A Novel Role for Fis1-mediated Mitochondrial Fission as a Senolytic Target

Liu, Seton (School: Bergen County Academies)

A new frontier in anti-aging research is the development of senolytics, drugs that selectively kill senescent cells an ameliorate age-associated disorders. A hallmark of senescence is the SAMD (senescence-associated mitochondrial phenotype) that includes impaired mitophagy and elongated mitochondria. A potential method to exploit this elongation and induce apoptosis in senescent cells is mitochondrial fission, a process that splits the mitochondria through fission mediator fis1. Cardiomyocytes were transfected with a mitochondrial fission protein 1 (fis1) plasmid in vitro to create a Fis1(+) cell line with upregulated fission. In vitro premature senescence was induced with the chemical D-galactose. Fis1(+) senescent cells had more Cytochrome c ($p<0.001$), an apoptosis-inducing protein generated by fission, less mitophagy PINK1 protein ($p<0.001$), and subsequent apoptotic caspase 3/7 activity ($p<0.001$), demonstrating fission has adversarial effects on mitophagy-impaired senescent cells. Senolytic treatment was then shown to upregulate fission, a possible apoptotic mechanism. Confocal images of mitochondrial morphologies were classified with DynaMito, a computer vision pipeline. Feature extraction, dimensionality reduction, and unsupervised clustering was utilized to label images in an unbiased manner. DynaMito classification with unbiased labeling achieved an accuracy of 83.3%, much higher than classification with treatments as labels. Extracted data was utilized in agent-based modeling of mitochondria to further supplement drug discovery in silico. This study demonstrates the potential of fission as a senolytic target mechanistically and allows for analysis of mitochondrial mophologies with DynaMito, greatly improving the current understanding and potential of senolytics.