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# Wnt Signaling in Neural Circuit Assembly

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## Key Words

migration, polarity, axon guidance, dendrite, synapse formation

## Abstract

The Wnt family of secreted proteins plays a crucial role in nervous system wiring. Wnts regulate neuronal positioning, polarization, axon and dendrite development, and synaptogenesis. These diverse roles of Wnt proteins are due not only to the large numbers of Wnt ligands and receptors but also to their ability to signal through distinct signaling pathways in different cell types and developmental contexts. Studies on Wnts have shed new light on novel molecular mechanisms that control the development of complex neuronal connections. This review discusses recent advances on how Wnt signaling influences different aspects of neuronal circuit assembly through changes in gene expression and/or cytoskeletal modulation.

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## INTRODUCTION

The function of the Wnt family of signaling proteins during embryonic development and disease has been well established. In recent years, it has become clear that Wnt signaling also plays a key role in the formation and modulation of neural circuits. Wnts regulate diverse cellular functions that include neuronal migration, neuronal polarization, axon guidance, dendrite development, and synapse formation, all of which are essential steps in the formation of functional neural connections. In addition, new emerging studies strongly suggest that Wnt signaling may also regulate synaptic function in the adult brain.

**Wnt:** *Wingless*  
*Integration*

**PCP:** planar cell  
polarity

Identifying the molecular principles of neuronal connectivity is central for understanding how complex neuronal circuits are formed and modulated but also how they can be repaired after brain injury. The Wnts' ability to stimulate neurite outgrowth and synaptic site formation suggests that Wnt activity modulation could be used to stimulate nerve regeneration and circuit repair. Elucidating the molecular mechanisms by which Wnts regulate diverse aspects of circuit formation will provide a basis for developing therapeutic approaches for nerve and brain regeneration after injury or disease.

This review focuses on recent findings on the function of Wnts in neuronal circuit assembly in different biological systems. Researchers have made substantial advances in identifying the Wnt molecular mechanisms of action during brain wiring. However, much of the progress on the role of Wnts in neuronal connectivity is relatively recent; therefore, many questions remain outstanding.

## WNT LIGANDS SIGNAL THROUGH DIFFERENT SIGNALING CASCADES

Wnt proteins activate a number of signaling pathways, resulting in different cellular responses through binding to many receptors at the cell surface. Binding of Wnts to Frizzleds (Fzs), seven-pass transmembrane receptors, activates at least three different signaling pathways: the canonical or  $\beta$ -catenin pathway and the noncanonical pathways, which include the planar cell polarity (PCP) pathway and the calcium pathway (for review see Gordon & Nusse 2006, Logan & Nusse 2004). Different Wnt signaling pathways can be activated by different receptors. In addition to the Fz receptors (10 Fzs in mammals), the low-density lipoprotein receptor-related protein (LRP-5/6) is required as a coreceptor in the canonical pathway but not in the noncanonical pathways. Wnts also signal through two other receptors, Ryk/Derailed, a receptor tyrosine-like protein with an inactive kinase domain, and the receptor tyrosine

kinase, Ror2 (Cadigan & Liu 2006). Although little is known about the signaling pathways downstream of these receptors, Ryk can form a complex with Frizzled and can signal through the canonical and noncanonical pathways depending on the cell or developmental context (Lu et al. 2004).

Binding Wnts to their receptors activates the cytoplasmic protein Dishevelled (Dvl), which brings together signaling components (Malbon & Wang 2006, Wallingford & Habas 2005). Downstream of Dvl, the pathway can branch into three different cascades. In the canonical pathway, Fz signals together with the LRP5/6 to activate Dvl. A key step in the canonical pathway is the inhibition of glycogen synthase kinase-3 (Gsk3), which phosphorylates the cytoplasmic protein  $\beta$ -catenin within a degradation complex containing Axin and adenomatous polyposis coli (APC). Canonical signaling increases the stability of  $\beta$ -catenin, which subsequently translocates to the nucleus, where it activates target gene transcription in association with transcription factors of the TCF/LEF family (Clevers 2006). A divergent canonical pathway in which transcription is not involved also operates in developing axons (Ciani et al. 2004) (see below). In the PCP pathway, Fz receptors are required, together with a number of core components such as Dvl, Flamingo, van Gogh, Diego, and Prickle, to activate Rac, Rho, and JNK (Jun N-terminal kinase) (for a review see Wang & Nathans 2007). This pathway regulates cell and tissue polarity through direct changes in the cytoskeleton. The calcium pathway, which also requires Fz receptors and Dvl, activates PKC (protein kinase C) and induces intracellular calcium mobilization and CAMKI activation (Kohn & Moon 2005). Documentation of cross-talk or interference between these pathways adds further complexity (Harris & Beckendorf 2007, Inoue et al. 2004, Mikels & Nusse 2006, Veeman et al. 2003, Wu et al. 2004). In neurons, both canonical and noncanonical pathways have been implicated in different aspects of embryonic patterning and also neuronal connectivity.

## WNT-FRIZZLED SIGNALING AND DIRECTIONAL NEURONAL MIGRATION IN *CAENORHABDITIS ELEGANS*

Neuronal migration controls neuronal positioning in the nervous system, which is a vital step in nervous system wiring. Neurons undergo extensive migration to arrive at their final anatomical positions. Neuronal migration is typically highly directional and is controlled by several guidance systems (Hatten 2002).

Initial work in *Caenorhabditis* linked Wnt signaling to neuronal migration. While studying the guidance mechanisms controlling Q neuroblast migration, investigators found that *wnt/egl-20*, *frizzled/lin-17*, and *frizzled/mig-1* were involved in proper directional migration. Q neuroblasts are a pair of sensory neuron precursors that migrate along the anterior-posterior (A-P) body axis. The Q cell on the right side of the body, QR, migrates anteriorly, whereas the cell on the left side, QL, migrates posteriorly. In *egl-20* and *lin-17* mutants, both QR and QL migrate randomly along the A-P axis. Canonical Wnt signaling controls the posterior migration of QL, whereas an unknown noncanonical pathway mediates the anterior migration of QR cells (**Figure 1**).

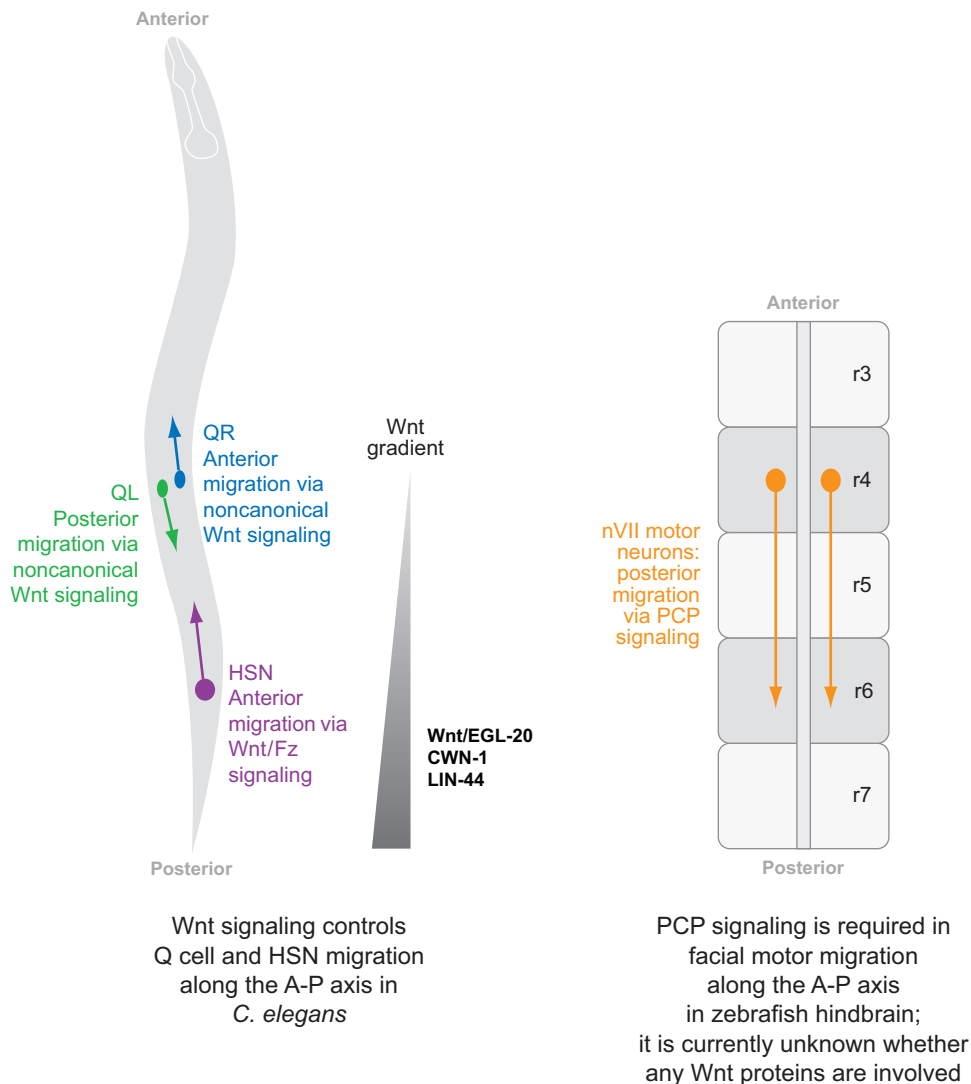
Is EGL-20 a directional cue for Q cell migration? Moving the source of EGL-20 from posterior to anterior did not reverse the direction of Q cell migration (Harris et al. 1996, Maloof et al. 1999, Whangbo & Kenyon 1999). Therefore, EGL-20 may not be a directional cue for Q cells because the QR descendants do not require graded EGL-20 protein. However, one could not exclude the possibility that other Wnts may still be directional cues for Q cells because other Wnts may contribute to A-P guidance of Q cell migration. Indeed, two other Wnts are expressed in a low to high A-P gradient (CWN-1 and LIN-44). More recent work showed that Wnt signaling is also required for the anterior migration of a different neuron class, the hermaphrodite-specific neurons (HSNs). Genetic analyses showed that all Wnts and Frizzleds play a role in HSN migration (**Figure 1**). Misexpression experiments showed

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**APC:** adenomatous polyposis coli

**TCF:** T-cell factor

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**Figure 1**

Neuronal migration along the anterior-posterior axis.

that at least Wnt/EGL-20 can act as a repellent for HSN neurons along the A-P axis (Pan et al. 2006). Therefore, Wnts can clearly act as directional cues in this case. Frizzleds likely mediate Wnt function in neuronal migration. *C. elegans* studies revealed that Frizzled signaling is rather complex. Frizzled/MIG-1 single mutation already results in HSN migration defects. Two other Frizzleds, MOM-5 and CFZ2, had no effect by themselves but en-

hanced the phenotypes of MIG-1, suggesting that they interact with MIG-1 somehow and assist the MIG-1 function. Another Frizzled, LIN-17, antagonized MIG-1 signaling. *Cfz-2* is also required cell nonautonomously for the anterior migration of anterior lateral microtubule (ALM) neurons (Zinovyeva & Forrester 2005). Therefore, further studies in this area will shed light on the complex Frizzled signaling networks.

Although many examples show that Wnt signaling controls the migration of normal and cancer cells in vertebrates, still unknown is whether Wnts are involved in vertebrate neuronal migration. Recent work in zebrafish hind-brain showed that components of the PCP pathway, strabismus (Stbm)/Van Gogh (Vang), Prickle 1, Frizzled3a, and Celsr2 (Fleming) are required for branchiomotor neuron migration along the A-P axis (Bingham et al. 2002, Carreira-Barbosa et al. 2003, Jessen et al. 2002, Wada et al. 2006). Facial motor neurons originate from rhombomere 4 and migrate caudally to rhombomere 6 of the developing hind-brain (**Figure 1**). Mutations of these PCP genes blocked the caudal migration, and the motor neurons either stay in rhombomere 4 or start abnormal radial migration. Wnts would be good candidates involved in this migration given that Wnt (Wnt11) is involved in vertebrate convergent extension, which also requires the same PCP components (Heisenberg et al. 2000). However, currently there is no direct evidence for or against a Wnt involvement in this process.

## WNTS AND FRIZZLED3 IN NEURONAL POLARITY

A fundamental feature of a vertebrate neuron is its highly polarized arrangement of axonal and dendritic processes. These polarized compartments are made of distinct components that mediate different cellular and physiological functions. Proper polarization of neuronal processes is essential for the development of neuronal connections and nervous system wiring. The mechanisms of neuronal polarity are beginning to be unveiled.

*C. elegans* neurons often do not have clear axon-dendrite distinction on a process having neighboring axonal and dendritic segments within the same process. In some neurons, such as the PLM neurons, however, the anterior and posterior processes have distinct functions and, therefore, have clear axon-dendrite polarity. Only the anterior process makes gap junctions and synapses, and there are no synapses in the

posterior process (**Figure 2**). *Wnt/lin-44* and *frizzled/lin-17* are required for proper polarization of the PLM neurons (Hilliard & Bargmann 2006, Prasad & Clark 2006). In *lin-44* and *lin-17* mutants, the polarity of PLM neurons is completely reversed, with synapses formed in the posterior process. LIN-17 is asymmetrically localized only to the posterior process and requires LIN-44 for that localization.

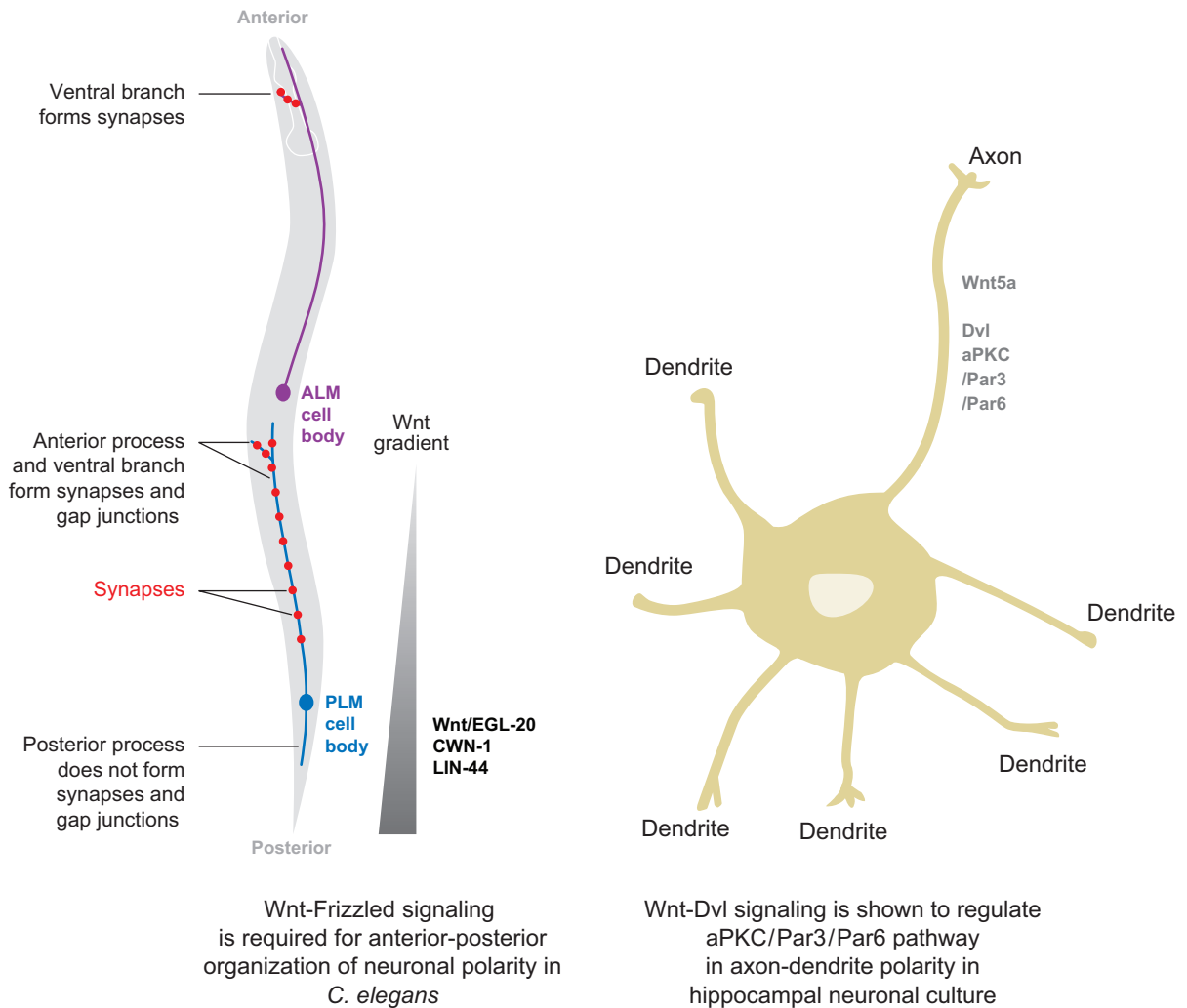
Is a Wnt gradient important for neuronal polarity? Some evidence demonstrates that Wnts provide directional information for neuronal polarity of some neurons such as the ALM, although research is still unclear about others such as the PLM (Hilliard & Bargmann 2006). A localized source of LIN-44 is apparently not essential for proper PLM polarization because LIN-44 can partially rescue PLM when expressed uniformly from a heat-shock promoter. However, the directional role for Wnts is still possible because two other Wnts, EGL-20 and CMN-1, may also regulate PLM polarity. The reason that LIN-44 can rescue A-P polarity of PLM may be that LIN-44 may sensitize its response to these two other Wnts and plays a permissive role; these two other Wnts are still present in an A-P expression gradient and are present nearby. This latter possibility is consistent with the observation that when EGL-20 was ubiquitously expressed, the polarity of another neuron, ALM, was reversed (Hilliard & Bargmann 2006). Different from PLM, ALM is located anteriorly, far away from posterior sources of the other two Wnts (CWN-1 and LIN-44), and perhaps EGL-20 misexpression is sufficient to alter the gradient. It is currently unknown which signaling pathway mediates cell polarization along the A-P axis. A good candidate would be a pathway similar to the PCP, although a Wnt protein has not been implicated in fly PCP.

Wnt signaling through Dvl may regulate neuronal polarity through the PAR (partitioning defective) polarity pathway in vertebrates. Studies using hippocampal cultures have suggested that the PAR3-PAR6-aPKC pathway is essential for axonal differentiation and neuronal polarity (Nishimura et al. 2004; Shi et al. 2003).

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**Neuronal polarity:** Neurons are highly polarized cells usually with axons and dendrites compartmentalized in distinct areas; in vertebrates, they typically grow out of opposite sides of the cell body

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**Figure 2**

Wnt signaling and neuronal polarity.

Upstream of this complex, both PAR1 and LKB-1 are required for neuronal polarization in mammals *in vivo*. *In vivo* evidence of PAR3-PAR6-aPKC regulating vertebrate neuronal polarity is still lacking (Barnes et al. 2007, Kishi et al. 2005, Shelly et al. 2007). In *Drosophila*, aPKC is not required for axon-dendrite polarity (Rolls & Doe 2004). A recent study using the same hippocampal culture system showed that Dvl may be upstream of this polarity pathway and that Wnt5a can stimulate the Dvl-mediated aPKC stabilization (Figure 2)

(Zhang et al. 2007). Overexpression of Dvl results in multiple axons, and aPKC mediates the Dvl-induced axon differentiation. This action potentially connects Wnt signaling to the PAR polarity pathway. The *in vivo* relevance of Wnts activating aPKC to regulate neuronal polarization awaits further investigation.

### WNT SIGNALING IN AXON GUIDANCE

A remarkable part of brain wiring is the highly controlled process of axon growth and

guidance. Neurons typically send out axons, which often navigate long distances to find their target area and then seek out their specific postsynaptic partners to make functional synapses. Many classes of axon guidance molecules have been discovered, including embryonic morphogens (Dickson 2002, Tessier-Lavigne & Goodman 1996, Zou & Lyuksyutova 2007). A large body of evidence from both *in vivo* and *in vitro* studies now demonstrates that Wnt proteins are guidance cues for axon pathfinding and target selection. In many cases, their biological functions and mechanisms are highly conserved between vertebrates and invertebrates.

Overexpression of *DWnt5* (previously known as *DWnt3*) disrupting commissural axon tracts (Fradkin et al. 1995) hinted that Wnts may affect axon growth in the *Drosophila* midline. Subsequent studies then showed that *DWnt5* is a repulsive cue through Derailed, a receptor-tyrosine-like protein that controls the crossing of commissural axons in the *Drosophila* embryonic central nervous system (Yoshikawa et al. 2003). *DWnt5* protein is enriched in the posterior commissure and prevents the Derailed-expressing axons from crossing the midline via the posterior commissure in each embryonic segment.

Studies in vertebrate spinal cord showed that Wnt signaling controls the direction of axon growth along the A-P axis of the spinal cord. *Wnt4* and *Wnt7b* are expressed in an A-P gradient in the ventral midline at midgestation and attract spinal cord commissural axons to turn anterior after midline crossing through an attractive guidance mechanism (Imondi & Thomas 2003, Lyuksyutova et al. 2003). In *Frizzled3* mutant mice, commissural axons turn randomly along the A-P axis. Recent studies suggest that atypical PKC signaling is required for Wnt attraction and that the anterior-posterior guidance of spinal cord commissural axons and PI3K may serve as an on switch for attractive Wnt responsiveness upon midline cross (Wolf et al. 2008). Remarkably, two other Wnts, *Wnt1* and *Wnt5a*, are expressed in an A-P gradient in the dorsal spinal cord in neonatal rodents, and they repel descending corti-

cospinal tract axons to grow down the spinal cord (Dickson 2005, Liu et al. 2005). Corticospinal tract axons are initially insensitive to Wnt repulsion. The onset of repulsion responsive to Wnts correlates with the timing of midline crossing (pyramidal decussation). After corticospinal tract axons have crossed the midline and entered the rostral spinal cord, they begin to respond to Wnts. Ryk, the vertebrate homolog of *Drosophila* Derailed, mediates this repulsion. The temporal expression pattern of Ryk correlates with the onset of Wnt repulsion. In the mammalian brain, Ryk mediates repulsive activity of *Wnt5a* to corpus callosum after they have crossed the midline and defines the tight fascicles of corpus callosum axons (Keeble & Cooper 2006). Ryk is also required for attractive Wnt response in dorsal root ganglion (DRG) cell axons. In Ryk-deficient mice created by an RNAi transgene, DRG axons failed to respond to *Wnt3* attraction (Lu et al. 2004).

Wnt signaling plays highly conserved biological roles in axon guidance both in A-P guidance in vertebrate and in *C. elegans* axon pathfinding. Three *C. elegans* Wnts are expressed in an A-P increasing gradient. Wnt signaling is important for A-P guidance and neuronal polarity of several neurons as well as migration of neuroblasts as previously discussed (Hilliard & Bargmann 2006, Pan et al. 2006, Prasad & Clark 2006). Although Wnts provide A-P directional information in both vertebrates and nematodes, there are several differences, including the direction of Wnt gradients along the A-P axis and the role of Frizzleds in attractive and repulsive responses to Wnts (Zou 2006).

Wnts are also highly conserved topographic mapping cues in vertebrates and *Drosophila*. In the chick retinectal system, Wnt signaling plays a role in medial-lateral topographic mapping by conveying positional information (Flanagan 2006, Luo 2006, Schmitt et al. 2006). Dorsal retina ganglia cell (RGC) axons target to lateral tectum, and ventral RGC axons project to medial tectum, forming a continuous spatial representation of the visual world along the dorsal-ventral axis. Computational

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**Morphogens:** diffusible signaling proteins that form gradients and determine cell fate on the basis of concentration

**Topographic mapping:** spatial information is smoothly and continuously represented from one part of the nervous system to another through ordered projections

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modeling suggested that for topographic maps to form, counterbalancing forces that oppose each other along each axis are necessary (Fraser & Hunt 1980, Fraser & Perkel 1990, Gierer 1983, Prestige & Willsaw 1975). Wnt3 is expressed in a medial-lateral decreasing gradient and Ryk is expressed in a dorsal-ventral increasing gradient. Wnt3 is a laterally directing mapping force, and the ventral axons are more sensitive to the lateral Wnt3 repulsion because of the higher Ryk expression level. The other opposing force is ephrinB1-EphB signaling, which is medially directed and whose activity is attractive. EphrinB1 is expressed at high medial and low lateral gradients in the tectum. EphB receptors are expressed by forming a low-dorsal and high-ventral gradient in the RGCs of the retina. Therefore, the more ventral RGCs are more sensitive to the medial ephrinB1 attraction, balancing the Wnt3 activity. The mechanisms by which these two molecular gradients act to balance each other are currently unknown. We also do not know whether the opposing gradient model is a general mechanism that applies to other maps. Wnt signaling also controls retinotopic mapping along the dorsal-ventral axis of the *Drosophila* visual system (Sato et al. 2006). The 750 ommatidia send axons from the fly compound eye to brain targets in a topographically organized way. Dorsal ommatidia axons project to the dorsal arm of the lamina, whereas ventral axons target to the ventral lamina, forming a continuous spatial map. DWnt4 is expressed in the ventral lamina and directs ventral axons toward the ventral lamina via DFz2 receptor. In *DWnt4*, *DFz2*, and *Dvl* mutants, ventral photoreceptor axons mistarget dorsally (Sato et al. 2006). Although the actual topographic organizations are different between vertebrates and fly, Wnt signaling plays essential roles in topographic organization along the same body axis. Moreover, the phenotype of a dorsal shift in the map when Wnt signaling is ablated suggests that an apposing dorsally directed force exists in the *Drosophila* visual system, which is yet to be identified (Zou & Lyuksyutova 2007).

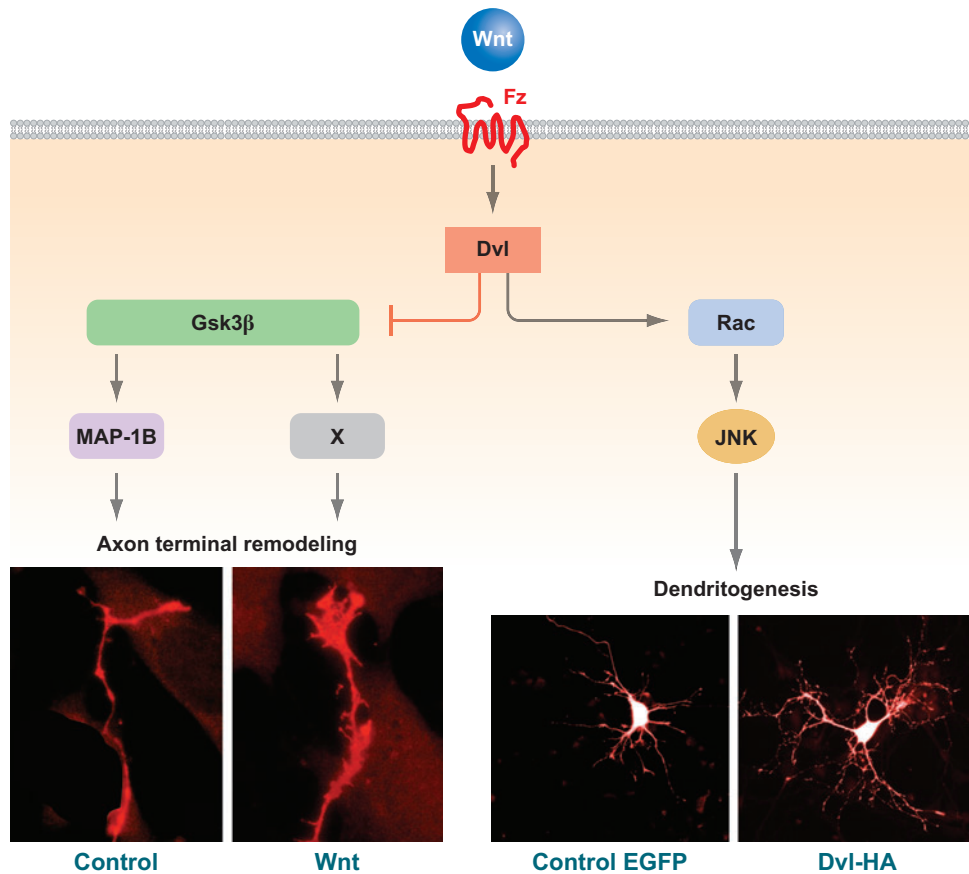
## WNT SIGNALING AND DENDRITE MORPHOGENESIS

Dendrite growth and branching are critical episodes in the formation of functional neuronal connections. A combination of intrinsic and environmental factors regulates the dendritic morphology of individual neurons through changes in the cytoskeleton (Parrish et al. 2007). Several extracellular cues that stimulate or inhibit dendritic growth and branching have been identified (McAllister 2000, Whitford et al. 2002). Intracellular molecules such as Rho GTPases have been implicated in dendritic development (Luo 2002, Van Aelst & Cline 2004), but little is known about how extracellular cues modulate these molecular switches.

Studies in hippocampal neurons led to the discovery that Wnt signaling regulates dendritic morphogenesis. Wnt7b, which is expressed during hippocampal dendritogenesis, increases the length and branching of cultured hippocampal neurons (Rosso et al. 2005). Wnt7b increases the number of secondary and tertiary branches, an effect that is blocked by the Wnt antagonist, Sfrp1. Sfrp1 on its own impairs dendritic development, which suggests that endogenous Wnts regulate this process (Rosso et al. 2005). Consistent with this finding, Yu & Malenka (2003) found that cultured hippocampal neurons release Wnt proteins into the conditioned media. These results indicate that endogenous Wnts contribute to the normal dendritic arborization of hippocampal neurons in culture.

A noncanonical Wnt pathway through Dvl and Rac regulates dendrite morphogenesis. Gain and loss of Dvl function studies showed that Dvl is required for dendrite outgrowth and branching (Rosso et al. 2005). Wnt7b and Dvl activate a noncanonical pathway through Rac. Activated Rac increases dendritic development, whereas dominant-negative Rac blocks the effect of Wnt or Dvl (Rosso et al. 2005). Wnt7b and Dvl also activate JNK to regulate dendritic morphogenesis. In hippocampal neurons, dominant-negative JNK or exposure to JNK inhibitors blocks the dendritogenic effect





**Figure 3**

Wnts regulate the terminal arborization of axons and dendritic morphogenesis. Activation of the divergent canonical pathway regulates the terminal arborization of axons through inhibition of Gsk3 and changes in the phosphorylation of MAP1B and possibly other targets (X). In contrast, activation of the Wnt planar cell polarity pathway regulates dendritic morphogenesis. Wnt and Dvl activate Rac1 and JNK to increase dendrite length and branching.

of Dvl1. In contrast, JNK activation by low levels of anisomycin mimics the Wnt effect (Rosso et al. 2005). Thus Wnt signaling through a non-canonical pathway that requires Rac and JNK regulates dendritic development (**Figure 3**).

$\beta$ -catenin, a component of the canonical pathway, also stimulates dendrite development. Expression of constitutively active  $\beta$ -catenin increases dendritic arborization in hippocampal neurons (Yu & Malenka 2003). However, this function is not dependent on  $\beta$ -catenin-mediated transcription. Instead, active  $\beta$ -catenin increases dendritic arborization

through its interaction with N-cadherin and  $\alpha$ N-catenin (Yu & Malenka 2003). Moreover, a dominant-negative  $\beta$ -catenin that impairs TCF function does not block Dvl function on dendrites (Rosso et al. 2005). Thus,  $\beta$ -catenin stimulates dendritic morphogenesis through a pathway that is independent of canonical signaling.

Electrical activity regulates dendritic development by stimulating the expression of Wnts. It is well documented that neuronal activity stimulates the growth and maintenance of complex dendritic arbors (Libersat & Duch 2004, Scott & Luo 2001, Yuste & Bonhoeffer

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**NMDA:** N-methyl-D-aspartic acid

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2001) and that activation of NMDA receptors and calcium release mediate this process (McAllister et al. 1996, Ruthazer et al. 2003, Sin et al. 2002, Wu et al. 1996). Recent studies showed that neuronal activity regulates dendrite growth by modulating the expression and/or release of Wnts. Indeed, conditioned media from depolarized hippocampal neurons contain higher levels of Wnt activity than does media from nonstimulated cells (Yu & Malenka 2003). More recently, Soderling and colleagues showed that Wnt2 expression is enhanced by neuronal activity (Wayman et al. 2006). Electrical activity activates CaMKK and CaMK1, triggering a signaling cascade that culminates with CREB-mediated transcriptional activation of Wnt2 (Wayman et al. 2006). Wnt2 is essential for activity-dependent dendritic growth and branching. Thus electrical activity enhances dendrite development through Wnt factors.

### TERMINAL AXON REMODELING BY WNT SIGNALING

Upon contact with their appropriate targets, axons decelerate their growth and remodel extensively to form synaptic boutons, presynaptic structures containing the machinery responsible for neurotransmitter release (for review see Goda & Davis 2003, McAllister 2007, Waites et al. 2005). In some neurons, remodeling occurs at the terminal growth cones, whereas in other neurons, the axon shaft remodeling results in the formation of *en passant* synapses. Although axon remodeling is an essential early step in synapse formation, little is known about the mechanisms that regulate this process (Prokop & Meinertzhagen 2006, Ziv & Garner 2004).

In the central nervous system, Wnt factors enhance the terminal axon remodeling. *Wnt7a* is expressed in cerebellar granule cells when these neurons contact their presynaptic targets, the mossy fibers (Lucas & Salinas 1997). Upon contact with granule cells, mossy fiber axons are extensively remodeled, becoming larger and irregular in shape, and spread areas appear along the axon shaft where *en passant* synapses as-

semble (Hamori & Somogyi 1983, Mason & Gregory 1984). Gain and loss of function studies using a combination of cultured neurons and *Wnt7a* and double *Wnt7a/Dvl1* mutant mice have demonstrated a key role for Wnt7a and Dvl1 in mossy fiber remodeling (Ahmad-Annar et al. 2006, Hall et al. 2000). Studies also found a similar function for Wnt3, which is released by lateral motoneurons and remodels proprioceptive DRG neurons (Krylova et al. 2002). In both systems, Wnts act as retrograde signals to regulate presynaptic remodeling.

How does Wnt signaling regulate axon remodeling? Profound changes in the organization and stability of microtubules seem to mediate this process. In actively growing axons, dynamic and stable microtubules form large bundles along the axon shaft that splay as they enter the growth cone (for review see Dent & Gertler 2003, Zhou & Cohan 2004). Growth cones contain many dynamic but few stable microtubules (Gordon-Weeks 2004, Dent & Gertler 2003). In the presence of Wnts, thicker bundles of microtubules form along the axon shaft with some unbundling at spread areas. At growth cones, both stable and dynamic microtubules form large loops in the central region (Hall et al. 2000). These findings suggest that Wnt signaling induces changes in microtubule stability and organization. Indeed, Dvl expression or Gsk3 inhibition mimics the Wnt remodeling effect (Ciani et al. 2004, Krylova et al. 2000, Lucas et al. 1998). Consistent with a role for the Wnt-Gsk3 pathway in terminal axon arborization, Gsk3 activity is required for proper arborization of retinotectal projections in the zebrafish (Tokuoka et al. 2002). Epistatic analyses revealed that Wnt-Dvl signaling regulates the microtubule cytoskeleton through a pathway that is independent of transcription (Ciani et al. 2004) (**Figure 3**). Axin, which functions as a negative regulator in the canonical Wnt pathway, collaborates with Dvl to regulate microtubule stability, and both bind very tightly to microtubules (Ciani et al. 2004, Krylova et al. 2000). These results suggest that the Wnt pathway directly signals to microtubules. Indeed, Wnt-mediated inhibition of Gsk3 changes

the level of MAP1B phosphorylation (Ciani et al. 2004, Lucas et al. 1998), a microtubule-associated protein that regulates microtubule dynamics (Goold et al. 1999, Tint et al. 2005) (**Figure 3**). Thus Wnt signaling increases microtubule stability by decreasing MAP1B phosphorylation through Gsk3.

More recent studies showed that Wnt signaling also regulates microtubule stability through JNK. Expression of Dvl activates endogenous JNK, whereas JNK inhibition blocks Dvl-mediated microtubule stability. Interestingly, Rac and Rho do not seem to be involved in JNK activation (Ciani & Salinas 2007), suggesting the involvement of an alternative non-canonical Wnt pathway. The findings are consistent with the view that JNK collaborates with Gsk3 to increase microtubule stability. As JNK phosphorylates a number of microtubule-associated proteins, including MAP1B (Chang et al. 2003), these findings collectively suggest that Wnt-Dvl signaling modulates microtubule dynamics during axon remodeling through both JNK activation and Gsk3 inhibition.

## WNT SIGNALING REGULATES THE FORMATION OF CENTRAL AND PERIPHERAL SYNAPSES

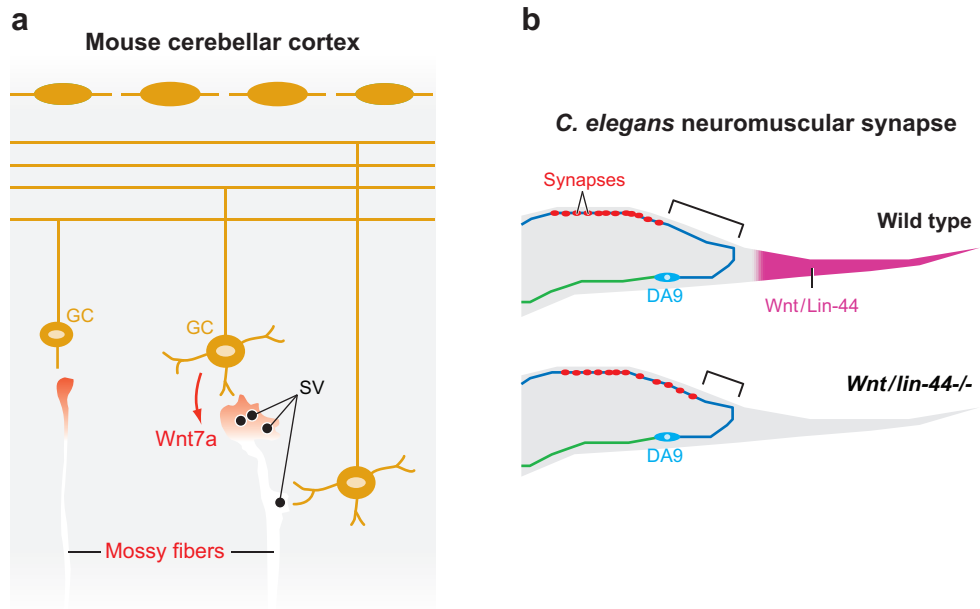
### Wnts Stimulate Central Synaptogenesis

The first indication that Wnts modulate presynaptic differentiation came from studies using cultured cerebellar neurons (Lucas & Salinas 1997). However, loss-of-function studies looking at the mossy fiber–granule cell synapse provided the first clear demonstration of a role for Wnt signaling in synaptogenesis (Hall et al. 2000). In this system, Wnt7a from granule cells induces a significant increase in presynaptic protein clustering, a hallmark of presynaptic assembly on mossy fiber axons (Hall et al. 2000) (**Figure 4a**). The cerebellum of the *Wnt7a* mutant mouse exhibits defects in synapse formation, manifested by decreased accumulation of presynaptic proteins (Ahmad-Annun et al. 2006, Hall et al. 2000). These findings collec-

tively demonstrate that Wnt7a acts as a retrograde signal to regulate presynaptic differentiation in the cerebellum.

Which pathway regulates synaptic differentiation? Dvl1 is required for Wnt7a function on synapse formation. Expression of Dvl1 mimics Wnt effects, whereas Dvl1 deficiency results in presynaptic differentiation defects manifested by the presence of fewer presynaptic sites in cultured mossy fibers. In vivo, the *Dvl1* mutant exhibits defects in the accumulation of presynaptic proteins as observed in the *Wnt7a* mutant. The double *Wnt7a/Dvl1* mutant mice exhibit more severe defects than do single-mutant mice (Ahmad-Annun et al. 2006), demonstrating a requirement for Dvl1 function. Wnt7a-Dvl signals through Gsk3 $\beta$ , as inhibitors of Gsk3 $\beta$  mimic the effect of Wnt in vitro (Hall et al. 2000, 2002). Although the signaling pathway downstream of Gsk3 $\beta$  remains poorly understood, conditional knockout of  $\beta$ -catenin in hippocampal neurons indicates that  $\beta$ -catenin is required for the proper localization of synaptic vesicles along the axon. However, this function of  $\beta$ -catenin is independent of TCF-mediated transcription (Bamji et al. 2003). In agreement, loss or gain of function of Wnt signaling does not affect the levels of many presynaptic proteins (Ahmad-Annun et al. 2006). It is worth noting that a similar Wnt-Gsk3 pathway operates presynaptically to regulate remodeling and presynaptic assembly, suggesting that both processes could be interconnected.

Which aspect of synapse formation is regulated by Wnt signaling? Waites et al. (2005) proposed that Wnt signaling regulates synaptogenesis indirectly by stimulating neuronal maturation through gene transcription. However, several findings do not support this suggestion. In cultured neurons, Wnt signaling rapidly increases the number and the size of synaptic vesicle recycling sites without affecting synaptic protein expression. In vivo, Wnt deficiency also affects the localization of synaptic proteins without affecting their levels (Ahmad-Annun et al. 2006). Taken together, these findings strongly support the view that Wnt signaling regulates synaptic assembly.



**Figure 4**

Wnts can function as pro- and antisynaptogenic factors. (a) In the mammalian nervous system, Wnts act as target-derived signals that regulate the assembly of synapses. In the cerebellum, Wnt7a induces the terminal remodeling of mossy fibre axons followed by the recruitment of synaptic components to remodeled axon areas. (b) In *C. elegans*, cholinergic DA9 motoneurons do not assemble synapses at the most posterior domain of the axon owing to the presence of Wnt/Lin-44, which is expressed in the posterior hypodermis.

Electrophysiological recordings at the mossy fiber–granule cell synapse using brain slices revealed that Wnt signaling could also regulate synaptic function. The *Wnt7a/Dvl1* double mutant exhibits a significant decrease in the frequency but not amplitude of miniature excitatory postsynaptic currents (mEPSCs), suggesting a presynaptic defect (Ahmad-Annuar et al. 2006). This mutant does not exhibit defects in the number or structures of active zones, suggesting that some aspects of synaptogenesis are normal. However, the decreased frequency of mEPSCs suggests a defect in neurotransmitter release (Ahmad-Annuar et al. 2006).

### Wnt Signaling at the Neuromuscular Synapse

In *Drosophila*, the Wg/Wnt signaling pathway through Gsk3 regulates the assembly of the

neuromuscular junction (NMJ). The finding that Wg protein is present at motoneuron terminals led Budnik and collaborators to test the function of Wg in synaptogenesis using a temperature-sensitive allele to bypass any patterning defects (Packard et al. 2002). Wg is released from motoneurons but signals to both pre- and postsynaptic terminals. Loss of *wg* results in severe defects in the number and shape of synaptic boutons. At the ultrastructural level, active zones are not properly assembled, and pre- and postsynaptic markers fail to colocalize properly. Postsynaptically, Wg binds to DFz2 receptors, resulting in its internalization and cleavage at its C-terminus portion. This cleaved receptor is subsequently transported to the nucleus (Ataman et al. 2006). Whether the nuclear localization of the DFz2 is important for transcription is unclear; however, disruption of this receptor pathway affects synaptic growth (Ataman et al. 2006, Mathew et al. 2005). Thus

**mEPSCs:** miniature excitatory postsynaptic currents

**NMJ:** neuromuscular junction

Wg signaling is required at both pre- and post-synaptic sides of the neuromuscular synapse.

Wg signals through shaggy/gsk3 to regulate the shape of boutons through changes in synaptic microtubules. An interesting feature of NMJ boutons is the presence of looped microtubules, which are decorated with the microtubule binding protein Futsch, the homolog of MAP1B (Hummel et al. 2000, Roos et al. 2000). Loss of *wg* function leads to changes in the localization of Futsch and to an increase in the number of boutons without loops or containing splayed microtubules (Packard et al. 2002). Similarly, *shaggy* mutants exhibit defects in bouton size and distribution (Franco et al. 2004). These findings demonstrate that the organization of presynaptic microtubules contributes to the shape and size of boutons. The great similarity between the function of Wnt7a and Wg on presynaptic microtubules suggests that a common mechanism regulates presynaptic remodeling in central and peripheral synapses.

No clear evidence has been presented to support a role of Wnts at the NMJ. However, some components of the pathway are associated with the postsynaptic machinery. Dvl1 interacts with MuSK (Luo et al. 2002), a receptor for Agrin, a secreted molecule required for vertebrate NMJ formation (for review see Burden 2002, Kummer et al. 2006, Strohlic et al. 2005). Antisense constructs for the three *Dvl* mouse genes block Agrin's ability to cluster the postsynaptic acetylcholine receptors (AChRs) in cultured myotubes. In this system, Dvl does not signal through the canonical pathway. Instead, Dvl interacts with the p21 kinase PAK1. Moreover, Agrin activates PAK, and this process depends on Dvl (Luo et al. 2002). Another component of the Wnt pathway, APC, colocalizes with AChRs at the mature vertebrate NMJ (Wang et al. 2003), and disruption of APC-AChR interaction decreases Agrin's ability to induce AChR clustering. Unfortunately, no Wnt ligand has been identified to regulate NMJ development. Further studies are necessary to elucidate a possible role for Wnt signaling at the vertebrate NMJ.

## Wnts as Antisynaptic Factors

In addition to promoting synaptogenesis, Wnts also inhibit synapse formation. Recent studies in *C. elegans* showed that Lin-44 (Wnt) (Herman et al. 1995), through its receptor Lin-17 (Frizzled) (Sawa et al. 1996), acts as an antisynaptogenic signal (Klassen & Shen 2007). The DA9 motoneuron, located on the ventral side of the animal, forms *en passant* synapses with muscles along the dorsal-most anterior regions of the axon. In contrast, a restricted area of the axon is completely devoid of synapses (Hall & Russell 1991, White et al. 1976). In *lin-44* and *lin-17* mutants, however, presynaptic puncta are present in this asynaptic area. The number of synaptic sites does not change, suggesting that Wnt signaling negatively regulates the distribution of neuromuscular synapses (Klassen & Shen 2007) (Figure 4b). Another interesting feature is the restricted localization of the Lin-17 receptor to the asynaptic area, and its distribution is dependent on Lin-44 (Klassen & Shen 2007). Lin-44 is secreted by four hypodermal cells in the tail forming a posterior-to-anterior gradient (Goldstein et al. 2006). However, when *lin-44* is ectopically expressed, the Lin-17 receptor localizes to axon areas close to the Lin-44 source (Klassen & Shen 2007). Thus the Wnt ligand regulates the localization of its receptor at specific domains within the axon. But how does Lin-44 inhibit synaptic assembly? One of the three dishevelled genes in the worm, *dsb-1*, is required in this process. However,  $\beta$ -catenin, TCF, and genes implicated in the PCP pathway are not required (Klassen & Shen 2007). Further studies are necessary to determine the pathway that regulates synaptic localization.

The assembly and distribution of synapses are crucial events in the formation of complex and elaborate neuronal circuits. Therefore, the discovery that Wnts act as pro- and antisynaptogenic factors is of great significance. A combination of Wnts and their receptors could sculpt complex neuronal networks. Although an antisynaptogenic activity for Wnts in vertebrates has not been reported, the absence of

secreted Wnt antagonists such as Sfrps and Dkk1 in the *C. elegans* and *Drosophila* genomes (Lee et al. 2006) suggests that the interplay between Wnts and their secreted antagonists regulates synaptic assembly and distribution in higher organisms.

## CONCLUSIONS

Although the field has made great progress in understanding the function of Wnt signaling in different aspects of neuronal circuit assembly, many issues remain outstanding. For example, during early embryonic patterning, Wnts can function as morphogens, wherein different levels of Wnt proteins can elicit different cellular responses within identical cells. Wnt gradients are apparently important in axon pathfinding and neuronal migration at later stages. How is this gradient used to control direction? Studies on retinotectal projection indicate that the Wnt gradients may convey positional information for the formation of axon termination zones within their correct topographic positions, but the underlying molecular mechanisms are still poorly understood. What is the interplay of different levels of Wnts, their receptors, and their secreted antagonists in axon guidance?

Wnts are clearly important for neuronal migration in *C. elegans*, conveying directional information in some neurons. It will be interesting to test whether Wnt signaling also plays a role in controlling vertebrate neuronal migration. Wnt signaling is also important for neuronal polarity in *C. elegans*. In vitro results suggest that Wnt5a may be a polarizing cue for vertebrate neurons. It will be important to determine whether Wnt signaling controls vertebrate neuronal polarity in vivo.

## DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

The discovery that Wnts can function as pro- and antisynaptogenic factors raises the intriguing and exciting possibility that a combinatorial function of different Wnts and their secreted antagonists plays a crucial role in determining the distribution of synapses within a neuron, thereby influencing the formation of complex patterned neuronal circuits.

Identification of a novel role for Wnt signaling in synaptic modulation is emerging. Wnts and their receptors are expressed throughout life, suggesting that Wnt signaling plays a role not only during early neuronal connectivity but also in synaptic modulation in the adult. The finding that Wnt deficiency leads to electrophysiological defects strongly suggests that Wnts regulate synaptic function (Ahmad-Annuar et al. 2006). Supporting this notion, further electrophysiological studies suggest that Wnts modulate synaptic transmission by regulating neurotransmitter release and long-term potentiation (LTP) (Beaumont et al. 2007, Chen et al. 2006). Although the mechanism by which Wnt regulates neurotransmitter release remains unknown, the finding that Wnts can increase presynaptic receptors, which modulate calcium entry (Farias et al. 2007), suggests a possible mechanism. The discovery that electrical activity can regulate Wnt expression and/or release (Wayman et al. 2006, Yu & Malenka 2003) and that Wnts might regulate neurotransmitter release suggests that Wnts could contribute to a positive feedback mechanism for synaptic modulation. Future studies using conditional genetic approaches will provide important insights into the function of Wnt signaling during the formation, maintenance, and modulation of neuronal circuits throughout an organism's life.

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## Errata

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