This Review is the Introduction of a new thematic series on **Wnts in Cardiovascular Development and Disease**, which includes the following articles:

An Updated Overview on Wnt Signaling Pathways: A Prelude for More

The Multiple Phases and Faces of Wnt Signaling During Cardiac Differentiation and Development

Wnt Signaling in Vascular Progenitor Cells and Angiogenesis

Wnt Signaling in Cardiac Hypertrophy and Remodeling

Wnt Signaling in Heart Failure and Aging

Wnt Signaling and Stem Cells

Michael Kühl, Guest Editor

An Updated Overview on Wnt Signaling Pathways
A Prelude for More

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Abstract: Growth factor signaling is required for cellular differentiation, tissue morphogenesis, and tissue homeostasis. Misregulation of intracellular signal transduction can lead to developmental defects during embryogenesis or particular diseases in the adult. One family of growth factors important for these aspects is given by the Wnt proteins. In particular, Wnts have important functions in stem cell biology, cardiac development and differentiation, angiogenesis, cardiac hypertrophy, cardiac failure, and aging. Knowledge of growth factor signaling during differentiation will allow for improvement of targeted differentiation of embryonic or adult stem cells toward functional cardiomyocytes or for understanding the basis of diseases. Our major aim here is to provide a state of the art review summarizing our present knowledge of the intracellular Wnt-mediated signaling network. In particular, we provide evidence that the subdivision into canonical and noncanonical Wnt signaling pathways solely based on the identity of Wnt ligands or Frizzled receptors is not appropriate anymore. We thereby deliver a solid base for further upcoming articles of a review series focusing on the role of Wnt proteins on different aspects of cardiovascular development and dysfunction. (*Circ Res*. 2010;106:1798-1806.)

Key Words: Wnt ■ frizzled ■ canonical ■ noncanonical

Wnt proteins are secreted glycoproteins acting as short or long range signaling molecules. To trigger a cellular response and to activate intracellular signal transduction, they bind to receptors of the Frizzled family and several coreceptors such as lipoprotein receptor–related protein (LRP)-5/6, Ryk, or Ror2.[1,2] In humans, 19 members of the Wnt family and 10 Frizzled receptors are known. Based on different biological readouts, Wnt ligands, as well as Frizzled receptors, were subdivided into different subclasses, eg, some Wnts are able to induce secondary body axes when injected into *Xenopus* embryos or to transform C57 mg cells, whereas other Wnts regulate cell adhesion and morphogenetic movements.

Wnt Proteins Activate Apparently Distinct Signaling Pathways

Canonical Wnt/β-Catenin Signaling

On a molecular level, these different biological activities are mediated through different intracellular signaling pathways (Figure 1). Axis duplication and cell transformation are based on the activation of the canonical Wnt pathway that involves the multifunctional protein β-catenin. In the absence of Wnt, β-catenin is targeted to a multimeric protein complex called destruction complex for its phosphorylation. This is achieved by CK1-mediated phosphorylation at Ser45, followed by

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Ser33, Ser37, and Thr41 phosphorylation by glycogen synthase kinase (GSK)3β.[3] This phosphorylation targets β-catenin for β-Trcp–mediated ubiquitination and its subsequent degradation by the proteasome. Deletion of these phosphorylation sites either by point mutations (eg, S33A) or by larger deletions, therefore, result in stabilization of β-catenin. A widely used mouse model is a floxed exon 3 of β-catenin allowing a conditional deletion of exon 3 that codes for these amino acids. This mouse model shows an increased β-catenin stability and T-cell factor (TCF)/lymphocyte enhancer factor (LEF)-dependent transcription.[4]

In the presence of some Wnt ligands, a cascade of events initiated at the plasma membrane by the binding of Wnt to the cysteine-rich domain of Frizzled receptors results in the disassembly of the destruction complex consisting of axin, adenomatous polyposis coli (APC), and GSK3β and the stabilization of β-catenin. This process also involves the phosphoprotein dishevelled. Cytoplasmic β-catenin accumulates and is eventually imported into the nucleus, where it serves as a transcriptional coactivator of transcription factors of the TCF/LEF family. In mice, deletion of exon 3 to 6 results in a β-catenin loss-of-function situation because this truncated form of β-catenin is not able to function in transcriptional activation.[4] TCF/LEF target genes are then involved in regulating cell proliferation, stem cell maintenance, or differentiation. Interestingly, β-catenin can also interact with other transcription factors such as Prop1, Oct-

Non-standard Abbreviations and Acronyms

APC	adenomatous polyposis coli
CaMKII	calcium/calmodulin-dependent kinase II
GSK	glycogen synthase kinase
JNK	jun N-terminal kinase
HDAC	histone deacetylase
LEF	lymphocyte enhancer factor
LRP	lipoprotein receptor–related protein
NFAT	nuclear factor of activated T cells
NLK	nemo-like kinase
PK	protein kinase
TCF	T-cell factor

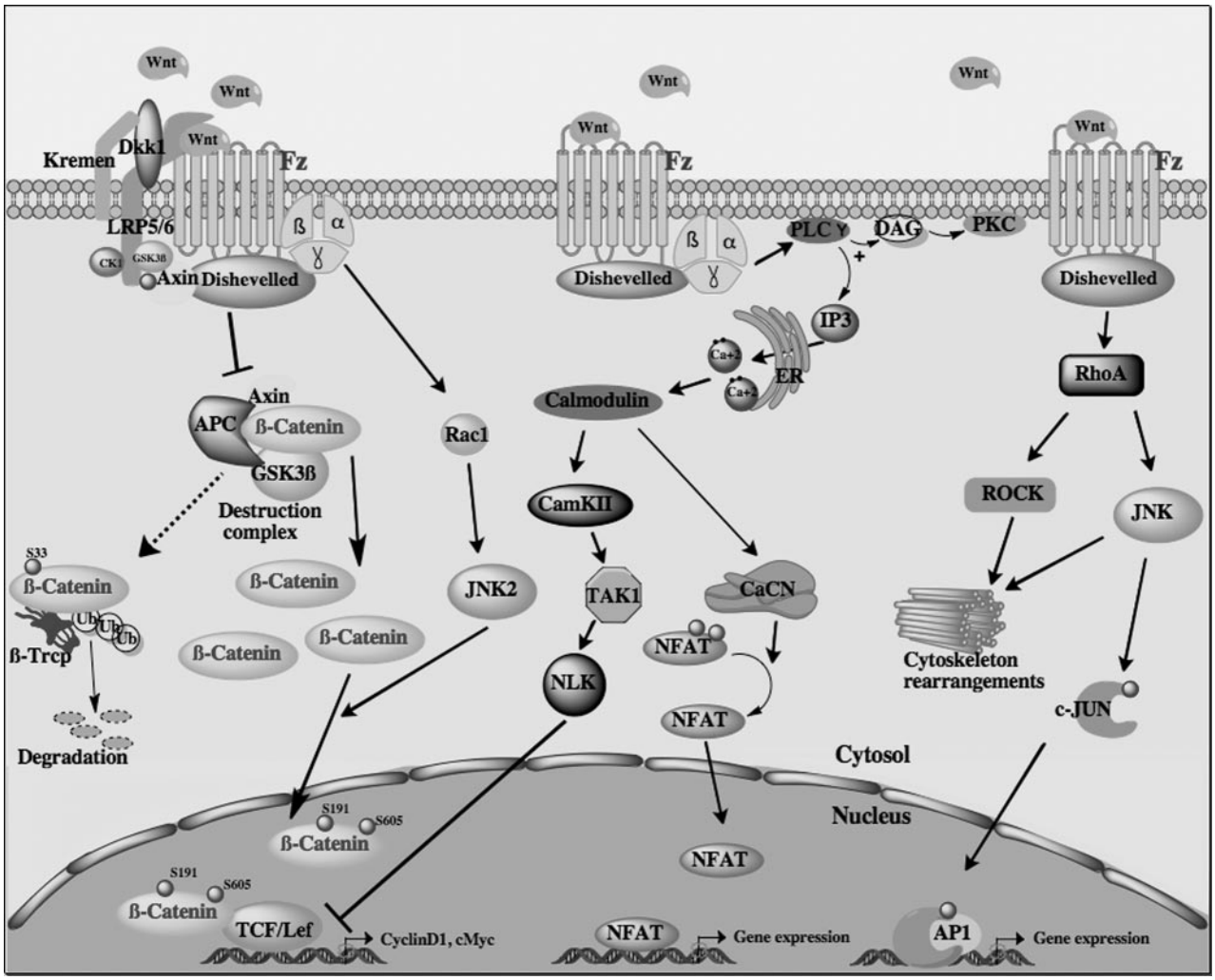

Figure 1. Overview of canonical (left) and noncanonical Wnt signaling pathways (right) as discussed in the text. CaCN indicates calcineurin.

3/4, Pitx2, or Mitf.[5–8] This pathway has been linked to cardiac development[9] and angiogenesis,[10] which are 2 aspects of cardiovascular development that will be discussed in 2 follow-up reviews.

β-Catenin As a Multifunctional Protein

One must keep in mind, however, that β-catenin is a multifunctional protein and interacts with additional proteins such as cadherins.[11] This interaction with β-catenin is essential for the function of cadherins in cell adhesion by establishing a link to the actin cytoskeleton. In this context, the closely related γ-catenin (plakoglobin) can also replace β-catenin. This interaction of cadherins with β-catenin is also tightly regulated by phosphorylation. Phosphorylation of β-catenin at Tyr654 through src kinase, as well as Thr112 and Thr120 by protein kinase (PK)D1, enhances the interaction with E-cadherin.[12] Conversely, phosphorylation of E-cadherin at Ser834, Ser836, and Ser842 by CK2 and GSK3β enhances its interaction with β-catenin. In contrast, phosphorylation at Tyr831 and Tyr860 by src kinase and Ser846 by CK1 inhibits the interaction of E-cadherin with β-catenin.[13] Taken together, these data indicate that the role of β-catenin in Wnt-mediated signal transduction and cell adhesion is highly dependent on its phosphorylation status at multiple sites.[14,15]

Members of the cadherin and catenin families are also required for adhesion between cardiomyocytes. This also includes the desmosomal cadherins desmocollin and desmoglein, the catenins plakoglobin (γ-catenin) and plakophilin2, or desmoplakin, which links the cadherin/catenin complex to intermediate filaments. Mutations in these components are the cause of arrhythmogenic right ventricular cardiomyopathies. In combination with wooly hair and palmoplantar keratoderma this congenital disease is also called Naxos disease.[16,17] This disease is characterized by ventricular arrhythmias and a progressive loss of cardiomyocytes that are replaced by fibrofatty tissue. Recent data suggested that this phenotype is not only caused by defects in cell adhesion. Loss of desmoplakin results in nuclear import of γ-catenin (plakoglobin) that negatively interferes with Wnt/β-catenin signaling.[18] Fine-tuned regulation of cadherin-mediated cell adhesion is also required for epithelial–mesenchymal or mesenchymal–epithelial transitions. The interplay of cadherin-mediated cell adhesion and Wnt signaling has recently also been reviewed in detail by others.[14]

β-Catenin–Independent Noncanonical Wnt Pathways

In contrast, all Wnt signaling activities that are apparently independent of β-catenin constitute different noncanonical Wnt signaling pathways. Depending on the major intracellular mediators used, those are called the Wnt/jun N-terminal kinase (JNK) or Wnt/calcium pathway, respectively. The Wnt/JNK pathway has a high degree of overlap with the planar cell polarity pathway originally described in *Drosophila.*[19] It involves activation of small GTPases of the rho family including rac, cdc42, and rho and further downstream protein kinases such as JNK or rho kinase. In this branch, Frizzled and dishevelled function in concert with other proteins to set up cellular polarity by asymmetrical and polarized protein localization. Those include classic and novel components of the planar cell polarity pathway like vangl/Strabismus,[20–22] Celsr,[23] Prickle,[24] or PTK7[25] in a context-dependent manner. Most of these proteins have been shown to regulate polarized cell movements (eg, during gastrulation, neural crest migration, or cardiac outflow tract development) and planar polarity of epithelial cells (eg, wing hair development in *Drosophila* or stereociliary bundles in the vertebrate cochlea). Furthermore, noncanonical Wnt signaling has also been linked to ciliogenesis.[26]

The existence of a calcium-mediated pathway that is directly activated by Wnt proteins was originally described in zebrafish and *Xenopus.*[27,28] These pathways have been linked to cardiac development in several settings,[29–33] as discussed in more detail in another review of this series. A long-lasting debate whether the observed intracellular release of calcium is a direct response or reflects some indirect effects was solved by showing that purified Wnt5a is able to activate calcium signaling in different cell culture models.[34–37] This process is very rapid and depends on heterotrimeric G proteins.[36] The released Ca^{2+} then activates calcium dependent enzymes like calcium/calmodulin-dependent kinase (CaMK)II, PKC or calcineurin.[38,39] In particular the regulation of PKC by Wnt ligands is important for cardiac differentiation.[29,40,41] PKC comes in different isoforms and a detailed analysis suggested PKCδ to play an important role during noncanonical Wnt signaling during cardiac differentiation.[40]

Through calcineurin the Wnt/calcium pathway connects to NFAT (nuclear factor of activated T cells) transcription factor[35,42] and gene expression. Interestingly, cardiac hypertrophy involves, beside other signaling pathways, calcineurin and its downstream target NFAT.[43] The involvement of both canonical and noncanonical Wnt signaling during cardiac hypertrophy and cardiac remodeling will therefore be discussed in great detail in a forthcoming review of this series.

On the other hand CaMKII can lead to activation of a nemo-like kinase (NLK), which interferes with β-catenin signaling.[44,45] Although not formally proven, the activation of CaMKII suggests that noncanonical Wnt signaling could modify the activity of histone deacetylase (HDAC). In particular, HDAC4 and -5 are regulated through CaMKII or CaMKIV,[46–50] and this is required for the expression of early cardiac genes such as Nkx2.5, MEF2C, or GATA-4.[46] This would not only provide an additional link to gene regulation through noncanonical Wnt signaling but suggests that a misregulation of noncanonical Wnt signaling could result in pathophysiological conditions in the heart that had been linked to CaMKII or HDACs.[48,51] One interesting finding here is that noncanonical Wnt signaling has been shown to modulate the activity of a histone lysine methyltransferase in a different setting.[52] Here, noncanonical Wnt signaling through the CaMKII-NLK axis results in H3-K9 methylation of histones to regulate gene expression.

Wnt Signaling at the Plasma Membrane

Wnt and Frizzleds: Monomers, Heterodimers, and Homodimers

Based on the biological assays mentioned, Wnts were subdivided into canonical or noncanonical Wnts, and the same

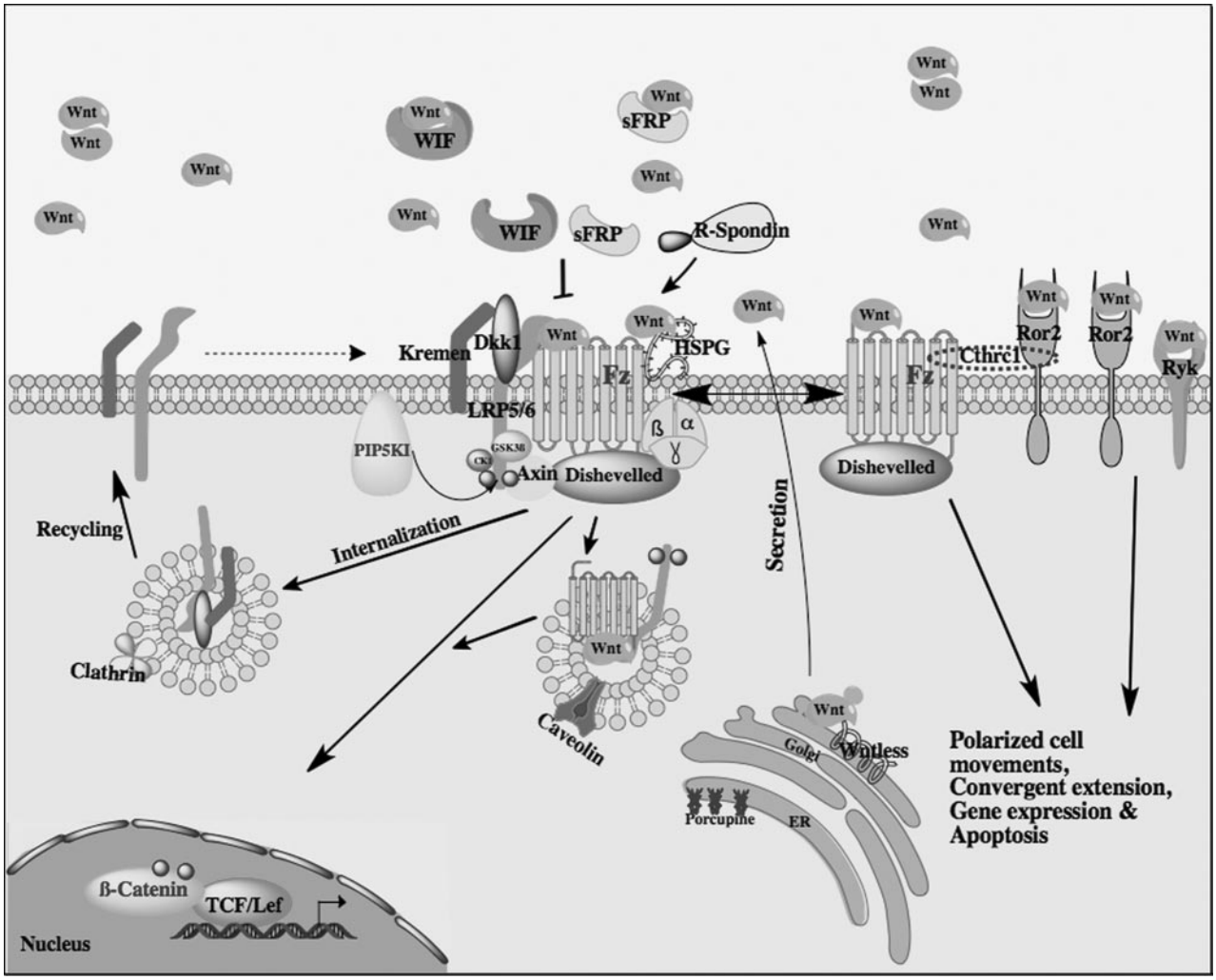

Figure 2. Wnt signaling at the membrane. Relative concentrations of different components determine pathway specificity.

holds true for Frizzled receptors,[39] eg, Wnt1, Wnt3a, or Wnt8 were considered to activate canonical Wnt signaling, whereas Wnt5a or Wnt11 are best known for their ability to trigger noncanonical Wnt signaling. This model of signaling specificity has been challenged by the finding that so-called noncanonical Wnt ligands can activate β-catenin signaling in the presence of appropriate Frizzled receptors and vice versa. "Canonical" Wnt3a has the ability to activate PKC during bone formation[53] and the bona fide "noncanonical" Wnt5a couples to canonical Wnt signaling in the presence of Frizzled-5.[54] Just recently noncanonical Wnt11 was shown to activate β-catenin signaling during axis specification in *Xenopus*.[55] These data indicate that differences in affinities of different Wnt and Frizzleds and their local concentrations (in vivo but also experimentally) would determine to which signaling branch a particular Wnt couples. Extending these earlier findings, it was recently shown that Wnt5a and Wnt11 proteins can interact physically[56] and thereby induce β-catenin signaling. Tyrosyl protein sulfotransferase-1–dependent *O*-sulfation of specific tyrosine residues of Wnt11 is required for this interaction with Wnt5a.[57] Similarly, Frizzled-4 has been shown to activate either β-catenin signaling[58] or noncanonical Wnt signaling branches.[59] There is also evidence for Frizzled dimers and multimers.[60–62] These findings indicate that the analysis of a particular Wnt ligand or Frizzled receptor in a certain biological context always requires an investigation of how the Wnt signal is transduced. However, this leaves with challenging questions: How is Wnt signaling initiated at the plasma membrane? And how is specificity achieved?

LRP Phosphorylation Generates a Docking Site for Axin

Activation of canonical Wnt/β-catenin signaling requires the interaction of a Wnt ligand with Frizzleds and LRP-5/6. The major outcome of pathway activation is the disintegration of the destruction complex, the release of β-catenin and its subsequent stabilization. This is achieved by binding of dishevelled and axin to Frizzleds and phosphorylated LRP-5/6, respectively (Figure 2). Wnt-induced phosphorylation of LRP5/6 is mediated by the concerted action of GSK3β and CK1.[63,64] A recent report indicated that in *Drosophila*, a cyclin-dependent kinase (CDK), L63, or its vertebrate homolog PFTK also phosphorylates LRP5/6.[65] This is an interesting finding because Wnt/β-catenin itself regulates the cell cycle by directly promoting c-Myc and cyclinD1 expression. Furthermore, β-catenin is required for centrosome

separation during mitosis.[66] Apparently, there is an intricate feedback between the cell cycle machinery and Wnt signaling to maintain a high-proliferative state as found in stem cells or tumor cells. Interestingly, some reports indicated that Wnt/β-catenin signaling is required to regulate cardiac progenitor cell proliferation, an issue that is also discussed in detail in a forthcoming review of this series.[67,68] A recent report also claims that Wnt3a stimulates the formation of phosphatidylinositol-4,5-bisphosphates [PtdIns(4,5)P_2] through Frizzled and dishevelled, the latter of which directly interacts with and activates PIP5KI.[69] PIP5KI then subsequently can phosphorylate LRP5/6. In addition, G protein–coupled receptor kinase 5/6 is able to phosphorylate LRP-5/6.[70] Some evidence suggests that LRP6 also antagonizes noncanonical Wnt signaling in vivo, possibly via competition for Wnt ligands[71] or by an unknown mechanism.[72]

Local Changes in pH Are Involved in Wnt Signaling

Frizzled binding of dishevelled as part of noncanonical Wnt signaling is pH-dependent.[73] The authors screened for molecules involved in dishevelled membrane recruitment and found that a Na^+/H^+ exchange activity of the plasma membrane exchanger, Nhe2, is a key player. Just recently, this model has been extended by showing that a local change in pH is also required for Wnt/β-catenin signaling. This is mediated by the prorenin receptor and a vacuolar H^+ATPase.[74]

Things at the Membrane Are More Complex: The Involvement of G Proteins

Frizzleds are 7-transmembrane proteins. Those are often associated with heterotrimeric G proteins to initiate intracellular signal transduction. Whereas noncanonical Wnt signaling has been linked to G proteins for a long time,[27,38,75] the lack of genetic evidence was used by some to argue against a role of G proteins in canonical Wnt signal transduction. These days, however, we have mounting evidence that they are involved in a key position. The first findings were obtained by experiments using inducible Frizzled receptors that indicated a requirement for G proteins in both canonical and noncanonical signaling branches, requiring $G_{\alpha o}$ and $G_{\alpha q}$ or $G_{\alpha o}$ and $G_{\alpha t}$, respectively.[76,77] Moreover, activation of a TCF/β-catenin–dependent reporter[78] is blocked by small interfering RNA targeting different G_α subunits[79] and Frizzled, dishevelled, and axin can directly interact with some G-protein subunits.[80,81] Also, genetic evidence argues for a requirement of G proteins in Wnt signaling.[82]

Dkk1: Beyond a Wnt Inhibitor

Dkk1 is among the best-characterized inhibitors of the canonical Wnt pathway. Dkk1 itself is a target gene of Wnt/β-catenin signaling, thereby establishing a negative-feedback loop. The Dickkopf family of secreted proteins is conserved among all vertebrates. They are also present in some invertebrates, such as urochordates and ascidians, but are noticeably missing in *Caenorhabditis elegans* and *Drosophila.*[83] Dkk1 consists of 2 cysteine-rich domains at the N and C terminus, respectively. The C-terminal cysteine-rich domain is shown to be responsible for the Wnt inhibitory function.[84,85] Dkk1 inhibits the formation of a ternary complex consisting of LRP5/6, Frizzled, and the Wnt ligand (Figure 2).[86] Others indicated that Dkk1, together with single pass transmembrane proteins of the Kremen family, mediates LRP5/6 internalization.[87] In the absence of Dkk1, however, Kremen activates Wnt signaling through LRP-5/6.[88] This is an interesting finding because it would allow for a steep gradient of pathway activation in the presence of a Dkk1 protein gradient.[89] Interestingly, inhibiting canonical Wnt signaling by Dkk1 resulted in an activation of noncanonical JNK signaling in some studies.[29,90,91] The N-terminal domain of Dkk1 has additional, not yet characterized signaling activities independent of β-catenin regulation. Interestingly, this activity is involved in regulating cardiogenesis.[92]

Internalization of LRP-5/6 is not only a mechanism to inhibit Wnt signaling by reducing the accessibility of LRP-5/6 for Wnt ligands, but is also required for Wnt signaling. This difference is mainly based on the mechanism by which LRP-5/6 is internalized. Whereas Dkk-induced clathrin-mediated internalization of LRP5/6[93] results in pathway inhibition, Wnt stimulates a caveolin-mediated LRP5/6 internalization that is involved in normal Wnt signaling.[93]

Atypical Receptor Kinases in Wnt Signaling

Members of the Ryk and Ror families are single span transmembrane receptors with an intracellular tyrosine kinase domain. They can interact with Wnt proteins through their extracellular cysteine-rich domain in the case of Ror proteins or their Wif domain in the case of Ryk proteins.[94–98] With respect to signal transduction, Ror2 has been placed upstream of small rho-GTPases and JNK,[99,100] whereas src is involved in Ryk signaling.[101] Interestingly, Ror2-mediated signal transduction also inhibits β-catenin signaling in a RTK-dependent manner.[96,102] Mutations in Ror2 result in Robinow syndrome, which is characterized by abnormal morphogenesis in the face and limb defects. Many patients also have heart defects,[103] further highlighting the role of noncanonical Wnt signaling in cardiac development.

Extracellular Modulation of Wnt Signaling

Wnt/β-catenin signaling can also be modulated by extracellular ligands other than Wnts. R-Spondins form a small family with 4 members. Initially, R-Spondin was shown to directly interact with Frizzled-8 and LRP5/6, thereby positively regulating β-catenin signaling.[104] Furthermore, R-Spondin positively regulates canonical Wnt signaling by competing with Dkk1 for binding to Kremen and LRP5/6.[105,106] R-Spondin3 supports angioblast development and vasculogenesis through β-catenin signaling.[107] Norrin is another extracellular protein that can activate β-catenin signaling through interaction with Frizzled-4.[58,108] Signaling through norrin and Fz-4 for example has been linked to vasculogenesis.[108] Furthermore, the extracellular collagen triple helix repeat–containing protein 1 (Cthrc1) interacts with some Wnts and Frizzleds and supports Wnt-Fz-Ror2 complex formation and at the same reduces Wnt-Fz-LRP complex formation. Thus, Cthrc1 might favor noncanonical Wnt signaling (Figure 2).[109]

An additional level of regulation comes in form of secreted Wnt inhibitors, such as Wif proteins and secreted frizzled-related proteins (Sfrps). Wifs and Sfrps can directly bind to

Wnt proteins in the extracellular space, thereby affecting receptor occupancy and, ultimately, the cellular response.[110] Finally, more and more evidence indicate a role for heparin sulfate proteoglycans (HSPG) in the transport, stabilization, and presentation of Wnt.[2] In *Drosophila*, absence of *Dally*, an HSPG,[111] and mutations in genes encoding enzymes that modify HSPG[112] generate phenotypes similar to *wingless* mutants.

In summary, all these reports consistently support the requirement for coordinated changes at the plasma membrane for Wnt mediated signal transduction. The major challenge in the field is to describe how all of these different pieces fit together in a unifying model of receptor activation explaining signaling specificity in vivo.

Nuclear Components of β-Catenin Signaling: From Transcription Factors to Chromatin Remodeling

Regulating Nuclear Localization of β-Catenin

The mechanisms underlying the nuclear import and export of β-catenin are not well understood but apparently do not require a nuclear localization signal.[113] A recent report indicated that the nuclear import of β-catenin is mediated by Wnt-induced activation of a Rac-JNK pathway by phosphorylation of β-catenin at Ser191 and Ser605.[114] On the other hand, APC and axin were shown to function in nuclear export of β-catenin.[115,116] Furthermore, RanBP3 has been shown to be involved in nuclear export of β-catenin.[117] In the nucleus, Bcl9 and pygopus play a role in retention of β-catenin.[118] In detailed fluorescence recovery after photobleaching experiments, it was recently shown that APC, axin, Bcl9, and TCF factors influence the cytoplasmic/nuclear localization of β-catenin mainly on the level of retention rather than active transport.[118]

β-Catenin and TCF/LEF Transcription Factors

In the absence on Wnt, TCF/LEF transcription factors bind to Wnt response elements, facilitating the recruitment of corepressors such as Groucho, CtBP, and HDACs to the particular genomic region. In the presence of Wnt, however, β-catenin is imported into the nucleus and binds to TCF/LEF, thereby replacing transcriptional repressors and recruiting additional transcriptional coactivators, in particular chromatin remodeling complexes such as swi/SNF. Those are brought to the TCF/β-catenin complex by Bcl-9/legless and pygopus.[119] Several posttranslational modifications like phosphorylation, sumoylation, ubiquitination, and acetylation modulate the potential of TCF/LEF transcription factors to interact with nuclear coactivators, repressors, or DNA.[120] For example, the phosphorylation of TCF/LEF by activated NLK/Nemo is thought to diminish the DNA-binding affinity of the β-catenin/TCF/LEF complex, thereby affecting transcriptional regulation of Wnt target genes.[44,45]

Interestingly, in some cases, a repressive function of TCF/β-catenin complexes has been described. In *Drosophila*, this apparently involves a different Wnt responsive element, whereas in vertebrates, the well-known consensus sequence is used.[121] These data indicate that the molecular mechanisms underlying the exchange of transcriptional repressors by transcriptional activators within a TCF/LEF-mediated transcriptional complex are far from being understood.

Intracellular Signaling Pathways: Toward an Integrative View of Wnt Signaling

The historical model of Wnt signaling assumed the existence of 3 completely separate signaling pathways. Within the last decade, however, many examples were found demonstrating that individual mediators of Wnt signaling are involved in several branches. This includes certain Frizzled receptors that obviously have the ability to elicit different intracellular responses,[58,59] G proteins that are involved in different signaling branches,[27,28,75–82] and continues with the protein disheveled that also links to all three signaling branches.[122] Furthermore, some components seem to favor one signaling pathway at the expense of the other. Finally, as mentioned above, it recently became evident that β-catenin signaling also relies on a simultaneous activation of the Wnt/JNK branch.[114] Given all of these issues, it seems more appropriate to talk of a Wnt signaling network of interwoven signaling branches. This new model of Wnt signaling has been discussed recently in more detail.[1,123] Depending on the cellular context, eg, concentrations of individual components, this would allow for the preferred activation of certain aspects of the network. This, however, has direct implications on the interpretation of experimental results because the status of the network must be analyzed in detail in each experimental setting and biological model.

Outlook

These discussions indicate that Wnt proteins have multiple functions on a cellular level, including regulation of gene expression via different mechanisms (and thus differentiation) and cell cycle and proliferation, as well as other nongenomic responses such as cell migration or cilia formation. As indicated, a critical analysis of Wnt function in a given context should always include an investigation of mediators used. A simple assignment based on the identity of Wnt ligands or Frizzled receptors is not sufficient. In the forthcoming reviews of this series, different authors will focus on different aspects of Wnt signaling during cardiovascular development and dysfunction, in particular, during cardiac differentiation and development, angiogenesis, and cardiac remodeling, as well as cardiac failure and aging.

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None.

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