Tata Institute of Fundamental Research
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Comprehensive Seminar

Regulation of DNA damage clamp, 9-1-1 recruitment, and its implications in ATR-mediated damage response

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To safeguard genomic integrity, cells have evolved sophisticated DNA damage response (DDR) pathways that detect and repair DNA lesions. Key proteins involved in these pathways include phosphoinositide-3-kinase-related kinases (PIKKs) like ATR, ATM, and DNA-PK, which coordinate the cellular response to different types of DNA damage.

ATR (Ataxia Telangiectasia and Rad3-related) is a central kinase in the DDR recruited to DNA damage sites which are characterised by stretches of single-stranded DNA coated with Replication Protein A (RPA). ATR signal transduction is tightly regulated and activated only when replication stress arises. ATR-mediated signal transduction can result in cell cycle arrest, dormant origin firing, transcriptional activation, and/or apoptosis through effector kinases.

In the initial steps of the ATR activation, the 9-1-1 checkpoint clamp is loaded onto 5'- junctions by the clamp loader Rad17-RFC2-5, which further recruits activators such as TOPBP1 to stimulate ATR kinase activity. The 9-1-1 complex is a heterotrimeric DNA damage clamp composed of Rad9, Rad1, and Hus1. However, we still do not understand the contribution of the checkpoint clamp, 9-1-1, in mediating origin firing through translocation. Further, whether damage-dependent recruitment of 9-1-1 facilitates local vs global ATR signalling is not defined. The relevance of 9-1-1 paralogs in ATR signalling is also not explored.

In this seminar, I will discuss the distinguishing features of the 9-1-1 clamp and the clamp loader. The presentation will also include biophysical and biochemical aspects of 9-1-1 recruitment to the DNA damage sites.

Wednesday, May 28th 2025

10:00 Hrs (Tea / Coffee 09:45 Hrs)

Seminar Hall, TIFRH