UC RIVERSIDE

Institute for Integrative Genome Biology Seminar Series

You are cordially invited to attend:

Dr. Matthew Sachs

Professor of Biology
Texas A&M University

Genetic control of ribosome movement in fungi

Date: Friday, April 7th
Time: 12:00 pm - 1:00 pm
Location: Genomics Auditorium 1102A

Host: Dr. Kathy Borkovich

Abstract:

Chemical compounds can target ribosome activity. We have analyzed high-resolution structures of ribosomes from *Neurospora crassa* and *Candida albicans* containing cycloheximide. *Neurospora* ribosomes, like most eukaryotic ribosomes, are naturally sensitive to the translation inhibitor cycloheximide, which blocks the elongation step of protein synthesis. Mutations confer cycloheximide resistance. In contrast, wild-type *C. albicans* ribosomes are naturally resistant to the drug. Analyses of the structures of these ribosomes, and analyses of the sequences and structures of ribosomal proteins near the nascent peptide exit tunnel from sensitive and resistant ribosomes, revealed both the elongation step at which translation is inhibited and the basis for cycloheximide resistance.

Ribosome activity can also be controlled by genetic elements that regulate translation. The coding capacities of eukaryotic mRNAs go well beyond the main open reading frame that specifies the gene product. Up to 50% of eukaryotic mRNAs contain upstream open reading frames (uORFs), but the roles of the vast majority of these uORFs remain undetermined. In some cases, this additional translational capacity is evolutionarily conserved and serves critical roles in controlling gene expression. An important emerging class of regulatory uORF-encoded peptides causes ribosomes to stall in response to metabolites. We discovered a uORF in the 5'-leaders of fungal mRNAs specifying the first enzyme necessary to synthesize the central metabolic molecule inositol, inositol-3-phosphate synthase. This uORF is conserved across fungal phyla and thus has been retained for the billion years since their divergence. While missing in some Saccharomycotina, this uORF is present in important fungal pathogens, including *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Coccidioides posadasii*. We have named the conserved uORF-encoded peptide the inositol regulatory peptide (IRP) based on experimental data. Analyses of IRP function are consistent with models for IRP regulation in which inositol or a closely related molecule interacts directly with ribosomes, the nascent IRP, or both to interfere with peptidyltransferase center activity. Stalling would act directly to reduce leaky scanning. Inositol-regulated ribosome stalling would thus regulate inositol-3-phosphate synthase biosynthesis and inositol metabolism.