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Fusion and Fission of Mitochondria Modulate Cellular Senescence

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Mitochondria are dynamic organelles that undergo continuous fission and fusion. The human protein hFis1 participates in mitochondrial fission by recruiting the dynamin-like GTPase, Drp1, into mitochondria. Using short hairpin RNAs, we reduced the expression levels of hFis1 in HeLa cells and characterized the cellular phenotypes. As expected, depletion of hFis1 mRNA in HeLa cells resulted in increase of elongated mitochondria. Interestingly, knockdown of hFis1 expression caused a significant morphological change such as enlarged and flattened cell shape with increased granularity, suggesting a possibility of cellular senescence. Indeed, senescence-associated b-galactosidase activity was significantly increased in these cells. Reintroduction of hFis1 gene or knockdown of Opa1, an important regulator of mitochondrial fusion, restored normal mitochondrial morphology and abrogated senescence-associated cellular changes. Sustained elongation of mitochondria in hFis1 depleted cells led to decrease in mitochondrial membrane potential and increase of reactive oxygen species (ROS) production. This is the first evidence demonstrating that modulation of mitochondria morphology controls cellular senescence via ROS generation.