Review

Wnt signaling in myogenesis

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The formation of skeletal muscle is a tightly regulated process that is critically modulated by Wnt signaling. Myogenesis is dependent on the precise and dynamic integration of multiple Wnt signals allowing self-renewal and progression of muscle precursors in the myogenic lineage. Dysregulation of Wnt signaling can lead to severe developmental defects and perturbation of muscle homeostasis. Recent work has revealed novel roles for the non-canonical planar cell polarity (PCP) and AKT/mTOR pathways in mediating the effects of Wnt on skeletal muscle. In this review, we discuss the role of Wnt signaling in myogenesis and in regulating the homeostasis of adult muscle.

A role for Wnt in muscle

Wnt signaling plays an essential role during embryonic muscle development and in the maintenance of skeletal muscle homeostasis in the adult. During embryonic development, Wnt signals control the expression of myogenic regulatory factors (MRFs), which are essential for myogenic lineage progression. In adult skeletal muscle, canonical Wnt signaling regulates the differentiation of muscle stem cells (satellite cells), whereas non-canonical signals mediate the self-renewal of satellite stem cells and the growth of muscle fibers. In the following sections, we provide a comprehensive overview of canonical and non-canonical Wnt signaling in myogenesis during development and in the adult.

Wnt signaling

Wnt proteins constitute a large family of secreted glycoproteins that are related to the *Drosophila* wingless gene [1] (see Glossary). In mammals, the Wnt family comprises 19 members that share homologies in their amino acid sequence but often have fundamentally distinct signaling properties [2]. All Wnt proteins share a signal sequence for secretion, several glycosylation sites, and a characteristic distribution of 22 cysteine residues [2].

Wnt proteins typically bind to Frizzled receptors (Fzd) located in the plasma membrane of target cells [1,3]. Fzd receptors are seven-transmembrane proteins containing a large extracellular cysteine-rich domain that is involved in Wnt binding. They are known to interact with Dishevelled (Dsh) and heterotrimeric G proteins, which are required for downstream signaling [4].

Wnt–receptor interactions can elicit various intracellular responses [5], the best understood and most widely studied being the activation of β-catenin/TCF transcriptional complexes. This process is known as canonical Wnt signaling (Figure 1, in pink). A key component of the canonical Wnt signaling pathway, also referred to as the classical Wnt signaling pathway, is β-catenin. β-catenin is associated with its own degradation complex, which comprises axin, adenomatous polyposis coli (APC) and the serine–threonine kinase glycogen synthase kinase-3 (GSK-3-β). In the absence of Wnt ligands, β-catenin is phosphorylated within the complex, leading to its ubiquitin-dependent degradation (Figure 1) [4]. When canonical Wnts bind to their respective Fzd receptors, heterotrimeric G proteins and Dsh become activated, leading to the recruitment of axin to the Fzd coreceptor low-density lipoprotein receptor-related protein (LRP) [6]. Subsequently, the degradation complex is inactivated and β-catenin accumulates in the cytoplasm. On its release, β-catenin translocates into the nucleus and binds members of the TCF and LEF family of transcription factors. β-catenin functions as a transcriptional coactivator to induce context-dependent Wnt/β-catenin target genes, whose transcription controls several biological processes such as early myogenesis in the somite [7].

By contrast to canonical Wnt signaling, non-canonical Wnt signaling does not require the transcriptional activity of β-catenin. Non-canonical Wnt signaling pathways are less well characterized and understood. Non-canonical Wnt pathways signal independently of β-catenin through Fzd receptors either in concert or independent of LRP. Additionally, Fzd-independent non-canonical Wnt signaling pathways have been proposed. Examples of non-canonical Wnt

Glossary

Dermomyotome: a dorsal–lateral sheet during embryogenesis that gives rise to skeletal muscle and the dermis.
Frizzled (Fzd) receptors: a family of seven-pass transmembrane receptors for Wnt ligands.
LDL receptor-related protein (LRP): coreceptor of Fzd in canonical Wnt signaling.
Muscle hypertrophy: an increase in myofiber size, either with or without addition of new myonuclei.
Myoblasts: skeletal muscle precursor cells that can differentiate into myocytes and further into myotubes.
Myofiber: a multinucleated muscle cell that contracts on stimulation.
Myogenesis: the process of functional muscle formation.
Satellite cells: adult stem cells of skeletal muscle.
Self-renewal: the process by which a stem cell gives rise to an identical daughter cell, through symmetric or asymmetric division.
Somite: a bilaterally paired structure during embryogenesis that gives rise to adult skeletal muscle and skeleton.
Wnt: a family of highly conserved secreted signaling molecules that typically bind to Fzd receptors.

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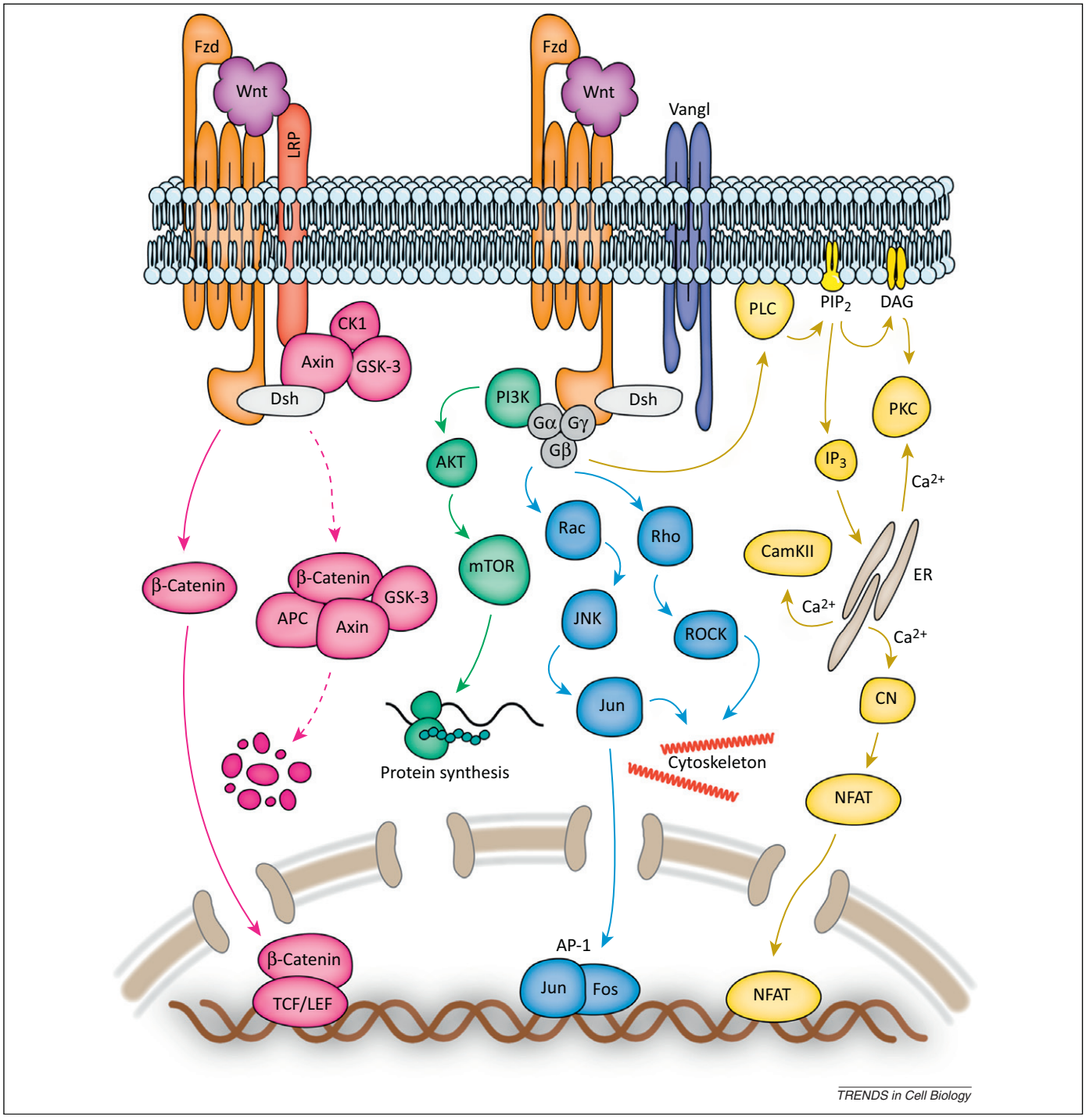

Figure 1. Overview of Wnt signaling cascades. Wnt signals can be transduced through either the canonical pathway (colored in pink) or different non-canonical pathways. Canonical Wnt signals are mediated by Frizzled (Fzd) receptors and their low-density lipoprotein receptor-related protein (LRP) coreceptors. In the absence of Wnt stimulation, β-catenin forms a degradation complex with adenomatous polyposis coli (APC), axin, and glycogen synthase kinase-3 (GSK-3) (dashed pink line). Phosphorylation of β-catenin by casein kinase I (CK1) primes β-catenin and GSK-3 for proteasome-mediated degradation. The presence of Wnt ligand results in the activation of Dishevelled (Dsh), which leads to phosphorylation-dependent recruitment of axin to the LRP coreceptor and disassembly of the β-catenin degradation complex. This leads to accumulation and stabilization of β-catenin in the cytoplasm and the nuclear translocation of β-catenin. β-Catenin complexes with the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF) and acts as a transcriptional coactivator to induce context-dependent Wnt/β-catenin target genes. Non-canonical Wnt signals are mostly transduced through Fzd receptors without involvement of LRPs. Stimulation of Fzd through Wnt can lead to the activation of phosphatidylinositol 3-kinase (PI3K), which then activates the AKT/mTOR pathway resulting in increased protein synthesis (shown in green). Other G protein-mediated pathways are the planar cell polarity (PCP) pathway (shown in blue) leading to the activation of Rac/Rho, c-Jun N-terminal kinase (JNK), and/or Rho-associated kinase (ROCK). JNK can induce Jun, which, together with Fos, forms the AP-1 early response transcription factor. Both PCP pathways have been implicated in cytoskeletal rearrangements. The Wnt/Ca^{2+} signaling pathway (colored in yellow) is defined by the activation of phospholipase C (PLC) through Wnt/Fzd, resulting in an increase in intracellular Ca^{2+} levels that activates protein kinase C (PKC) and calcium–calmodulin-dependent kinase II (CamKII) or calcineurin (CN), a phosphatase that activates the transcription factor nuclear factor of activated T cell (NFAT).

signaling pathways include the PCP, the Wnt/Ca^{2+} and the PI3K/AKT/mTOR signaling cascades (Figure 1, in green) [8–10]. The PCP signaling pathway was first discovered in *Drosophila* and has been shown to be critical for epithelial and mesenchymal cell polarity in various organisms [11,12]. Wnt/PCP signaling mediates changes in cytoskeletal organization that are a prerequisite for migration and cell polarization; for instance, controlling the orientation of hair cells