The molecular details of how lamin A influences 53BP1 stability and inhibits formation of p130/E2F4 repressor complexes remain to be identified. Lamins may directly bind to and affect these proteins, or these effects may be indirect. Altogether, the study by Redwood et al. provides a glimpse of novel functions of lamin A in both the transcription and stabilization of DNA damage repair components. Lamin A thus seems to also be involved in regulating the intricate cross talk between the different DSB repair pathways.

References

1. Stracker TH, et al. Nat Rev Mol Cell Biol 2011; 12:90-103.
2. Dechat T, et al. Cold Spring Harb Symp Quant Biol 2010; 75:533-43.
3. Dechat T, et al. Genes Dev 2008; 22:832-53.
4. Liu Y, et al. J Cell Sci 2006; 119:4644-9.
5. Manju K, et al. J Cell Sci 2006; 119:2704-14.
6. Varela I, et al. Nature 2005; 437:564-8.
7. Gonzalez-Suarez I, et al. EMBO J 2009; 28:2414-27.
8. Dimitrova N, et al. Nature 2008; 456:524-8.
9. Redwood AB, et al. Cell Cycle 2011; 10:2550-6.

New role for Spinophilin in tumor suppression

Comment on: Ferrer I, et al. Cell Cycle 2011; 10:2751–62

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Spinophilin was initially identified as a regulatory subunit of the PP1 protein phosphatase, responsible for its targeting to specific substrates in dendritic spines.[1,2] In the years after this discovery, the spectrum of Spinophilin partners and functions has expanded but has remained mostly in the field of neurobiology. The general picture emerging from these studies identifies Spinophilin as a scaffold protein that connects signal transduction to cell architecture, regulating processes critical for neural function, like spine morphology and density, synaptic plasticity and neuronal migration.[2]

In an article in the August 15th issue of *Cell Cycle*, Ferrer et al.[3] revealed that, in addition to its well-established role in neurophysiology, Spinophilin has a previously unappreciated role in cancer biology, acting upon the two major tumor suppressor circuits in mammals, the p53 and Rb pathways. Prompted by the location of the Spinophilin locus in a region of frequent LOH, Ferrer et al. set out to elucidate the potential role of this protein in tumorigenesis. Among the long list of PP1 substrates, they focused on the Retinoblastoma protein (Rb), an attractive candidate to mediate the tumor suppressive action of Spinophilin. Consistent with a role for Spinophilin and PP1 in phosphorylation of Rb and control of the G_1/S transition, Spn-knockout fibroblasts failed to fully dephosphorylate Rb at quiescence and showed premature entry into S phase after serum re-stimulation. Interestingly, this phenotype was paralleled by reduced PP1 activity.

Remarkably, Ferrer et al. showed that Spinophilin is also functionally linked to p53 in a variety of p53-mediated responses. MEF immortalization typically involves one of two equally frequent events: p53 mutation or inactivation of p19Arf or the entire Ink4a/Arf locus, reflecting the essential role of the ARF-p53 axis in senescence of this cell type. Spn-deficient fibroblasts underwent senescence and immortalization at normal rates. However, immortalization occurred in all cases through p53 mutation in a clear deviation from the pattern of wild-type MEFs. In additional experiments, loss of Spn accentuated p53-mediated cell-cycle arrest or the response to genotoxic agents, while silencing of Spinophilin enhanced the transformed phenotype of p53-deficient cells. Taken together, these observations clearly support a functional link between Spinophilin and p53, but they also suggest that the specific outcome can be context-dependent. Spinophilin loss may be beneficial by potentiating p53 in response to acute stress, but it can be deleterious under sustained mitogenic stress (as in serial passage or tumor formation), presumably because it poses a selective pressure that ultimately leads to p53 inactivation and increased tumorigenesis.

An interesting question is whether the links of Spinophilin to Rb and p53 are connected. It is conceivable that Rb deregulation due to Spn loss can provoke mitogenic stress that, in turn, leads to ARF-mediated p53 activation. In support of this model, ARF seems to mediate the enhanced p53 activation by oncogenic stress in Spn-deficient MEFs.[3] Also, the interaction between ARF and Spinophilin has been reported,[4] although its functional relevance is unclear. However, this has to be reconciled with unusually infrequent ARF loss in immortalized Spn-deficient MEFs or effects of Spinophilin on ARF-independent p53 responses. The involvement of PP1 in DNA damage signaling[5] could account for p53 regulation by Spinophilin in some cases. Even p53 or Rb-independent mechanisms could be considered, because Spinophilin can inhibit the growth of cells defective in either tumor suppressor.[3]

Can we extend these observations to the context of tumor formation? Spinophilin can restrain self-renewal of brain tumor initiating cells[6] and anchorage-independent growth of glioma cell lines.[7] Furthermore, the combined inactivation of Spinophilin and p53 correlates with increased tumorigenicity in vivo, as shown in two recent reports. First, Spinophilin-knockout mice display spontaneous mammary benign lesions, and this phenotype is exacerbated in mice expressing mutant p53 in mammary glands, leading to increased incidence of carcinomas.[8] Also, a subset of human lung tumors show reduced Spinophilin levels, which correlate with p53 inactivation and poor prognosis.[9] It would be interesting to extend these studies to other tumor types to establish the generality of these findings. In summary, although several interesting questions remain open, this report clearly identifies Spinophilin as a new player in tumorigenesis, in connection with PP1, Rb, and p53, and sets the basis for future work on the role of this protein in tumor biology.