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Review

The regulation of Notch signaling in muscle stem cell activation and postnatal myogenesis

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Abstract

The Notch signaling pathway is an evolutionarily conserved pathway that is critical for tissue morphogenesis during development, but is also involved in tissue maintenance and repair in the adult. In skeletal muscle, regulation of Notch signaling is involved in somitogenesis, muscle development, and the proliferation and cell fate determination of muscle stems cells during regeneration. During each of these processes, the spatial and temporal control of Notch signaling is essential for proper tissue formation. That control is mediated by a series of regulatory proteins and protein complexes that enhance or inhibit Notch signaling by regulating protein processing, localization, activity, and stability. In this review, we focus on the regulation of Notch signaling during postnatal muscle regeneration when muscle stem cells ("satellite cells") must activate, proliferate, progress along a myogenic lineage pathway, and ultimately differentiate to form new muscle. We review the regulators of Notch signaling, such as Numb and Deltex, that have documented roles in myogenesis as well as other regulators that may play a role in modulating Notch signaling during satellite cell activation and postnatal myogenesis.

Keywords: Myogenesis; Satellite cell; Notch; Numb; Deltex

Contents

Abbreviations: Arf6, ARF ribosylation factor 6; bHLH, basic helix-loop-helix; CSL, CBF1, Supressor of Hairless, Lag-1; DSL, Delta, Serrate, Lag-2; E(spl), Enhancer of Split; JNK, jun N-terminal kinase; MADS, MCM1, agamous, deficiens, serum response factor; MEF2, myocyte enhancer factor 2; MRF, myogenic regulatory factor; NICD, Notch intracellular domain; PRR, proline-rich region; PTB, phosphotyrosine binding; SCF, Skp1–Cullin–F-box; Su(dx), Suppressor of Deltex; Su(H), Supressor of Hairless

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1. Introduction

Notch signaling plays an important role in tissue morphogenesis both during development and during postnatal regeneration of skeletal muscle, regulating such diverse processes as proliferation, differentiation, and cell fate decisions [1]. The focus of this review is to summarize the current evidence of the role of Notch in postnatal myogenesis, to focus on how regulation of this pathway guides effective muscle regeneration and repair, and finally to discuss specific regulators of Notch signaling that may be critical for the myogenic program.

The Notch signaling pathway is an evolutionarily conserved pathway that plays a critical role in tissue development in organisms ranging from nematodes to mammals. The canonical Notch signaling pathway is initiated by the binding of one of the DSL (named for Delta, Serrate, and Lag-2) family of ligands to the one of the members of the Notch family of transmembrane receptors [2,3]. Ligand binding leads to sequential enzymatic cleavage of the Notch receptor and release of the active form of the protein, also known as NICD (Notch intracellular domain), into the cytoplasm. NICD then translocates to the nucleus where it binds members of the CSL (named for CBF1 (also known as RBP-J), Supressor of Hairless (Su(H)), and Lag-1) family of transcriptional repressors, converting them to transcriptional activators [1,4–6]. The targets of these transcription factors are typified by the Enhancer of Split (E(spl)) complex in Drosophila and the Hes and Hey genes in vertebrates [1,4–6]. In Drosophila development, the basic helix-loop-helix (bHLH) proteins encoded by the E(spl) complex serve to inhibit differentiation programs, such as those necessary for neurogenesis and myogenesis [1].

2. Notch and myogenic differentiation

Myogenesis, whether during development or during postnatal regeneration, involves the expansion of mononucleated progenitor cells, their progression along a myogenic lineage pathway to become fusion-competent myoblasts, their migration and alignment, and finally their differentiation. The differentiation of myoblasts results in both profound morphological and biochemical changes. Morphologically, myoblasts fuse to form multinucleated myotubes which further develop to become the myofibers of mature skeletal muscle. Biochemically, myogenic differentiation is characterized by the coordinate upregulation of genes encoding proteins that subserve the fundamental functions of mature muscle, proteins such as myosin, sarcomeric actin, and creatine kinase. This biochemical differentiation is regulated by two families of transcription factors: (i) the bHLH myogenic regulatory factors (MRFs), which include MyoD, myogenin, Myf-5, and MRF4; and (ii) myocyte enhancer factor 2 (MEF2) proteins, which belong to the MADS (MCM1, agamous, deficiens, and serum response factor)-box family [7,8]. Members of both families are able to bind directly DNA to activate transcription. The binding of each factor to its DNA binding site helps to recruit and stabilize the binding of the other factor via protein–protein interactions [9]. This cooperative activation of transcription is facilitated by the close proximity and coordinated positioning of the binding sites for MRFs and MEF2 in promoters of muscle-specific genes [10]. Each MRF can initiate myogenesis in a variety of non-myogenic cells [11–13], but this myogenic conversion requires the function of the MEF2 family [14,15]. However, MEF2 proteins are not sufficient to induce myogenesis [9,15,16].

Each of the MRFs has been shown to heterodimerize with the ubiquitous bHLH E proteins, including E12 and E47 (generated by alternative splicing of E2A), ITF-2, and HEB [13,17,18]. The MRF/E protein heterodimers bind to DNA at E-boxes (CANNTG) that are present in the promoters of many skeletal muscle-specific genes such as desmin, creatine kinase, troponin I, alpha-actin, and acetylcholine receptor subunits [19–21]. MRF/E protein heterodimers interact with MEF2 proteins to cooperatively and synergistically activate myogenesis [16,22].

Activation of the Notch pathway inhibits myogenic differentiation [23,24]. The differentiation of the murine myogenic C2C12 cell line is markedly inhibited by the ectopic expression of NICD [5,25], but not by expression of full-length Notch [25]. Similar results have been reported in MyoD- or Myf5-converted fibroblasts in which NICD has been overexpressed [25]. The co-culture of C2C12 cells with cells expressing one of the Notch ligands also inhibits differentiation [26,27]. Notch-mediated inhibition of myogenesis is accompanied by a down-regulation of myogenin and myosin light chain 2 [23,26–28]. Removal of the two nuclear localization signals present in NICD inhibits its nuclear translocation and abolishes the ability of NICD to inhibit differentiation [25], presumably due to the failure to activate CSL-dependent gene expression, including the induction of Hes gene expres-