McGill UNIVERSITY

Department of Anatomy and Cell Biology

Hosted by Dr. Huy Bui

"Structural basis for the activation of PINK1 and Parkin, two proteins implicated in mitochondrial quality control and Parkinson's disease."

Jean-François Trempe, PhD

Assistant Professor, Department of Pharmacology & Therapeutics, McGill University

Mutations in Parkin and PINK1 cause an early-onset autosomal recessive form of Parkinson's disease (PD). PINK1 is a mitochondrial kinase that builds up on damaged mitochondria and initiates Parkin-mediated quality control. Parkin is basally auto-inhibited in the basal state through a series of interdomain interactions (Trempe et al. 2013). PINK1 recruits and activates Parkin by phosphorylating ubiquitin and the ubiquitin-like domain of Parkin (Sauvé et al. 2015 & 2018). We have shown how Parkin enables selective mitophagy via a distinct series of activation step that include release of the Repressor Element of Parkin (REP) and catalytic domain RING2 (Tang et al. 2017). However, what triggers PINK1's activity remain unclear. Using structural and proteomics tools, we discovered that PINK1 auto-phosphorylation at Ser228 occurs only *in trans*, and is a pre-requisite to ubiquitin and Parkin phosphorylation (Rasool et al. 2018). This property provides a sensitization mechanism to prevent premature initiation of mitophagy. Moreover, we show that the first target of PINK1 consists of ubiquitin chains located on Mfn2. Finally, we investigate how the substrate specificity of Parkin is dictated by the location of phospho-ubiquitin chains, which explains why Parkin ubiquitinates primarily Mfn2. These results have implications in our understanding of PD and how we could manipulate the Parkin-PINK1 pathway to treat this disease.

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11:30 am

Strathcona Anatomy Building
3640 University Street
Room 2/36

www.mcgill.ca/anatomy/seminars
anatomysec.med@mcgill.ca