

## **Translational control of gene expression: The cancer connection.**

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Dysregulated expression of factors that control global protein synthesis rates, and that of specific mRNAs, is associated with poor prognosis of many cancers, but the underlying mechanisms are not well defined. Therefore polysome profiling was used to examine global changes in the translome of cells derived from patients with diffuse large B-cell lymphoma (DLBCL) and in cells treated with agents that cause bulky adduct DNA damage that are used therapeutically e.g. cisplatin.

Analysis of the DLBCL translome revealed selective up-regulation of mRNAs encoding anti-apoptotic and DNA repair proteins. We showed that enhanced synthesis of these proteins in DLBCL was mediated by the relief of repression that is normally imposed by structure in the 5' UTRs of their corresponding mRNAs. This process was driven by signaling through mTOR resulting in increased synthesis of eIF4B, a known activator of the RNA helicase eIF4A. Reducing eIF4B expression alone was sufficient to decrease synthesis of proteins associated with enhanced tumor cell survival, including DAXX and BCL2 and the critical DNA repair enzyme ERCC5. Importantly, eIF4B-driven expression of these key survival proteins directly correlated with patient outcome and eIF4B, DAXX and ERCC5 were identified as new prognostic markers for poor survival in DLBCL.

Analysis of the translome following bulky adduct DNA damage showed that translational up-regulation of many critical components of the nucleotide excision repair pathway was mediated by RNA regulatory elements within the 5' and 3' UTRs of mRNAs that remain polysomally associated. Importantly, we identified a common polymorphism in a uORF in the 5' UTR of ERCC5 that determines sensitivity to platinum-based chemotherapy by controlling ERCC5 translation.

Taken together these data illustrate the importance of post-transcriptional control pathways in cancer progression and how a greater understanding these regulatory pathways will lead to novel therapeutic approaches.