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The temporal specific role of WNT/β-catenin signaling during myogenesis

Akiko Suzuki[1,2], **Anne Scruggs**[1], and **Junichi Iwata**[1,2,3,*]

[1]Department of Diagnostic & Biomedical Sciences, the University of Texas Health Science Center at Houston School of Dentistry, USA

[2]Center for Craniofacial Research, the University of Texas Health Science Center at Houston School of Dentistry, USA

[3]The University of Texas Graduate School of Biomedical Sciences at Houston, USA

Abstract

Disruption of WNT/β-catenin signaling causes muscle developmental defects. However, it has been unclear how WNT/β-catenin signaling regulates each step of myogenesis. The *in vitro* culture of primary myoblasts and C2C12 cells (a myoblast cell line) has the ability to differentiate into myofibers in culture with differentiation inducers. These *in vitro* systems are useful to investigate each step of muscle development, ranging from cell proliferation to homeostasis, under the control of experimental conditions. Our recent study shows that WNT/β-catenin signaling can regulate myogenesis in a temporal specific manner by controlling the gene expression of cyclin A2 (*Ccna2*) and cell division cycle 25C (*Cdc25c*) during myoblast proliferation and fermitin family homolog 2 (*Fermt2*) during myoblast fusion and differentiation, respectively. In the well-differentiated myofibers, WNT/β-catenin signaling plays a role in the maintenance of their structure through a cadherin/β-catenin/actin complex formation, which is important for connecting a myofiber's cytoskeleton to the surrounding extracellular matrix. Thus, our recent study coupled with previous findings indicates that WNT/β-catenin signaling regulates myogenesis in a variety of ways, and any failure of these steps of myogenesis causes muscle developmental defects.

Keywords

WNT signaling; cell cycle; myoblast fusion; muscle homeostasis

Muscle development

Skeletal muscle has extensive metabolic and functional plasticity as well as a robust regenerative capacity. The process of skeletal muscle formation, beginning with muscle progenitor cell activation and ending with myofiber formation, is complex and highly regulated in both development and regeneration [1]. These developmental and regenerative processes are affected by a variety of muscle disorders and atrophy [2,3]. Muscle precursor

*Corresponding Author. Junichi Iwata, Ph.D., Junichi.Iwata@uth.tmc.edu.

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cells (*aka* satellite cells in the adult) are the major source of myoblasts for the growth of skeletal muscles [3]. During development and regeneration muscle precursor cells proliferate, at which stage they are referred to as myoblasts, and subsequently differentiate into myofibers [3]. Among skeletal muscles, muscles in the tongue are the most developed muscles at birth for the purpose of suckling, compared with the other craniofacial and trunk muscles [4,5]. There are many lines of evidence for differences between craniofacial and trunk skeletal muscles. For example, the origin of myoblasts and satellite cells, and fibroblasts in the craniofacial region is occipital somites derived from paraxial mesoderm, and cranial neural crest (CNC) cells, respectively. In contrast, the origin of myoblasts and satellite cells, and fibroblasts in the trunk region is somites derived from paraxial mesoderm, and lateral plate mesoderm, respectively [6].

Embryonic myogenesis (*aka* primary myogenesis) is necessary to establish the basic muscle pattern at embryonic day (E) E11-E14 in mice. The following fetal myogenesis (*aka* secondary myogenesis) is characterized by growth and maturation of each muscle anlagen and by the onset of innervation at E14.5-E17.5 in mice [7]. PAX3 (paired box 3, a transcription factor) and PAX7 (paired box 7, a paralogue of *Pax3*) are critical for myogenic potential, survival, and proliferation of muscle progenitor cells, but differentially contribute to myogenic lineages in the craniofacial and trunk regions [8]. PAX3 is required for myogenic specification upstream of myogenic differentiation 1 (MYOD1; *aka* MEF3) and myogenic factor 5 (MYF5), somite segmentation, dermomyotome formation, and limb musculature development. Interestingly, mice lacking *Pax3* and *Myf5* fail to develop skeletal muscle in the trunk and limb, although craniofacial muscles form normally [9]. Pax7 is crucial for the specification and survival of muscle satellite cells in adults [10]. Mice with ablation of *Pax7* (*Pax7*$^{-/-}$ mice) exhibit compromised myogenesis and regeneration in adults, but fetal myogenesis is not affected in *Pax7*$^{-/-}$ mice [7]. In *Pax3*$^{-/-}$;*Pax7*$^{-/-}$ double knockout mice, the early embryonic muscle of the myotome forms, but all subsequent steps of skeletal muscle formation are compromised by a failure of cell survival or cell fate determination of Pax3^{+} or Pax7^{+} expressing cells. These studies indicate that PAX3 is essential for embryonic myogenesis and PAX7 is crucial for adult myogenesis in growth and regeneration; however, both PAX3 and PAX7 share redundant functions during fetal myogenesis. Taken together, the source of muscle supporting cells is different between cranial and trunk muscles, and the contribution and distribution of PAX3^{+} progenitor cells are different between cranial and trunk muscles. These findings suggest that the molecular mechanism of craniofacial muscle development likely differs from that of trunk and limb muscles.

After myogenic specification, the determination and terminal differentiation of muscle cells are regulated by myogenic regulatory factors (MRFs), which are basic helix-loop-helix (bHLH) transcription factors. MRFs consist of MYF5, muscle-specific regulatory factor 4 (MRF4; *aka* MYF6), MYOD1, and myogenin (MYOG; *aka* MYF4) [11]. In parallel, muscle cells (myoblasts, myotubes and myofibers) express myosin heavy chain (MyHC), which is the actin motor protein. The proper MyHC isoform is crucial for specialized muscle function and myofibril stability [12].

WNT/β-catenin signaling

The WNT family consists of 21 secreted glycoprotein ligands that are essential to activate canonical (β-catenin-dependent) and/or non-canonical (β-catenin-independent) pathways in various physiological and pathological conditions [13]. Without WNT ligands, β-catenin is incorporated into a destruction complex containing AXIN, adenomatous polyposis coli (APC) and the serine-threonine kinase glycogen synthase kinase-3 (GSK3β). The destruction complex phosphorylates β-catenin and leads it to be degraded by the ubiquitin-proteasome system [13]. With binding of WNT ligands to a frizzled receptor (FZD) and the low-density lipoprotein receptor-related protein 5/6 (LRP5/6), the destruction complex is inactivated, and β-catenin can be stabilized and translocate into the nucleus [13]. Increased nuclear β-catenin interacts with transcriptional co-activators, such as members of the T-cell factor/Lymphocyte-enhancement factor-1 (TCF/LEF-1) family, and it regulates transcription of target genes [14] (Figure 1). In addition, cytoplasmic β-catenin is involved in cell-cell interactions in combination with cadherin and actin [15]. In chick embryos WNT promotes trunk myogenesis, but blocks myogenesis in the branchial arches [16]. Thus, β-catenin has multiple functions in regulating gene expression and cytoskeletal complex formation; however, the molecular mechanism of WNT/β-catenin signaling during muscle development is still largely unknown.

Role of WNT/β-catenin signaling in early muscle specification and myoblast proliferation

Mice with deficiency of WNT/β-catenin signaling (*Ctnnb1*$^{-/-}$ mice) are embryonic lethal by E8.5 with increased cell death [17]. During axial myogenesis, WNT/β-catenin signaling is crucial for dermomyotome and myotome formation [2,18–20]. WNT ligands can positively regulate the number of dermomyotomal Pax3 and Pax7 expressing (Pax3^{+}/Pax7^{+}) progenitors [21–23]. Mice with conditional depletion of β-catenin in muscle precursor *Pax7*$^{+}$ cell lineage (*Pax7-Cre;Ctnnb1*$^{\Delta/fl2\text{-}6}$ mice) show reduced formation of slow myofibers during fetal myogenesis [2]. Mice with constitutively activated β-catenin in *Pax7*$^{+}$ lineage (*Ctnnb1* $^{\Delta ex3}$*;Pax7-Cre* mice) exhibit reduced muscle fiber size, excessive nerve defasciculation and branching, and increased number of motor axon at E18.5, resulting in neonatal lethality [2,24]. Thus, the studies of both loss-of-function and gain-of-function of β-catenin indicate that precise amounts of WNT/β-catenin signaling activity is important for myogenesis of Pax7^{+} progenitor cells.

Furthermore, WNT ligands can induce *Myf5* and *Myod1* expression *in vitro* [25–28]. WNT ligands regulate both the specification of skeletal myoblasts in the paraxial mesoderm and the induction of location-specific expression of MRFs that govern the determination and terminal differentiation of muscle cells [29]. Our recent study shows that during myoblast proliferation, gene expression of *Ccna2* and *Cdc25c* is specifically downregulated by the inhibition of WNT/β-catenin signaling in both C2C12 cells and primary mouse myoblasts isolated from the tongue and the hind limb muscle [30] (Figure 2). Importantly, WNT/β-catenin activation also induces satellite cell proliferation during skeletal muscle regeneration [31]. Furthermore, treatment with secreted frizzled-related protein 3 (sFRP3), a soluble WNT antagonist, reduces skeletal myogenesis in a dose-dependent fashion in mouse

embryos [32]. Altogether, WNT/β-catenin signaling plays a crucial role in myogenic proliferation in both development and regeneration.

Role of WNT/β-catenin signaling in myoblast fusion

Pharmacological activations of WNT/β-catenin signaling can facilitate the differentiation of satellite cells and myoblasts [33–35]. During myoblast fusion, the cell signaling pathway is tightly regulated and controls downstream target molecules involved in membrane fusion and cytoskeletal remodeling [36]. Members of the R-spondin (RSPO) family of secreted cysteine-rich proteins (RSPO1, -2, -3, and -4) and their cognate receptors, members of leucine-rich repeat-containing G protein-coupled receptors 4, 5, and 6 (LGR4/5/6), have emerged as new regulatory components of the WNT signaling pathway [36]. Interestingly, RSPOs activate WNT/β-catenin signaling at the receptor level and promote myogenic differentiation and hypertrophic myotube formation in C2C12 cells through gene expression of the TGFβ antagonist Follistatin (*Fst*) in C2C12 cells, primary myoblasts from the hind limb muscle, and mouse embryos [37,38]. This suggests that cell signaling network of WNT/β-catenin and TGFβ may be crucial for myogenic differentiation and fusion.

The destruction complex containing AXIN, APC, and GSK3β can regulate the stability of β-catenin and the following WNT/β-catenin signaling activity. In the absence of WNT ligands, GSK3β is activated (phosphorylated) and can phosphorylate β-catenin for ubiquitination and degradation by the proteasome. WNT-mediated GSK3β inactivation by WNT3A or LiCl (lithium chloride; pharmacological WNT/β-catenin signaling inducer) promotes myoblast fusion during muscle differentiation in C2C12 cells [39]. Furthermore, treatment with insulin and a specific inhibitor of GSK3β or WNT/β-catenin signaling activator LiCl leads to enhanced differentiation of C2 myoblasts [35]. These studies indicate that WNT/β-catenin signaling can regulate myoblast differentiation, including fusion of myoblasts.

It is important to identify specific cell signaling cascades and molecules for the fusion of myoblasts. Our recent study shows that gene expression of *Fermt2* is regulated by WNT/β-catenin signaling during myogenic differentiation and fusion [30]. RNAi knockdown of *Fermt2* in C2C12 cells results in a failure of early myoblast differentiation and/or myoblast fusion [30,40]. These findings indicate that WNT/β-catenin-mediated *Fermt2* expression is crucial for myogenic differentiation, including myoblast fusion (Figure 2). This is also supported by the fact that mice with disruption of *Fermt2* exhibit early embryonic lethality with musculature developmental defects [41].

Role of WNT/β-catenin signaling in muscle homeostasis

Muscle homeostasis includes maintenance of the number and shape of muscle fibers and the metabolic function and movement. β-catenin is involved in both transcriptional regulation and cell-cell adhesion (*aka* adherens junction formation) through the formation of cadherin/β-catenin/actin complex. Our recent study shows that a blockade of WNT/β-catenin signaling results in disrupted cell adhesion via loss of cadherin/β-catenin/actin complex formation during muscle maturation/maintenance [30] (Figure 2). The extracellular region of cadherin binds to the extracellular molecules in a Ca^{2+}-dependent manner. Through extracellular interactions, opposing cadherin dimers can integrate the actin cytoskeletons.

Stabilization of intracellular adhesion requires the cytoplasmic domain of cadherin, which binds to β-catenin and can be an anchor for a number of cytoskeletal proteins. Thus, β-catenin co-localizes with cadherin in membranes and plays dual roles in WNT/β-catenin signaling and in cadherin-mediated cell adhesion [42,43].

Cadherin family molecules exhibit distinctly regulated tissue distribution and control morphogenesis. Skeletal muscle cells express both N-cadherin (encoded by *Cdh2*) and M-cadherin (encoded by *Cdh15*) throughout myogenesis, from progenitors to myofibers, in both development and regeneration [44,45]. Mice with deletion of *Cdh2* or *Cdh15* ($Cdh2^{-/-}$ or $Cdh15^{-/-}$ mice) exhibit normal myogenesis; therefore, N- and M-cadherins may be functionally redundant. A future study of $Cdh2^{-/-};Cdh15^{-/-}$ double knockout mice will address this question.

The actin family is categorized into six unique isoforms. Based on their predominant tissue-specific location, actins are categorized into four muscle-specific isoforms (α-skeletal, α-cardiac, α-smooth, and γ-smooth) and two ubiquitously expressed isoforms (β-cytoplasmic and γ-cytoplasmic) [46]. Mice with deficiency of α-skeletal actin ($Acta1^{-/-}$ mice) are indistinguishable from their littermates at birth but die in the early neonatal period (postnatal day 1 to 9) with skeletal muscle defects including reduced muscle strength and growth deficits [47]. This is because most muscles develop postnatally, although tongue muscles are well differentiated in newborns. Therefore, this suggests that the actin complex in the tongue plays a crucial role in muscle homeostasis, but not proliferation and differentiation. However, the actin complex in other muscles may be important for differentiation and maturation.

Altered WNT/β-catenin signaling is implicated in multiple malformations and syndromes including muscle disorders (ex. oculopharyngeal muscular dystrophy, facioscapulohumeral muscular dystrophy, Duchenne muscular dystrophy) in humans [48–51].

Conclusions

WNT/β-catenin signaling plays important roles in muscle development and homeostasis by regulating gene expression of cell cycle regulators and complex formation of cadherin/β-catenin/actin, respectively. This indicates that WNT/β-catenin signaling has unique target molecules in each stage of development. Thus, the *in vitro* studies with small molecules and genetic manipulation are very useful in determining the step-specific molecular mechanisms during muscle development. Our recent findings on the mechanisms of temporal specific action of WNT/β-catenin signaling may offer several intriguing possibilities into the potential for therapeutic interventions. Genetic approaches *in vivo* will further validate the functions of target molecules identified in the *in vitro* studies.

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Abbreviations

APC	adenomatous polyposis coli
ChIP	chromatin immunoprecipitation
FZD	Frizzled receptor
GSK3β	serine-threonine kinase glycogen synthase kinase-3
H&E	Hematoxylin and Eosin
IP	immunoprecipitation
LEF-1	Lymphocyte-enhancement factor-1
LRP5/6	low-density lipoprotein receptor-related protein 5/6
MyHC	myosin heavy chain
NCBI	National Center for Biotechnology Information
sFRP3	secreted Frizzled-related protein 3
TCF	T-cell factor

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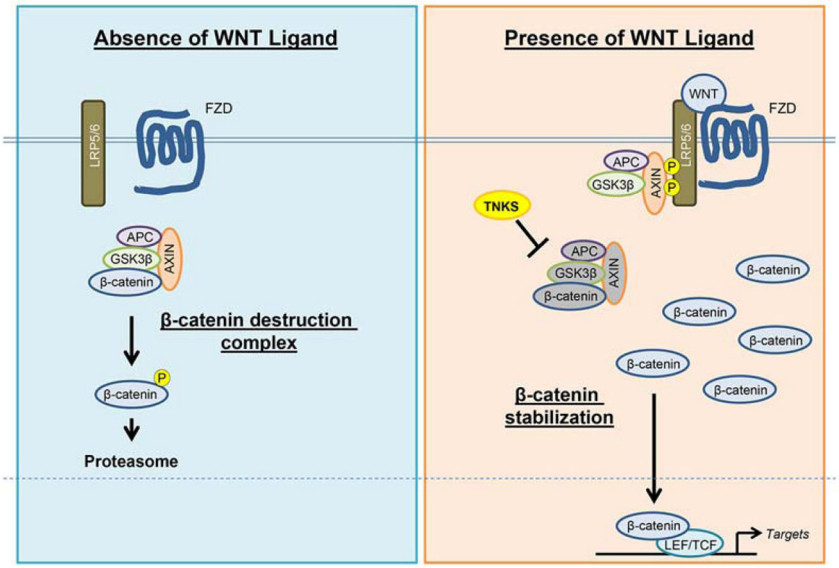

Figure 1.

WNT/β-catenin signaling pathway. In the absence of WNT ligands, β-catenin is incorporated into a destruction complex containing AXIN, adenomatous polyposis coli (APC) and the serine-threonine kinase glycogen synthase kinase-3 (GSK3β). The destruction complex phosphorylates β-catenin and leads it to be degraded by the proteasome. In the presence of WNT ligands, WNT ligands bind to a Frizzled receptor (FZD) and the low-density lipoprotein receptor-related protein 5/6 (LRP5/6). The destruction complex is inactivated, and then β-catenin can be stabilized and translocate into the nucleus. Increased nuclear β-catenin interacts with transcriptional co-activators such as members of the T-cell factor/ Lymphocyte-enhancement factor-1 (TCF/LEF-1) family and regulates transcription of target genes.

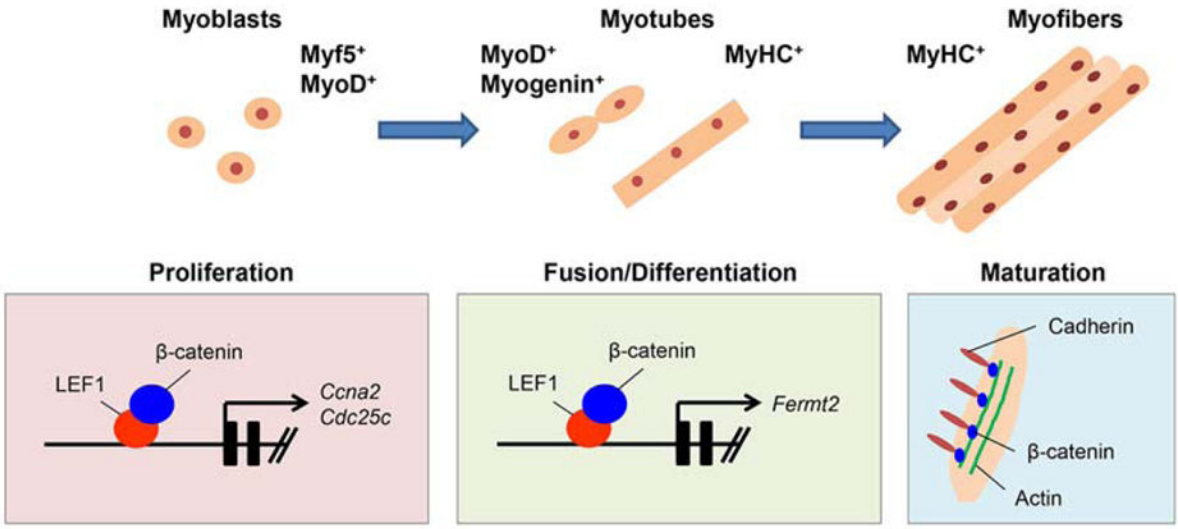

Figure 2.

Model of WNT/β-catenin signaling during myogenesis. The schematic diagram depicts our model of the mechanism of WNT/β-catenin signaling pathway during myogenesis. WNT/β-catenin signaling regulates gene expression of *Ccna2* and *Cdc25c* in the cell proliferation stage. WNT/β-catenin signaling regulates gene expression of *Fermt2* in the differentiation stage. Beta-catenin forms a complex with cadherin and actin to elongate the myofiber. Disruption of the complex formation results in disorganized myofiber morphology.