Regulation of PARN mediated deadenylation

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The process of synthesis of RNA molecules from DNA is called transcription. There are many types of RNA molecules present in cell, messenger RNAs (mRNA), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs) and also some small RNAs (SnRNAs, miRNAs, snoRNAs and scaRNAs). All these RNAs are required for the synthesis of proteins which is called translation, in which mRNA gets translated into amino acids to form proteins. Removal of mRNA tail (poly(A) tail) which is called deadenylation is the primary step in the degradation of eukaryotic mRNAs. Poly(A)-specific ribonuclease (PARN) is a major mammalian deadenylating enzyme that removes the poly(A) tail. The aim of this study was to investigate how PARN mediated deadenylation is regulated. This was studied in two approaches; in one set of experiments our aim was to identify RNAs that are regulated by PARN activity by studying the relative changes of potential PARN target RNAs in primary fibroblasts deficient in PARN expression. In a separate approach our aim was to identify potential micro RNAs (miRNAs) that could be involved in targeting PARN to certain mRNAs.

The abundance of the PARN mRNA and its protein was reduced in the PARN deficient fibroblast cells compared to normal primary fibroblast cells. Recent studies show that some proto-oncogenes (which can produce deleterious proteins) were identified as PARN target mRNAs, the relative levels of these RNAs were reduced in the PARN deficient fibroblast cells compared to normal fibroblast cells. This reduction in the levels of these proto-oncogenes could be either due to the down regulation of transcription in order to avoid over-production of harmful mRNA products when regular PARN mediated deadenylation is not working properly or the cells may have activated alternative deadenylation machinery. PARN is also involved in the maturation of some small RNAs such as snoRNAs and scaRNAs. The relative levels of the oligoadenylated snoRNAs and scaRNAs were up regulated in the PARN deficient cells compared to normal cells. We hypothesize, in agreement with a recent study and, that the enrichment of these oligoadenylated small RNAs is due to the deficiency in PARN expression. Furthermore, the misregulation in scaRNA and snoRNA biogenesis could lead to deficiencies in the maturation and processing of rRNAs and SnRNAs that can ultimately shows effect on protein synthesis of the cell. In another approach, to get an insight into mechanisms of regulation of PARN, we also tried to isolate potential miRNAs associated with PARN using an in vitro reversible cross-linking immunoprecipitation (CLIP) approach; however this was not successful due to background problems.

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