MBG FOCUS TALK

hosted by Erik Østergaard Jensen

MBG Focus Talks in Molecular Biology

Monday 22 June 2015 at 1:15 - 2:00 pm

The conference room, building 3130-303, Gustav Wieds vej 10c

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Dynamic cellular transitions: New RNA- and protein players in post-transcriptional regulation

Most cellular processes rely on intricate and tight regulation of gene-expression at both transcriptional and post-transcriptional levels. Dynamic cellular transitions forced for example by cellular stress and differentiation cues, rapidly reprogram the cell to mount an appropriate response and to allow for continued cell development and homeostasis. Many of these transitions are controlled by regulation RNA decay rates and translation efficiency. Using cell-biological, biochemical and bioinformatical approaches, we have studied processes including rapid cellular stress-responses, neuronal cell differentiation and disease-causing genetic alterations and assessed how these impact cell biology and gene-expression. In this talk, I will first present mechanistic insights into the process of translational repression during cellular stress, which is linked to key signaling pathways, including 'mammalian target of rapamycin' (mTOR) and 'general control nonderepressible 2' (GCN2). Although these pathways regulate global translation, our results uncover how three RNA binding proteins (TIA-1, TIAR and LARP1) 'sensitize' and co-regulate an entire class of mRNAs containing 5'-terminal oligo-pyrimidines (TOP mRNAs), which primarily encode ribosomal proteins. Repression of TOP mRNAs involves occlusion of key initiation factors from these mRNAs and induces assembly of repressed mRNPs in cytoplasmic stress granules. This system allows the cell to efficiently shut down ribosome biosynthesis and mount an efficient stress response. Secondly, I will introduce a recently identified class of circular RNAs (circRNAs) of which at least one, 'circular RNA Sponge for miR-7' (ciRS-7), can function as a potent miRNA-regulator. Using global RNA sequencing analyses, we have now identified >5000 circRNAs, which are differentially expressed during neuronal differentiation. Interestingly, our dataset shows that several hundred circRNAs are massively upregulated during differentiation. Aside from functioning as miRNA sponges, evidence suggests that most circRNAs may possess alternative functions. We are therefore currently defining the circRNA-interacting proteome by specific circRNA pull-down assays, which have revealed that a number of RNA-binding proteins robustly associate with specific circular RNAs. Given their conserved nature, differential and very high expression level in neuronal cells, we predict an important functional impact of circRNAs on neuronal differentiation.