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### The ins and outs of nitrogen-responsive gene regulation in *Saccharomyces cerevisiae*

Yeast cells have evolved to maintain steady internal nitrogen homeostasis in the face of continuous and drastic transitions in its environmental nitrogen supply. Cells are able to take full advantage of luxurious nitrogenous environments, while retaining the ability to successfully cope with those that are more austere. This Nitrogen Catabolite Repression (NCR) sensitive control is achieved through the regulation of the GATA-binding transcription activators, Gln3 and Gat1. In nitrogen replete conditions Gln3 and Gat1 are efficiently sequestered in the cytoplasm and as a result, NCR-sensitive transcription is minimal. As nutritional conditions deteriorate, Gln3 and Gat1 relocate to the nucleus and dramatically increase GATA factor-mediated transcription of the genes required to import and catabolize poor nitrogen sources scavenged from the environment. TorC1 kinase complex was originally thought to be the principle contributor to NCR-sensitive Gln3 regulation. However, Gln3 responds to 5 distinct physiological conditions each exhibiting a unique set of regulatory requirements. This argued that NCR-sensitive control was more complex than appreciated. Using amino acid substitutions throughout the disordered Gln3 protein, we show that nitrogen-responsive TorC1 control only partially accounts for NCR-sensitive regulation. Uncharged tRNA-activated, Gcn2 kinase-mediated General Amino Acid Control (GAAC) is equally critical with the Gcn2 and TorC1 kinases functioning independently and in opposition to one another. Epistasis experiments indicate Gcn2 likely functions upstream of Ure2, whereas the 14-3-3 proteins Bmh1/2, also required for nuclear Gln3 localization, likely function downstream. Nuclear Gln3 import is also more complex than previously appreciated requiring two additional Nuclear Localization Sequences (NLS) in addition to the previously reported NLS1 as well as a newly identified Ure2 Relief Sequence. A third level of Gln3 regulation is imposed within the nucleus. In high glutamine, Gln3 exits from the nucleus in the absence of binding to its GATA targets within NCR-sensitive promoters. In contrast, as glutamine levels decrease, GATA binding becomes requisite for Gln3 to exit from the nucleus. It is only through the concerted actions of this full array of regulatory components that NCR can effectively manage intra-cellular homeostasis in the face of unreliable environments.

#### Speaker Biography

Terrance G Cooper investigated Avian Oil Droplets as an undergraduate and obtained his MS in Chemistry studying carboxylase enzyme mechanisms at Wayne State and his PhD at Purdue University. He first discovered that Π-oxidation occurs in peroxisomes rather than mitochondria with Magasanik at MIT. He investigated the mechanism of carbon catabolite repression in E. coli. While there he and Patricia Whitney discovered yeast urea amidolyase to be a multifunctional protein consisting of urea carboxylase and allophanate hydrolase. Moving to the University of Pittsburgh, he and his students elucidated the reactions of the allantoin degradative pathway, proposed nitrogen catabolite repression (NCR) as controlling nitrogen-responsive gene expression and he authored "*The Tools of Biochemistry*". He learned the intricacies of yeast genetics from Sye Fogel and cloning from John Carbon. His group identified, mapped and cloned and sequenced the allantoin pathway structural and four GATA-transcriptional regulatory genes. As Harriet S Van Vleet Professor at the University of Tennessee, he founded and directed the Molecular Resource Center and was Chair of Microbiology and Immunology for 15 years. His students identified the promoter structures of the NCR-sensitive genes, binding sites for their four regulatory transcription factors and now the regulatory pathways controlling Gln3 localization and intra-nuclear regulation. He served 17 years on and chaired NIH and ACS study sections, chaired the AAMC Council of Academic Societies, served on the AAMC Executive Committee, Multiple Editorial Boards and as Treasure and American Representative to the International Conference of Yeast Genetics and Molecular Biology. He is currently a member of the UT Board of Trustees.

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