

Weekly Colloquium

Tuesday, 1/9/2018, 12:30pm, Billings Building – Rosedale Conference Room

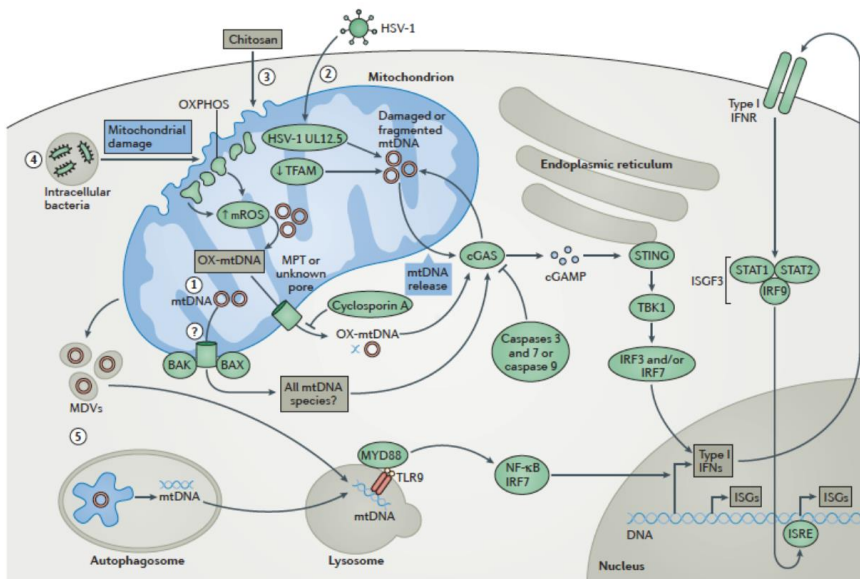
"Mitochondrial Stress Signaling in Disease, Aging and Immunity"

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Abstract:

My research focuses on the role of mitochondria in disease, aging and the immune system. My group has 1) made seminal contributions to the current understanding of mitochondrial gene regulation and mtDNA metabolism, 2) pioneered aging studies showing that mitochondrial respiration and ROS signaling are key components of conserved longevity pathways, and 3) developed and analyzed novel cell and animal models of mitochondrial stress and disease. For example, we identified mitochondrial dysfunction and oxidative-stress signaling as key elements of the multi-factorial, neurodegenerative disease Ataxia-Telangiectasia and developed a mouse model of maternally inherited deafness. Hearing loss in the latter is due to activation of tissue-specific, pro-apoptotic AMPK-E2F1 signaling by mitochondrial ROS, an unprecedented mitochondrial-to-nucleus signaling mechanism of disease pathogenesis. We also discovered that mtDNA stress is a trigger for the innate immune response and a cell-intrinsic antiviral signal that has implications for autoimmune diseases, cancer and age-related pathology. Our studies demonstrate that the role of mitochondria in disease and aging transcends simple energetic decline and ROS damage and involves complex interactions with cellular stress pathways, where ROS (and other mediators) serve as context-dependent signaling molecules. My plan going forward to bring this exciting new area to the forefront of biomedical research, where I am convinced novel treatments will emerge for common human diseases and age-related pathology that involve deregulation of mitochondrial and metabolic pathways.



Publications:

West AP, Tal MC, Staron M, Pineda CM, Lang SM, Bestwick M, Raimundo N, Khoury-Hanold W, MacDuff DA, Duguay BA, Smiley JR, Kaech SM, Means RE, Iwasaki A & Shadel GS. (2015)

Mitochondrial DNA Stress Primes the Antiviral Innate Immune Response. *Nature* 520:553-557.

Shadel GS & Horvath TL. (2015) Mitochondrial ROS signaling in organismal homeostasis. *Cell*, 163:560-569.

West AP & Shadel GS. (2017) Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nature Reviews Immunology*, 17:363-375