SINGAPORE RNA SEMINAR SERIES

RNA STABILITY AS A KEY LINK BETWEEN GENETIC VARIANTS AND HUMAN DISEASE

Tuesday 19 March 2024
10am (SGT , GMT+8)

Via Zoom

About the speaker

Xinshu (Grace) Xiao, Ph.D., is the Maria R. Ross Professor in the Department of Integrative Biology and Physiology at UCLA, and Chair of UCLA's Bioinformatics Interdepartmental Program. Dr. Xiao completed her PhD degree at MIT where she worked in the research group of Dr. Richard Cohen focusing on computational and mathematical models of physiological systems. She did postdoctoral work in the lab of Dr. Chris Burge at MIT from 2005-2008 where she studied RNA splicing. Her laboratory has developed a number of computational methods for understanding gene regulation, such as GIREMI for identification of RNA editing sites, scAllele for single-cell allele-specific splicing, and BEAPR for allele-specific binding of RNA-binding proteins. They have also developed experimental assays to study the global RNA binding profile of the dsRNA-binding protein ADAR and massively parallel reporter assays for post-transcriptional RNA regulation. The lab has contributed to the understanding of RNA editing, splicing regulatory elements, protein-RNA interaction, and alternative RNA processing in health and disease. Her lab's current research focuses on the effects of RNA editing on innate immunity, large-scale analysis of functional genetic variants in disease, and computational and experimental methodology development for post-transcriptional gene regulation.

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About the seminar

Identifying genetic variants that regulate gene expression is a crucial approach to understanding the biological mechanisms driving traits and diseases. While it is acknowledged that both transcriptional regulation and the variable stability of transcripts play vital roles in determining mRNA abundance at steady state, the focus has predominantly been on the former. By employing metabolic labeling data (Bru/BruChase-seq) alongside a novel computational pipeline, RNAtracker, we have successfully distinguished between allele-specific RNA stability (asRS) and allele-specific RNA transcription (asRT) events. Our analysis has demonstrated that RNA stability influences allelic imbalance to a degree comparable to transcriptional regulation. Notably, asRS variants were found to be enriched in events involving allele-specific protein-RNA binding and miRNA target sites, with asRS genes predominantly associated with immune-related pathways. Through integration with GWAS and TWAS, our research highlights RNA stability as a key factor in the link between genotype and disease. Furthermore, we introduced a high-throughput reporter assay, MapUTR, designed to identify functional genetic variants within 3′ UTRs that affect post-transcriptional regulation of gene expression. MapUTR not only confirmed the functionality of asRS variants but also unveiled thousands of rare non-coding variants impacting mRNA abundance, presumably through mechanisms of RNA stability regulation. Notably, many of these functional variants are present in cancer driver genes, establishing a crucial connection between mutations in 3′ UTRs and cancer progression.

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