Subject: Dissertation Defense - Purva Gade, PhD Biosciences
Date: Thursday, July 10, 2025 at 9:47:09 AM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
To: SSB-FACULTY-LIST-L@LISTSERV.GMU.EDU

Dissertation Defense Announcement
To: the George Mason University Community

Candidate: Purva Vinayak Gade

Program: PhD in Biosciences

Date: Monday July 21, 2025

Time: 1:00 PM Eastern Time (US and Canada)

Location: In Person: IABR conference room 1004, Science & Tech campus

and via zoom
Join Zoom Meeting
https://gmu.zoom.us/j/97642695882?pwd=KVhSJPdeuGxRMrzLnv91Hn28jN4Vru.1
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Committee Chair: Dr. Lance Liotta

Committee Members: Dr. Fatah Kashanchi, Dr. Amanda Haymond, Dr. Remi Veneziano

Title : Secretory Mitophagy: A Novel Cancer Cell Survival Mechanism for Oxidative Stress Adaptation and Tumor Suppressor Clearance

Abstract:
Mitophagy is a critical survival mechanism that enables cells to remove toxic, aged, or

defective mitochondria via lysosomal degradation. Cancer cells, which experience high oxidative stress and energy demands, rely on mitophagy to maintain mitochondrial health. However, excessive oxidative stress can generate an overwhelming volume of damaged mitochondria, exceeding the capacity of lysosomal and proteasomal degradation pathways. To counter this, we propose a novel adaptive mechanism, secretory mitophagy, in which cancer cells export damaged mitochondrial segments via extracellular vesicles (EVs) rather than degrading them intracellularly. Using multiple cancer cell lines, we demonstrate that oxidative stress induced by carbonyl cyanide-3-chlorophenylhydrazone (CCCP) triggers secretory mitophagy. This process is further enhanced by Bafilomycin A1, which blocks mitophagosome-lysosome fusion, leading to increased secretion of PINK1-positive EVs. These exported mitochondria contribute to enhanced cell survival, improved mitochondrial ATP production, and reduced oxidative damage, highlighting secretory mitophagy as a new class of cancer pro-survival mechanism. Additionally, we show that PINK1-mediated secretory mitophagy exports key tumor suppressors including phosphorylated p53 and Merlin, within EVs. Merlin, a key regulator of cell shape, growth, and contact inhibition in nervous tissue, is mutated in neurofibromatosis type II (NF2), and its loss has been implicated in tumor progression. This suggests that secretory mitophagy not only facilitates mitochondrial quality control but also actively contributes to cancer progression by removing tumor-suppressive signals. We hypothesize that PINK1-regulated secretory mitophagy serves as an "overload release valve", allowing cancer cells to manage oxidative stress when mitophagy demand exceeds lysosomal capacity. Furthermore, EVs may act as mediators of cell-cell communication, transferring mitochondrial components and oncogenic signals between tumor cells, thereby supporting metabolic plasticity and survival in the tumor microenvironment. By identifying secretory mitophagy as a novel tumor survival mechanism, our study provides crucial insights into how cancer cells evade oxidative stress-induced damage while simultaneously eliminating the tumor suppressors. Targeting EV-mediated export of damaged mitochondria and activated tumor suppressor proteins represents a new therapeutic strategy to sensitize tumor cells to chemotherapy radiotherapy and molecular therapy.

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