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

Comprehensive Seminar

Oxidative stress and G-quadruplexes in the regulation of transcription and translation

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DNA is constantly subjected to reactive oxygen species (ROS) causing a variety of oxidative modifications in the bases. These lesions are non-helix distorting and removed by a mechanism called base excision repair (BER). The DNA base modification 7,8-Dihydro-8-oxoguanine (8oxoG) is the most abundant form of oxidative DNA lesion and potentially mutagenic, causing G-C -> T-A transversions. Although classically thought of as a DNA damage marker, 8oxoG has also been referred to as an epigenetic marker due to its roles in the regulation of transcription. 8oxoG lesions are enriched in GC- rich regions. When guanines are present in repeating tracts of four or more nucleotides, they can form secondary structures called G-quadruplexes (G4s). G4s have also been found enriched in the promoters of many genes and recent studies have suggested a mechanism by which oxidative stress induces the folding of G4s and regulates transcription. However, these observations are dependent on plasmid constructs with engineered 8oxoG lesions and do not report on this mechanism under direct oxidative stress in the chromatin context. In addition, the exact mechanism of transcriptional activation is unknown and base excision repair proteins as well as G4s themselves may be responsible in the binding and assembly of transcription factors. Besides DNA, RNA can also form G4s and these were found enriched on mRNA UTRs. Some studies have implicated their roles in translation, including of ribosomal protein mRNAs. RNA-G4s have also been found ubiquitously on rRNAs in ribosomes. These studies suggest roles for G4s in the regulation of translation. DNA G4s have also been observed to co-localize with cytoplasmic stress granule markers under conditions of stress and this can be a further mechanism of global translational regulation. However, most of these studies are in vitro or bulk, ex vivo readouts. Potential links between oxidative stress mediated translational regulations by RNA G4s have also not been explored. Both 8oxoG and G4s may be present in ribosomal DNA and RNA, hinting at regulatory roles for these nucleic acid features. We aim to address these lacunae as a part of this proposal. We have standardised the use of antibodies to detect both 8oxoG lesions and G4s in cells. Using these and other proposed tools, we hope to explore detailed mechanisms of oxidative damage induced transcriptional and translational regulation mediated by G-quadruplexes.

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09:30 AM (Tea / Coffee 09.15 AM)

Auditorium, TIFR-H