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Wnt Signaling in Bone and Muscle

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Introduction

Wnt signaling plays central roles in many aspects of development and alterations in the pathway are commonly associated with human disease. The first Wnt gene was identified by Nusse and Varmus in 1982 based on its location in a chromosomal region enriched for integration sites in mouse mammary tumor virus (MMTV)-induced mammary adenocarcinomas [1]. It was originally referred to as Integration site-1 (*int-1*) because of this relationship with MMTV and inferred to be a secreted protein based on the presence of a signal peptide. The protein proved difficult to purify in biologically active form [2], so the initial identification of downstream signaling components was based on genetic systems. A key system in which this was examined was the development of embryonic segment polarity in *Drosophila melanogaster*. This was based on the fact that the *Drosophila* *Wingless* gene was found to be a close homolog of the mouse *int-1* gene [3]. The observation that *Wingless* was a component of the well-defined segment polarity pathway allowed several other genes to be functionally linked to the *Wingless/int-1* gene (reviewed in [4]). Because of the homology between *int1* and *Wingless*, the gene was renamed as *Wnt1* (*W*ingless + *int*1) [5] and was eventually recognized as the founding member a large Wnt gene family encoded by 19 different genes in humans and mice. Wnt proteins share characteristics as cysteine-rich glycoproteins dependent on the addition of a lipid modification for function [6].

In this review, we will briefly describe the components of signaling pathways induced by Wnt ligands and then describe the current state of research as this applies to aspects of development and disease as it relates to skeletal muscle and bone. We will conclude with a discussion of the parallels and differences in Wnt signaling in these two contexts and how these pathways are being (or could potentially be) targeted for therapeutic treatment of musculoskeletal diseases.

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Wnt-Induced Signaling Pathways

The requirement for Wnt signaling in the establishment of *Drosophila* embryonic segment polarity helped define the core components of one signaling pathway initiated by Wnt ligands during the early to mid-1990s. This specific Wnt pathway, dependent on the β -catenin protein (*armadillo* in *Drosophila*), is referred to as the “canonical” pathway (reviewed in [7, 8]) (**Fig. 1**). In this pathway, a Wnt ligand engages a receptor complex that includes a member of the Frizzled family of seven transmembrane receptor proteins and either the Low density lipoprotein related receptors 5 and 6 (Lrp5/6). In the absence of this receptor complex, the cytoplasmic and nuclear levels of the β -catenin protein are reduced or absent due to Glycogen synthase kinase 3 (GSK3)-dependent phosphorylation of residues near its N-terminus which targets the protein for ubiquitin-dependent proteolysis. GSK3 has numerous putative substrates, but in the context of canonical Wnt signaling its activity is regulated by the formation of a multiprotein complex which includes the Adenomatous polyposis coli (APC) protein and Axin. Upon Wnt binding to the LRP5/6;Frizzled receptor complex, the cytoplasmic tail of the Lrp5/6 component becomes phosphorylated creating a binding site for Axin. Recruitment of Axin to this site results in inhibits GSK3-mediated phosphorylation of β -catenin, allowing β -catenin levels to increase in the cytoplasm. In some cell types, additional pathways downstream of Wnt ligands may be required for nuclear localization of β -catenin. Upon entering the nucleus, β -catenin interacts with members of the LEF/TCF family of DNA binding proteins to bind to and activate target gene transcription.

The historical focus on the “canonical” Wnt/ β -catenin pathway has resulted in relatively less attention being played to the myriad of other signaling pathways activated by Wnt ligands. The shared characteristic of these pathways is that they signal in a β -catenin-independent manner [9] (**Fig. 1**). These pathways can be induced by activation of several alternative Wnt receptors such as Ror2 and Ryk, but may also be initiated by engagement of Frizzled receptors by Wnts, often in the absence of co-engagement of Lrp5/6. One of the best known of these pathways is referred to as the planar cell polarity (PCP) pathway. This pathway, like the “canonical” pathway, was originally characterized in *Drosophila melanogaster*. Here frizzled activation signals through the small GTPase, RhoA, and Jun N-terminal kinase (JNK) to regulate cell-cell communication required for the proper orientation of wing hair and the ommatidia of the compound eye [10]. The PCP pathway also influences cytoskeletal remodeling, cell adhesion, and motility in mammalian systems [11]. Other β -catenin-independent pathways induced by Wnts include those that activate Protein Kinase C [12], Protein Kinase A [13], mTOR [14], and PI3K/Akt [15].

The activation of receptor complexes by Wnts is also under complex regulatory control. For example, the four members of the Secreted family of frizzled proteins (sFRPs), can inhibit Wnt-induced signaling by preventing the interaction between Wnts and the Frizzled component of the co-receptor [16]. In addition, proteins such as members of the Dickkopf family [17] and Sclerostin [18] inhibit β -catenin-dependent, canonical signaling by preventing Wnt ligands from binding to Lrp5/6. An interesting recent development in this context is the demonstration that Lrp4 acts within the local microenvironment to bind Sclerostin and present it to Lrp5/6 to facilitate inhibition of Wnt signaling [19].

Recently, the processes involved in the production and secretion of Wnts have become more defined. Again, the foundation for this work was based on *Drosophila* genetics which identified the requirement for the gene, *Porcupine*, in Wnt-producing cells for establishment of embryonic segment polarity [20]. The protein encoded by *Porcupine* was subsequently identified as a member of the membrane-bound O-acyl transferase family required to acylate Wnt ligands [21]. Lipid-modified Wnts are then bound by a protein referred to as Wntless (also known as *GPR177* or *Sprinter*) to allow transit to the plasma membrane and subsequent secretion [22]. All naturally occurring Wnt proteins are thought to require lipid modification by Porcupine and Wntless-mediated transport for secretion.

Role of Wnt Signaling in Bone Development and Homeostasis

The intense interest in understanding the role of Wnt signaling in regulating bone development and homeostasis can be traced to three seminal manuscripts in the early 2000s. The first reported that the underlying cause of Osteoporosis pseudoglioma (OPPG), a syndrome in which affected patients have extremely low bone mass, was homozygosity for loss of function mutations in *LRP5* [23]. Shortly after this, two groups independently reported that a point mutation in *LRP5* (G171V) was the underlying cause of a dominantly inherited high bone mass (HBM) trait [24, 25]. The mechanistic explanation for high bone mass is that the G171V mutation produces an LRP5 protein that can no longer interact with inhibitors such as DKK1 and Sclerostin [26-30] (as well as other proteins such as MeSD [31, 32]). While some individuals with HBM suffer from complications such as headaches [33], the fact that they do not appear to be predisposed to carcinogenesis spurred a great deal of interest on the part of biotechnology and pharmaceutical companies in developing agents that mimicked the results of this alteration. Subsequent studies have reported additional mutations in the *LRP5* gene that increase or decrease human bone mass (for example see [34]).

Mouse models in which *Lrp5* was globally deleted demonstrated reduced bone mass [35-37], further validating that loss of *LRP5* was the underlying cause of OPPG. In addition, osteoblast-specific expression of *LRP5*^{G171V} resulted in the predicted high bone mass [38]. The link between LRP5 and β -catenin lead to an examination of the roles of other components of the canonical Wnt pathway in bone development and disease. For example, conditional deletion of *Ctnnb1* (which encodes β -catenin) in osteoblasts or osteocytes resulted in severely low bone mass, while conditional activation of β -catenin by either cre-mediated expression of a non-degradable form of β -catenin or via deletion of *Apc* lead to dramatically increased bone mass [39-41]. In both cases, further work linked alterations in β -catenin signaling to dysregulation of the OPG/RANKL signaling axis. Specifically, OPG was shown to be a direct transcriptional target of β -catenin [39]. Thus, changes in bone mass seen in the context of altered Wnt signaling within osteoblasts, at least in part, may be due to alterations in osteoclast function or differentiation caused by changes in RANKL-induced signaling. There are several additional mechanisms by which Wnts derived from osteoblasts or other cells in the skeletal microenvironment influence osteoclast function. For example, osteoblast-derived Wnt5a can enhance osteoclast differentiation and activated via activation of the ROR2 receptor [42]. Also, the demonstration that dynamic regulation of β -catenin is

required for proper osteoclast differentiation suggests that Wnt ligands may have stage-specific effects during osteoclastogenesis [43].

Osteoblast-specific deletion of the *Lrp5* and *Lrp6* genes also lead to significant reductions in bone mass [44], consistent with a role for canonical Wnt signaling within the osteoblast lineage in controlling bone mass. However, an alternative explanation in which Lrp5-mediated regulation of serotonin production by the enterochromaffin cells of the intestine has also been proposed [45-47]. At early stages of osteoblast differentiation, canonical Wnt signaling is required for commitment to the osteoblast lineage. Deletion of either *Ctnnb1* [48-50] or *Lrp5* and *Lrp6* [51] results in a failure to efficiently form bone.

Alterations in known negative regulators of the canonical signaling pathway have also been clearly linked to changes in bone mass in both humans and mice. For example, alterations in the function of the Sclerostin (*SOST*) locus, which encodes a protein that inhibits canonical Wnt signaling, are causally linked to two syndromes associated with high bone mass, Sclerosteosis and van Buchem's disease [52, 53]. This association was also validated in mouse models. In addition, mouse models with impaired Dkk1 function, another negative regulator of the pathway, also develop high bone mass [54].

In addition to work on the roles of the Wnt receptor complex and signaling components downstream of its activation, recent work has revealed key roles for specific Wnt ligands and components regulating its secretion from Wnt-producing cells in establishing and/or maintaining normal bone mass. For example, a meta-analysis of SNPs associated with alterations in human bone mineral density identified the genomic region where Wntless/GPR177 is located as containing SNPs significantly associated with changes in bone mineral density [55]. The importance of GPR177 has been validated using several mouse models which demonstrate that loss of GPR177 results in low bone mass [56-58]. Finally, recent work on the genetic causes of Osteogenesis imperfecta, a disease characterized by the presence of brittle bones, identified putative causative mutations in *WNT1* [59-61]. This establishes a key role for Wnt1 in establishing and maintaining human bone mass, however the precise mechanisms by which this occurs await further study.

Perhaps because OPPG, Sclerosteosis, and van Buchem's disease were also associated with alterations in bone mass correlating with changes in β -catenin signaling, non-canonical Wnt pathways have received less attention in the context of bone development. However, it is clear that non-canonical pathways also contribute to this process. For example, mouse models demonstrate that Wnt5a secreted from cells of the osteoblast lineage activates ROR2 on osteoclasts to regulate their differentiation and function [42]. In addition, mice lacking Frizzled 9 have reduced bone mass due to alterations in signaling pathways that are independent of β -catenin [62, 63]. Also, Wnt signaling acting through PKC promotes bone formation [64]. These are just some examples of the demonstrated roles for noncanonical Wnt signaling in bone development, and there are undoubtedly additional examples that will emerge as we learn more about the functions of these pathways in other systems. Nowhere is this more apparent than in our understanding of muscle cell regeneration.

Wnt Signaling in Myogenesis

Skeletal muscle is derived from somites during embryonic development [65], and myogenic specification in somatic cells is regulated by signals from the surrounding tissues (**Fig. 2**). Expression of Wnt-1, -3a, -4, -6, -7a and 11 from dorsal neural tube or ectoderm is critical for the induction, initiation and progression of myogenesis in the presomitic mesoderm and early somites [66, 67]. Within the embryonic myogenic progenitors, Wnts also regulate the expression of Pax3/7, MyoD and Myf5, key transcription factors involved in myogenesis [68-72]. Genetic studies have demonstrated the role of several Wnt molecules and β -catenin in the normal development of skeletal muscles [73, 74]. Therefore, canonical and non-canonical Wnt signaling pathways play multiple essential roles in embryonic myogenesis.

The role of canonical Wnt/ β -catenin signaling in the regulation of postnatal satellite cell function and skeletal muscle regeneration has been controversial. Satellite cells are muscle resident stem cells responsible for postnatal regeneration of injured muscles. Canonical Wnt activation has been suggested to induce satellite cell proliferation during skeletal muscle regeneration [75]. However, contradictory results showing that activation of canonical Wnt signaling is necessary to counteract Notch signaling to induce myogenic differentiation were also reported [76]. Furthermore, in the aged niche, elevated systemic Wnt molecules impede myogenic differentiation and facilitate satellite cell fate conversion to fibroblastic cell lineages [77]. Recently, a thorough genetic study in adult satellite cells demonstrated that it is not activation of Wnt/ β -catenin signaling but rather silencing that is important for muscle regeneration [76].

Adult skeletal muscles contain heterogeneous types of muscle fibers that can be broadly divided into slow- and fast-twitch myofibers. In the limb muscles, the slow-twitch myofibers express type I myosin heavy chain (MyHC), while the fast-twitch myofibers express type IIa, IIx and IIb MyHC isoforms [78]. During early stages of myofiber generation in chicks, Wnt11 promotes fast myofiber formation, whereas Wnt5 enhances slow myofiber generation [79]. Wnt4 similarly stimulates fast myofiber formation in chicks [80]. Activation of β -catenin induced myofiber hypertrophy followed by degeneration of fast myofibers in zebrafish [81]. In mice, depletion of β -catenin during myogenesis in Pax7-lineage cells led to reduced slow myofibers and overall reduction of muscle mass [82]. During fetal development in mice, Wnt/ β -catenin signaling induces BMP4 expression in myoblasts which in turn induces slow myofibrogenesis (Skelet Muscle. 2013 Mar 5;3(1):5. doi: 10.1186/2044-5040-3-5). Together, these studies suggest that Wnt signaling plays diverse roles in regulating slow-versus fast-twitch myofiber formation during development.

Role of Wnt Signaling in Muscle Growth and Regeneration

Satellite cells located beneath the basal lamina of myofibers are required for the growth and regeneration of skeletal muscle [83]. Molecular genetic studies in mice have established that a small subset of the satellite cell population are stem cells that are capable of reconstituting the satellite cell population following transplantation, of long-term self-renewal, and of giving rise to committed myogenic progenitors through asymmetric apical-basal cell divisions [84, 85]. Cre-LoxP lineage tracing in mice using *Myf5-Cre* and *R26R-YFP* alleles

allows the discrimination between committed satellite myogenic cells that have expressed *Myf5-Cre* (YFP⁺), and a small subpopulation (<10 %) of satellite stem cells that have never expressed *Myf5-Cre* (YFP⁻) [84].

Satellite stem cells also express high levels of Fzd7 and signaling through the Wnt7a/Fzd7 planar-cell-polarity (PCP) pathway drives the symmetric expansion of satellite stem cells to accelerate and augment muscle regeneration [86]. Closer examination showed that administration of recombinant Wnt7a markedly stimulated the symmetric expansion of satellite stem cells but did not affect the growth or differentiation of myoblasts. Conversely, silencing of Fzd7 abrogated Wnt7a binding and stimulation of stem cell expansion. Wnt7a signaling was shown to induce the polarized distribution of the planar cell polarity effector Vangl2, and silencing of Vangl2 abrogated Wnt7a action on satellite stem cell expansion. Wnt7a overexpression enhanced muscle regeneration and increased both the number of satellite cells and muscle mass. Conversely, mice lacking Wnt7a exhibited a decrease in satellite cell number following regeneration. Therefore, Wnt7a signaling through the PCP pathway controls the homeostatic level of satellite stem cells and hence regulates the regenerative potential of muscle.

Over-expression of Wnt7a results in a significant hypertrophic response of skeletal muscle [15]. Wnt7a/Fzd7 signalling in myofibers was found to directly activate the Akt/mTOR growth pathway thereby inducing hypertrophy. Notably, the Fzd7 receptor complex was associated with Gαs and PI3kinase and these components were required for Wnt7a to activate the Akt/mTOR growth pathway in myotubes. Surprisingly, Wnt7a/Fzd7 activation of this pathway was completely independent of IGF-receptor activation. Together, these experiments demonstrate that Wnt7a/Fzd7 activates distinct pathways at different developmental stages during myogenic lineage progression, and together identify a novel non-canonical anabolic signalling pathway for Wnt7a and its receptor Fzd7 in skeletal muscle [15].

The remodeling of the stem cell niche in muscle by satellite cells expressing fibronectin (FN) plays an unexpected role in Wnt7a signaling and satellite stem cell expansion [87]. Syndecan-4 (Sdc4) and Fzd7 form a co-receptor complex in satellite cells and binding of the ECM glycoprotein FN to Sdc4 stimulates the ability of Wnt7a to induce the symmetric expansion of satellite stem cells. Newly activated satellite cells dynamically remodel their niche by transient high-level expression of FN. Knockdown of FN in prospectively isolated satellite cells severely impairs their ability to repopulate the satellite cell niche. Conversely, *in vivo* over-expression of FN with Wnt7a dramatically enhances the expansion of satellite stem cells in regenerating muscle. Therefore, activating satellite cells remodel their niche through autologous expression of FN that provides feedback to stimulate Wnt7a signalling through the Fzd7/Sdc4 co-receptor complex. Thus, FN and Wnt7a together regulate the homeostatic levels of satellite stem cells and satellite myogenic cells during regenerative myogenesis [87].

Wnt7a/Fzd7 also acts at another level during muscle growth and repair to increase the polarity and directional migration of murine satellite cells and human myogenic progenitors through activation of Dvl2 and the small GTPase Rac1 [88]. Importantly, these effects can

be exploited to potentiate the outcome of myogenic cell transplantation into dystrophic muscles. A short 3h Wnt7a treatment resulted in a marked stimulation of tissue dispersal and engraftment of transplanted satellite cells leading to significantly improved muscle function. Moreover, myofibers at distal sites that fused with Wnt7a-treated cells were hypertrophic suggesting that the transplanted cells deliver activated Wnt7a/Fzd7 signaling complexes to recipient myofibers. Interestingly, satellite cells and their daughter progenitors take up Wnt7a/Fzd7 complexes by clathrin-dependent endocytosis into long-lived intracellular vesicles and delivery of these complexes to myofibers after fusion of the migrating progenitors stimulates hypertrophy. Taken together, these findings describe a viable and effective *ex vivo* cell modulation process that profoundly enhances the efficacy of stem cell therapy for skeletal muscle [88].

Thus, Wnt7a acts at multiple levels as an intrinsic factor to positively regulate regeneration: First, Wnt7a stimulates the symmetric expansion of the satellite stem cell compartment via the non-canonical PCP-signaling pathway; Second, Wnt7 signaling simulates the polarity and motility of satellite cells and myogenic progenitors via non-canonical PCP-signaling; Third, Wnt7a directly induces myofiber hypertrophy by activating the AKT/mTOR growth pathway.

Wnt7a treatment of the *tibialis anterior* (TA) muscle in an *mdx* mouse resulted in a significant increase in strength, as determined by generation of specific force per unit mass, and markedly reduced levels of contractile damage, likely due to a shift towards slow-twitch fiber type [89]. Wnt7a induced myotube hypertrophy and a shift towards slow-twitch fiber type in human primary myotubes. Taken together, these findings suggest that Wnt7a is a promising candidate for development as an ameliorative treatment for patients with DMD.

Duchenne Muscular Dystrophy (DMD) is a devastating genetic muscular disorder of childhood manifested by progressive debilitating muscle weakness and wasting, and ultimately death in the second or third decade of life [90]. Wnt7a treatment was found to efficiently induce satellite cell expansion and myofiber hypertrophy in treated muscles of *mdx* mice [89]. Importantly, Wnt7a treatment resulted in a significant increase in strength of the muscle as determined by generation of specific force. Furthermore Wnt7a reduced the level of contractile damage likely by inducing a fiber type shift towards slow-twitch. Wnt7a similarly induced myotube hypertrophy and a shift in fiber type towards slow-twitch in human primary myotubes. Therefore, Wnt7a appears to be a promising candidate for development as an ameliorative treatment for muscular dystrophy [89].

Opportunities for Therapeutics

The Wnt pathway has emerged as a therapeutic target for many diseases [91]. In the context of bone and muscle, therapies are being developed and evaluated that aim to increase the activity of the pathway. This is contrast to therapeutic programs in the oncology space which aim to treat several tumor types by blocking Wnt signaling activity. For example, Porcupine inhibitors are currently in clinical trials to treat several types of cancer [92]. It would not be surprising based on mouse models in which Wnt secretion from osteoblasts has been blocked by deletion of *Wntless*/GPR177 [58] if patients being treated with these inhibitors

are susceptibility to side effects associated with decreasing bone mass. Conversely, clinicians should be appropriately cognizant of the potential for Wnt activating therapies to predispose to inappropriate cellular growth. Thankfully, this has not been a problem to date perhaps due to the specificity of some of the therapies. For example, Sclerostin is primarily expressed from mature osteocytes and is thought to act in the local environment, so the effects of anti-sclerostin therapies would be predicted to be limited to the skeleton [18].

Several agents which upregulate canonical Wnt signaling are being developed. These include strategies to block the function of Sclerostin or DKK1 which are currently being tested in human clinical trials [93]. In addition, recent studies characterizing the activity of antibodies designed to modulate Lrp6-mediated activation of β -catenin signaling have potential future promise [94, 95]. In addition, the direct application of liposomal vesicles packaged with purified Wnt3a stimulates bone regeneration and engraftment [96-98]. Finally, treatment with lithium chloride, which stabilizes β -catenin via its inhibition of GSK-3 activity [99], can also enhance fracture healing [100, 101].

An obstacle to the use of Wnt7a in recombinant protein therapy is its hydrophobicity caused by the palmitoylation of the protein during post-translational processing prior to secretion. The recently solved crystal structure of a Wnt/Frizzled complex was consistent with the concept that the lipid-modification of Wnt was necessary for function as the Frizzled protein contains a cleft that specifically interacts with this lipid modification [102]. This lipid modification is also consistent with the difficulty in purifying biologically active Wnt proteins as the purification protocols resulted in Wnt proteins lacking the Wnt modification. This lipid modification also complicates the development of Wnt proteins for potential therapeutic use as the associated hydrophobicity creates challenges for delivery.

Recently, however, one of the authors of this review developed a variant of Wnt7a that is comprised of the final carboxyl-terminal 137 amino acids (Wnt7aCT), and entirely lacks lipidation sites [103]. Wnt7aCT exhibits similar or superior effect on muscle regeneration relative to full length Wnt7a, is readily expressed to high levels, and exhibits improved dispersal in tissue, and bioavailability. This work is significant because it will potentially transform the utility of Wnts for biotherapeutic applications.

Understanding how Wnt signaling controls the growth and repair of bone and muscle tissue is clearly highly relevant to understanding the regenerative processes that occur in patients with degenerative diseases such as osteogenesis imperfecta and muscular dystrophy. Without question, mechanistic studies are providing novel insights into the biology of bone and muscle regeneration and this knowledge is being actively translated towards having clinical impact. Such mechanistic insights are key to the development of new modalities of therapeutic intervention that will include protein biologics but also small drugs that target these pathways.

Recent work has focused increased attention on the mechanisms by which muscle and bone interact to maintain musculoskeletal health [104]. Emerging information suggests that Wnt ligands may mediate some aspects of the interaction between these tissues. For example, Wnt3a secreted from osteocytes may support myogenesis and maintenance of muscle

function. Muscle tissue appears to secrete factors that can inhibit osteocyte apoptosis in association with elevated levels of β -catenin [105]. Further evaluation of how Wnt signaling may mediate muscle-bone crosstalk, as well as assessment as to how applicable Wnt signaling mechanisms identified in either myocytes and osteoblasts are to other cell types will provide additional opportunities for insights into this critical signaling pathway.

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Highlights

Canonical Wnt signaling is critical for normal bone and muscle development

Non-canonical Wnt pathways are key to muscle repair processes associated with satellite cells Understanding of these processes will be critical for developing effective therapeutic strategies

Figure 1. Overview of Wnt Signaling Pathways

A. Canonical signaling pathways are typically defined as those that are dependent on the stabilization of the β -catenin protein. In this context, Wnt ligands bind to a receptor complex that includes a member of the Frizzled family of seven transmembrane proteins and either Lrp5 or Lrp6. The engagement of this receptor complex leads to the phosphorylation of serine residues in the cytoplasmic tail of Lrp5/6 creating a binding site for the Axin protein. Axin is a component of a multi-protein complex which also includes the adenomatous polyposis coli (APC) protein and the serine/threonine protein kinase, Glycogen synthase kinase 3 (GSK3). In the absence of an upstream Wnt signal, this multiprotein complex facilitates the GSK3-dependent phosphorylation of β -catenin, targeting it for ubiquitin-dependent proteolysis. When Axin is recruited to the plasma membrane via its association with phosphorylated Lrp5/6, GSK3-mediated phosphorylation of β -catenin is inhibited, leading to increased levels of cytoplasmic β -catenin. β -catenin then can undergo nuclear translocation and lead to target gene activation. **B.** Non-canonical signaling pathways refer to the group of pathways induced by Wnt ligands that act via β -catenin-independent mechanisms. These include a pathway that activates the small GTPases, RhoA and Rac1, resulting in cytoskeletal rearrangement and activation of Jun N terminal kinase (JNK) and a pathway that induces PI3K and subsequent activation of Akt. Adapted from [106].

Figure 2. Wnt signaling and the embryonic development of skeletal muscle

Wnt signaling from surrounding tissues influences the development of muscle in a spatiotemporal manner. The dorsal regions of the neural tube express Wnt1, Wnt3a and Wnt4 whereas the dorsal ectoderm expresses Wnt4, Wnt6 and Wnt7a. The epaxial dermomyotome expresses Wnt11.