**Topic**

Transcriptional mechanisms regulating skeletal muscle differentiation

**Phosphorylation and alternative splicing of MEF2C, a dual switch function in muscle regeneration.**

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Muscle regeneration is a multistep process that is regulated by a restricted number of transcription factors whose activity is modulated at multiple levels. However, how different layers of regulation are coordinated to promote adult myogenesis is not yet understood. Here we show that the MEF2C transcription factor controls multiple steps of muscle regeneration, including myogenic progression of satellite cells and muscle maturation of newly generated myofibers, exhibiting multiple functions that depend on alternative splicing and post-translational modifications. Inclusion of the 1 exon in *Mef2c* transcripts is upregulated in proliferating mouse satellite cells and in the early phases of muscle regeneration. The encoded MEF2C1 isoform stimulates expansion of primary myoblasts *ex vivo* and *in vivo*. The pro-proliferative activity of MEF2C is mediated by phosphorylation of two phosphoserines located in exon 1. Subsequent terminal differentiation and growth of newly formed myofibers are promoted by dephosphorylated MEF2C1 and MEF2C2. Our results thus reveal an important role for regulatory interactions between alternative splicing and post translational modifications of a single transcription factor in the control of the multilayered regulatory programs required for adult myogenesis.