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Review Article

Myostatin regulation of muscle development: Molecular basis, natural mutations, physiopathological aspects

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ABSTRACT

Since its identification in 1997, myostatin has been considered as a novel and unique negative regulator of muscle growth, as *mstn*–/– mice display a dramatic and widespread increase in skeletal muscle mass. Myostatin also appears to be involved in muscle homeostasis in adults as its expression is regulated during muscle atrophy. Moreover, deletion of the myostatin gene seems to affect adipose tissue mass in addition to skeletal muscle mass. Natural myostatin gene mutations occur in cattle breeds such as Belgian Blue, exhibiting an obviously increased muscle mass, but also in humans, as has recently been demonstrated. Here we review these natural mutations and their associated phenotypes as well as the physiological influence of the alterations in myostatin expression and the physiopathological consequences of changes in myostatin expression, especially with regard to satellite cells. Interestingly, studies have demonstrated some rescue effects of myostatin in muscular pathologies such as myopathies, providing a novel pharmacological strategy for treatment. Furthermore, the myostatin pathway is now better understood thanks to in vitro studies and it consists of inhibition of myoblast progression in the cell cycle, inhibition of myoblast terminal differentiation, in both cases associated to protection from apoptosis. The molecular pathway driving the myogenic myostatin influence is currently under extensive study and many molecular partners of myostatin have been identified, suggesting novel potent muscle growth enhancers for both human and agricultural applications.

Contents

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Introduction

Myogenesis involves a multiplicity of complex processes enabling the growth and maintenance of muscle tissue. Myoblast differentiation is one of the major steps of muscle development. After an active proliferative phase, myoblasts irreversibly exit from the cell cycle to fuse into multinucleated myotubes. This event is associated to a coordinated expression of a set of muscle-specific proteins involved in particular in the organization of the muscle contractile apparatus. These early stages of muscle development are regulated by muscle-specific bHLH transcription factors (Myf5, MyoD, MRF4 and myogenin). Knockout studies in mice have established that, whereas MyoD and Myf5 are involved in determination of the muscle lineage [1–3], myogenin plays a key role in myoblast terminal differentiation and MRF4 could regulate muscle fiber maturation [4–7]. However, a novel double MyoD/Myf5 knockout recently revealed that MRF4 is also probably involved in determination events [8].

Cloning of myostatin in 1997 focused great attention on a novel and unique negative regulator of muscle growth because the myostatin gene knockout in mice leads to a dramatic and widespread increase in skeletal muscle mass. This new factor, also called the growth and differentiation factor 8 (GDF8), has been identified by a PCR approach on murine DNA using degenerated oligonucleotides corresponding to highly conserved sequences among the members of the TGFβ family. The complete cDNA sequence was obtained by screening a murine skeletal muscle library. The deducted myostatin protein sequence contains all hallmarks of members of the TGFβ superfamily, including a signal sequence for secretion, a proteolytic processing site and a carboxy-terminal region containing the conserved pattern of 9 cysteine residues, the cysteine knot, essential for TGFβ activity. As other members of the TGFβ superfamily, myostatin is synthesized as a 376 amino acid precursor protein containing a signal sequence, an N-terminal propeptide domain and a C-terminal domain that consisting of the active ligand [9] (Fig. 1). Proteolytic processing between the propeptide domain and the C-terminal domain gives rise to an N-terminal propeptide and the mature form of myostatin, a 12-kDa carboxy-terminal fragment. Both unprocessed and mature myostatin form disulfide-linked dimers and the processed myostatin dimer represents the only active form of the protein.

In mice, myostatin is predominantly expressed in developing muscle, as early as 9.5 days postcoitum, and in adult skeletal muscle [9]. However, several studies in different animal species have also reported the occurrence of myostatin mRNA or protein in other tissues and in plasma [10–12].

Myostatin has been also detected in several fish species, which in some cases revealed the existence of two distinct myostatin genes [11,13,14]. Fish myostatin is detected in numerous tissues including muscles, eyes, gill filaments,

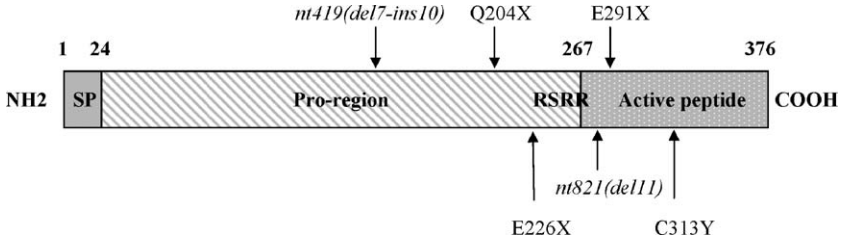

Fig. 1 – Structure of myostatin protein and natural mutations occurring in the bovine myostatin gene. The three domains represented in this scheme are the signal peptide (SP), the pro-region, which will be cleaved by proteasic digestion at the RSRR site during maturation, and the active peptide at the C-terminal part of the myostatin precursor. The arrows indicate the position of inactivating mutations that are responsible for the increased muscle growth observed in some cattle breeds.