Department of Biological Sciences

JOB TALK

Speaker: Dr. Atul K Singh, PhD

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Date/Time: Tuesday, 1st May, 2018 at 04:00 pm
Venue: L-8, LHC

title "Molecular insights into Parkinson's disease: deciphering the mechanism of Parkin E3 ligase and PINK1 kinase"

Abstract:

Parkinson's disease (PD) is a neurodegenerative disorder with severe motor and non-motor symptoms. Mutations on several genes associated with various structural and functional components of neurons cause loss of neurons which results in PD. However, two genes PARK2 and PARK6 are found most frequently mutated causing more than 50% of the familial form of the disease. PARK2 gene encodes an E3 ubiquitin ligase Parkin, and PARK6 encodes PTEN-induced Kinase 1 (PINK1). Parkin is an auto-inhibited enzyme mediated by its ubiquitin like (Ubl) domain. During stress condition, PINK1 is stabilised on mitochondria and phosphorylates Ser65 on UBL domain of Parkin and ubiquitin. Phosphorylation of Parkin and ubiquitin results in fully active Parkin which clears the damaged mitochondria however, underlying molecular mechanism of PINK1 and Parkin signalling is poorly understood. I have determined human Parkin structures in both in-active state (apo-Parkin) & active state (phospho-mimic Parkin & in complex with phospho-ubiquitin (pUb)). My research on Parkin reveals how Ubl domain cause inhibition, and how Parkin is allosterically activated by pUb binding. My research reveals an intriguing mechanism of catalysis of Parkin and propose a similar mechanism for other members of RBR family E3 ligase which are activated by different activators. I have also solved the first crystal structure of PINK1 and identified a unique insertion in the kinase domain responsible for ubiquitin/UBL recognition, specifically. Mapping of mutations on PINK1 and Parkin structures suggest that mutations are present in important functional regions perturbing their function and causing Parkinson's. The study provides molecular rationale for therapeutics purpose, and presents scope for future research towards identifying key enzymes involved in phospho-ubiquitin signalling along with establishing the role of other genes associated with the disease.