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

Seminar

When Proteins Go Bad: Oncogenic HEY1::NCOA2 Fusion Condensates Override Gene Regulation

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The HEY1::NCOA2 fusion oncoprotein, observed in ~80% of mesenchymal chondrosarcoma cases, forms nuclear condensates associated with aberrant gene activation. We demonstrate that these nuclear condensates are transcriptional hubs, formed through phase separation by a C-terminal intrinsically disordered region (C-IDR) of NCOA2. Both DNA binding and condensate formation are essential for HEY1::NCOA2-dependent gene activation and resulting oncogenic cellular phenotypes. Importantly, HEY1::NCOA2 condensates incorporate CBP and p300, enhancing chromatin acetylation at activated genes. Through multi-site mutagenesis of the C-IDR, we show graded changes in condensate formation correlate with similarly graded change in DNA binding, super-enhancer chromatin acetylation and gene expression, without affecting interactions with CBP and p300. While global chromatin structure remains unaltered, HEY1::NCOA2 expression caused AB compartment changes and focal DNA looping at activated genes, dependent on both its DNA binding and condensate formation. Remarkably, substitution mutagenesis showed that the physicochemical properties of the C-IDR, rather than its specific amino acid sequence, govern HEY1::NCOA2-dependent gene expression. These findings reveal how HEY1::NCOA2 exploits phase separation to focally remodel the chromatin landscape and reprogram transcriptional networks.

Monday, Nov 4th 2024

11:30 Hrs (Tea / Coffee 11:15 Hrs)

Auditorium, TIFR-H