NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

SBS Seminar Announcement

New aspects of the TDP 43 self-regulation mechanism and its connection with protein aggregation and neurological disease

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Abstract

TDP-43 nuclear factor is the major protein component of the intracellular inclusions occurring in the neurons of patients affected by neurodegenerative diseases such as familial and sporadic Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). This protein is essential for cell survival playing a critical role particularly in RNA metabolism (RNA splicing, RNA stability, miRNA processing, etc.)

The cellular levels of TDP 43 are tightly controlled and the mechanism involves, like for many other RNA binding proteins, interaction of the protein with its transcript. Similarly to other systems the binding of TDP 43 to its own pre-mRNA triggers a specific alternative splicing. However unlike the other examples the Non Sense Mediated Decay (NMD) process does not play a role in TDP 43 self regulation.

The induction in tissue culture cells of higher levels of a transgenic TDP 43 dramatically decrease the endogenous gene expression. The mechanism of this shut off involves binding of TDP 43 to a specific TDP binding region (TDPBR) in the 3'UTR of its transcript. There are several pathways that seem to be involved in this process. There is evidence of: RNA Pol II pausing at the TDBPR, a variation in splicing that eliminates the TDPBR and the main Poly A site that is within it. The removal of this intron leads to a change in poly A site usage. There may also be a contribution from early termination and exosome activation. In addition recent evidence obtained in our lab indicate that the role of the splicing event may be the more critical one for the whole self regulation process.

From the point of view of the pathogenic mechanisms of ALS/FTD, the self-regulation loop of TDP- 43 is likely to play a role in the growth of the TDP- 43 brain aggregates identified as the end point of these neurodegenerative diseases. In fact, these aggregates may act as a TDP-43 "sink" that captures the protein in the cytoplasm, lowering TDP-43 concentrations in the nucleus, and signaling to the cell to increase TDP-43 production, thus establishing a harmful cycle of events.

In parallel to our studies on the self regulation loop we have set up experimental models to study the effect of aggregate formation in the disruption of TDP-43 self-regulation and other TDP 43 functions. In particular, our work has demonstrated that the introduction of multiple repetitions of residues 331-369 from TDP-43 (a Q/N rich region), caused the induction of aggregates that were able to recruit TDP-43, both in cell lines and neuronal cells. The deletion of the Q/N region from TDP-43 prevented its recruitment to the aggregates.

The elucidation of the steps involved in the self regulation process and the understanding of the factors that trigger or prevent aggregation are key issues for developing innovative therapeutic strategies for these neurodegenerative diseases.

Tuesday, 19 Feb 2013 11.00am to 12.00pm SBS Classroom 7 (SBS-B1n-17)

Host: Assistant Professor Eugene Makeyev