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DISSERTATION

"Bioinformatic Studies of Mechanisms and Consequences of Alternative Cleavage and Polyadenylation"

by

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Molecular Biology, Genetics, & Cancer Track

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Thursday, April 16th, 2020
11:00 A.M.
WebEx

ABSTRACT

Characterization of regulation of transcriptome diversity is important for understanding basic biology and human diseases. Alternative cleavage and polyadenylation (APA) generates mRNA isoforms with diverse 3′ untranslated regions (3′UTRs) and/or coding regions from a single gene, contributing to transcriptome diversity. Changes in 3′UTR composition of mRNAs can alter mRNA metabolism by regulating subcellular localization, stability, and protein synthesis. Most eukaryotic protein-coding genes exhibit APA, which is regulated extensively in cell differentiation, under stress, and in cancer and other diseases. Studies have shown that brain cells tend to express long 3′UTR isoforms by using distal cleavage and polyadenylation sites (PASs). In this thesis, four bioinformatic studies have been carried out to understand the regulatory mechanisms and consequences of APA, focusing mostly on the neuronal system. In the first study, a computational method was developed to examine APA events by using RNA-seq data from brain cells. A key finding of this study is that neurons globally express longer 3′UTRs than other cell types in the brain, such as microglia and endothelial cells. Further analysis of APA regulation during differentiation of embryonic stem cells into neurons indicates that a large fraction of the APA events regulated in neurogenesis are similarly modulated in myogenesis, but to a much greater extent. In the second study, APA regulation during neuronal activation was identified by using 3′ region extraction and deep sequencing (3′READS) with chemical long-term potentiation (cLTP) in mouse hippocampal CA3-CA1 synapses. A general trend of 3′UTR shortening and activation of intronic APA (IPA) isoforms was observed. Additionally, specific APA regulatory events were shown to impact the expression of two genes with known functions during LTP, including 3′UTR APA of *Notch1* and intronic APA of *Creb1*. In the third study, 3′READS data of newly made and steady-state RNAs in different human cell lines were analyzed, including HEK293T, HepG2, and SH-SY5Y. Neuronal SH-SY5Y cells showed many stability differences compared to other cell types. Regression analysis showed that GC content in 3′UTRs was stabilizing features in SH-SY5Y cells. Furthermore, long 3′UTR isoforms in general were less stable in all three cell lines compared to short 3′UTR isoforms. Moreover, intronic APA isoforms were less stable overall, and 5′splice site strength, intron position and size were found to be the important features regulating their stability. In the last study, over 100 RNA binding proteins (RBPs) were systematically studied for their binding around the PAS, by using ENCODE eCLIP data, RNA-seq data and our cell type-specific 3′READS data. Among those RBPs, T-cell intracellular antigen-1 (TIA1) showed a strong binding at the PAS. Importantly, knockdown of TIA1 and its paralog TIAR led to 3′UTR shortening, whereas overexpression of TIA1 led to 3′UTR lengthening. Overall, this thesis develops a new bioinformatic method to profile APA using RNA-seq data, reveals APA regulation in neurogenesis and neuronal activation, elucidates differences in APA isoform stabilities, and uncovers a potential role of TIA1 in APA regulation.