National Institute of Animal Biotechnology

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NIAB Seminar

11th August 2014

"cAMP-induced phosphorylation of the 26S proteasome enhances degradation of misfolded proteins"

Speaker

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Education and Training :

INSTITUTION AND LOCATION	DEGREE	MM/YYYY	FIELD OF STUDY
Harvard Medical School, Boston, MA, USA	Postdoc	11/2012-Present	Medicine
Nanyang Technological University, Singapore	PhD	01/2008-10/2012	Molecular Biology
Sri Krishnadevaraya University, AP, India	MSc	08/2005-05/2007	Biotechnology

Abstract:

Rates of proteins degradation by the ubiquitin-proteasome pathway (UPS) are determined by rates of ubiquitination. To learn if proteasomal degradation of ubiquitin conjugates is also regulated, we studied the effects of cAMP-dependent protein kinase (PKA) on proteolysis by the UPS. In cells, agents that raise cAMP and activate PKA promoted degradation of shortlived cell proteins generally, several model UPS substrates, and aggregation-prone proteins associated with neurodegenerative diseases including FUS, SOD1 and TDP43. However, PKA activation didn't enhance degradation of long-lived proteins. 26S proteasomes purified from treated cells degraded ubiquitinated proteins, small peptides, and ATP more rapidly than control, and multiple 19S subunits were phosphorylated. Treating proteasomes with PKA caused a similar activation, which was reversed by protein phosphatase treatment. We also investigated the effects of abnormal tau accumulation on proteasome function in the brains of a mouse model of tauopathy (rTg4510) and in a cross to a UPS reporter mouse (rTg4510/UbG76V-GFP). Accumulation of insoluble tau correlated with a progressive decrease in the activities of brain 26S proteasomes, while levels of ubiquitinated proteins and undegraded UbG76V-GFP increased. After affinity purification, the soluble 26S proteasomes were less active. This loss of proteasome activity was prevented by administering an activator of cAMP/PKA signaling and thus phosphorylates the several proteasome subunits. Enhancing proteasome function led to reduce levels of aggregated tau and improved cognitive performance in early stage tauopathy. Thus, proteasome function and degradation of proteins are regulated by cAMP through PKA, and activation of proteasomes by this mechanism may be useful in treating neurodegenerative diseases.

Venue: Auditorium, NIAB, D. No. 1-121/1, 4th & 5th Floors, Axis Clinicals Building, Opp. Talkie Town, Miyapur, Hyderabad

Time: 4 PM to 5 PM

All are cordially invited. **Director, NIAB**