ROS driven mitochondrial-telomere dysfunction during environmental stress

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USA

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ROS driven mitochondrial-telomere dysfunction during environmental stress

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telomere, Reactive Oxygen Species, TERF1 gene, Mitochondria, Stress

Research Abstract

? DESCRIPTION (provided by applicant): Maintenance of mitochondrial and telomere function are critical for healthy aging, and significant cross-talk occurs between these distinct compartments. Many environmental factors cause mitochondrial dysfunction and subsequent reactive oxygen species (ROS) generation that particularly damage the telomeres. This project will directly test the hypothesis that oxidative damage at telomeres cause mitochondrial dysfunction, and conversely that oxidative damage to mitochondrial DNA cause telomere

dysfunction, and that this reciprocal damage contributes to several environmentally-induced human disease, including neurodegeneration in Parkinson’s disease (PD). We will monitor ROS flux in distinct cellular compartments using a highly innovative system consisting of fluorescent protein tagging and visible light to rapidly induce ROS, and fluorogen-activating peptides (FAPs) with unique chemical sensors to detect ROS. These FAPs will also be used with different chemical moieties to generate different types of ROS. We will use an environmental pesticide associated with PD as a mitochondrial toxicant to examine ROS flux and subsequent telomere damage. The R21 phase will develop and validate this approach first in human cells and will generate transgenic animals for applying this system to zebrafish. Aim 1 will use the KillerRed ROS-generating system to examine how ROS generation in mitochondria impacts telomere function, and reciprocally how ROS generation at telomeres alters mitochondrial function. Aim 2 will develop the FAP system for sensing and producing ROS within the mitochondria or telomeres, and will use this technology to examine ROS flux from the mitochondria to the telomeres. We will create transgenic zebrafish driver lines for localized FAP-mediated ROS sensing and generation in the mitochondria or telomeres. The R33 phase will apply the targeted ROS sensing/producing system toward investigating the underlying mechanisms of dysfunctional mitochondria and telomere cross-talk in human neuronal cells (Aim 3), in transgenic zebrafish embryos (Aim 4) and in a specific zebrafish model of PD (Aim 5). These innovative studies will measure the temporal and spatial generation of ROS in living cells and provide mechanistic insight into how dysfunctional telomeres or mitochondria influence each other in the process of environmentally-induced human diseases, including PD. This project builds tools and capacity for examining ROS-mediated flux and mitochondrial cross-talk in response to environmental stressors. Completion of this project will lay the foundation for developing new interventions to better mitigate the negative effects of environmental exposures on telomere and mitochondria function, serving to ameliorate or delay aging-related diseases and pathologies.

Further information available at:

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