BIOMEDICAL & VETERINARY SCIENCES

GRADUATE PROGRAM

ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Swagatika Paul

"The Non-canonical Function and Regulation of TBK1 in the Cell Cycle"

Thursday, August 31st, 2023
10:00AM
Life Science 1
Room Number 101

Bio

Swagatika Paul is originally from the state of Odisha in India. She graduated with a Bachelor of Science in Physics, Chemistry and Mathematics from the RTM Nagpur University, Maharashtra. Next, she obtained her Master of Science in Bioinformatics and Applied Biotechnology from the University of Mysore, Karnataka. She joined the graduate program in Biomedical and Veterinary Sciences at Virginia Tech in August 2018. Under the guidance of Dr. Alicia Pickrell, her Ph.D. research has focused on understanding the less explored role of a multifunctional serine/threonine kinase TBK1 during cell division. Following the completion of her Ph.D., Swagatika will join the University of Washington, Seattle as a postdoc to continue her passion in the field of proteomics.

Funded by

National Institutes of Health Grants GM142368 (AMP)
Departmental startup funds (AMP)
VMCVM Office of Research and Graduate Studies

Lay Language Abstract

Defective cell division is the underlying cause for many human health maladies such as birth defects and cancer. Investigation into the proteins that are abnormally expressed in cancer can help us identify their physiological roles in regulating the cell cycle. Tank Binding Kinase 1 (TBK1) is often overexpressed in several types of cancer such as glioblastomas, breast, and lung cancers. It has also been extensively studied in the process of removing damaged cytosolic components from cells called autophagy. During cancer progression, cells often hijack the autophagy machinery to their advantage for abnormal cell proliferation. However, we do not completely understand the role of TBK1 in cancer pathogenesis or during normal cell division. Each cell duplicates its genomic contents and divides its organelles and cytosolic components during cell division. Centrosomes organize microtubules to attach to the duplicated genomic material to equally segregate the DNA between two daughter cells. Previous studies have shown that TBK1 is active on the centrosomes during mitosis, and the loss of TBK1 leads to reduced cell proliferation. However, the function of TBK1 and what regulates its activation on the centrosomes are unknown. Using a combination of genetic, biochemical, and molecular biology techniques, we found that an immune response protein Nak Associated Protein 1 (NAP1/AZI2) binds to TBK1 and activates it on the centrosomes during cell division. Furthermore, our study demonstrates that the loss of either NAP1 or TBK1 exhibits a multitude of different types of defects in the process of cell division. We further identified TBK1 substrates in a phosphoproteomic screen indicating that TBK1 regulates the activity of other major cell division kinases. We show that defects in autophagy machinery result in the mislocalization and overactivation of TBK1 resulting in defects during chromosome segregation, and in the formation of micronuclei. Together our study shows that an established immune response protein NAP1 regulates the function of TBK1 during cell division and there exists a connection between TBK1 activity and disrupted autophagy.

Publications

Paul S, DeFoor N, Zavar L, Biswas S, Soto Y, Pickrell AM. Impaired autophagy results in the formation of micronuclei driven by mitotic errors due to the abnormal activation of TBK1. (*In preparation*)

Paul S, Sarraf SA, Nam K, Zavar L, Biswas S, Fritsch LE, DeFoor N, Yaron TM, Johnson JL, Huntsman EM, Cantley LC, Ordureau A, Pickrell AM. NAK associated protein 1/NAP1 is required for mitosis and cytokinesis by activating TBK1. *bioRxiv 2022.03.09.483647 doi: https://doi.org/10.1101/2022.03.09.483647 (Under revision at JCB)*

Fritsch LE, Kelly C, de Jager C, Wei X, Brindley S, Kaloss AM, DeFoor N, Paul S, O'Malley H, Ju J, Olsen ML, Theus MH, Pickrell AM. Acute STING signaling from microglia and peripheral white blood cells drive neutrophil infiltration influencing brain injury. *(Under revision at J Neuroscience)*

DeFoor N, Paul S, Li S, Basso EKG, Stevenson V, Browning JL, Prater AK, Tao G, Pickrell AM. Remdesivir increases mtDNA copy number causing mild alterations to oxidative phosphorylation. *(Under revision at Scientific Reports)*

Fritsch LE, Ju J, Basso EKG, Soliman E, Paul S, Chen J, Kaloss AM, Kowalski EA, Tuhy TC, Somaiya RD, Wang X, Allen IC, Theus MH, and Pickrell AM. Type I Interferon Response is Mediated by NLRX1-cGAS-STING Signaling in Brain Injury. *Frontiers in Molecular Neuroscience. 2022 (PMID: 35283725)*

Paul S, and Pickrell AM. Hidden phenotypes of PINK1/Parkin knockout mice. *Biochim Biophys Acta Gen Subj. 2021 (PMID: 33571581)*

Paul S, Zhang X, He JQ, "Homeobox gene Meis1 modulates cardiovascular regeneration. *Semin Cell Dev Biol. 2020 (PMID: 31623926)*

Bawa PS, Ravi S, Paul S, Chaudhary B, Srinivasan S. A novel molecular mechanism for long non-coding RNA PCAT92 implicated in prostate cancer. *Oncotarget. 2018 (PMID: 30197753)*

Presentations

Oral Presentations

Paul S, Sarraf SA, Nam K, Zavar L, Biswas S, Fritsch LE, DeFoor N, Yaron TM, Johnson JL, Huntsman EM, Cantley LC, Ordureau A, Pickrell AM. NAK associated protein 1 (NAP1) is required for mitosis and cytokinesis through TBK1 activation.
Spotlight session speaker at the American Society for Biochemistry and Molecular Biology Annual Meeting, ASBMB 2023, Seattle.

Paul S, Sarraf SA, Nam K, Zavar L, Fritsch LE, DeFoor N, Ordureau A, Pickrell AM. Nak Associated protein 1 (NAP1) activates Tank Binding Kinase 1 (TBK1) to regulate mitosis.
Mini symposium speaker at American Society for Cell Biology, ASCB Cell Bio Dec 2021.

Paul S, Sarraf SA, Nam K, Zavar L, Fritsch LE, DeFoor N, and Pickrell AM, A proteomic approach to unravel TBK1 signaling during mitosis.
Fall 2021 BMVS RIP Seminar series, Virginia Tech.

Paul S, and Pickrell AM, NAP1 Mediated Activation of TBK1 at the Centrosomes is necessary for Cell Division.
37th GSA Annual Research Symposium & Exposition March 2021, Virginia Tech (Virtual).

Paul S, and Pickrell, AM. In the Quest for Discovering the Tank Binding Kinase 1 (TBK1) Adaptor Protein during Mitosis.
Annual Research Retreat Aug 2020, School of Neuroscience, Virginia Tech (Virtual).

Paul S, and He JQ. Endothelial Cell Specific Knockout of Meis1 Improves the Cardiac Function of Infarcted Heart in the Mouse Model.
6th Annual Meeting DC, MD & VA Chapter of the American Physiological Society Oct 2019, Washington DC.

Presentations continued

Paul S, and He JQ. Understanding the Molecular Role of Meis1 in the Mammalian Vascular Network.
Spring 2019 BMVS RIP Seminar series, Virginia Tech.

Poster Presentations

Paul S, DeFoor N, Zavar L, Pickrell AM. Impaired autophagy results in the formation of micronuclei driven by mitotic errors due to the abnormal activation of TBK1.
12th Salk Cell Cycle Meeting 2023, San Diego.

Paul S, Sarraf SA, Nam K, Zavar L, Biswas S, Fritsch LE, DeFoor N, Yaron TM, Johnson JL, Huntsman EM, Cantley LC, Ordureau A, Pickrell AM. NAK associated protein 1 (NAP1) is required for mitosis and cytokinesis through TBK1 activation.
32nd Annual BMVS Research Symposium 2023, Virginia Maryland College of Veterinary Medicine, Virginia Tech.

Paul S, Sarraf SA, Nam K, Zavar L, Fritsch LE, DeFoor N, Ordureau A, Pickrell AM. NAP1/AZI2 activates TBK1 to regulate mitosis and cytokinesis.
EMBO Workshop – Chromosome Segregation and Aneuploidy, May 2022 Vienna, Austria.

Paul S, Sarraf SA, Pickrell, AM. NAP1/AZI2 Regulates Cell Cycle via TBK1 Activation at the Centrosomes.
Salk Institute 11th Cell Cycle Meeting June 2021 (Virtual).

Paul S, Pickrell, AM. Deciphering the Mechanism of Tank Binding Kinase 1 (TBK1) Activation During Mitosis.
31st Annual BMVS Research Symposium 2021, Virginia Maryland College of Veterinary Medicine, Virginia Tech.

Presentations continued

Paul S, He JQ. Endothelial Cell Specific Knockout of Meis1 Seems to Improve the Cardiac Function of Infarcted Heart in the Mouse Model.
8th Annual International Symposium on Regenerative Rehabilitation Oct 2019, Charlottesville.

Paul S, He JQ. Endothelial Cell Specific Knockout of Meis1 Seems to Improve the Cardiac Function of Infarcted Heart in the Mouse Model.
30th BMVS Annual Research Symposium Nov 2019, Virginia Maryland College of Veterinary Medicine, Virginia Tech.

Awards and Adademic Achievements

- Graduate student researcher travel award - *American Society for Biochemistry and Molecular Biology Annual Meeting, ASBMB 2023, Seattle.*

- Virginia Tech GPSS Travel Fund Award, Spring 2022 for travel to *Vienna, Austria in May 2022 to attend EMBO workshop on Chromosome Segregation and Aneuploidy.*

- Best abstract award at the *6th Annual Meeting DC, MD & VA Chapter of the American Physiological Society 2019, Washington DC.*

Examination Graduate Committee

Major Advisor/Chair:

Alicia Pickrell, PhD
Associate Professor, School of Neuroscience
Virginia Tech

Graduate Advising Committee Members:

Michelle Theus, PhD
Professor; Director of Neurotrauma Research Program
Department of Biomedical Sciences and Pathobiology
Virginia Tech

Daniela Cimini, PhD
Professor, Department of Biological Sciences
Virginia Tech

Paul Morton, PhD
Assistant Professor, Department of Biomedical Sciences and Pathobiology
Virginia Tech

VIRGINIA TECH™