Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Students' Annual Seminar

HP1α driven phase separation contributes to the repair pathway choice in response to heterochromatin DNA damage

Darshika Bohra

Double strand breaks pose a severe threat to genomic stability and need immediate attention from the DNA damage repair (DDR) machinery. DDR in heterochromatin has distinctive features owing to the nature of chromatin organisation. Heterochromatin Protein 1 (HP1) which contributes significantly to the organisation, maintenance, and functionality of heterochromatin can shed light on the various molecular processes. Mammalian HP1 has three isoforms, α, β, and γ, which possess significant homology to each other yet have diverse functions.

In order to investigate DDR in heterochromatin, we focused on HP1 isoforms α and β. Using tools of fluorescence recovery after photobleaching, live cell imaging and immunofluorescence, we show that the dynamics of HP1α and HP1β differ at the site of damage. Cells overexpressing HP1α or HP1β showed differential recruitment of repair proteins at the site of damage with HP1α promoting the recruitment of proteins involved in a more error-free repair pathway [Homologous Recombination (HR)] and HP1β promoting the recruitment of proteins supporting more error-prone repair pathway [Non-homologous End Joining (NHEJ)]. Readouts of HR also differ in the two cases. The ability of HP1α to undergo phase separation may affect these damage repair outcomes. In order to address this, we have utilized mutants of HP1α that perturb different functions of the protein. Our data suggests that the ability of HP1α to be phosphorylated on the serine residues in the N terminal extension region, which contributes to its ability to form phase-separated liquid droplets, also controls the ability to recruit HR factors at the site of damage. This provides a link between phase-separation and DDR based roles of HP1α. I will also present preliminary data to indicate that the site of damage in heterochromatin behaves like a phase separated domain within the cell. Further in this study we aim to determine how the regulation of repair pathway choice contributes to the heterochromatin DDR, maintenance of genomic integrity and cell survival.

Friday, May 12th 2023

2:00 PM (Tea / Coffee 1.45 PM)

Seminar Hall, TIFR-H