The tricks neurons use to express their genes: jumping genes, zero-length exons and RNA loops

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How are RNAs important for gene expression in neurons?

mRNA

miRNAs

RNA duplex

mRNAs are transported to allow localised protein synthesis

neurons

Longer mRNAs in neurons up to 10000nt

<1000nt elsewhere

motor neuron disease

No cure available 1/232 deaths in 2012

Mutations in six RNA-binding proteins

RNA duplex
What proteins bind to an RNA?

How do these proteins control synthesis of other proteins?

RNA splicing, stability, translation

How mutations disrupt protein-RNA interactions.

Disease models

iPS-derived motor neurons

Integrate regulation

Interpret mutations

Measure interactions

New techniques

hiCLIP & iCLIP
Zero-length exons
Splicing makes an mRNA
Splicing makes an mRNA
Recursive splicing makes same mRNA
Recursive splicing makes same mRNA

recursive splice site
Recursive splicing makes same mRNA

recursive splice site
Recursive splicing makes same mRNA
Genes expressed in the brain are extremely long

Recursive splice sites are present within some of the longest genes

Definition of the cryptic exon is required for recursive splicing

Recursive sites are followed by cryptic poison exons

Recursive site prevents inclusion of the cryptic exon

MG:

P1: YYYYYAG GTAAGC... GTAAA...
P1-m1: YYYYYAG GTAAGC... ATAAA...
P1-m2: YYYYYAG GCAGCC... GTAAA...

Suggested model for the mechanism of recursive splicing in vertebrates

recursive splice site
Suggested model for the mechanism of recursive splicing in vertebrates
Suggested model for the mechanism of recursive splicing in vertebrates
Suggested model for the mechanism of recursive splicing in vertebrates
Suggested model for the mechanism of recursive splicing in vertebrates
The cryptic exon is included if preceded by another cryptic exon.
Recursive splicing detects upstream cryptic exons
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Recursive splicing detects upstream cryptic exons
Cryptic exon detects other cryptic exons due to recursive splicing
Jumping genes
Formation of exons from antisense Alu elements

- Alus are transposable elements
  - 10% of human genome
  - 650k in introns

- Alus resemble exons when in antisense
  - Cryptic splice sites
  - poly-U tracts

- Alus are an important source of new exons in primates
  - ~5% of human alternative exons

Keren et al, *Nat Rev Gen* 2010
hnRNP C represses splicing of Alu exons

Zarnack et al, Cell, 2013
Alu exons can cause human diseases

Vorechovsky et al., Human Genetics 2010
hnRNP C controls the emergence of \textit{Alu}-derived cryptic exons

\textbf{Alu} exon repressed

\textit{Zarnack et al, Cell, 2013}
hnRNP C represses damaging cryptic Alu exons
RNA loops
mRNAs have a structure
...to form mRNPs
Example 1: RNA structures can act as thermometers

Mortimer et al, Nat Rev Gen, 2014
RNA duplexes in 3’ UTR lead to formation of long RNA loops

- 3,530 duplexes in 3’ UTRs
- 894 duplexes in coding regions
- 84 duplexes in 5’ UTRs

Loop length

1000 2000 3000 8000
Long-range RNA duplexes are not computationally predicted

Sugimoto et al, Nature 2015
STAU1 regulates cytoplasmic splicing of the XBP1 mRNA

We identified an RNA duplex in the XBP1 3’UTR

The RNA duplex is required for STAU1 binding to XBP1 mRNA

STAU1 is required for efficient cytoplasmic splicing of XBP1 mRNA during UPR

Sugimoto et al, Nature 2015
Staufen binds RNA duplexes that form long-range contacts in 3’UTRs. mRNAs localised to neuronal dendrites have longest 3’UTRs up to 10000nt in neurons.

Sugimoto et al, Nature 2015
RBPs regulate the time and space of neuronal gene expression