Quaking and PTB control overlapping splicing regulatory networks during muscle cell differentiation.

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Public Summary:
Alternative splicing is a critical step in proper gene expression. Muscle cell differentiation is accompanied by a complex change in alternative splicing patterns, but a complete set of muscle-specific alternative splicing regulators and the way they control each other are unknown. Genomic studies in our laboratory and others found that the RNA sequence “ACUAA” is present near alternative exons such as exon 9 in Capzb (a gene encoding an important muscle protein) that are regulated in muscle. Mass spectrometry of muscle precursor cell (myoblast) proteins that bound to Capzb exon 9 intron RNA identifies Quaking (QK), a protein known to bind the ACUAA RNA sequence. We find that QK regulates the alternative splicing of Capzb exon 9 in opposition to another splicing factor called polypyrimidine tract-binding protein (PTB) which controls more than a thousand exons in muscle cells. Genomic studies show that QK controls at least 406 cassette exons through their nearby ACUAA. Combined analysis of the PTB- and QK-splicing regulatory networks during muscle cell differentiation (myogenesis) suggests that 39% of all exons regulated in developing muscle cells are under the control of one or both of these splicing factors. This work provides the first evidence that QK is a global regulator of splicing during muscle development in vertebrates and shows how overlapping splicing regulatory networks contribute to gene expression programs during differentiation. Furthermore, enumeration of the regulators of gene expression in differentiating muscle will be necessary to understand muscle development and regeneration.

Scientific Abstract:
Alternative splicing contributes to muscle development, but a complete set of muscle-splicing factors and their combinatorial interactions are unknown. Previous work identified ACUAA ("STAR" motif) as an enriched intron sequence near muscle-specific alternative exons such as Capzb exon 9. Mass spectrometry of myoblast proteins selected by the Capzb exon 9 intron via RNA affinity chromatography identifies Quaking (QK), a protein known to regulate mRNA function through ACUAA motifs in 3' UTRs. We find that QK promotes inclusion of Capzb exon 9 in opposition to repression by polypyrimidine tract-binding protein (PTB). QK depletion alters inclusion of 406 cassette exons whose adjacent intron sequences are also enriched in ACUAA motifs. During differentiation of myoblasts to myotubes, QK levels increase two- to threefold, suggesting a mechanism for QK-responsive exon regulation. Combined analysis of the PTB- and QK-splicing regulatory networks during myogenesis suggests that 39% of regulated exons are under the control of one or both of these splicing factors. This work provides the first evidence that QK is a global regulator of splicing during muscle development in vertebrates and shows how overlapping splicing regulatory networks contribute to gene expression programs during differentiation.

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