA, et al. Nat Rev Mol Cell Biol 2013; 14:297-306; PMID:23594950; http://dx.doi.org/10.1038/nrm3567
3. Narita M, et al. Cell 2003; 113:703-16; PMID:12809602; http://dx.doi.org/10.1016/S0092-8674(03)00401-X
4. Talluri S, et al. Mol Cell Biol 2010; 30:948-60; PMID:20008551; http://dx.doi.org/10.1128/MCB.01168-09
5. Vernier M, et al. Genes Dev 2011; 25:41-50; PMID:21205865; http://dx.doi.org/10.1101/gad.1975111
6. Adams PD. Gene 2007; 397:84-93; PMID:17544228; http://dx.doi.org/10.1016/j.gene.2007.04.020