Frontiers in Biological Chemistry

BK-BRL International Symposium

February 16, 2022

Department of Chemistry, Pusan National University,

Busan, Republic of Korea

Organized by
> Department of Chemistry, PNU
> Education and Research Center for Molecular Materials, PNU
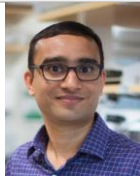> Chemistry Institute for Functional Materials, PNU
> Basic Research Lab (Biophysical chemistry lab for overcoming neurodegenerative diseases), PNU

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Time	Topic	Speaker	
9:20-9:30	Welcoming Remark		
9:30-10:10	RNA aggregation in neurodegenerative disease	Ankur Jain Massachusetts Institute of Technology	
10:10-10:50	Coupling between intra-species and community-level population dynamics in a mammalian gut microbiome	Adrian Serohijos University of Montreal	
10:50-11:30	How do cells maintain ribosome concentration during starvation?	Heeseon An Memorial Sloan Kettering Cancer Center	
11:30-12:10	Regulate gene expression by RNA splicing modulators	Jingxin Wang University of Kansas	
12:10-12:50	Imaging molecular force with DNA sensors	Isaac Li University of British Columbia	
12:50-13:00	Closing Remark		

Zoom Link: https://pusan.zoom.us/j/89486697402?pwd=bDVvL2tyakUwT0xqbHUyd09aeitEZz09

Abstracts

RNA aggregation in neurodegenerative disease

Ankur Jain

Department of Biology, Massachusetts Institute of Technology, USA

Expansions of short nucleotide repeats are associated with at least 30 degenerative diseases such as Huntington disease, myotonic dystrophy, and amyotrophic lateral sclerosis. The RNA transcribed from the repeats can contribute to the pathology via at least two routes: i) the RNA can accumulate in the nuclei as foci and sequester various RNA binding proteins, and ii) the RNA can undergo repeat-associated non-ATG translation often in all three reading frames. In a previous study, we reported that RNA foci result from sol-gel phase transitions of the repeat-containing RNA. Here, I will present new findings on how the genomic context of the repeats affects RNA localization and its propensity to undergo RAN translation. Interestingly, the repeat-containing RNA co-aggregate with RAN translation products. Inhibition of RAN translation prevents cytoplasmic RNA aggregation and also alleviates cell toxicity. Our findings provide a cogent explanation for aberrant cytoplasmic localization of RNA binding proteins and implicate cis-acting flanking sequences in mediating RAN translation and disease.

Coupling between intra-species and community-level population dynamics in a mammalian gut microbiome

Adrian Serohijos

Canada Research Chair in Evolutionary Biophysics and Population Dynamics

Department of Biochemistry, Université de Montréal, Canada

Evolution is a unifying theme in the urgent medical and public health problems we face today including cancer, the rise of antibiotic resistance, and the spread of viral pathogens. But the ability to predict evolution remains a major challenge because it requires bridging several scales of biological organization. Potential evolutionary pathways are determined by the cellular "fitness landscape" (the genotype-phenotype relationship), but how this landscape is explored depends on the principles of population genetics and ecology. In this seminar, I will describe a chromosomal barcoding technique that allows simultaneous tracking of $\sim 10^6$ distinct bacterial cell lineages in an evolving bacterial population. We used this approach to study microbial populations evolving under sub-inhibitory antibiotic concentrations and consequently to quantify the balance between drift, mutation, and selection. Additionally, I will show how the barcoding technology reveals the coupling between intra-species and community-level dynamics during bacterial colonization and antibiotic treatment in mammalian gut.

How do cells maintain ribosome concentration during starvation?

Heeseon An

Chemical Biology Program, Memorial Sloan Kettering Cancer Center

Ribosomes are targets of translational control during nutrient stress and have also been suggested to be a source of amino acids and nucleotide precursors via autophagy. However, the precise contributions of biosynthetic and degradative mechanisms to ribosomal protein (r-protein) abundance is poorly understood. In this study, we investigated how the ribosome concentration in mammalian cells is maintained or altered after nutrient stress by employing systematic quantitative proteomics methods. From the unbiased data analysis, we found that r-protein abundance during nutrient stress is primarily shaped by translational suppression, with dilution and non-autophagosomal turnover playing contributing roles. Ribophagic flux, however, accounts for a very small fraction of r-protein turnover. Our data is inconsistent with a role for NUFIP1, a previously reported ribophagy receptor, in mediating autophagic turnover of a large fraction of ribosomes. The quantitative inventory of r-proteins in this study provides a framework for examining the interplay between nutrient availability and cellular biosynthetic and degradative systems. There is significant interest in selective turnover of proteins and organelles via autophagy. This work is central to understanding how various organelles are remodeled due to the depth of proteome analysis which encompasses the contributions from global protein translation, the UPS- and autophagy-mediated degradations, and cell division rate control. The usefulness of our integrated dataset extends far beyond our focus on ribosomes.

Regulate gene expression by RNA splicing modulators

Jingxin Wang

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas USA.

Precursor messenger RNA (pre-mRNA) splicing is essential for almost all eukaryotic genes to generate mature mRNA for RNA translation. Modulating RNA splicing by small molecules is an emerging pharmacological modality to control gene expression. This approach is well exemplified by two recent blockbuster drugs that act through direct binding to the target pre-mRNAs: risdiplam for the treatment of spinal muscular atrophy (SMA) (approved in 2020) and branaplam for Huntington's disease (Phase 2 clinical trial). Risdiplam upregulates a gene named survival of motor neuron 2 (SMN2) by including an exon that stabilizes the SMN protein. On the other hand, branaplam induces a disruptive pseudo-exon in the mutated huntingtin (HTT) gene. The inclusion of this pseudo-exon caused a reading frameshift and early termination of HTT. These two drugs showcase the broad utility of splicing modulators in controlling gene expression. We previously investigated the mechanism of risdiplam and elucidated that a G/A-rich sequence in the SMN2 exon is induced into a double-loop structure for the compound binding, which is required for the RNA-binding selectivity of risdiplam analogs. The Wang group is now further improving risdiplam's selectivity and expanding the drug modality to other genes.

Imaging molecular force with DNA sensors

Isaac Li

Department of Chemistry, University of British Columbia Okanagan, Canada

Adhesion molecules on cell surfaces help cells attach to their environment and transduce mechanically-coupled biochemical signal. To understand the mechanical forces involved at the molecular scale, molecular force sensors have been used to probe forces at cell-substrate interfaces. Several classes of force sensors have been developed in the past few years including the DNA-based Tension Gauge Tether (TGT). TGTs rely on the force-dependent dissociation of complementary dsDNA strands to probe forces where the mechanical stability can be semi-quantitatively tuned by DNA sequence and pulling geometry. We will provide an overview of the field to show the advantages and disadvantages of different classes of current force sensors. We will then show applications of TGT in studying fast dynamic molecular adhesion processes involved in cell rolling adhesion. Lastly, we will introduce a framework to quantify molecular forces using the TGTs.