CHEMICALLY AND GENETICALLY INDUCED ACCUMULATION OF FARNESYLATED PRELAMIN A DIFFERENTIALLY AFFECT OXIDATIVE STRESS AND MITOCHONDRIAL POTENTIAL

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Abstract

The cell nucleus is structurally and functionally organized by lamins, intermediate filament proteins that jointly make up the nuclear lamina. Point mutations that interfere with proper maturation of a specific subset of lamins, the A-type lamins, are the prime cause for a spectrum of diseases termed laminopathies. Recent evidence points to a role for A-type lamins in intracellular redox management. To decipher whether different lamin perturbations differentially affect intracellular oxidative stress, we have analyzed basal levels of reactive oxygen species (ROS), sensitivity towards oxidative stress, mitochondrial potential and expression of ROS defusing enzymes in human fibroblasts in which we experimentally induced accumulation of different prelamin A variants. Using a quantitative single cell imaging workflow, we measured a significant increase in basal ROS levels upon chemically induced, but not upon genetically induced accumulation of prelamin A. Since both chemical and genetic induction of prelamin A lead to mitochondrial hyperpolarization, chemical treatments may have lamin-independent effects that aggravate ROS production or impair ROS defusing capacity. In contrast, reduction of mature lamin A via siRNA-mediated knockdown caused a highly significant rise in basal ROS levels and an even more prominent increase in sensitivity towards ROS, but had no effect on mitochondrial potential, consistent with a direct ROS-buffering capacity of mature lamins. Hence, different lamin intermediates exert distinct roles in cellular redox management.