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

Internal Seminar

Understanding the Spatiotemporal Regulation of Mammalian Genome Replication Initiation

Muntaish Bashir

TIFR, Hyderabad

Replication of genetic material is considered a fundamental process for the sustenance and perpetuation of living organisms. It is the highest priority of the cell to reproduce an error-free copy of DNA and execute this process in a regulated and time-bound manner. DNA replication in all organisms is known to commence from a given site on the genome called the origin of replication. However, owing to the large size of the genome existing as multiple chromosomes in eukaryotes and also for the purpose of efficient replication, the number of these origin sites multiplies towards the highly evolved genome of the mammalian cells with the loss of sequence specificity. It is estimated that there are about 50,000 to 100,000 origin sites spread across the entire genome of mammalian cells. Among the thousands of origins, nevertheless, only around 10% are involved in active genome replication during early, mid, and late S-phase in an unperturbed condition inside the cell while the rest of the origins remain dormant unless signalled to turn active during stress.

Our study aims to explore the factors and basis for deciding the replication initiation sites in the mammalian genome and the mechanism for the spatiotemporal pattern of origin firing. Furthermore, it aims to understand the regulatory pathway which ensures that the genome is neither re-replicated from an origin nor under-replicated in a given cell cycle to prevent genome instability. We are modelling the mutations guided by structure and Meier-Gorlin Syndrome in the essential replication proteins as CDT1, CDC45, and MCM10 at the endogenous genome location in the mammalian cells (HEK) to modulate these factors at different stages of origin to fork transition.

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09:30 AM

Venue: Auditorium