TIFR Centre for Interdisciplinary Sciences
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Seminar

New Paradigms in protein Post Translational Modifications in yeast

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Yeast, a versatile organism, serves as a workhorse for unraveling nature's secrets. Right from germ cell development and understanding the mechanism of protein synthesis to oxidative stress response, yeast can be used as a choice organism. In corollary, protein Post Translational Modifications (PTMs), known to regulate biological processes can be studied in the yeast *Saccharomyces cerevisiae*.

Germ cell development is a transformative process yet a process wherein the onus of hereditary lineage is enshrined in it. Yeast sporulation is conceptually similar to spermatogenesis in higher eukaryotes as it is also a highly regulated process wherein a diploid cell gives rise to four haploid gametes. We have identified histone H4 Ser1 phosphorylation, a highly stable and ubiquitously present mark during sporulation. A histone H4 S1A substitution mutant forms aberrant spores and has reduced sporulation efficiency. Deletion of sporulation-specific yeast Sps1, a member of the Ste20 family of kinases, nearly abolishes the sporulation-associated H4 S1ph modification. We believe that H4 S1ph may promote chromatin compaction while absence of it results in increased DNA volume in spore nuclei. Most importantly, H4 S1ph is present during *Drosophila melanogaster* and mouse spermatogenesis. Thus, H4 S1ph may be an evolutionarily ancient histone modification to mark the genome for gamete-associated packaging.

Peptide methionine sulfoxide reductases are conserved enzymes that reduce oxidized methionines in protein(s). Although these reductases have been implicated in several human diseases, there is a dearth of information on the identity of their physiological substrates. By using *Saccharomyces cerevisiae* as a model, we show that of the two methionine sulfoxide reductases (MXR1, MXR2), deletion of mitochondrial MXR2 renders yeast cells more sensitive to oxidative stress than the cytosolic MXR1. Our earlier studies showed that Mge1, an evolutionarily conserved nucleotide exchange factor of Hsp70, acts as an oxidative sensor to regulate mitochondrial Hsp70. We show that MXR2 regulates Mge1 by selectively reducing MetO at position 155 and restores the activity of Mge1 both in vitro and in vivo. Mge1 M155L mutant rescues the slow-growth phenotype and aggregation of proteins of MXR2Δ strain during oxidative stress. By identifying the first mitochondrial substrate for MXRs, we add a new paradigm to the regulation of the oxidative stress response pathway.

Thus the yeast *Saccharomyces cerevisiae* provides a valuable system to gain insights into the regulatory aspects of the highly conserved biological pathways.

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4:00 PM (Tea/Coffee at 3:45 PM)

Seminar Hall, TCIS