Protein family review
The Wnts
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Summary
The Wnt genes encode a large family of secreted protein growth factors that have been identified in animals from hydra to humans. In humans, 19 WNT proteins have been identified that share 27% to 83% amino-acid sequence identity and a conserved pattern of 23 or 24 cysteine residues. Wnt genes are highly conserved between vertebrate species sharing overall sequence identity and gene structure, and are slightly less conserved between vertebrates and invertebrates. During development, Wnts have diverse roles in governing cell fate, proliferation, migration, polarity, and death. In adults, Wnts function in homeostasis, and inappropriate activation of the Wnt pathway is implicated in a variety of cancers.

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The Wnt family of secreted protein growth factors is a large family of Wnt genes that are highly conserved between vertebrates and slightly less conserved between vertebrates and invertebrates. During development, Wnt proteins have diverse roles in governing cell fate, proliferation, migration, polarity, and death. In adults, Wnts function in homeostasis, and inappropriate activation of the Wnt pathway is implicated in a variety of cancers.

Gene organization and evolutionary history

Gene organization
In humans, 19 WNT genes have been identified and the chromosomal locations of each is known (see Table 1) [1-6]. Several human WNT genes are located very close to each other in the genome [7,8]; these include WNT6 and WNT10a, which are located immediately adjacent to one another on chromosome 2 (about 6.4 kilobases (kb) apart), and WNT1 and WNT10b, which are located adjacent to each other on chromosome 12 (about 8.1 kb apart). WNT6 and WNT10a are transcribed in opposite directions, whereas WNT1 and WNT10b are expressed from the same strand of DNA. Several additional pairs of WNT genes are also clustered within the human genome, including WNT2 and WNT16 (about 4 megabases (Mb) apart), WNT3a and WNT14 (about 250 kb apart), and WNT3 and WNT15. In the mouse, there are at least 18 Wnt genes and the locations of all but two of them have been determined [1-3,5,6]. As in humans, the mouse Wnt1/Wnt10b, Wnt6/Wnt10a, and Wnt3/Wnt15 gene pairs are each located on the same chromosomes, and in the case of the Wnt1/Wnt10b and Wnt6/Wnt10a pairs the close proximity of these genes has been conserved from mouse to human. Interestingly, in the Drosophila genome, the paralogous genes wingless (wg), DWnt6 and DWnt10, are located immediately adjacent to one another on the second chromosome and are all transcribed in the same orientation. Thus, it is possible that there was an ancient cluster of Wnt genes consisting of Wnt1, Wnt6 and Wnt10 in a common ancestor of vertebrates and arthropods. In vertebrates, this cluster may have been duplicated with subsequent loss of Wnt1 from one cluster and Wnt6 from the other.

The majority of human WNT genes contain four coding exons, with exon 1 containing the initiation methionine (Figure 1a) [8]. WNT proteins that differ from this pattern include WNT14, with three exons, WNT2, WNT5b, and WNT11, with five exons, and WNT8b with six exons. Several WNTs - WNT2b/13, WNT8a/d, and WNT16 - have alternative amino or carboxyl termini, which result from the use of alternative 5’ or 3’ exons.

Evolutionary history
The deduced evolutionary relationships of 18 of the 19 known human WNT genes are shown in Figure 2. The majority of Wnt proteins share about 35% amino-acid sequence identity, although members of a subgroup (those with the same numeral, such as WNT3 and WNT3a) share increased sequence identity (from 58% to 83%) and some overlapping sites of expression. Members of subgroups are not closely linked within the genome, however, suggesting that they were generated by gene-translocation or genome-duplication events, not by local duplication events.
Wnt genes have been identified in vertebrates and invertebrates, but appear to be absent from plants, unicellular eukaryotes such as Saccharomyces cerevisiae and from prokaryotes. To date, in vertebrates, 16 Wnt genes have been identified in Xenopus, 11 in chick, and 12 in zebrafish [5]; in invertebrates, Drosophila has seven Wnt genes, Caenorhabditis elegans five and Hydra at least one [5]. The apparent evolutionary relationships between selected invertebrate and vertebrate Wnt genes are shown in Figure 2b. In vertebrates, the orthologs in different species are highly similar in sequence. For example, human WNT1 and mouse Wnt1 are 98% identical, and human WNT5a and Xenopus Wnt5a are 84% identical at the amino-acid level. Phylogenetic analyses of vertebrate and invertebrate Wnts demonstrate orthologous relationships between several human and Drosophila Wnts (Figure 2b). The sequence identity between orthologous proteins in humans and flies ranges from 21% between human WNT8a/d and Drosophila DWnt8 to 42% sequence identity between human WNT1 and Drosophila Wingless (Wg). The evolutionary relationship between the five C. elegans Wnt genes and human WNT genes is less apparent, making it difficult to determine which C. elegans Wnt genes may have orthologs in the human genome.

### Characteristic structural features

Human WNT proteins are all very similar in size, ranging in molecular weight from 39 kDa (WNT7a) to 46 kDa (WNT10a) [3]. Drosophila Wnt proteins are also similar to this, with the exception of Wg, which is approximately 54 kDa and has an internal insert not found in vertebrate Wnts, and DWnt3/5, which is about 112 kDa [3]. Very little is known about the structure of Wnt proteins, as they are notoriously insoluble, but all have 23 or 24 cysteine residues, the spacing of which is highly conserved (Figure 1b), suggesting that Wnt protein folding may depend on the formation of multiple intramolecular disulfide bonds. Analysis of the signaling activities of chimeric Wnt proteins has shown that the carboxy-terminal region of Wnt proteins may play a role in determining the specificity of responses to different Wnts [9]. Furthermore, deletion mutants lacking the carboxy-terminal third of a Wnt protein can act as

### Table 1

**Chromosomal locations of WNT genes in human and mouse**

| Gene         | Human Location | Mouse Location | References | Accession numbers | Human Accession | Mouse Accession |
|--------------|----------------|----------------|------------|-------------------|-----------------|-----------------|
| WNT1         | 12q13          | Wnt1           | 15         | [87-91]           | X03072          | K02593          |
| WNT2         | 7q31           | Wnt2           | 6 (4.2 cM) | [92,93]           | X07876          | AK012093        |
| WNT2b/13     | 1p13           | Wnt2b/13       | 3 (49.0 cM)| [94-96]           | XM052111, XM052112 | AF070988       |
| WNT3         | 17q21          | Wnt3           | 11 (63.0 cM)| [97-100]          | AY009397        | M32502          |
| WNT3a        | 1q42.13        | Wnt3a          | 11 (32.0 cM)| [101-103]         | AB060284        | X56842          |
| WNT4         | 1p35           | Wnt4           | 4          | [100,104]         | AY009398        | M89797          |
| WNT5a        | 3p14-p21       | Wnt5a          | 14 (14.8 cM)| [104-106]         | L20861          | M89798          |
| WNT5b        | 12p13.3        | Wnt5b          | 6 (56.2 cM)| [104,107]         | AB060966        | M89799          |
| WNT6         | 2q35           | Wnt6           | 1          | [104,108,109]     | AY009401        | M89800          |
| WNT7a        | 3p25           | Wnt7a          | 6 (39.5 cM)| [104,106,110,111]| D81715          | M89801          |
| WNT7b        | 22q13.3        | Wnt7b          | 15 (46.9 cM)| [100,104,112,113]| AB062766        | M89802          |
| WNT8a/d      | 5q31           | Wnt8a          |           | [114,115]         | AB057725, AY009402 | Z68889        |
| WNT8b        | 10q24          | Wnt8b          | 19 (43.0 cM)| [116-118]         | Y11094          | AF130349        |
| WNT10a       | 2q35           | Wnt10a         | 1          | [109,119]         | AB059569        | U61969          |
| WNT10b/12    | 12q13.1        | Wnt10b         | 15 (56.8 cM)| [106,119-124]     | U81787          | U61970          |
| WNT11        | 11q13.5        | Wnt11          | 7          | [106,125]         | Y12692          | X70800          |
| WNT14        | 1p42           | -              | 136        | [103,126]         | AB060283        |                 |
| WNT15        | 17q21          | Wnt15          | 11         | [126]             | AF028703        | AF031169        |
| WNT16        | 7q31           | Wnt16          |           | [127,128]         | XM031374, XM004884 | AF172064    |

*Locations of mouse genes give the chromosome and the distance in centimorgans (cM) from the telomere. †Accession numbers are for GenBank [3].
The amino terminus contains a signal sequence (S). All Wnts contain 23 alternatively used 5’ exons. (b) Structural features of the Wnt protein. The amino terminus contains a signal sequence (S). All Wnts contain 23 or 24 conserved cysteine residues (C) with similar spacing, suggesting that the folding of Wnt proteins depends on the formation of multiple intramolecular disulfide bonds.

Subcellular localization
Once secreted, Wnt proteins associate with glycosaminoglycans in the extracellular matrix and are bound tightly to the cell surface [19,20]. Although Wnts are found in tight association with the plasma membrane, it is possible to collect active Wnt from the medium of cultured cells [21,22]. Beyond this information, the localization of Wnt proteins in vertebrates is poorly understood. Examination of the localization of Wg in Drosophila, however, has provided critical insights into the subcellular distribution of Wnt proteins and the importance of this distribution for signaling activity. In the embryonic epidermis, Wg is found inside cells that secrete Wg and in association with the plasma membrane of secreting cells and non-secreting cells several cell diameters from the Wg source [23]. Wg is also prevalent in vesicles and multi-vesicular bodies of non-Wg-producing cells anterior to the source of Wg, suggesting that Wg is endocytosed [23,24]. This idea is supported by examination of shibire embryos, which have a mutation in dynamin, a critical component of the endocytic machinery; these mutants have defects in Wg distribution, and Wg signaling activity is compromised [25]. Similarly, expression of a dominant-negative form of shibire also reduces Wg activity [26]. Endocytosis may also help to limit the distribution of Wg signal. In contrast to cells anterior to the Wg source, cells posterior to Wg-producing cells have much lower levels of Wg in endocytic vesicles, and this asymmetry in distribution mirrors the observation that Wg acts over a much shorter range towards the posterior than towards the anterior. This difference in Wg distribution appears to be due to rapid degradation of endocytosed Wg in posterior cells [27]. The spatially restricted pattern of Wg degradation is regulated by signals through the epidermal growth factor (EGF) receptor that hasten the destruction of Wg in posterior cells [27].

Localization and function
Post-translational modifications and secretion
Wnt proteins have an amino-terminal signal sequence, which can act in a cell non-autonomous manner, and are present in the secretory pathway, indicating that they are secreted proteins [11]. In addition, genetic analyses of Wg signaling in Drosophila uncovered mutations in the porcupine gene that show a lack of Wg activity due to the retention of Wg protein in the endoplasmic reticulum [12-14]. The porcupine gene is predicted to encode a protein with eight transmembrane domains and has a perinuclear localization in transfected cells [14]; overexpression of porcupine does not increase levels of secreted Wg but does change the pattern of Wg glycosylation [14]. In worms, mom-1 encodes a porcupine homolog and, when mutated, phenocopies mutants of mom-2, which encodes a Wnt, suggesting that the function of porcupine is conserved [15,16]. Although size chromatography suggests that Wg is secreted as a multimer, it remains unclear whether Wnt proteins in general are secreted as monomers, oligomers, or as part of a multi-protein complex [17]. Wnt proteins are glycosylated, but mutation of some or all of the predicted glycosylation sites in mouse Wnt1 does not abolish its activity in cultured cells [18]; these modifications may thus be unimportant for Wnt function.
Biology

Sequences were aligned using the ClustalW program; trees were constructed from the alignments using the neighbor-joining method and selected human sequence is available. Numbers indicate branch lengths.

Predicted evolutionary relationships between members of the Wnt gene family. (a) Predicted relationships between 18 of the 19 known human WNT protein sequences; WNT15 was omitted because only a partial sequence is available. (b) Predicted evolutionary relationships between selected human WNT proteins (representing each large grouping shown in (a)) and Wnt proteins from mouse, Xenopus, Drosophila, and Caenorhabditis elegans. Sequences were aligned using the ClustalW program; trees were constructed from the alignments using the neighbor-joining method and are diagrammed using midpoint rooting. Numbers indicate branch lengths.

Polarized distribution of wg transcripts in embryonic epithelial cells is also required for optimal signaling activity. High-resolution in situ hybridization analyses demonstrate that wg transcripts are localized apically in the embryonic epidermis and that this distribution is mediated by two cis-acting elements found in the 3’ UTR of the wg mRNA [29]. Mutation of these elements results in uniform localization of wg transcripts and impaired Wg protein distribution and signaling. The asymmetric distribution of wg transcripts is dependent on dynein-mediated microtubule transport [30].

Function

Wnts and Wnt receptors

Reception and transduction of Wnt signals involves binding of Wnt proteins to members of two distinct families of cell-surface receptors, members of the Frizzled (Fzd) gene family and members of the LDL-receptor-related protein (LRP) family [31,32]. The canonical Fzd receptor has an aminoterminal cysteine-rich domain (CRD) that binds Wnt, seven transmembrane domains and a short cytoplasmic tail containing a consensus PDZ domain binding motif (S/T-X-V in the single-letter amino-acid code) at the carboxyl terminus. The CRD forms a novel protein fold with a conserved dimerization interface that may be important for Wnt binding [33]. Fzd receptors have been identified in vertebrates and invertebrates; there are ten known members in humans and mice, four in flies, and three in worms. The general structure of Fzd receptors resembles that of seven-transmembrane G-protein-coupled receptors, suggesting that Fzd proteins may use heterotrimeric G proteins to transduce Wnt signals. Several recent studies provide evidence consistent with this idea, showing that a subgroup of Fzd receptors can signal through the pertussis-toxin-sensitive subclass of heterotrimeric G proteins to stimulate an increase in intracellular Ca2+ and activate protein kinase C (PKC) [34-38]. Heterotrimeric G proteins do not appear to be involved in transducing Wnt/Fzd signals that regulate the cytoskeleton-associated protein β-catenin, however (see below).

Two members of the vertebrate LRP family, LRP-5 and LRP-6, can bind Wnts and may form a ternary complex with a Wnt and a Fzd [39]. Mutations in LRP-6 in mice result in developmental defects similar to those seen in mice deficient for several individual Wnt genes [40], and overexpression of LRP in Xenopus can activate the Wnt pathway [39]. In Drosophila, arrow, the ortholog of LRP5 and LRP6, is required for optimal Wg signaling [41]. Although the mechanism of LRP signaling is unclear, recent evidence suggests that binding of the cytoplasmic domain of LRP to the Wnt antagonist Axin may play a role in Wnt pathway activation [42].
In addition to the Fzd and LRP receptors, cell-surface proteoglycans also appear to have a role in the reception of Wnt signals. For example, genetic analyses in Drosophila have shown that several genes required for optimal Wg signaling encode cell-surface proteoglycans of the glypican family [43, 44] and proteins involved in proteoglycan synthesis [45-47]. Furthermore, QSuII, an avian protein related to heparan-specific N-acetyl glucosamine sulfatas, has also been shown to regulate heparan-dependent Wnt signaling in cultured cells [48]. It is unclear at this time how proteoglycans modulate Wnt signaling, but current suggestions include concentrating Wnt proteins at the cell surface or preventing Wnt ligands to cell-surface receptors.

**Secreced modulators of Wnt signaling**

Wnt signals are modulated extracellularly by diverse secreted proteins, including members of the Frizzled-related protein (FRP or FrzB) family [49], Wnt-inhibitory factor-1 (WIF-1) [50], Cerberus [51], and Dickkopf (Dkk) [52]. FRPs, WIF-1, and Cerberus can bind Wnts directly and are thought to antagonize Wnt function by preventing their interaction with Fzd receptors. FRPs can also interact with Fzds, suggesting that a second way in which FRPs might antagonize Wnt signaling is through the formation of a non-functional complex with Fzd receptors. Humans have at least five FRP genes, and the specificity of each FRP for different Wnts remains to be determined. Dkk does not bind Wnts but instead interacts with the extracellular domain of LRPs, thereby blocking activation of Wnt signaling [42, 53-54]. Four Dkk genes have been identified in vertebrates, including Dkk2, which does not act as a Wnt antagonist but rather can stimulate Wnt signaling [55].

**Intracellular signaling pathways**

Wnt signals are transduced through at least three distinct intracellular signaling pathways including the canonical ‘Wnt/β-catenin’ pathway, the ‘Wnt/Ca2+’ pathway, and the ‘Wnt/polarity’ pathway (also called the ‘planar polarity’ pathway) [5, 56-62]. Distinct sets of Wnt and Fzd ligand-receptor pairs can activate each of these pathways and lead to unique cellular responses. The Wnt/β-catenin pathway primarily regulates cell fate determination during development, whereas the major function of the Wnt/polarity pathway is regulation of cytoskeletal organization. The biological function of the Wnt/Ca2+ pathway is unclear.

The canonical Wnt/β-catenin pathway is intensely studied, and on the basis of current literature I propose the model illustrated in Figure 3a [59, 63, 64]. Signaling through this pathway depends on the levels of β-catenin in the cell. In the absence of Wnt, β-catenin is targeted for degradation by a multi-protein destruction complex. Wnt signaling antagonizes the destruction complex, leading to the accumulation of β-catenin and activation of target genes. Up-to-date lists of proteins involved in Wnt/β-catenin signaling and the potential roles of each of these proteins can be found on the worldwide web [5, 60, 62].

The Wnt/Ca2+ pathway involves an increase in intracellular Ca2+ and activation of PKC; it can be activated by a distinct group of Wnt ligands and Fzd receptors from those that activate other pathways, including Wnt5a, Wnt11 and Fzd2 (Figure 3b) [58, 61, 62]. The Wnt/Ca2+ pathway involves activation of a heterotrimeric G protein, an increase in intracellular Ca2+, and activation of calcium/calcmodulin-regulated kinase II (CamKII) and PKC [34, 35, 37]. The downstream targets of CamKII and PKC are currently unknown, but it has been shown that activation of the Wnt/Ca2+ pathway can antagonize the Wnt/β-catenin pathway in Xenopus, although it is unclear at what level this interaction occurs [65].

Wnt/polarity signaling regulates the polarity of cells through regulation of their cytoskeletal organization (Figure 3c) [56, 57, 62]. In vertebrates, Wnt/polarity signaling is thought to control polarized cell movements during gastrulation and neurulation [66-70]. In Drosophila, Wnt/polarity signaling...
Figure 3 (see the legend on the previous page)
These molecules are required for the appropriate orientation of trichomes - or hairs - of the adult wing and for appropriate chirality of ommatidia in the eye, and may regulate asymmetric cell divisions of certain neuroblasts [56,71,72]. The only molecules known to function in both the vertebrate and the invertebrate Wnt/polarity pathways are members of the Fzd family and the cytoplasmic scaffold protein Dsh. The regulation of gastrulation movements in vertebrates also requires the activity of Wnt11, which may signal through Fzd7 to regulate protrusive activity during convergent extension [66,67]. In flies, genetic analyses have identified a number of potential components of the Wnt/polarity pathway in addition to DFz3 and Dsh, including the small GTPase DrhoA, Drosophila rho-associated kinase (Drok), Jun N-terminal kinase (JNK), myosin II, myosin VIIA, and the products of the novel genes flamingo/starry night, fuzzy, inturned, and strabismus/van gogh [56,72]. A Wnt ligand for the Wnt/polarity pathway has not been identified in flies, however, and it remains to be seen how much of the intracellular signaling mechanism has been conserved between vertebrates and invertebrates.

Several studies have suggested that distinct classes of Wnts signal through either the Wnt/β-catenin pathway or the Wnt/Ca2+ pathway [58]; for example, overexpression studies in Xenopus have shown that XWnt1, XWnt3a, XWnt8, and XWnt8b can stimulate the Wnt/β-catenin pathway whereas XWnt4, XWnt5a, and XWnt11 can stimulate the Wnt/Ca2+ pathway [58]. Furthermore, the separation of Wnts into these two distinct functional classes is mirrored by the classification of Fzds proteins into similar functional groups on the basis of their ability to activate one or other pathway in overexpression assays. Although this classification of Wnts, which partially mirrors their evolutionary relationships, may provide a useful tool for predicting the function of Wnts and Fzds, the relationship between specific Wnts and the intracellular pathway they use is not fixed. For example, overexpression of XWnt5a in combination with human FZD5 in Xenopus embryos results in activation of the Wnt/β-catenin pathway [73], suggesting that the activity of Wnts in vivo will be determined by the repertoire of Fzds receptors present at the cell surface.

### Important mutants and developmental functions

Loss-of-function mutations in 9 of the 18 mouse Wnt genes have been generated, and the phenotypes of mutant embryos demonstrate the diverse functions of Wnt genes during embryogenesis (Table 2). For example, knocking out Wnt1 results in a dramatic loss of a portion of the midbrain and deletion of the rostral cerebellum [74,75]. Inactivation of Wnt4 results in the absence of kidneys [76], masculinization of mutant females (absence of the Müllerian duct and continued development of the Wolffian duct) [77], and defects in mammary gland morphogenesis during pregnancy [78]. Targeted knockout of Wnt7a also has pleiotropic effects, including ventralization of the limbs

| Gene   | Natural allele | Phenotype of knockout or other functions                                                                 | References                        |
|--------|----------------|-------------------------------------------------------------------------------------------------------|-----------------------------------|
| Wnt1   | swaying        | Loss of a portion of the midbrain and cerebellum                                                      | [74,75,129,130]                   |
|        |                | Deficiency in dorsal neural-tube derivatives, including neural-crest cells in double knockout with Wnt3a | [131]                             |
| Wnt2   |                | Placental defects                                                                                   | [132]                             |
| Wnt3   |                | Defects in axis formation and gastrulation                                                           | [84]                              |
|        |                | Defects in hair growth and structure                                                                  | [133,134]                         |
| Wnt3a  | vestigial tail | Defects in somite and tailbud development                                                            | [102,135-137]                     |
|        |                | Deficiency in dorsal neural-tube derivatives, including neural crest cells in double knockout with Wnt1 | [131]                             |
|        |                | Loss of hippocampus                                                                                 | [138]                             |
| Wnt4   |                | Defects in kidney development                                                                       | [76]                              |
|        |                | Defects in female development; absence of Mullerian duct, ectopic synthesis of testosterone in females | [77]                              |
|        |                | Defects in mammary gland morphogenesis                                                              | [78]                              |
| Wnt5a  |                | Truncated limbs, shortened anterior-posterior axis, reduced number of proliferating cells            | [139]                             |
| Wnt7a  | postaxial hemimelia | Defects in limb polarity                                                                             | [79]                              |
|        |                | Female infertility due to failure of Mullerian duct regression                                       | [80,140]                          |
|        |                | Defects in uterine patterning                                                                       | [141]                             |
|        |                | Defects in synapse maturation in the cerebellum                                                      | [81]                              |
| Wnt7b  |                | Placental defects                                                                                   | [142]                             |
| Wnt10b |                | Inhibition of adipogenesis                                                                        | [143]                             |
female infertility due to failure of Müllerian-duct regression [80], and a delay in the morphological maturation of glomerular rosettes in the cerebellum [81].

Overexpression and antisense ‘knockdown’ analyses in Xenopus have shown that the Wnt/β-catenin pathway is required for the specification of dorsal cell fates [82]. A debate is ongoing, however, over whether a maternal Wnt ligand is required to activate this pathway in dorsal cells. In support of a role for a Wnt ligand, a recent study has shown that XFzd7 is important for establishing dorsal cell fates [83], thereby implicating a Wnt ligand in this process. Furthermore, targeted knockout of Wnt3 in mice results in defects in axis formation and gastrulation, suggesting a conserved role for Wnts in regulating the establishment of the dorsal-ventral axis in vertebrates [84]. On the other hand, overexpression of a dominant-negative form of Xwnt8 in oocytes does not suppress formation of dorsal cell fates, arguing against the requirement for a maternal Wnt in axis specification [10]. Further studies are necessary to resolve the role of Wnts in vertebrate early axial development.

In flies, Wnt signaling has a variety of functions during development. The wg gene is required for cell-fate choices in the ventral epidermis during embryogenesis, as well as for many other functions, and DWnt2 is required for testis and adult muscle development [17]. In C. elegans, genetic analyses have defined a number of roles for Wnts, including establishment of polarity and endodermal cell fates in the early embryo and regulation of cell migration, among many others [85]. A comprehensive list of Wnt genes and their mutant phenotypes in vertebrates and invertebrates can be found at the Wnt gene homepage [5].

**Wnt signaling and cancer**

In addition to the many roles for Wnt signaling during development and in adult tissues, it is also involved in tumorigenesis in humans [59,64]. Although mutation or misexpression of a Wnt gene has not been linked directly to cancer in humans, mutation of several intracellular components of the Wnt/β-catenin pathway is thought to be critical in many forms of cancer. Most notably, patients with familial adenomatous polyposis (FAP) develop multiple intestinal adenomas early in life and have germline mutations in the APC gene. In addition, mutation of APC is associated with more than 80% of sporadic colorectal adenomas and carcinomas. More than 95% of germline and somatic mutations of the APC gene are nonsense mutations that result in the synthesis of a truncated protein lacking the region of APC that is important for its function in the destruction complex. Significantly, these truncations in APC remove binding sites for β-catenin and Axin, as well as putative phosphorylation sites for GSK3; as a result, the mutant APC protein cannot efficiently promote degradation of β-catenin. Mutations in the third exon of the human β-catenin gene (CTNNb1) that make it refractory to phosphorylation-dependent degradation and lead to inappropriate accumulation of β-catenin have also been identified in a large number of primary human cancers (see [64] for a table of β-catenin mutations in human cancers). Interestingly, mutations in CTNNb1 and APC are rarely found in the same tumor; for example, in colon cancer, in which the vast majority of tumors have mutations in APC, the overall frequency of CTNNb1 mutations is relatively low, but colorectal tumors lacking APC mutations are much more likely to have mutations in CTNNb1. Recently, Axin has also been shown to act as a tumor suppressor; mutations in the Axin1 gene have been found in human hepatocellular cancers [86]. Importantly, mutations in Axin1 and CTNNb1 found in hepatocellular carcinomas also show mutual exclusivity similar to that seen for APC and CTNNb1 in colon cancers. Together, these data strongly argue that mutations resulting in the stabilization of β-catenin can promote cancer in many tissue types.

**Frontiers**

The large number of Wnt genes and the many roles that Wnt signaling plays in development and human disease pose many unresolved issues for researchers. One of the major unanswered questions is the specificity of interactions between different Wnt ligands and Fzd receptors and also which downstream pathways these many different ligand-receptor pairs stimulate. It also remains unclear how Wnt signals are transduced by the Fzd-LRP receptor complex and what role proteoglycans play in this process. Inside the cell, many questions regarding the transduction of Wnt signals remain, including how receptor activation stimulates Dsh and how Dsh discriminates between different Wnt signals to activate either the Wnt/β-catenin or the Wnt/polarity pathway. Furthermore, many roles of Wnts during development remain to be determined. This challenge will require detailed analyses of knockout mice, in addition to biochemical, cell-biological and genetic analyses in other model systems, to characterize the functions of Wnts and the signaling pathways they use during embryogenesis. Finally, the identification and characterization of mutations in Wnt-pathway genes involved in human disease is ongoing and these studies, together with a greater knowledge of the molecular mechanism of Wnt signal transduction, promise future clinical therapies for devastating human afflictions such as colon cancer. Thus, although there is so much still to learn, the importance and widespread occurrence of Wnt signaling guarantees the rapid increase in our understanding of the normal and abnormal functions of the Wnts.

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The Genome Database (GDB) is the official central repository for genomic mapping data resulting from the Human Genome Initiative.

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The Stanford Online Universal Resource for Clones and ESTs (SOURCE) compiles information from several publicly accessible databases, including...
The authors investigated whether distinct domains of XWnt8 and XWnt5a were required in mediating Wg signaling. The authors expressed int-1 (Wnt1) in fibroblasts and found that it could not be detected in the culture medium but instead was found in tight association with the extracellular matrix. They also presented evidence that Wnt1 can bind heparin in vitro, suggesting that Wnt proteins may associate with glycosaminoglycans at high concentrations.

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This paper describes a novel endocytic compartment in Drosophila embryos termed argosomes that may represent a specialized exovesicle important for transcytosis and movement of signaling molecules through epithelia. Wg protein was found to co-localize with argosomes, suggesting that argosomes may represent a novel vehicle for the transport of Wnt ligands through epithelia.

29. Simmonds AJ, dos Santos G, Livne-Bar I, Krause HM: Apical localization of wingless transcripts is required for wingless signaling. Cell 2001, 105:197-207.

Using high-resolution in situ hybridization analyses, the authors show that wingless transcripts are apically localized in several tissues during Drosophila development. This polarized distribution was dependent on two cis-acting elements found in the 3' UTR of the wingless transcript. Mutation of these elements resulted in mis-localization Wg protein as well as a reduction in Wg signaling activity.

30. Willkie GS, Davis T: Drosophila Argosomes and pair-rule transcripts localize apically by dynein-mediated transport of RNA particles. Cell 2001, 105:209-219.

This paper demonstrates that wingless transcripts assemble into cytoplasmic particles that are transported to apical regions of the cell via microtubules and dynein motors.

31. Bejsovec A: Wnt signaling: an embarrassment of receptors. Curr Biol 2000, 10:R919-R922.

This review and [32] discuss the recent identification of LRP as a Wnt co-receptor.

32. Parand P, Kuhl M: An arrow for wingless to take-off. BioEssays 2001, 23:207-210.

This paper discusses Wnt signal transduction.

33. Dann CE, Hsieh JC, Rattner A, Sharma D, Nathans J, Leahy DJ: Insights into Wnt binding and signaling from the structures of two Frizzled cysteine-rich domains. Nature 2001, 412:86-90.

The structure of the cysteine-rich domains (CRDs) of mouse Fz8d and secreted Fzd-related protein-3 (FRP3). The CRD was shown to form a novel protein fold, and the design and interpretation of CRD mutations identified a Wnt-binding site. The CRDs were also found to exhibit a conserved dimer interface that may be a feature of Wnt signaling.

34. Sheldahl LC, Park M, Malbon CC, Moon RT: Protein kinase C is differentially stimulated by Wnt and Frizzled homologs in a G-protein-dependent manner. Curr Biol 1999, 9:695-698.

This paper builds on a previous observation that signaling by Wnt5a and Fzd2 leads to an increase in intracellular Ca2+ and demonstrates that Wnt5a and Fzd2 also activate PKC in Xenopus embryos. The authors also show that distinct subsets Wnt ligands and Fzd receptors stimulate either the Wnt/β-catenin or the Wnt/β-catenin pathway in Xenopus.

35. Liu X, Liu T, Slusarski DC, Yang-Snyder J, Malbon CC, Moon RT, Weng H: Activation of a frizzled-2/β-adrenergic receptor-chimeric protein vectorizes Wnt signaling and directs signaling of mouse F9 teratocarcinoma cells via Gαm and Gαq. Proc Natl Acad Sci USA 1999, 96:14383-14388.

The authors engineered a rat Fzd2 chimera responsive to β-adrenergic agonist by fusing the ligand-binding domains of the β(3)-adrenergic receptor to the intracellular loops of Fzd2. Isoproterenol-induced activation of the Fzd2 chimera in F9 embryonic teratocarcinoma cells was blocked by pertussis toxin and by oligodeoxynucleotide antisense to Gαm or Gαq, demonstrating the involvement of two pertussis toxin-sensitive G proteins for signaling by the Fzd2 receptor.

36. Liu T, Liu X, Wang H, Moon RT, Malbon CC: Activation of rat frizzled-1 promotes Wnt signaling and differentiation of mouse F9 teratocarcinoma cells via pathways that require Galphai(q) and Galphai(o) function. J Biol Chem 1999, 274:33539-33544.

This paper demonstrated that stimulation of F9 teratocarcinoma cells expressing rat Fzd1 with Xenopus Wnt8-conditioned media results in differentiation into primitive endoderm, Fzd1/Wnt18-dependent differentiation could be blocked by pertussis toxin, depletion of Gαm or Gαq, inhibition of PKC, and inhibition of mitogen-activated protein kinase (MAPK), suggesting that signaling by Fzd1 in F9 cells involves activation of heterotrimeric G-proteins, PKC and MAPK.

37. Kuhl M, Sheldahl LC, Malbon CC, Moon RT: Ca(2+)/calmodulin-dependent protein kinase II is stimulated by Wnt and Frizzled homologs and promotes ventral cell fates in Xenopus. J Biol Chem 2000, 275:12701-12711.

This paper demonstrates that expression of a subset of Wnt ligands (Wnt5a and Wnt11) and Fzd receptors (including rat Fzd2) in Xenopus embryos leads to the stimulation of CamKII. Using chimeric β-adrenergic/Fzd2 receptors, the authors also show that activation of CamKII occurs within 10 minutes following receptor stimulation and is sensitive to pertussis toxin.

38. Liu T, DeCostanzo AJ, Liu X, Wang H, Hallagan S, Moon RT, Malbon CC: G protein signaling from activated rat frizzled-1 to the β-catenin-Lef/Tcf pathway. Science 2001, 292:1718-1722.

This paper shows that stimulation of a chimeric β-adrenergic/Fzd1 receptor expressed in mouse F9 teratocarcinoma cells with isoproterenol results in the stabilization of β-catenin and activation of a β-catenin-responsive reporter gene. Both of these effects could be blocked by pertussis toxin, indicating that heterotrimeric G proteins may be involved in transducing signals from Fzd1 to the Wnt/β-catenin pathway.

39. Tamai K, Semenov M, Kato Y, Spokony R, Liu C, Katsuyama Y, Hess F, Saint-Jeannet JP, He X: LDL receptor-related proteins in Wnt signal transduction. Nature 2000, 407:530-535.

This paper demonstrates that the LRP6 can act as a Wnt receptor in Xenopus embryos. Overexpression of LRP6 in Xenopus resulted in axis duplication and activation of Wnt-responsive genes while overexpression of a truncated form of LRP6 blocked Wnt activity in the same assays. Furthermore, LRP6 can bind Wnt and interacts with Fzd in a Wnt-dependent manner.

40. Pinson KL, Brennan J, Monkley S, Avery BJ, Skarnes WC: An LDL-receptor-related protein mediates Wnt signaling in mice. Nature 2000, 407:535-538.

This paper provides evidence that LRP6 can act as a Wnt receptor in mice. Embryos homozygous for a mutation in the LRP6 gene exhibit developmental defects that are a striking composite of those caused by mutations in individual Wnt genes. Furthermore, the authors show a genetic enhancement of the vestigial tail (Wnt3a) phenotype in mice lacking one functional copy of LRP6.

41. Wehrli M, Dougan ST, Caldwell K, O’Keefe L, Schwartz S, Vaizel-Ohayon D, Scheijer E, Tonilinson A, DiNardo S: Arrow encodes an LDL-receptor-related protein essential for Wingless signaling. Nature 2000, 407:527-530.

This paper demonstrates that the arrow gene is necessary for all Wg signaling events in Drosophila. The authors also provide genetic evidence that arrow gene function is essential in cells receiving Wg input and that it acts upstream of Dsh.

42. Mao J, Wang J, Liu B, Pan W, Farr GH 3rd, Flynn C, Yuan H, Takekada S, Kimelman D, Li L, et al: Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway. Mol Cell 2001, 7:801-809.

This paper shows that the intracellular domain of LRPS binds Axin. Wnt signals were found to cause recruitment of Axin to the membrane and enhanced the interaction of Axin with LRPS. Together, these data suggest that activation of the Wnt/B-catenin pathway may involve direct interaction of Axin with the Wnt receptor complex.

43. Lin X, Perrimon N: Dally cooperates with Drosophila Frizzled 2 to transduce Wingless signalling. Nature 1999, 400:281-284.

The authors show that mutation of dally, a member of the glycan family of heparan sulfate proteoglycans, results in phenotypes similar to partial loss of wingless function. Loss of dally was also found to enhance loss-of-function Dfz2d phenotype.

44. Tsuda M, Kamimura K, Nakato H, Archer M, Staatz W, Fox B, Humphrey M, Olson S, Fucht T, Kalzu M, et al: The cell-surface proteoglycan Dally regulates Wingless signaling in Drosophila. Nature 1999, 400:276-280.

Similar to the results reported in [43] this paper describes genetic evidence that dally plays a role in the reception of Wg signals.

45. Binari RC, Staveley BE, Johnson WA, Godavarti R, Sassekharan R, Manoukian AS: Genetic evidence that heparin-like glycosaminoglycans are involved in wingless signaling. Development 1997, 124:2623-2632.

This paper shows that injection of heparin into Drosophila embryos results in the degradation of heparin-like glycosaminoglycans and a wingless-like cuticular phenotype, suggesting the proteoglycans are involved in Wnt signaling.

46. Hacker U, Lin X, Perrimon N: The Drosophila sugarless gene modulates Wingless signaling and encodes an enzyme involved in polysaccharide biosynthesis. Development 1997, 124:3565-3573.

This paper describes genetic evidence that the sugarless gene, a Drosophila homolog of vertebrate UDP-glucose dehydrogenase, is required for optimal Wg signaling. UDP-glucose dehydrogenase is essential for the biosynthesis of various proteoglycans, suggesting that
47. Haerry TE, Heslip TR, Marsh JL, O’Connor MB: Defects in glucuronate biosynthesis disrupt Wingless signaling in Drosophila. Development 1997, 124:3055-3064.

The authors describe the identification and characterization of the Drosophila suppankescher (skk) gene that encodes a UDP-glucose dehydrogenase required for production of glucuronic acid. Genetic analyses show that the phenotype skk mutant embryos resemble that of wingless deficient embryos and that skk interacts with both wingless and dishevelled.

48. Dhoot GK, Gustafsson MK, Ai X, Sun W, Standiford DM, Emerson CP Jr.: Regulation of Wnt signaling and embryo patterning by an extracellular sulfatase. Science 2001, 292:1663-1666.

The identification of Qsuf1, an avian ortholog of an evolutionally conserved protein family related to heparan-specific N-acetyl glucosaminyl sulfatases. In cultured C2C12 myogenic progenitor cells Qsuf1 was found to facilitate Wnt signaling, suggesting that Qsuf1 can modulate Wnt signals by desulfation of cell-surface proteoglycans.

49. Moon RT, Brown JD, Yang-Snyder JA, Miller JR: Structurally related receptors and antagonists compete for secreted Wnt ligands. Cell 1997, 88:725-728.

This paper describes the discovery and function of FRPs with a focus on the role of FRPs during early Xenopus development.

50. Hsieh JC, Kodjabachian L, Rebert ML, Rattner A, Samos CH, Nusse R, Dawid IB, Nathans J: A new secreted protein that binds to Wnt proteins and inhibits their activities. Nature 1999, 398:431-435.

The authors describe the identification of Wnt-inhibitory factor-1 (WIF-1), a secreted Wnt antagonist, and show that overexpression of WIF-1 in Xenopus embryos perturbs somitogenesis.

51. Piccolo S, Ageus E, Lyley LA, Bhattacharyya S, Grunz H, Bouwmeester T, de Robertis EM: The head inducer Cerberus is a multifunctional antagonist of Nodal, BMP and Wnt signals. Nature 1999, 397:707-710.

This paper shows that the Cerberus protein can bind to Nodal, BMP and Wnt proteins via independent sites, suggesting that it functions as a multivalent growth-factor antagonist. Based on overexpression experiments in Xenopus, the authors propose that Cerberus functions to block Nodal, BMP, and Wnt signals involved in trunk formation thereby promoting head formation in anterior regions of the embryo.

52. Nusse R: Developmental biology. Making head or tail of Wnt signaling. Nature 1999, 399:123-128.

This comment article summarizes data presented in [53].

53. Bafico A, Liu G, Yaniv A, Gazit A, Aaronson SA: Novel mechanism of Wnt signalling inhibition mediated by Dickkopf-1 interaction with LRPS/Arrow. Nat Cell Biol 2001, 3:683-686.

This paper demonstrates that Dickkopf-1 (Dkk1), a secreted Wnt antagonist, blocks Wnt signaling by binding to the extracellular domain of the Wnt receptors LRPS and LRP6.

54. Semenov MV, Tamaki K, Brott BK, Kuhl M, Sokol S, He X: Head inducer Dickkopf-1 is a ligand for Wnt coreceptor LRPS6. Curr Biol 2001, 11:1591-1596.

The authors show that Dickkopf-1 (Dkk-1) is a high-affinity LRPS6 ligand that inhibits Wnt signaling by blocking Wnt-induced Fzd-LRPS6 complex formation.

55. Wu W, Glinka A, Delius H, Niehrs C: Mutual antagonism between dickkopf1 and dickkopf2 regulates Wnt/beta-catenin signalling. Curr Biol 2000, 10:1611-1614.

This paper shows that dickkopf2 (Dkk2) and Wnt act synergistically in Xenopus embryos to activate the Wnt/beta-catenin pathway. Thus, unlike other members of the DKK family that act as Wnt antagonists, Dkk2 appears to function as a stimulatory co-factor for Wnt signaling.

56. Adler PN, Lee H: Frizzled signaling and cell-cell interactions in planar polarity. Curr Opin Cell Biol 2001, 13:635-640.

This review provides a current summary of the role of Fzd and Dsh in regulating planar polarity during gastrulation. It provides a detailed analysis of the effects of the truncated form of Dsh on cell movements and demonstrate that Dsh regulates the polarization of cells along the medial-lateral axis as well as the dynamics and polarity of cellular protrusions during gastrulation.

57. Boutrous M, Mlodzik M: Dishevelled: at the crossroads of divergent intracellular signaling pathways. Mech Dev 1999, 83:27-37.

This review provides a summary of the function of Dsh in Wnt signaling and discusses how Dsh discriminates between different Wnt inputs to modulate distinct downstream cellular responses.

58. Kuhl M, Sheldahl LC, Park M, Miller JR, Moon RT: The Wnt/Ca2+ pathway: a new vertebrate Wnt signaling pathway takes shape. Trends Genet 2000, 16:279-283.

This review provides a synopsis of our current understanding of the Wnt/Ca2+ pathway and presents an interesting tale describing the apparently mutually exclusive ability of different Fzd receptors to stimulate either the Wnt/beta-catenin or Wnt/Ca2+ pathways.

59. Miller JR, Hocking AM, Brown JD, Moon RT: Mechanism and function of signal transduction by the Wnt/beta-catenin and Wnt/Ca2+ pathways. Oncogene 1999, 18:7860-7872.

This review provides a detailed summary of our current understanding of the molecular mechanisms underlying signaling through the Wnt/beta-catenin or Wnt/Ca2+ pathways. Particular attention is paid to the function and regulation of the Axin/APC/GSK3 destruction complex and the involvement of Wnt pathway genes in human cancer.

60. Science’s STKE Connections Map [http://stke.sciencemag.org/cm/]

This website is an excellent source of up-to-date information on a variety of cell-signaling topics and includes an interactive connections map for several Wnt pathways.

61. A Pond in Seattle: Xenopus and Zebrafish Research in the lab of Dr. Randall Moon [http://faculty.washington.edu/rmoon/]

This website contains several flash animated movies of Wnt signaling and an excellent source for DNA constructs useful for studying Wnt signaling.

62. Wnt World [http://www.gcd.med.unm.edu/millerlab/Wnt/wntworld.html]

This website, maintained by my lab, is a new venture aimed at providing up-to-date information on the mechanism of Wnt signaling and the function of Wnt signaling during development and in human disease.

63. Wodarz A, Nusse R: Mechanisms of Wnt signaling in development. Annu Rev Cell Dev Biol 1998, 14:59-88.

This review provides a comprehensive view of the role of Wnt signaling during development.

64. Polakis P: Wnt signaling and cancer. Genes Dev 2000, 14:1837-1851.

This review provides an excellent synopsis of our current understanding of the role of Wnt signaling in human cancer. It also contains a table describing Wnt mutations found in various human cancers and is an excellent source for DNA constructs useful for studying Wnt signaling.

65. Torres MA, Yang-Snyder JA, Purcell SM, DeMarais AA, McGrew LL, Moon RT: Activities of the Wnt-1 class of secreted signaling factors are antagonized by the Wnt-5A class and by a dominant-negative cadherin in early Xenopus development. J Cell Biol 1996, 133:1223-1237.

The authors demonstrate that overexpression of XWnt5A can inhibit signaling by Xwnt8 in Xenopus embryos through a mechanism that may involve changes in cell-cell adhesion.

66. Heisenberg CP, Tada M, Rauch G, Saude L, Concha ML, Geisler R, Stemple DL, Smith JC, Wilson SW: Silberblick/Wnt11 mediates convergent extension movements during zebrafish gastrulation. Nature 2000, 405:76-81.

This paper describes the characterization of the silberblick/Wnt11 gene in zebrafish. The authors demonstrate that silberblick/Wnt11 is required for convergent-extension movements and that overexpression of a truncated form of Dsh active in Wnt/polarity signaling but not Wnt/beta-catenin signaling can compensate for the loss of silberblick/Wnt11 function.

67. Taipale M, Smith JC: Xwnt11 is a target of Xenopus Brachyury: regulation of gastrulation movements via Dishevelled, but not through the canonical Wnt pathway. Development 2000, 127:2227-2238.

The authors demonstrate that overexpression of a dominant-negative form of Xwnt11 in Xenopus embryos inhibits convergent extension movements. Co-expression of wild-type Dsh or a truncated form of Dsh that cannot signal through the Wnt/beta-catenin pathway can overcome this inhibitory effect.

68. Wallingford JB, Rowling BA, Vogeli KM, Rothenbacher U, Fraser SE, Harland RM: Dishevelled controls cell polarity during Xenopus gastrulation. Nature 2000, 405:81-88.

This paper demonstrates that overexpression of a truncated form of Dsh that inhibits Wnt/Polarity signaling, but not Wnt/beta-catenin signaling, disrupts convergent extension movements in Xenopus. The authors provide a detailed analysis of the effects of the truncated form of Dsh on cell movements and demonstrate that Dsh regulates the polarization of cells along the medial-lateral axis as well as the dynamics and polarity of cellular protrusions during gastrulation.

69. Marsden M, DeSimone DW: Regulation of cell polarity, radial intercalation and epiboly in Xenopus: novel roles for integrin and fibronectin. Development 2001, 128:3635-3647.

This paper shows that integrin-dependent binding of blastocoel roof cells to fibronectin is sufficient to drive membrane localization of Dsh-GFP, suggesting that a convergence of integrin and Wnt signaling pathways acts to regulate morphogenesis in Xenopus embryos.
70. Wallingford JB, Harland RM: Xenopus Dishevelled signaling regulates both neural and mesodermal convergent extension: parallel forces elongating the body axis. Development 2001, 128:2581-2592. This paper shows that spatially restricted expression of Dissh mutants that block Wnt/Polarity signaling, but not Wnt/β-catenin signaling, to neural or mesodermal tissues inhibited either neural or mesodermal convergent extension. Targeted expression of other Wnt signaling antagonists also inhibited neural convergent extension in whole embryos without affecting cell fate, suggesting that Wnt/Polarity signaling regulates morphogenesis of both mesodermal and neural tissues during vertebrate development.

71. Adler PN, Taylor J: Asymmetric cell division: plane but not simple. Curr Biol 2001, 11:R233-R236. This review discusses the role of Fzd receptors in the regulation of asymmetric cell divisions in Drosophila embryos.

72. Strutt D: Planar polarity: getting ready to ROCK. Curr Biol 2001, 11:R506-R509. This review summarizes recent advances in our understanding of how Fzd and Dsh regulate planar polarity in Drosophila focusing on the role of the rho-associated kinase ROCK in this process.

73. He X, Saint-Jeannet JP, Wang Y, Nathans J, Dawid I, Varmus H: A pregnancy. They also found that Wnt3 activity regulates cell fate decision in the developing kidney regulated by Wnt-4. Nature 1994, 372:679-683. This paper describes the expression pattern of Wnt4 and the knockout phenotype of embryos lacking Wnt4 activity. Wnt4 mutant mice fail to form pretubular cell aggregates in the developing kidney, suggesting that Wnt4 regulates the mesenchyme to epithelial transition that underlies nephron development.

74. McMahon AP, Bradley A: The Wnt-1 (int-1) proto-oncogene is required for development of a large region of the mouse brain. Cell 1990, 62:1073-1085. This paper describes the knockout of Wnt1 in the mouse and demonstrates that Wnt1 is required for the development of the midbrain and cerebellum.

75. Thomas KR, Musci TS, Neumann PE, Capecci MR: Swaying is a mutant allele of the proto-oncogene Wnt-1. Cell 1991, 67:969-981. The authors show that swayng phenotype is caused by deletion of a single base pair from Wnt1 that results in premature termination of translation, eliminating the carboxy-terminal half of the Wnt1 protein.

76. Stark K, Vainio S, Vassileva G, McMahon AP: Epithelial transformation of metanephric mesenchyme in the developing kidney regulated by Wnt-4. Nature 1994, 372:679-683. This paper describes the expression pattern of Wnt4 and the knockout phenotype of embryos lacking Wnt4 activity. Wnt4 mutant mice fail to form pretubular cell aggregates in the developing kidney, suggesting that Wnt4 regulates the mesenchyme to epithelial transition that underlies nephron development.

77. Vainio S, Heikila M, Kispert A, Chin N, McMahon AP: Female development in mammals is regulated by Wnt-4 signalling. Nature 1999, 397:405-409. This paper demonstrates that Wnt4 is required for the development of sexual dimorphism. Females lacking Wnt4 fail to form the Müllerian duct while the Wolffian duct continues to develop.

78. Brissen C, Heineman A, Chavarria T, Elenbaas B, Tan J, Dey SK, McMahon A, McMahon AP, Weinberg RA: Essential function of Wnt-4 in mammary gland development downstream of progesterone signaling. Genes Dev 2000, 14:650-654. The authors perform transplantation studies to demonstrate that mammary tissue lacking Wnt4 fails to undergo side branching during pregnancy. They also found that Wnt4 expression is regulated by progesterone. Together these data suggest that Wnt signaling is necessary to mediate progesterone function during mammary gland morphogenesis.

79. Parr BA, McMahon AP: Dorsalizing signal Wnt-7α required for normal polarity of D-V and A-P axes of mouse limb. Nature 1998, 374:350-353. This paper describes the knockout phenotype of mice lacking Wnt7a focusing on the role of Wnt7a in the limb. Mutant embryos display defects in limb patterning characterized by a dorsal-to-ventral transformation of cell fate, indicating that Wnt7a is a dorsalizing signal.

80. Parr BA, McMahon AP: Sexually dimorphic development of the mammalian reproductive tract requires Wnt-7a. Nature 1998, 395:707-710. This paper demonstrates that Wnt7a is required for establishment of sexual dimorphism. Male mice lacking Wnt7a fail to undergo reprogramming of the Müllerian duct due to the absence of the receptor for Müllerian-inhibiting substance. The authors also show that mutation of Wnt7a affects development of female-specific tissues. Wnt7a-deficient females are infertile because of abnormal development of the oviduct and uterus.

81. Hall AC, Lucas FR, Salinas PC: Axonal remodeling and synaptic differentiation in the cerebellum is regulated by WNT-7a signaling. Cell 2000, 100:525-535. This paper shows that the Wnt antagonist sFRP-1 can block endogenous signals produced by granule cells that induce axon and growth cone remodeling in mossy fibers. In contrast, Wnt7a, which is expressed by granule cells, can mimic the endogenous signal.

82. Moon RT, Kimelman D: From cortical rotation to organizer gene expression: toward a molecular explanation of axis specification in Xenopus embryos. Curr Biol 2000, 10:171-180. A comprehensive review summarizing the role of Wnt signaling in the establishment of the dorsal-ventral axis in Xenopus.

83. Sumanas S, Stroge P, Heasman J, Ecker SC: The putative wnt receptor Xenopus frizzled-7 functions upstream of beta-catenin in vertebrate dorsoventral mesoderm patterning. Development 2000, 127:1981-1990. The authors show that reducing Fzd7 function with antisense oligonucleotides in early Xenopus embryos results in defects in dorsal development. These data suggest that Fzd7 regulates the specification of dorsal cell fates and provides circumstantial evidence that a Wnt ligand is also required for this process.

84. Liu P, Wakamiya M, Shea MJ, Albrecht U, Behringer RR, Bradley A: Requirement for Wnt3 in vertebrate axis formation. Nature Genet 1999, 22:361-365. This paper describes the expression pattern of Wnt3 in mice and the phenotype of embryos lacking Wnt3. The authors find that Wnt3+/− mice develop a normal egg cylinder but do not form a primitive streak, mesoderm or node, indicating that Wnt3 plays an important role in axial patterning in the early embryo.

85. Thorpe CJ, Schlesinger A, Bowerman B: Wnt signalling in Caenorhabditis elegans: regulating repressors and polarizing the cytoskeleton. Trends Cell Biol 2000, 10:10-17. This review summarizes our knowledge of the role of Wnt signaling in regulating early cell fate decisions in the soil worm, C. elegans. The review discusses the interesting findings that C. elegans Wnt signals regulate cell fate choices via two pathways: one that involves activation of a mitogen activated protein kinase and another that involves a heterotrimeric G-protein and polarization of the mitotic spindle.

86. Satoh S, Dajo Y, Furukawa Y, Kato T, Miwa N, Nishiwaki T, Kawase T, Ishiguro H, Fujita M, Tokino T, et al.: AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. Nat Genet 2000, 24:245-250. This paper demonstrates that mutations in the AXIN1 gene are associated with hepatocellular carcinomas. These data indicate that Axin, like APC, is a tumor suppressor gene and strengthen the idea that genes involved in Wnt signaling play a critical role in human disease.

87. Nusse R, Varmus HE: Many tumors induced by the mouse mammary tumor virus contain inserts of proviral DNA inserted in the same region of the host genome. Cell 1982, 31:99-109. This paper examines the mechanism by which mouse mammary tumor virus causes mammary tumors and the authors find that proviral integration within the Wnt-1 (Wnt-1) locus.

88. Nusse R, van Ooyen A, Cox D, Fung YK, Varmus H: Mode of proviral activation of a putative mammary oncogene (int-1) on mouse chromosome 15. Nature 1984, 307:131-136. This paper demonstrates that integration of mouse mammary tumor virus into the int-1 (Wnt-1) is a virus provirus insertion into the int-1 (Wnt-1) and results in a provirus inserted within the int-1 (Wnt-1) locus.

89. van Ooyen A, Nusse R: Structure and nucleotide sequence of the putative mammary oncogene int-1; proviral insertions leave the protein-encoding domain intact. Cell 1984, 39:233-240. This paper presents the sequence of the int-1 (Wnt-1) gene and describes the sites of proviral insertion in the 5’ and 3’ untranslated regions associated with tumorigenesis.

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91. Arheden K, Mandahl N, Strombeck B, Isaksson M, Mitelman F: Chromosome localization of the human oncogene INT1 to
12q13 by in situ hybridization. **Cytogenet Cell Genet** 1988, 47:86-87.

This paper describes the chromosomal location of the human INT1 (WNT1) gene to 12q13 a position involved in chromosomal rearrangements in lipomas, myxoid liposarcomas, pleomorphic adenomas, and myomas.

92. Wainwright BJ, Scambler PJ, Stanier P, Watson EK, Bell G, Wicking C, Etxebarria X, Courtoy M, Boue A, Pedersen FS, et al.: Isolation of a human gene with protein sequence similarity to human and murine int-1 and the Drosophila segment polarity mutant wingless. *EMBO J* 1988, 7:1743-1748.

This paper describes the cloning, sequence, and expression pattern of the human WNT2 gene.

93. McMahon JA, McMahon AP: Nucleotide sequence, chromosomal localization and developmental expression of the mouse int-1-related gene. Development 1989, 107:643-650.

The authors describe the cloning, sequence, and expression pattern of the mouse Wnt2 gene. Adult expression of mouse Wnt2 is restricted to the heart, lungs, and fetal expression, to the pericardium of the heart, to the umbilicus and associated allatotic mesoderm, and to the ventral lateral mesenchyme tissue surrounding the umbilical vein.

94. Kato M, Hirai M, Sugimura T, Terada M: Cloning, expression and structure of the mouse Wnt gene family. Oncogene 1996, 13:873-876.

This paper describes the cloning, sequence and mapping of the human WNT1 and 2 genes to 1p13. The authors also show that WNT1 is expressed in several cell lines including HeLa (cervical cancer), MKN28 (gastric cancer), and KATO-III (gastric cancer) cells.

95. Grove EA, Tole S, Limon J, Yip L, Ragsdale CW: The hem of the embryonic cerebral cortex is defined by the expression of multiple Wnt genes and is compromised in Glis3-deficient mice. Development 1998, 125:2315-2325.

This paper describes the cloning and mapping of the human WNT13 gene to 1p13. The authors also show that WNT13 is expressed in several cell lines including Hela (cervical cancer), MKN28 (gastric cancer), and KATO-III (gastric cancer) cells.

96. Zakik JD, Mazan S, Maury M, Martin N, Guenel JL, Brulet P: Structure and expression of Wnt13, a novel mouse Wnt2 related gene. Mech Dev 1998, 73:107-116.

This paper describes the cloning and expression of the mouse Wnt2b gene and expression analysis of Wnt2b, Wnt3a, Wnt5a and Wnt7a in the telencephalon, Wnt2b, Wnt3a, and Wnt5a were found to be expressed in the hem of the cerebral cortex and expression is absent in the extra-toes mutant mouse.

97. Roesink H, Wagenaar E, Lopes da Silva S, Nusse R: Wnt-3, a gene activated by proviral insertion in mouse mammary tumours, is homologous to int-1/Wnt-1 and is normally expressed in mouse embryos and adult brain. Proc Natl Acad Sci USA 1999, 91:11011-11015.

The authors describe the characterization of the mouse Wnt3 gene on chromosone 11 as a site for mouse mammary tumor provirus insertion. The paper also presents expression data for Wnt3.

98. Chandrasekharappa SC, King SE, Freedman ML, Hayes ST, Bowcock AM, Collins FS: The CA repeat marker D17S791 is located within 40 kb of the WNT3 gene on chromosome 17q21. *Genomics* 1995, 21:677-680.

This paper describes the genomic localization of the human WNT3 gene close to a CA repeat marker on chromosome 17q.

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This paper describes the characterization of the human WNT3 gene and its localization to chromosome 17q21. Analysis of the WNT3 gene in a collection of mammary tumor samples failed to detect rearrangements or amplification.

100. Hunt M, Bicker El, McMahon JA, McMahon AP, Bicknell R, Harris AL: Differential expression of human Wnt genes 2, 3, 4, and 7B in human breast cell lines and normal and disease states of human breast tissue. *Cancer Res* 1994, 54:2615-2621.

The authors report the expression of WNT3, WNT4, and WNT7B in human breast cell lines and WNT2, WNT3, WNT4, and WNT7B in human breast tissues. WNT3a and WNT7a were not expressed in the examined tissue. In addition, several of these genes, including WNT2, WNT4 and WNT7B, showed increased expression in breast tumors.

101. Roesink H, Nusse R: Expression of two members of the Wnt family during mouse development - restricted temporal and spatial patterns in the developing neural tube. *Genes Dev* 1991, 5:381-388.

This paper describes the cloning and expression patterns of the mouse Wnt3 and Wnt3a genes. The authors compare and contrast the expression of the two genes in the developing nervous system and find that despite their high degree of sequence identity, Wnt3 and Wnt3a are expressed in discrete regions of the spinal cord and brain.

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The authors present genetic and expression analyses demonstrating that the vestigial tail mutation is allelic to Wnt3a.

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The authors used a PCR-based strategy to isolate six Wnt genes (Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a and Wnt7b) expressed in fetal mice.

105. Clark CC, Cohen I, Eichstetter I, Cannizzaro LA, McPherson J, Wasmuth JJ, lozzo RV: Molecular cloning of the human proto-oncogene Wnt-5A and mapping of the gene (WNT5A) to chromosome 3p14-p21. *Genomics* 1993, 18:249-260.

This paper describes the cloning and mapping of the human WNT5A gene. RT-PCR expression analysis of a variety of embryonic, neonatal, and adult cell and/or tissues showed that WNT5A was detected only in neonatal heart and lung.

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The authors cloned the mouse Wnt11 and Wnt12 (Wnt6b) genes by degenerate PCR and mapped both of these Wnt genes as well as the Wnt5a and Wnt7a genes. Wnt11 mapped to chromosome 7, Wnt12 (Wnt6b) to chromosome 15 close to Wnt1, Wnt5a to chromosome 14, and Wnt7a to chromosome 6.

107. Saïtoh T, Kato M: Molecular cloning and characterization of human WNT5B on chromosome 12p13.3 region. *Int J Oncol* 2001, 19:347-351.

Expression analysis shows that WNT5B is expressed in adult prostate and fetal brain, and weakly expressed in fetal lung, kidney, adult liver, ovary, and small intestine. WNT5B is also expressed in the gastric cancer cell lines MKN7, MKN45, KATO-III, and a teratocarcinoma cell line NT2.

108. Rankin J, Strachan T, Lako M, Lindsay S: Partial cloning and assignment of WNT6 to a human chromosome band 2q35 by in situ hybridization. *Cytogenet Cell Genet* 1999, 84:50-52.

This paper reports the cloning of a partial CDNA encoding WNT6 and its mapping to chromosome 2q35.

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This paper describes the cloning and mapping of the human WNT6 and WNT10A genes. The two genes are clustered in the 2q35 region separated by only 7 kb. Both genes are expressed in a variety of tissues, including kidney, placenta, and spleen, and cancer cell lines.

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This paper describes the characterization of the human WNT7A gene and its expression in placenta, kidney, testis, uterus, fetal lung, and fetal and adult brain.

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113. Kikuchi H, Sekihara H, Katoh M: Molecular cloning and characterization of human WNT7B. Int J Oncol 2001, 17:779-783.

The authors describe the characterization of the human WNT7B gene and its expression in fetal brain, lung and kidney, and in adult brain, lung and prostate. WNT7B is also expressed in a lung cancer cell line A549, esophageal cancer cell lines TE2, TE3, TE4, TES, TE7, TE10, TE12, a gastric cancer cell line TMMK1, and pancreatic cancer cell lines BxPC-3, A431 and HS747. In addition, WNT7B was found to be up regulated in 50% of primary gastric cancers.

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The authors describe the cloning of the mouse Wnt8 gene and its expression during embryogenesis. Wnt8 is expressed in the posterior region of the neural plate, in the mesoderm and in the somites. Wnt8 is also transiently expressed in the mesoderm.

115. Saitoh T, Katoh M: Molecular cloning and characterization of human WNT8A. Int J Oncol 2001, 19:123-127.

This paper presents the sequence and expression of the human WNT8A gene. Expression analysis of WNT8A in various human tissues and cell lines only detected transcripts in NT2 teratocarcinoma cells.

116. Lako M, Strachan T, Curtis AR, Lindsay S: Isolation and characterization of WNT8A, a novel human Wnt gene that maps to 12q13. Genomics 1996, 35:386-388.

This paper and [117] describe the cloning, mapping, and expression analysis of the human WNT8A gene and [117] presents expression data for the mouse Wnt8b gene. Both the human and mouse Wnt8b genes were restricted to the developing brain, with the majority of expression being found in the forebrain.

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The authors characterize the human WNT11 gene, mapping it to 11q13.5 and demonstrating its expression in the perichondrium of the developing skeleton, lung mesenchyme, the tips of the ureteric buds and other areas of the urogenital system and the cortex of the adrenal gland.

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This paper describes the cloning and mapping of human WNT14 and WNT15 and show that WNT13 (WNT2B) is expressed in mammary tissue.

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The authors characterize the human WNT16 gene and show that it is activated by the E2A-Pbx1 fusion protein in pre-B acute lymphoblastic leukaemia. WNT16 is normally expressed in the spleen, appendix, and lymph nodes, but is not expressed in bone marrow. However, WNT16 transcripts are highly expressed in bone marrow and cell lines derived from pre-B ALL patients carrying the E2A-Pbx1 fusion suggesting that inappropriate expression of WNT16 plays a role in leukaemia.

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The authors map human WNT16 to 7q31 and characterize the differential expression of two distinct WNT16 isoforms. The isoforms were shown to utilize different 5'-UTRs and first exons.

121. McMahon AP, Gavin BJ, Parr B, Bradley A, McMahon JA: The Wnt family of cell signalling molecules in postimplantation development of the mouse. Ciba Found Symp 1992, 165:199-212.

This paper summarizes the phenotype of the Wnt1 knockout mice. See [74].

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This paper builds on [74] and provides a detailed characterization of the phenotype of Wnt1 deficient mice focusing on possible perturbations in structures adjacent to the presumptive midbrain and cerebellum.

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The authors show that mice mutant for both Wnt1 and Wnt3a show a dramatic decrease in the number of neural crest progenitors, normally derived from the dorsal neural tube.
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This paper examines the phenotype of Wnt2 knockout mice and show
that mice lacking Wnt2 display runting and approximately 50% died
perinatally. Mutant mice were found to have defects in the size and
structure the placenta with notable perturbation of the vascularization
of the placenta.

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mouse embryo. Genes Dev 1994, 8:174-189.

This paper and [136] describe the phenotype of mice lacking the
Wnt3a gene. Wnt3a-/- embryos lack caudal somites, have a disrupted noto-
chord, and fail to form a tailbud. Mutant mice also possess an ectopic
neural tube suggesting that Wnt3a plays a critical role in specifying
paraxial mesoderm and that in its absence these cells adopt neural fates.

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absence of Wnt-3a signaling promotes neuralization instead of paraxial mesoderm development in the mouse. Dev Biol 1997, 183:234-242.

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A: Wnt-3a regulates somite and tailbud formation in the
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This paper shows that the T-box gene, brachyury, is down regulated in
mice lacking Wnt3a. Transgenic analysis of the brachyury promoter
further demonstrates that brachyury is a direct target of the Wnt
pathway acting downstream of Wnt3a.

136. Lee SM, Tole S, Grove E, McMahon AP: A local Wnt-3a signal is
required for development of the mammalian hippocampus.
Development 2000, 127:457-467.

The authors examine the role of Wnt3a in the developing brain and
show that in mice lacking Wnt3a, caudomedial progenitor cells in the
cerebral cortex underproliferate. By mid-gestation, this defect leads to
the absence of the hippocampus or very small populations of residual
hippocampal cells.

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This paper shows that the T-box gene, brachyury, is down regulated in
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This paper characterizes the phenotype of Wnt5a knockout mice
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ears and genitals.

140. Parr BA, Avery EJ, Cygan JA, McMahon AP: The classical mouse
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hemimelia (px) mutant and show by morphological analysis and breed-
ing experiments that the px phenotype is caused by a mutation in the
Wnt7a gene. Molecular analysis demonstrates that px mice harbor a
515-bp deletion in the Wnt7a gene that results in the production of a
truncated Wnt7a protein.

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patterning during the development of the mouse female
reproductive tract. Development 1998, 125:3201-3211.

This paper examines the defects associated with loss of the Wnt7a
gene in female mice. The authors demonstrate that Wnt7a is required
for appropriate patterning of the oviduct and uterus as well as disorga-
nization of the uterine smooth muscle.

142. Parr BA, Cornish VA, Cybulsky MI, McMahon AP: Wnt7b regulates
placental development in mice. Dev Biol 2001, 237:324-332.

This paper shows that targeted disruption of the mouse Wnt7b gene
results in placental defects including inhibition of the normal fusion of
the chorion and allantois, perhaps due to the loss of integrin alpha-4.