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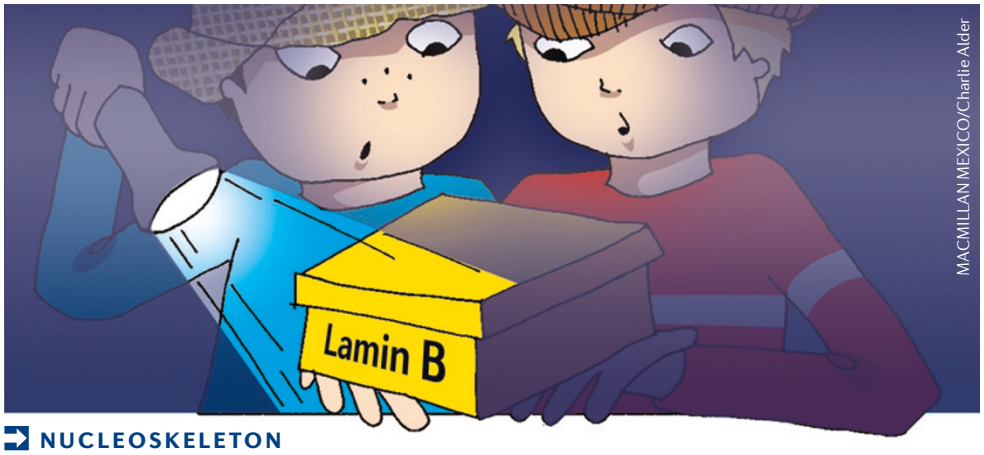

NUCLEOSKELETON

Uncovering roles for lamin B

Lamins are intermediate filament proteins found in the nuclear lamina and throughout the nucleoplasm that regulate nuclear structure, transcriptional regulation and chromatin organization. Two new studies have sought to more precisely delineate the roles of B-type lamins, and they reveal that these proteins have key functions in spindle orientation during mitosis and in cell proliferation and senescence.

Kim *et al.* initially set out to confirm whether B-type lamins are essential for transcriptional silencing during embryonic stem (ES) cell differentiation, as had been suggested previously. They generated knockout mice lacking lamin B1, lamin B2 or both B-type lamins. Lamin B-null mice died at birth, owing to difficulties in breathing, and showed several phenotypic abnormalities. However, ES cells from these mice had apparently normal nuclear envelopes and had similar growth rates and expression patterns of pluripotency markers to those of controls. These findings indicate that B-type lamins are not required for the lineage specification of ES cells but may have a role in organogenesis.

Indeed, further investigation showed that B-type lamins are involved in brain development. Specifically, lamin B1 and lamin B2 were found to be required for proper spindle orientation during the division of neuronal progenitors; this is presumably mediated through their previously shown interaction with the dynein regulator NudEL, which is known to have a role in this process. Furthermore, lamin B-null neurons showed defective migration, remaining closer to the ventricular and subventricular zones than controls, which suggests that B-type lamins may also help to define the brain tissue architecture.

Shimi *et al.* focused on the role of lamin B1 in human diploid fibroblast cell proliferation. They observed that silencing lamin B1 led to a significant decrease in cell proliferation and an eventual increase in the number of cells undergoing premature senescence, whereas lamin B1 overexpression increased cell proliferation. Consistent with this, senescent cells showed lower lamin B1 expression levels than actively proliferating cells, which were caused by reduced lamin B1 mRNA transcript levels, possibly mediated by the action of retinoblastoma protein.

So how does decreased lamin B1 expression lead to decreased proliferation and senescence? To identify the mechanism, Shimi *et al.* assessed how gene expression levels change following lamin B1 silencing, and found that, among others, p53 and its target p21 were altered. Indeed, p53 inactivation or downregulation abrogated the effect of lamin B1 depletion, with lamin B1-silenced cells showing similar proliferation rates and expression of senescence markers to those of control cells. Interestingly, p53 targets that act as antioxidants were upregulated in lamin B1-deficient cells and, consistently, reactive oxygen species (ROS) levels decreased. Shimi *et al.* hypothesized that this decrease may underlie the reduced proliferation rates in lamin B1-deficient cells, as moderate increases in ROS levels are known to enhance proliferation. Indeed, under hypoxic conditions, when ROS levels are high, the proliferation rates of lamin B1-deficient cells and control cells were comparable, and addition of a ROS scavenger eliminated this effect.

These two studies provide important insights into the cellular roles of B-type lamins during normal development and ageing, but further work is needed to delineate their roles in tissue building and to determine the link between ROS signalling and lamin B1 function.

Rachel David

> “key functions in spindle orientation during mitosis and in cell proliferation”

ORIGINAL RESEARCH PAPERS Kim, Y. *et al.* Mouse B-type lamins are required for proper organogenesis but not by embryonic stem cells. *Science* 24 Nov 2011 (doi:10.1126/science.1211222) | Shimi, T. *et al.* The role of nuclear lamin B1 in cell proliferation and senescence. *Genes Dev.* 8 Dec 2011 (doi:10.1101/gad.179515.111)