NANYANG TECHNOLOGICAL UNIVERSITY SINGAPORE

School of Biological Sciences
College of Science

Seminar Announcement

Speaker:

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Roles of phase separation in biology and disease

Date : 29 October 2019

Time : 11 a.m.

Venue : Classroom 4, SBS

Hosted By : Assoc Prof. Oliver Mueller-Cajar

Abstract

Phase separation is now understood to mediate the compartmentalization of biological macromolecules throughout the cell. One example is the nucleolus, the largest membraneless organelle, which forms in the nucleus through interactions between the genes that encode ribosomal RNAs (rRNAs), the rRNAs themselves, and ribosomal and non-ribosomal proteins that together drive the process of liquid-liquid phase separation (LLPS). A major constituent of the nucleolus is the protein nucleophosmin (NPM1). NPM1 undergoes LLPS via three distinct mechanisms; homotypically with other NPM1 molecules, heterotypically with arginine-rich (R-rich) proteins, and/or nucleic acids, particularly rRNA. In a series of studies, we have elucidated the molecular features underlying the role of NPM1-mediated nucleolar LLPS in ribosome biogenesis, and how this is altered in neurodegeneration. We show that NPM1 undergoes complex coacervation with rRNA and R-rich nucleolar proteins such as SURF6. We propose transient molecular hand-offs combined with countercurrent RNA and protein fluxes within the nucleolus drive the assembly and efflux of ribosomal subunits. NPM1 interactions with R-rich proteins are driven by tracts of acidic residues in the NPM1 central intrinsically disordered region (IDR). In Amyotrophic Lateral Sclerosis (ALS), these acidic tracts interact with toxic R-rich dipeptide repeat (DPR) polypeptides that are aberrantly expressed. R-rich DPRs are highly localized to nucleoli, where they bind rRNA and sequester NPM1 within soluble complexes leading to nucleolar disruption and stalled ribosome biogenesis. The ability of NPM1 to interact and phase separate with R-rich proteins and rRNA is critical for its roles in ribosome biogenesis, while enabling hijacking by toxic DPRs in common forms of ALS. We will present our latest findings on the diverse roles of NPM1 in nucleolar biology and disease, and will highlight the use of a wide array of methods, from structural and biophysical methods to quantitative *in vitro* and live cell microscopy, in our studies.

Biography

Dr. Kriwacki received his PhD at Yale University in Chemistry/Biophysics and performed postdoctoral studies in Molecular Biology at the Scripps Research Institute. He has longstanding interest intrinsically disordered proteins and how disorder mediates diverse biological functions, including cell cycle regulation, apoptosis and ribosome biogenesis. Recently, he and others discovered that the process of liquid-liquid phase separation by proteins and nucleic acids mediates the formation of membrane-less organelles and other liquid-like cellular bodies. Current studies seek to understand how proteins undergo phase separation, how phase separation mediates biological functions, and how this process goes wrong in human disease.