



COMBINED SEMINAR SERIES

Department of Biochemistry,
Microbiology & Immunology and
PRISM Research Centre

Thursday, October 21
11:30 am – 12:30 pm

(Zoom Meeting)



Dr. Timothy Wai

Head of Structure

Mitochondrial Biology Group

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“Mitochondrial dynamics in health and disease”

Mutations in OPA1 cause autosomal dominant optic atrophy (DOA) as well as DOA+, a phenotype characterized by more severe neurological deficits. OPA1 deficiency causes mitochondrial fragmentation and disrupts cristae, respiration, mitochondrial DNA (mtDNA) maintenance, and cell viability. It has not yet been established whether phenotypic severity can be modulated by genetic modifiers of OPA1. To better understand the genetic regulation of mitochondrial dynamics, we established a high-throughput imaging pipeline using supervised machine learning (ML) to perform unbiased, quantitative mitochondrial morphology analysis that was coupled with a bespoke siRNA library targeting the entire known mitochondrial proteome (1531 genes), providing a detailed phenotypic screening of human fibroblasts. In control fibroblasts, we identified known and novel genes whose depletion promoted elongation or fragmentation of the mitochondrial network. In DOA+ patient fibroblasts, we identified 91 candidate genes whose depletion prevents mitochondrial fragmentation, including the mitochondrial fission genes, but also genes not previously linked to mitochondrial dynamics such as Phosphatidyl Glycerophosphate Synthase (PGS1), which belongs to the cardiolipin (CL) synthesis pathway. PGS1 depletion reduces CL content in mitochondria and rebalances mitochondrial dynamics in OPA1-deficient fibroblasts by inhibiting mitochondrial fission, which improves defective respiration, but does not rescue mtDNA depletion, cristae dysmorphology or apoptotic sensitivity. Our data reveal that the multifaceted roles of OPA1 in mitochondria can be functionally uncoupled by modulating mitochondrial lipid metabolism, providing novel insights into the cellular relevance of mitochondrial fragmentation.

Zoom Meeting Details:

Meeting link: <https://usask-ca.zoom.us/j/91011870496?pwd=R284NEFk3bExpMnZ5dHRRWnlIOVZDUT09>

Meeting ID: 910 1187 0496

Passcode: 92137406

Join by phone

Find your local number here: <https://usask-ca.zoom.us/u/acaQnWkPtO>

Everyone Welcome