BDR SEMINAR (Kobe & online hybrid)

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Thursday, May 15, 2025

11:00-12:00

1F Auditorium, DB Building C, Kobe / Broadcast online via Zoom

Zoom meeting URL will be announced on the event day by e-mail.

※This seminar is open only to BDR members.

Imaging, Quantifying and Mapping Human Chromatin Remodeler Dynamics: From Phase-separation-mediated Intranuclear Organization to Cancer-mutant-specific Regulatory Landscape

Summary

SWI/SNF chromatin remodelers are a key family of multi-subunit complexes that regulate genome access via nucleosome translocation/ejection. Despite their prevalent implications in human cancers, their intranuclear dynamics *in vivo* and how misregulation of such dynamics could underpin cancers remain poorly understood. Herein, using single-molecule tracking (SMT), we systematically quantified the live-cell diffusion and chromatin-binding dynamics of the fully assembled SWI/SNF remodeler complexes. Leveraging a novel super-resolved density mapping strategy, we further revealed heterogenous, nanoscale remodeler binding "hotspots" across the nucleoplasm, pointing to a model where successive binding events preferentially clustered within these "hotspots" could lead to sustained productive remodeling. To further elucidate the underlying mechanism that drives such intranuclear organization, we showed that BRG1, the core ATPase/translocase subunit common to all major subtypes of the SWI/SNF family, undergoes phase separation both *in vitro* and in live cells, mediated by its IDR-rich C-terminus ($BRG1_C$). Condensates of $BRG1_C$ form across a wide range of (including endogenous) expression levels, are highly dynamic, and spatially colocalize with nucleolus. Sequence pattern analysis unveiled a specific molecular grammar governing the formation, localization and liquid-like properties of $BRG1_C$ condensates. Moreover, live-cell SMT revealed differential diffusional and chromatin-binding dynamics of $BRG1_C$ in a condensate-specific and chromatin-acetylation-dependent manner. These findings shed critical insights into a multi-modal, phase-separation-mediated landscape for organizing remodeler dynamics in space and time, and provide unique, mutant-specific signatures that establish the biophysical basis for aberrant remodeler–chromatin interactions underpinning diverse cancer-associated remodeler mutations.

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