ARMI EXTERNAL SEMINAR SERIES 2019

ARMI AUSTRALIAN REGENERATIVE MEDICINE INSTITUTE

10 YEARS 2009–19

Mitochondrial herniation triggered by Bak/Bax-mediated damage

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Abstract

mtDNA that has escaped the mitochondria is a potent pro-inflammatory stimulus. We recently demonstrated that activation of the intrinsic apoptosis pathway leads to mtDNA release into the cytoplasm of dying cells. During apoptosis, the pro-death proteins BAX and BAK permeabilize the outer mitochondria membrane and form macropores through which the inner mitochondrial membrane balloons out into the cytoplasm. We refer to this event as mitochondrial herniation. In the absence of caspases, released mtDNA triggers the cGAS/STING innate immune signalling cascade which drives type I interferon production and secretion by the dying cell. To understand the events that occur post-herniation, we have engineered mice and cell lines with fluorescently tagged mitochondria-associated proteins. These systems allow us to image mitochondrial behaviour in both primary and immortalised cells. Cryo-EM studies of apoptotic cells have revealed the presence of herniated mitochondria that are partially, and in some cases, fully encapsulated by double membraned vesicle structures. Points of contact between the mitochondrial inner membrane and the inner vesicle membrane are apparent. These observations suggest that a mitophagic response is triggered during intrinsic apoptosis, with the mitochondrial inner membrane being specifically recognised upon exposure to the cytoplasm. Whether this is mediated by the PINK1–Parkin or receptor-mediated mitophagy pathway, or an alternative mechanism, is the subject of ongoing investigation.

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Bio

Ben is Head of the Department of Anatomy and Developmental Biology, Monash University, in Melbourne, Australia. An NHMRC Principal Research Fellow, Ben trained at the Walter and Eliza Hall Institute (WEHI), where he obtained his PhD in 2001. After postdoctoral studies with Professor Monica Justice at Baylor College of Medicine in the USA, he returned to WEHI in 2004, establishing an independent research group in 2008. The Kile lab moved to Monash in 2017. The lab is focused on the molecular regulation of blood cell formation and function, with a particular interest in the role of cell death pathways in hematopoietic development and survival. Recent work has centred on the mitochondria as a source of innate immune signals during apoptosis.

EVENT DETAILS

DATE:

Tuesday, 16th July

TIME:

1:30pm

VENUE:

G19
Ground Floor
15 Innovation Walk
Monash University
Clayton Campus

HOST:

Professor Peter Currie

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The Australian Regenerative Medicine Institute (ARMI) acknowledges the generous support of Monash University and the Victorian State Government.