The Messenger's Tale: Decoding Post-transcriptional Gene Regulation in the 3'UTR

3'-untranslated regions (3'UTRs) specify post-transcriptional fates of mammalian mRNAs, yet knowledge of the underlying sequences and mechanisms is largely incomplete. For example, biochemical and comparative genomic studies have demonstrated that mammalian 3′UTRs contain a multitude of protein binding sites and conserved sequence tracts, respectively, yet only a small fraction corresponds to recognized regulatory elements. To identify functional 3′UTRs elements, we created a high-throughput screen that exploits integrated single-copy reporters, expressed and processed as endogenous genes. Using this system, we found hundreds of novel functional sequences, including both positive and negative regulatory elements. To complement our high-throughput studies, we performed a comprehensive analysis of the regulatory logic of the mammalian 3′UTR of Hmga2. We identified the complete set of regulatory elements within a single 3′UTR, most of which are novel, and, determined that the majority of sites function independently of one another. Amongst the elements we have found, we focused on two related repressive motifs. These motifs are interchangeable, specify transcript degradation via mRNA deadenylation, and are active only within 3'UTRs, where they are common and preferentially conserved. We identified the trans factors required for transcript degradation. Interestingly, the motifs are most active within the distal portion of 3'UTRs, suggesting that their role can be abrogated by alternative mRNA processing resulting in truncated 3'UTRs. Together, these studies demonstrate that human 3′UTRs contain many previously unrecognized regulatory elements, and that the post-transcriptional fate of an mRNA is largely due to the independent actions of multiple individual elements within its 3′UTR.