Tata Institute of Fundamental Research
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Seminar

Effects of nuclear mechanics and YAP relocalisation on DNA Damage Responses (DDR)

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Yes-associated protein (YAP), a 65 kDa transcriptional coactivator, plays a crucial role in controlling cell proliferation, development and organ size. Its function as a downstream regulator of Hippo pathway has been well studied. Nuclear localisation of YAP is essential to its function. Beyond post-translational modifications of YAP downstream of canonical DDR kinases like ATM (Ataxia Telangiectasia Mutated), recently nuclear mechanics has been shown to be critical for YAP nuclear localisation. Given that ATM and ATR (Ataxia Telangiectasia and Rad3-related) — the upstream kinases in DDR — are themselves responsive to nuclear mechanical forces, we investigated whether DNA double strand breaks (DSBs) can induce alterations in nuclear mechanics to influence both nuclear YAP levels and the ability to respond to DNA damage via ATM/ATR signalling. In this talk, I will discuss my findings on how DSB-induced changes in nuclear mechanics can regulate YAP levels in the nucleus. This relocalisation is not incidental and has a bearing on DNA damage response outcome, and knockdown of YAP changes relative induction of DDR markers. In addition to mechanics-dependent global eviction of YAP upon high levels of DNA damage, we observe site-specific enrichment of YAP at DNA damage sites and explore the potential roles of such recruitment. Our current model suggests two ways by which YAP can affect DNA damage responses: 1) Global eviction of YAP from the nucleus through changes in nuclear mechanics with increase in ATM and ATR activity and potential downregulation of pro-proliferative programs, 2) Enrichment of YAP at the sites of clustered DSBs facilitating recruitment of repair factors. Together, these ensure efficient repair of the damaged DNA. Together nuclear mechanics, YAP localisation and DDR kinase activity ensure optimal repair outcomes.

Tuesday, Jun 24th 2025

09:30 Hrs (Tea / Coffee 09:15 Hrs)

Auditorium, TIFRH