Regulation of cryptic splice sites in neuronal differentiation and disease

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Contact information of fellow
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Regulation of cryptic splice sites in neuronal differentiation and disease

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Motor neurone diseases

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Research Abstract

A recent era of RNA research discovered complex RNA regulatory networks that involve RNA binding proteins (RBPs) and RNA. These networks are particularly dynamic and complex in the central nervous system, and can lead to neurologic diseases if deregulated. The host lab

studies the regulatory networks that control alternative splicing in the brain. Recently, the lab identified thousands of cryptic splice sites that are bound by the spliceosome, but do not lead to active splicing in the adult brain. In the present project, I will assess if splicing at some of these cryptic sites is regulated during brain development or disease. Moreover, I will determine the importance of such regulation for neuronal differentiation.
Most of the cryptic splice sites are present within long introns of genes that are only expressed in the brain. Therefore, I will employ genome-wide experimental and computational methods to study the regulation of cryptic splice sites in mouse embryonic stem cells (mESCs) and mouse brain from several developmental stages. It is known that binding of RBPs to target pre-mRNAs can actively repress cryptic splicing, which ensures expression of stable mRNAs. FUS and TDP-43 are two RBPs that regulate alternative splicing and lead to amyotrophic lateral sclerosis (ALS) when mutated. They have increased binding to the long introns and their depletion leads to decreased expression of long genes. I will therefore assess changes in splicing at cryptic sites upon depletion of FUS or TDP-43 in mESCs, in ALS mouse models, and in induced pluripotent stem cells (iPSCs) from ALS patients. Since de-repression of cryptic splice sites would lead to aberrant mRNAs, this may unravel the mechanism explaining how FUS and/or TDP-43 regulate the expression of long genes.
The study of genome-wide cryptic splicing regulation might uncover a novel mechanism controlling neuronal development, and explain how misregulation of long genes contributes to ALS neuropathology.

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