

Review

A Review on the Genetic Regulation of Myogenesis and Muscle Development

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Abstract: Myogenesis of muscle tissues is known as a very complex and delicate process including many cellular differentiation and development events in animals. Here, the courses of cellular fate determination and terminal differentiation of muscle cells are systematically elaborated and the genetic regulatory network of muscle genesis is well conceived in animal organic growth and development through literature retrieval. Furthermore, the principal roles of myogenic regulatory factors, Myostatin, fibroblast growth factor, insulin-like growth factor and other muscular regulatory factors interrelated and reported in the myogenesis relevant studies are also reviewed. In addition, the interactions of these muscular specific factors and their possible relevant regulative pathways and interactions among them are included and developed too.

Keywords: Myogenesis, Molecular Interaction, Regulatory Network, Myogenic Regulatory Factor, Myostatin, Fibroblast Growth Factor

Introduction

In the past 50-60 years, a great progress has been made in the genetic selection of lean meat rate, growth rate and feed efficiency of domesticated animals. The meat production levels of domesticated animals have been continuously improved and their marketing cycles have been gradually shortened, but the internal genetic regulation mechanism of meat type animals during this genetic selection is not clear yet. With the intersection and development of these research fields of modern genetics and molecular biology and developmental biology, the perceiving and understanding of myogenesis and development of animal muscle tissues gradually enter into the molecular biology level, such as the genetic control of double muscle phenomena in pigs, cattle and sheep and the genetic selection of lean muscle mass in animal development have been related and referred to candidate genes of Myostatin (firstly reported in cattle and sheep) and IGF-II (Insulin-Like Growth FactorII, firstly reported in cattle and pigs) and CLPG (Callipyge, firstly reported in sheep and goat) in many short reports and/or detailed studies (McMurtry *et al.*, 1997; Andersson and Georges, 2004; Georges, 2007). However, the underlying genetic mechanism and interactions involved in myogenesis and development of animal muscle tissues are still unclear.

The formation and patterning of three muscle types are usually found in vertebrates, i.e. smooth, cardiac and skeletal muscles (Robson, 2017). All these three muscle types share the property that they contract to move substances around the body (smooth and cardiac) or move and stabilize the skeleton or skeletal (Robson, 2017). Specifically, the skeletal muscles are very important economic genetic traits in domestic animals (Aiello *et al.*, 2018; Dou *et al.*, 2018), such as the breast and leg muscles in commercial broiler chicken. In general, muscle cells of vertebrates originate from the mesoderm which is one of the early emerging cell types in initial myogenesis and development of muscle tissues. In vertebrates, the mesoderm is induced and brought about by some members of the BMP signaling molecule family. Molecular genetics and developmental biology studies showed that, myogenic regulatory factors (MRF), as the central regulatory target factors and other key regulatory molecules involved in the fate control of mesodermal cells mainly referred to many following signaling channels and/or pathways (Alfonso and Alison, 2002), i.e. Wnt signaling pathway, Shh (sonic hedgehog) signaling pathways, TGF β /BMP (transforming growth factor beta and bone morphogenetic factor super-family) signaling pathway, Notch/Delta signaling pathway, RTK/Ras (tyrosine receptor kinase) signaling pathway

and other various growth factor families, such as Myostatin (belonging to TGF β /BMP signaling pathways) and MAPK kinases (belonging to RTK/Ras signaling pathways). Once the genesis of mesoderm is formed, the signaling pathways of Wnt, TGF β /BMP, FGF and IGF and other signaling molecules of these growth factor families will jointly program to determine the differentiated developmental fate of muscle cells. For instance, the interaction between the Wnt and Shh signaling pathways synergistically promotes the occurrence of muscle tissues, which is manifested as the presence or absence of muscle mass, whereas myogenic regulatory factors MyoD and Myf5 and pax-3 are actually the targets at the intersecting ends of these signaling pathways.

The process of myogenesis starts with the transcription and translation of a number of transcription factors that are expressed by some mesodermal cells. These initial transcription factors will regulate the expressions of critical genes that code for muscle specific skeletal components (e.g. myosin), cytoplasmic enzymes (e.g. creatine kinase) and other cellular proteins that are essential for the electrophysiological processes of muscle cells. Depending on the specific combination of these essential proteins, different types of muscle cells are formed and exhibit functional differentiation (e. g., the myocardial and smooth muscle and striated muscle tissues in vertebrates and the trunk muscle and viscera muscle tissues in insects and other invertebrates). It is speculated that there was a complex gene regulation network (Fig. 1) existed in the processes of animal myogenesis induced by signals from surrounding tissues

(Molkentin and Olson, 1996; Nabeshima, 1996; Palacios and Puri, 2006; Ochi and Westerfield, 2007; Maqbool and Jagla, 2007; Haye *et al.*, 2014; Rossi *et al.*, 2016). In particular, the gene regulatory network framework of myogenesis and muscular development was proposed in the studies of zebrafish and fruit fly (Ochi and Westerfield, 2007; Maqbool and Jagla, 2007; Haye *et al.*, 2014). However, at present, there are still unclear and lack of research reports and/or in-depth studies for the exploration and explanation of the genetic network of various growth factors and regulators and their interactions with some specific cellular receptor and signaling pathways in the transduction and differentiation and regulation of myogenesis and muscular development in animals. Furthermore, the genetic regulation of myogenesis and muscular development and growth of animal muscle tissues is a highly complex and comprehensive successive process, which is affected by many genetic and physiological and environmental influencing factors, such as the genotype and/or haplotype and gender of animal species and/or strains (genetics), endocrine status (physiology), dietary feed level (nutrition), living and feeding environment and other internal and external factors. The effects of genetics and physiology and nutrition and other factors on the growth and development of animal muscle mass are finally implemented through the functional integration of myogenic regulatory factors and their receptors (Odle *et al.*, 2017; Rossi *et al.*, 2016).

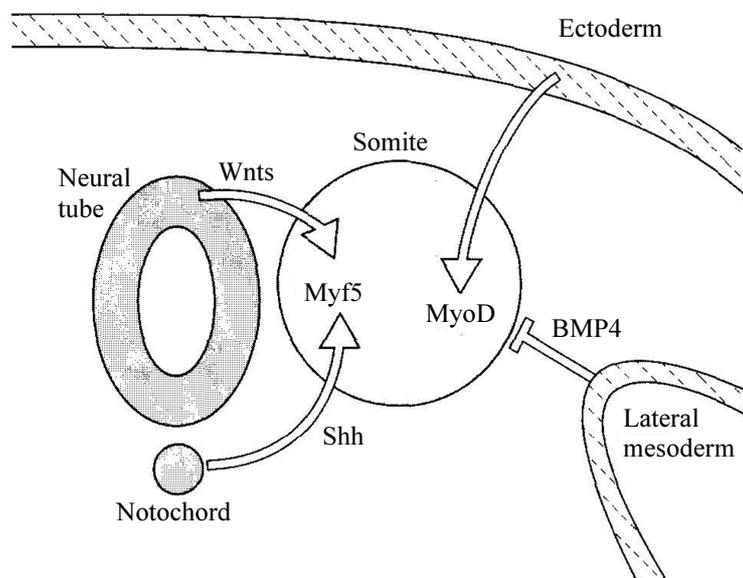


Fig. 1: A hypothetical inducing model of myogenesis in somites by signaling factors from surrounding tissues, adapted from the article by Molkentin and Olson (1996). These signaling factors act in combination along with those signaling factors from the ectoderm (top) to induce the gene expression of myogenic regulatory factors in the semite myotome. MyoD or Myf5 are expressed in proliferating myoblasts where their activity is inhibited by Cdk4 or cyclin-D

In the recent years, muscle-specific promoters have been extensively tested and many signal transduction factors and regulatory factors have been reported as involved in muscle development research. The embryonic genetic studies of mice, birds, fish and frogs have obtained some protein and/or gene interactive networks that regulate the intergeneric myogenic signals or regulatory interactions between those signal transduction factors and regulatory factors in muscle cells, including the regulatory network and/or signaling information that drive muscle-specific gene activation in animal muscle tissues. However, our understanding of the detailed processes of myogenin and muscle development remains limited. The following parts give a full review of MRFs, Myostatin, FGF, IGF and their receptors and corresponding binding proteins in recent myogenesis and muscle development studies.

The Origin and Developmental Differentiation of Muscle Cells

The time-ordered development of muscle tissues usually begin with a variety of transcription factors expressed in some mesoderm cells. These transcription factors regulate the expression and translation of muscle-specific proteins necessary for the electrophysiological processes of muscle cells, such as skeletal components and cytokines. The muscle cells (alias muscle fibers) of animals are classified into three types, i.e., red slow-shrinking muscle fibers (type I), white fast-shrinking muscle fibers (type II A) and intermediate fibers (type II B), according to their different metabolic modes. Different types of muscle cells (or muscle fibers) gradually appear functionally differentiated depending on the different combinations of expressed component proteins that are transcribed and translated. Thus, the amount of muscle depends on the number and size of muscle cells (or muscle fibers). However, the number of myofibroblasts will not change once the vertebrate is born. Therefore, the growth of muscle mass and tissues in animals after birth depends mainly on the length and diameter of the postnatal muscle fibers, rather than the change in the number of muscle cells.

In practice, the process of myogenesis of muscle cells is more complicated. This process is generally divided into three stages: the first early differentiation stage, in which the mesenchymal cells undergo terminal differentiation and begin to synthesize muscle-specific proteins; the second mature stage with the muscle-specific synthesis of constitutive proteins, including contractile proteins like actin and myosin, myogenic regulatory proteins like myogenin, muscle cytoplasmic enzymes like creatine kinase and some special membrane proteins and their receptors; the third late differentiation stage, in which muscle cells adapt to different types of muscle fibers with different types of proteins synthesized and gradually differentiate into various muscle tissues.

The Transcription Factors and Signal Transduction Involved in the Regulation of Gene Transcriptional Activity during Myogenesis and Muscle Development

In the process of myogenesis and muscle development, the muscle cells undergo a series of phenotypic and cellular and molecular changes, resulting in the cell lineages at various stages and finally form a diversity of myogenic cells through the terminal differentiation. Ultimately, the muscle cells differentiate into multiple kinds of fast and slow muscle fibers and a variety of muscle-specific transcription factors and inhibitors have been identified and reported in these cells.

The Role of Myogenic Regulatory Factors in the Cellular Determination and Differentiation of Muscle Cell

The differentiation of myoblasts (alias myocytes) is one of the key steps in myogenesis and muscle development. In the early stages of muscle development, differentiation of the myogenic cell lineage is regulated by muscle cell-specific MRFs (myogenic regulatory factors). After an active period of cell proliferation, those myogenic cells will irrevocably withdraw from the cell cycle and fuse into multinucleated myotubes.

The myogenic regulatory factor family (alias the MyoD family) is a class of proteins containing the basic helix-loop-helix (bHLH) domains, including Myf4, Myf5, MyoD and MyoG (myogenin) that play a key role in the development of muscle cells. These transcription factors are initially found and reported in mouse and rat myoblasts and myotubes during the myogenesis and development of muscle cells. They mainly coordinate with two regulatory factors called MEF and E proteins, whereas these two proteins bind to muscle-specific genes and promote and regulate the genes' expression in embryos. The identification of myogenic regulatory factors in vertebrates stems from the research for genetic mutations that trigger the development of cultured muscle cells (Berkes and Tapscott, 2005; Rossi *et al.*, 2016). Without these factors, muscle cells in the culture medium will not activate the program of muscle development and regeneration (Berkes and Tapscott, 2005; Rossi *et al.*, 2016).

The Discovery of Myogenic Regulatory Factors

MyoD is the earliest MRF gene identified and analyzed among vertebrates (Choi *et al.*, 1990; Berkes and Tapscott, 2005; Rossi *et al.*, 2016). Studies on the induction of C3h10t1/2 in embryonic cell lines using the demethylation reagent 5-heterocytoside showed that the embryonic cells underwent changes with stable genetic effects to form muscle stem cells and four members of the MRF family (MyoD, myogenin, myf-5 and myf-4) were then identified (Choi *et al.*, 1990; Edmondson and

Olson, 1993; Huang *et al.*, 1998; Berkes and Tapscott, 2005; Rossi *et al.*, 2016), in which myogenin was regarded as a key factor in the terminal differentiation of muscle stem cells into myocytes.

In vivo, each MRF is efficiently bound to a site containing CANNTG sequence (E box), which occurs in the promoter and enhancer regions of muscle-specific genes (Berkes and Tapscott, 2005; Rossi *et al.*, 2016). Intensive expression of MRF protein in cultured non-muscle cells can induce myogenic differentiation, but the respective efficiencies are different. However, the four MRFs showed distinct but overlapping functions *in vitro*. In developing mouse embryos, Myf5 is induced to express in the dorsal intermediate segment, which will develop into the trunk and intercostal muscles, followed by the expression of MyoD in the dorsal ganglion of the back which will develop into the muscles of the body wall and limbs. During the differentiation phase of muscles, MRF regulates the expression of contractile proteins and protein isoforms at different stages, allowing muscle cells to differentiate into different types of muscle fibers.

Transcriptional Regulation of the Myogenic Regulatory Factor Family

In mice, the expression of MyoD and Myf5 is a key event to the differentiation of pluripotent stem cells into muscle cell lineages (myofibril or myoblasts). Knockout or mutation of the two genes (i.e. MyoD and Myf5) in mice will result in the loss of skeletal muscle myogenic cells (Rudnicki *et al.*, 1993; Huang *et al.*, 1998). The absence of a mutation in either MyoD or Myf5 does not affect the normal development of the muscle, indicating a degree of redundancy in function of these two genes. Myf5 and MyoD genes control the determination of the muscle cell lineages above the axial axis (epaxial) and below the spinal axis (hypaxial) respectively (Kablar *et al.*, 1998), while myogenin is only work in terminal differentiation of myogenic cells (Wang and Jaenisch, 1997). The functional regions (protein motifs or domains) of MyoD and Myf5 that activates a silent muscle-specific gene is the helix structure located at the C-terminal region. Therefore, the MRF4's developmental role is complex and it is regarded as a potential impacting factor in the determination and terminal differentiation of muscle cell lineages. With the sequent expression of Myf5, MRF4 was observed to be transiently expressed in mouse sarcomere at 9.0 days (E9.0) and faded at 11.5 days (E11.5) and re-expressed at 16.0 days (E16.0) in mouse muscle fibers.

In addition, in the experiment of myogenin promoter-MRF4 transgenic mice, the replacement of myogenin with MRF4 partially rescued the myogenesis of myogenin^{-/-} homozygous mutant embryos (Zhu and Miller, 1997; Wang and Jaenisch, 1997), confirming that MRF4 played a role in the differentiation of muscle cells into terminal myocytes. Furthermore, the over-expression of MRF4 in embryonic stem cells (ES Cells)

lacking myogenin resulted in the well-differentiated muscle fibers, whereas the over-expression of MyoD did not (Sumariwalla and Klein, 2001; Myer *et al.*, 2001). Since the MRF4 and Myf5 genes are located in tandem sequences of DNA molecules and the experiments *in vitro* on the function of MRF4 are complicated, there is presently no clear conclusion of MRF4's function. Later, a series of complex Myf5 mutants have been obtained and some of these mutants can express MRF4 in the absence of Myf5 (Kassarduchosoy *et al.*, 2004; Berkes and Tapscott, 2005; Rossi *et al.*, 2016). Particularly, in the experiment of mice lacking both Myf5 and MyoD, the expression of MRF4 was unaffected, suggesting that MRF4 may be involved in the maturation of muscle fibers (Kassarduchosoy *et al.*, 2004). Myogenin was then functionally inferred as distinct from Myf5 and MyoD (Rawls *et al.*, 1995).

The previous studies mentioned above suggested the importance of MyoD and Myf5 in the establishment of muscle cell lineages. MyoD and Myf5 determine the fates of final muscle phenotypes, whereas myogenin plays a role in the terminal differentiation of muscle cells. Furthermore, MRF4 can partially promote these two regulatory processes. The functional roles of MyoD and Myf5 can be regarded as the specification of muscle cell lineages, whereas myogenin's functional role is the differentiation of muscle cells. And thus, MRF4 has some partial overlapped functions in these two aspects.

The Functional Interaction between Different Regulatory Proteins or Transcription Factors

MRF belongs to a kind of bioactive protein containing basic-helix-loop-helix (bHLH) structure of motif or domain, which is a typical type II transcription factor with tissue specific expression. MRFs can synthesize homodimers or bind to other type I factors containing bHLH structures to form heterodimers (Brennan *et al.*, 1991; Wang and Jaenisch, 1997; Black *et al.*, 1998; Penn *et al.*, 2004; Berkes and Tapscott, 2005; Haye *et al.*, 2014; Rossi *et al.*, 2016). Particularly, type I factors mainly include protein molecules whose base regions are necessary for binding to DNA sequences, such as HEB/HTF4, E2-2/ITF-2 and E12/E47, whereas the HLH structures mediate heterodimerization between different bHLH motif containing proteins. In brief, all of the bHLH protein dimers bind to the consensus sequence CANNTG sequence of E box, in which each monomer in the protein dimers can recognize half of the E box site (i.e. CANNTG), respectively.

In addition to E proteins, the Id proteins belonging to the bHLH protein super-family can also bind to other bHLH containing protein or transcription factor to form heterodimers. Actually, the Id proteins have an intact bHLH domain, but they cannot bind to DNA sequences due to the lack of a critical amino acid residue in their

basic domains, thereby inhibiting the terminal differentiation of muscle cells (Murre *et al.*, 1989; Atchley and Fitch, 1997; Berkes and Tapscott, 2005; Haye *et al.*, 2014; Rossi *et al.*, 2016). Another key transcription factor interacting with bHLH motif containing proteins is the members of MEF2 family including MADS box proteins or MADS domain transcription factors identified during skeletal muscle development (Wilson-Rawls *et al.*, 1999; Dichoso *et al.*, 2000). Such protein factors are expressed in several mesoderm and non-mesodermal cell lineages (Wilson-Rawls *et al.*, 1999; Dichoso *et al.*, 2000). Although they do not promote muscle development by themselves, they are able to interact with bHLH motif structure containing proteins to promote the processes of myogenesis and muscle development. In the specialization of skeletal and/or cardiac muscle cells, MEF2 family members interact with E protein and myogenic bHLH motif containing proteins to form heterodimers, but they cannot directly form heterodimers with E proteins (Wilson-Rawls *et al.*, 1999; Dichoso *et al.*, 2000).

Activators and Inhibitors in Myogenesis and Muscle Development

As mentioned above, MRFs usually bind to the MEF proteins and other muscle-specific and/or non-muscle-specific protein regulatory factors. In addition, the MRFs can act as co-activators or co-suppressors during myogenesis and muscle development to control the tissue-specific expression of related genes.

Co-activators of the Muscle Tissue Specific Gene Transcription

The cellular factors that regulate or activate MyoD and other MRFs are functionally diverse, such as the transcription factor Pax (a paired box protein), the MEF2 proteins (Lin *et al.*, 1997; Black *et al.*, 1998) and the members of Six family (Heanue *et al.*, 1999) and the cell cycle regulators (Lin *et al.*, 1997). Although most of these genes induced by MyoD were expressed at different times, chromatin immuno-precipitation experiments showed that MyoD can directly bind to corresponding regulatory elements of these genes expressed during cell differentiation of muscle tissues (Penn *et al.*, 2004).

Members of the MRF transcription factor family, such as MyoD, Myf5, MRF4 and myogenin, were isolated by the transfection-induced developmental experiments of muscle tissues (Murre *et al.*, 1989; Berkes and Tapscott, 2005; Haye *et al.*, 2014; Rossi *et al.*, 2016). Meanwhile, the same experiments also identified the regulatory protein Pax3 (Murre *et al.*, 1989; Berkes and Tapscott, 2005), a transcription factor containing a PRD homeodomain. MyoD, Myf5 and Pax-3 are the target genes for Wnt and Shh signaling pathways. In fact, the transcription factor Pax-3 is a 479 amino acid protein encoded by the Pax

gene, including two conserved DNA binding units, one consisting of a 128 amino acid amino end pairing domain and the other consisting of a 60 amino acid homeodomain. Actually, Pax-3 protein is involved in the proliferation, specialization and migration of anterior sarcomere cells in limbs. In mice and chickens, skeletal muscle cells were deduced to originate from the dermis sarcomere cells. The Pax3 gene is inferred to be expressed in a rather early dermal sarcomere, since pax-3 and the related pax-7 gene are expressed at the paraxial mesoderm before the formation of somites. Pax-3 is a key regulator of myogenesis and development of muscle cells because it activates the expression of MyoD gene in the somite and/or somatic ganglia (Rawls and Olson, 1997). The expression of Pax3 gene in the sarcomere and/or myogenic ganglion is a synthetic result of the combination of Wnt, Shh, FGF and BMP signaling factors (Pownall *et al.*, 2002). To explain the weak muscle developmental disorder caused by a single mutation of Myf5 or MyoD or Pax3, a genetic model was proposed in mutant mice (Tajbakhsh *et al.*, 1997), in which Myf5 and Pax3 synergistically activate MyoD expression in the myogenic segment. In the model, the regulatory effect of MyoD occurs at the downstream of the other two genes (i.e. Myf5 and Pax3) and then MyoD initiates a series of feedback regulation loops to maintain and adjust the expression levels of the three genes (Tajbakhsh *et al.*, 1997).

Co-Repressors of the Muscle Tissue Specific Gene Transcription

In the cell culture system of muscle tissues *in vitro*, MyoD is expressed just prior to the activation of its target gene. Several post-translational modification models have been proposed to prevent the premature activation of MyoD, including binding to co-repressors or to other proteins that enable MyoD to detach from DNA. Many proteins identified in experiments as antagonists that inhibit muscle development directly bind to E box proteins or MRFs, preventing them from binding to E box proteins or preventing their transcriptional activation of the muscle-specific gene promoters. Such inhibitors are themselves the proteins containing bHLH domains, including Id, Twist, MyoR and Mist-1. In addition, MyoD is also a terminal target protein for Myostatin, a key regulatory factor.

The presence of high cellular concentrations of Id proteins inhibits the activity of MRFs because Id proteins can efficiently bind to E box proteins to form the heterodimers that block and prevent the interaction of E box proteins with isolated MRFs (Benezra *et al.*, 1990; Parrinello *et al.*, 2001; Berkes and Tapscott, 2005). Id proteins can also form the heterodimers with MRFs, but at a very low efficiency (Benezra *et al.*, 1990; Parrinello *et al.*, 2001). Since Id proteins lack a base which binds to DNA sequences, the MRF/Id protein heterodimer is considered

to be completely lacking transcriptional activity. The results and data obtained in an experiment in which Id protein was strengthened by the MyoD-E47 protein dimer, i.e. the genetic fusion of MyoD and E47 in the same peptide chain to counteract the inhibitory activity of Id protein, supports this hypothesis (Neuhold *et al.*, 1993). Similar to Id protein, Twist is also an HLH protein which binds to E box protein to form a dimer and prevents the complex interactions between E box protein and MRF (Spicer *et al.*, 1996). Unlike Id protein, Twist has one base, whereas this base binds to the base of MRF without binding to DNA sequences, preventing the mutual interaction of the E box region with specific MRF and its homologues on the muscle-specific promoters (Hamamori *et al.*, 1997). Twist also inhibits the cell propagation of muscle tissues by interacting directly with the HLH binding regions of MEF2 proteins (Spicer *et al.*, 1996).

In addition to Id and Twist, MyoR and Mist-1 and Mdf1 are the inhibitors of myogenesis and muscle development too. These regulatory factors contain a base region and can form a dimer with MRFs. For instance, the heterodimers MRF/MyoR and MRF/Mist-1 bind to the E box consensus sequence, but these dimers do not activate the transcription and translation of specific genes when linked to DNA (Lemercier *et al.*, 1998; Lu *et al.*, 1999). Furthermore, Mdf1 is actually a negative regulator of MRFs, which functions differently from other negative regulators of the proteins containing HLH structural. Mdf1 is a cytoplasmic protein whose function is to bind and isolate MRFs in the cytoplasm to prevent their transport into the nucleus (Chen *et al.*, 1996).

Myostatin

Myostatin, also known as growth factor 8 (GDF8), is a member of the TGF β /BMP super-family. The intact precursor Myostatin is a 376 amino acid long protein containing a signal peptide with an N-terminal peptide domain and a C-terminal peptide domain of an active ligand. The C-terminal peptide domain of Myostatin includes a 12 kDa peptide fragment. Both the unprocessed precursor Myostatin and the mature Myostatin can form a disulfide-linked dimer through this peptide fragment, but the processed mature Myostatin dimer is the only active protein form of dimerized Myostatin to bind to the cell membrane's receptors. Myostatin has been recognized as the only negative regulator of muscle growth and development in animals, since Mcpherron *et al.* (1997) firstly reported the mutagenic effect of Myostatin gene (or MSTN) in cattle. Myostatin has been identified as a negative regulator of skeletal muscle mass and inactivating mutations in the MSTN gene are responsible for the development of a hypermuscular phenotype, because Myostatin^(-/-) mutant mice exhibit a generally and significantly increased skeletal muscle mass in which muscle atrophy

occurs (Mcpherron *et al.*, 1997; Kawada *et al.*, 2001; Mcfarlane *et al.*, 2006; Chelch *et al.*, 2009), Myostatin is also regarded to play important roles in the maintenance of muscle homeostasis and regeneration (Mcpherron *et al.*, 1997; Kawada *et al.*, 2001; Mcfarlane *et al.*, 2006; Chelch *et al.*, 2009; Odle *et al.*, 2017; Rossi *et al.*, 2016). If Myostatin is knocked out in laboratory animals, the animal mutation would affect both the growth and development of adipose tissues and skeletal muscle tissues. The naturally occurring mutations of Myostatin gene in cattle herd, such as the homozygous mutation of 11th bp in the third exon of Myostatin gene resulted in an enlarged phenotype of double muscles in the Belgian blue cattle herd (Mcpherron *et al.*, 1997; Mcfarlane *et al.*, 2006). Recent researches reported in myostatin-null mice revealed that PI3K and apoptotic pathways were regarded as possible Myostatin targets and Myostatin-deficiency in mice increases global gene expression at the Dlk1-Dio3 locus in the skeletal muscle (Chelch *et al.*, 2009; Hitachi and Tsuchida, 2017; Lessard *et al.*, 2018). Myostatin acts at key points during pre- and post-natal life of amniotes that ultimately determine the overall muscle mass of animals selected for high growth rate and muscularity (Aiello *et al.*, 2018; Dou *et al.*, 2018). Mutations in domestic animals have already demonstrated the impact of attenuating Myostatin activity on muscle development and a number of large animals, including cattle, sheep, goat, horse, pig, rabbit and chicken, display the double muscled phenotype or enlarged muscle mass due to mutations in the Myostatin gene (Aiello *et al.*, 2018; Dou *et al.*, 2018). The most recent research investigated the relations between muscle (breast and leg) myostatin mRNA expression and body and muscle growth among commercial broiler chickens (Dou *et al.*, 2018). They found the expression of Myostatin genes was correlated negatively with body weight from day 90 to 150 and the carcass weight and muscle mass from day 90 to 150 in Avian broiler chickens (Dou *et al.*, 2018).

In another case of mouse 9. 5-day embryos and adult skeletal muscle tissues, Myostatin is expressed preferentially in embryonic developing muscles (Dominique and Cabello, 2006). Changes in the expression amount of Myostatin have a particularly large effect on astrocytes, which may be the direct target cells of Myostatin (Cossu and Biressi, 2005; Dominique and Cabello, 2006). The Myostatin signaling pathway, which plays a inhibitory role in myogenesis and muscle development, is undergoing extensive research. A theoretical model of Myostatin signaling pathway has been proposed (Heldin *et al.*, 1997; Franck *et al.*, 2001; Franck and Mauviel, 2002; Dominique and Cabello, 2006; Rossi *et al.*, 2016; Lessard *et al.*, 2018), mainly including many cellular ligands, type I and type II receptors, Smad proteins or receptors, among which the ligands are mainly activins, Myostatin, TGF- β , BMP

proteins and growth factors (Fig. 2). However, no receptor of Myostatin and other growth factors has been found in muscle development and regeneration so far. The most recent research shows that c-Jun N-terminal kinase (JNK) regulates muscle remodeling via myostatin/SMAD inhibition (Lessard *et al.*, 2018). JNK is a molecular switch to active and stimulate muscle fibers to grow, resulting in increased muscle mass (Lessard *et al.*, 2018). However, when the muscle JNK activation is suppressed and the alternative remodeling program is initiated, resulting in smaller, more oxidative muscle fibers and enhanced aerobic fitness (Lessard *et al.*, 2018).

In addition, there is a limited and incomplete understanding of the TGF- β signaling pathway and its members in previous studies and reports, in which most of the subjects mainly target TGF- β and its receptors like Myostatin and there is lack of systematic research on the entire TGF- β signaling pathway. In recent years, the molecular activities and interactions of TGF- β 1 signaling pathway in fibroblasts have been extensively studied (Heldin *et al.*, 1997; Franck *et al.*, 2001; Franck and Mauviel, 2002; Rossi *et al.*, 2016; Lessard *et al.*, 2018). In the case of skin trauma or injury or muscle pathology, TGF- β 1 is firstly associated and bound with the Type II

receptor (TGF- β RII) on fibroblast membranes and then the conformation of TGF- β 1 molecule changes which can be recognized by Type I receptor (TGF- β RI) to form the TGF- β -receptor trimer complex of Type I receptor and TGF- β 1 and Type II receptor. In this trimer complex, the Type I and Type II receptors will act on the cytoplasmic Smad proteins (i.e. Smad2 and Smad3) to activate them by phosphorylation upon the activation of TGF- β receptors' phosphorylation, whereas the phosphorylated Smad proteins (i.e. P-Smad2 and P-Smad3) form a heterotrimer with SMAD4 and transport it to the nucleus (Heldin *et al.*, 1997; Franck *et al.*, 2001; Franck and Mauviel, 2002; Rossi *et al.*, 2016; Lessard *et al.*, 2018). Then, two inhibitors of this signaling have been identified, i.e. Smad7 and Smurf1. Smad7 represses the myostatin signal by binding its MH2 domain to activated receptors, thus preventing recruitment and activation of R-Smads and Smurf1 is an E3 ubiquitin ligase that mediates ubiquitination and consecutive degradation of the R-Smads (Lessard *et al.*, 2018). Thus, SMAD4 cooperates with internal transcription factors in the nucleus or independently regulates the expression of downstream target genes and promotes the synthesis of collagen and other structural components of muscle fibers.

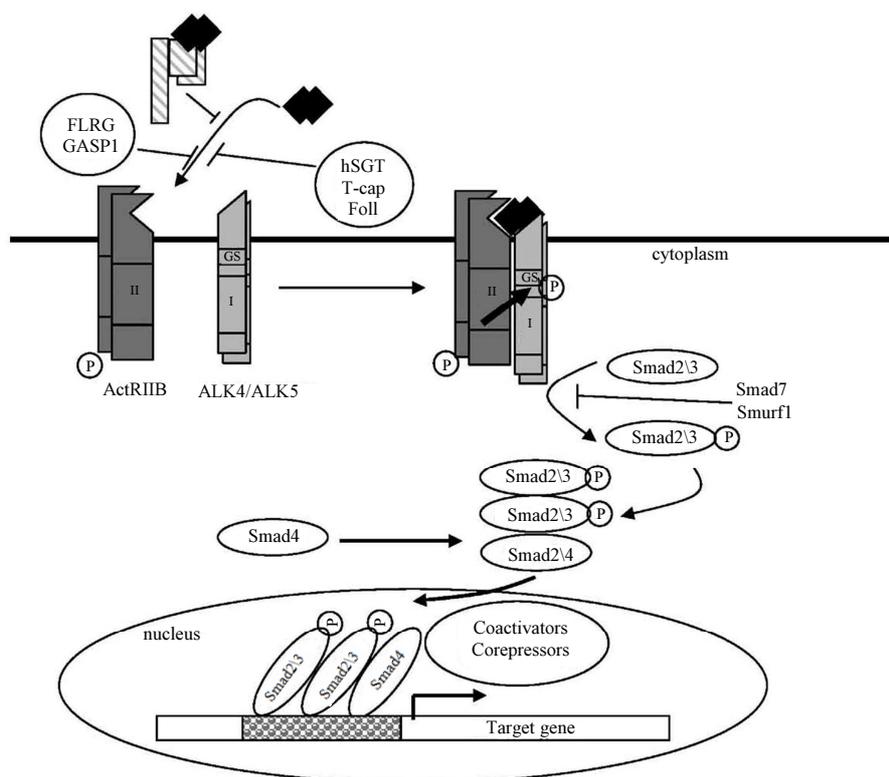


Fig. 2: A framework of Myostatin signaling pathway adapted from the article by Dominique and Cabello (2006). Those putative elements of the myostatin pathway were shown with the speculated Smad proteins and their corresponding targets and/or ligands. Myostatin can be found in serum or locally in an inactive state when bound to FLRG, GASP-1, hSGT, T-cap, or follistatin, etc.

When the external stimulating signals of TGF- β 1 signaling pathway is over, the P-Smad proteins rapidly dephosphorylate and deactivated and the cellular Smad proteins in the cytoplasm and nucleus is rapidly metabolized by the ubiquitin-proteasome system to return to the pre-phosphorylation level before the signal action.

Fibroblast Growth Factors (FGFs)

Fibroblast Growth Factor (FGF) is a crucial signaling molecule that interacts with many proteins and receptors of the intracellular MAP kinase signaling pathway to promote various aspects of embryonic development through the FGF receptors and binding proteins (Ornitz and Itoh, 2001; Fisher *et al.*, 2002; Itoh and Ornitz, 2011). Fibroblast growth factors and their receptors constitute a large family of polypeptide growth factors whose members are versatile (Szebenyi and Fallon, 1999; Fisher *et al.*, 2002; Itoh and Ornitz, 2011). In the body, the expression level of FGFs is relatively constant and their roles are to respond to tissue repair and injury. FGFs will transduce their signaling mainly through four transmembrane tyrosine kinase receptors (FGFRs), i.e. FGFR1, FGFR2, FGFR3, FGFR4 (Szebenyi and Fallon, 1999). The cell culture studies of muscle tissues shown that FGFs can promote the proliferation of fibroblasts and inhibit the differentiation and myogenesis of myogenic cells. Most recent studies reported that the FGF signaling pathway directly activates the gene expression of MyoD in *Xenopus* (Fisher *et al.*, 2002). Among the members of the FGF family, FGF6 (fibroblast growth factor 6) and FGF8 (fibroblast growth factor 8) and FGF24 (fibroblast growth factor 24) have been widely studied.

In the case of *Fgf6*($-/-$) mutant mice, FGF6 was mainly expressed in the myogenic cell lines of adult muscle and developing muscle (Kästner *et al.*, 2000; Armand *et al.*, 2005; Mcfarlane *et al.*, 2006; Armand *et al.*, 2006), suggesting that it might be associated with somite formation. Indeed, the components of FGF signaling pathway were found correlated to the regeneration of adult mouse muscles. In the *Fgf6*($-/-$) mutant mice, muscle fibers of the posterior squamous muscles of the regenerated calf showed swelling compared to those of the wild-type mice (Mynarcik *et al.*, 1996; Kästner *et al.*, 2000). It was surmised that Insulin-like growth factor II (IGF-II) might play a key role in the hyperplasia of this mutant mice (Mynarcik *et al.*, 1996; McMurtry *et al.*, 1997; Armand *et al.*, 2005; Mcfarlane *et al.*, 2006; Armand *et al.*, 2006; Headey *et al.*, 2004; Whittaker *et al.*, 2002). In order to clarify the exact functional roles of FGF6 in muscle development and enlargement, two different laboratories produced the same FGF6 homozygous knockout individuals to analyze the regeneration process of skeletal muscle in FGF6($-/-$) mutant mice, but contradictory results emerged (Floss *et al.*, 1997; Fiore *et al.*, 1997; 2000; Armand *et al.*, 2005). At

present, the exact role of FGF6 in mouse muscle development and enlargement remains unclear (Armand *et al.*, 2005). However, the FGF signaling pathway composed and its receptors FGFR1 (fibroblast growth factor receptor 1) and FGFR4 (fibroblast growth factor receptor 4) play important roles in the growth and development of muscle cells (muscle fibers). In the cellular experiment, muscle cells containing FGFR1 or FGFR4 were observed to alternately switch to different signaling pathways (Armand *et al.*, 2006), whereas *in vivo* study indicated that both FGF6 and FGFR4 were exclusively expressed in myofibroblasts and astrocytes and FGFR1 was widely expressed in myogenic cells and all the cells (Kästner *et al.*, 2000; Armand *et al.*, 2005; Mcfarlane *et al.*, 2006; Armand *et al.*, 2006). In contrast, inhibition of FGFR4 signaling *in vitro* often led to the retention of muscle precursor cells' differentiation (Marics *et al.*, 2002; Armand *et al.*, 2005; Mcfarlane *et al.*, 2006; Armand *et al.*, 2006; Zipora *et al.*, 2015). In addition to FGF6, many other FGFs are also expressed in skeletal muscles, including FGF2, FGF5 and FGF7. Most *in vivo* experiments have reported that these FGFs can induce the proliferation of myogenic cells and muscle satellite cells, whereas FGF1, FGF4, FGF2 and FGF6 can promote the cell proliferation of muscle astrocytes too (Marics *et al.*, 2002; Armand *et al.*, 2005; Mcfarlane *et al.*, 2006; Armand *et al.*, 2006; Zipora *et al.*, 2015).

In another case of chicken muscles, FGFs regulated the differentiation of myogenic precursor cells, rather than alter the proliferative capacity of myogenic precursor cells (Duclos, 1998; Duclos *et al.*, 1999; Duclos, 2005; Marics *et al.*, 2002; Fisher *et al.*, 2002). However, in reported studies, it is currently still unclear how do FGFs regulate the differentiation and myogenesis of myogenic precursor cells and muscle fibers. In the studies of zebrafish muscles, FGF8 and FGF24 work together during the developmental formation of mesoderm (Ochi and Westerfield, 2007). The cellular expression of FGF8 was detectable at the edge of the blastoderm during the 30% outsourcing period, whereas a back-abdominal gradient was formed during the 50% outsourcing period with the highest expression level observed on the dorsal side of the embryonic membrane. On the contrary, the earliest expression of FGF24 was detected at the edge of the blastoderm during approximately 50-60% outsourcing period too (Ochi and Westerfield, 2007). During the period of zebrafish segmental segmentation, the expression of FGF8 extends to the late period of mesoderm before that of somite formation. FGF8 is also observed to be expressed in somites, whereas the expression of FGF24 is not detected in somites (Ochi and Westerfield, 2007). In the zebrafish FGF8 cerebellar mutant embryos, the expression of MyoD is reduced in the paraxial but remains unchanged in the somite,

whereas the functional inhibition of FGF24 will suppress the formation of late mesoderm the FGF8 mutant embryos and the expression of MyoD was essentially removed and eliminated (Ochi and Westerfield, 2007), suggesting that FGF8 and FGF24 work together to regulate the formation of mesoderm and the gene expression of MyoD in zebrafish.

Conclusion and Outlook

At present, there are a considerable amount of studies and reports on the transcriptional regulation of animal myogenesis and muscle development (mostly skeletal muscles), but most of them are genetic and/or developmental analyses at the embryonic or cellular levels. There are lack of studies and/or reports on the gene expression networks and individual phenotypic effects. Furthermore, the research in depth on the myogenesis and development of muscle cells is presently not ample and elaborate enough. Particularly, the research on the roles of complex gene regulatory networks and underlying signaling pathways in myogenesis and muscle development is lack of systematic analyses. Although the framework of myogenesis and genetic network of skeletal muscle development has been proposed in the studies of zebrafish and fruit fly (Ochi and Westerfield, 2007; Haye *et al.*, 2014), it is still only an ideal model and the specific studies and/or reports has not yet been fully carried out and reported.

In the future, if one is willing to conduct a comprehensive and systematic study on the relationship between myogenic regulatory genes' regulation and transcription factors' interaction during myogenesis and muscle development like genetic analyses in yeast, the high throughput sequencing technologies and modern genome level or genome-wide scale research techniques would be referred to simultaneously obtain a large number of biological data and bioinformation on the genetic expression levels of specific genes and their interactions. Fortunately, there are already such technologies, such as gene-chip or DNA microarray, SAGE (Serial Analysis of Gene Expression), MPSS (Massively Parallel Signature Sequencing), RNA-seq (RNA sequencing) and scRNA-seq (Single-cell RNA-sequencing) and a series of analyzing techniques like bioinformatics and "Omics" techniques. Predictably, with the application of these biological technologies and/or techniques to the differential expression and analysis of specific genes involved in animal myogenesis and muscle development, the future research will provide a comprehensive and systematic information available for us, such as transcriptome and gene methylation. Of course, there will be more complete and systematic biological data and bioinformation enough for elaborated and in depth studies and/or reports on

myogenesis and muscle development. This may be one of the promising directions of future research on the genetic regulation of animal muscle mass.

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Ethics

This is original and unpublished article. There are no animals dealt in the study and the author declared that no competing interests and no ethical issues involved. The corresponding author confirms that the author has read and approved the manuscript.

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