

Conclusions

The cytokine human Leukemia inhibitory Factor (LIF) has been found to play key roles in myriads of cellular processes demanding tight yet subtle regulatory controls of its mRNA and protein expression levels. A deep insight into the molecular mechanisms underlying the post-transcriptional regulation of expression of this gene has been elucidated through this study in the context of PMA induction of human hystiocytic lymphoma cell line U937.

The *lif* 3'UTR has been characterized in terms of cross-species homology and known *cis*-acting element content into five regions, of which, functional characterization revealed the proximal non-canonical ARE region (*lif*-B) and the distal canonical ARE (*lif*-E) to be the most potent elements in *lif* mRNA stability.

Stabilization and enhanced polysome association of *lif* mRNA is mediated by stabilizing proteins Nucleolin and PCBP1 that are primarily nuclear in localization but undergo cytosolic translocation upon PMA treatment, bind *lif*-3'UTR directly at *lif*-B, thereby increasing *lif* mRNA half-life.

The role of *lif*-E in regulating *lif* mRNA stability in context of PMA treatment in U937 cells involve the interplay of multiple mechanisms that synergistically brings about *lif* mRNA stabilization. *hsa-mir-181* mediated repression of *lif* mRNA is reduced while cytoplasmic translocation of HuR is promoted which binds *lif* mRNA further protecting it from decay.

The overall regulation of *lif* mRNA stability is a very complicated process involving several effectors (*trans*-acting factors) whose co-ordinated behavior in response to a particular stimulus (PMA treatment in this case) influences the fate of mature *lif* mRNA in the cytosol. The functional characterization of *lif* 3'UTR in terms of identifying potent *cis*-acting elements in mRNA stability and further elucidating their respective *trans*-acting factors (proteins and micro RNAs) will not only facilitate the modulation of *lif* mRNA levels in different cellular and disease contexts, but will also serve as a template to further the understanding of underlying principles of mRNA stability in general.