Protein family review

The Frizzled family: receptors for multiple signal transduction pathways
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**Summary**

Frizzled genes encode integral membrane proteins that function in multiple signal transduction pathways. They have been identified in diverse animals, from sponges to humans. The family is defined by conserved structural features, including seven hydrophobic domains and a cysteine-rich ligand-binding domain. Frizzled proteins are receptors for secreted Wnt proteins, as well as other ligands, and also play a critical role in the regulation of cell polarity. Frizzled genes are essential for embryonic development, tissue and cell polarity, formation of neural synapses, and the regulation of proliferation, and many other processes in developing and adult organisms; mutations in human frizzled-4 have been linked to familial exudative vitreoretinopathy. It is not yet clear how Frizzleds couple to downstream effectors, and this is a focus of intense study.

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**Gene organization and evolutionary history**

The frizzled genes were first identified in Drosophila in a screen for mutations that disrupt the polarity of epidermal cells in the adult fly [1]. Subsequently, frizzleds have been found in diverse metazoa [2], including at least ten in vertebrates, four in Drosophila, and three in Caenorhabditis elegans. Frizzleds have also been identified in primitive metazoa, including the sponge Suberites domuncula [3] and in Hydra vulgaris [4], but they have not been described in protozoans. They have been shown to encode receptors for Wnt proteins [5]. The smoothened (smo) gene, which functions in the Hedgehog signaling pathway in various developmental processes, is distantly related to frizzled genes. Additional information on the Wnt pathway can be found on the Wnt gene homepage [6] and in various comprehensive reviews [1,7-9].

Sequence analysis suggests that the ten human frizzled (FZD) genes fall into four main clusters [10]. FZD1, FZD2, and FZD7 share approximately 75% identity; FZD5 and FZD8 share 70% identity; FZD4, FZD9, and FZD10 share 65% identity; and FZD3 and FZD6 share 50% amino acid identity [10]. Frizzled genes from different clusters share between 20% and 40% sequence similarity. A dendrogram of human and selected invertebrate frizzled genes is shown in Figure 1. The overall genomic organization of frizzled genes does not appear to be highly conserved across this broad species diversity. Several frizzled genes appear to lack introns, however, including vertebrate orthologs of human FZD1, FZD2, and FZD7 to FZD10 (this is also a feature of many G-protein-coupled receptor (GPCR) genes); other frizzled genes, such as human FZD5 and Drosophila frizzled2 (Dfz2), contain one intron but the entire open reading frame is encoded by a single exon. Interestingly, the intron-deficient frizzled genes appear to be derived from a common ancestor, as they cluster into a subfamily that includes Dfz2 (Figure 1).

**Characteristic structural features**

Frizzled proteins range in length from about 500 to 700 amino acids (Figure 2). The amino terminus is predicted to
be extracellular and contains a cysteine-rich domain (CRD) followed by a hydrophilic linker region of 40-100 amino acids. The proteins also contain seven hydrophobic domains that are predicted to form transmembrane \( \alpha \)-helices.

The intracellular carboxy-terminal domain has a variable length and is not well conserved among different family members [2].

The CRD, which is necessary and sufficient for binding to Wnt molecules, consists of 120-125 residues with ten conserved cysteines, all of which form disulphide bonds [5,11]. The crystal structures of the CRDs from mouse Frizzled 8 (mFz8) and mouse secreted Frizzled-related protein 3 (sFRP-3) reveal that CRDs are predominantly \( \alpha \)-helical and form a previously unknown protein fold [11]. A ligand-binding interface, involving a single region of the CRD surface, was predicted from analysis of the crystal structure integrated with comprehensive mutagenesis. Within the crystal, the CRDs form a conserved dimer interface, although in solution they appear to exist as monomers. Whether dimerization of the CRD has a role in ligand binding in vivo is not yet known [11].

The presence of seven hydrophobic domains has raised speculation that these receptors are related to the GPCR superfamily. The sequence similarity to GPCRs is low, however, and is limited to the hydrophobic domains, which might be expected to have some similarity because of the shared higher frequency of hydrophobic residues. An intriguing sequence similarity, potentially derived from evolutionary conservation, has been described between Frizzleds and members of the Taste2 subfamily of taste receptors (which are GPCRs) [10].

A motif (KTXXXW) located two amino acids after the seventh hydrophobic domain is highly conserved in Frizzleds and is essential for activation of the Wnt/\( \beta \)-catenin pathway [12]. Point mutations affecting any of the three conserved residues are defective in Wnt/\( \beta \)-catenin signaling (see below for more details on this pathway). A peptide derived from this conserved motif interacts in vitro with a peptide from the PDZ domain of mouse Dishevelled 1 - an intracellular signal-transduction protein - suggesting that this motif might mediate interaction between Frizzled proteins and Dishevelled proteins, although an interaction between the full-length proteins has not yet been demonstrated [13]. Apart from the KTXXXW motif, the carboxy-terminal tail is not well conserved among Frizzleds. The carboxy-terminal S/T-X-V motif found in some Frizzleds is apparently not required for Frizzled function [14]. The distantly related protein Smo also contains an amino-terminal CRD and seven hydrophobic domains, but it lacks the KTXXXW motif and does not bind Wnts [5,15].
Localization and function
Frizzled proteins are found exclusively at the plasma membrane. They are located at the surface of Wnt-responsive cells, although recent evidence has suggested that they may be internalized as part of a mechanism for regulating the extracellular level of Wnt protein and/or the cellular response to Wnts [16,17]. The tissue-specific expression of frizzled genes is complex, given that numerous frizzleds have been described in metazoans. In general, frizzleds are widely and dynamically expressed and, indeed, it is rare to find a cell that does not express one or more frizzleds. Specific expression patterns of frizzleds in model organisms have been described [2,6,14,18].

Frizzleds function in three distinct signaling pathways, known as the planar cell polarity (PCP) pathway, the canonical Wnt/ß-catenin pathway, and the Wnt/calcium pathway. The PCP pathway is defined by the ability of overexpressed Wnts and Frizzleds to cause increases in intracellular calcium. As discussed above, the frizzled gene (fz) was first identified genetically from mutations that cause a PCP phenotype in Drosophila [1]. Asymmetric subcellular distribution of Frizzled has a central role in establishing cell polarity in flies, and most likely in other organisms as well. The dorsal epidermis of the adult fly shows a highly polarized pattern referred to as planar cell polarity, in which a single hair extends from the posterior end of each cell and points from anterior to posterior. The PCP pathway also regulates the organization of photoreceptor cells in the Drosophila eye. Frizzled and Dishevelled proteins become asymmetrically localized at the distal boundary of each papillae wing cell during the generation of polarity [7,8]. Furthermore, polarization of sensory organ precursor (pI) cells in developing bristles requires fz, and Frizzled protein is localized to the posterior apical cortex of the pI cell prior to mitosis. The C. elegans frizzled genes lin-17 and mom-5 are also required for asymmetric cell divisions (Table 1) [14]. A role for frizzleds in vertebrate gastrulation movements was first suggested by the observation that expression of a truncated form of Xenopus fz8 that encodes just the CRD, which inhibits full-length Fz8 function, blocks convergent-extension movements in Xenopus gastrulae [19], in a similar way to overexpression of Wnt-5α [20] and a dominant-negative form of Dishevelled [21]. Subsequent work in zebrafish and Xenopus suggested this convergent-extension phenotype arises through disruption of a PCP pathway that orients cell movements during gastrulation [7].

The first evidence that Frizzled proteins can function as receptors for canonical Wnt signaling was the observations that Drosophila frizzled-2 (Dfz2) can make Drosophila S2 cells responsive to the Wnt protein Wingless (Wg); these cells normally do not respond to Wg [5]. Although fz interacts genetically with dishevelled in the PCP pathway, a fz loss-of-function mutant does not disrupt canonical Wnt signaling in the fly, as fz and Dfz2 are functionally redundant for canonical signaling [22]. Evidence that frizzleds are required for Wnt signaling therefore required removing both fz and Dfz2, which was accomplished by RNA interference against Dfz2 in an fz mutant background, by analysis of chromosomal deficiencies that delete Dfz2 (see Table 1), and by identifying mutations in Dfz2 and crossing these mutants to fz flies [22]. In vertebrates, overexpression studies suggest that different Frizzleds function in either the canonical or the noncanonical pathways [23], but at least some vertebrate frizzleds appear to function in multiple pathways, including the PCP, Wnt/calcium, and canonical Wnt/ß-catenin pathways [12].

Description of the Wnt/calcium pathway derives originally from the observations that overexpression of Wnt5a or rat frizzled2 can cause an increase in intracellular calcium in zebrafish and can activate protein kinase C and calcium/calmodulin-dependent protein kinase (CaM kinase) in Xenopus [7]. This pathway appears to require G proteins and Dishevelled, although a distinct Wnt/calcium pathway has also been proposed to regulate protein kinase C independently of Dishevelled in a frizzled7 pathway that maintains the separation of mesoderm and ectoderm during gastrulation in Xenopus [24].

The specific functions of Frizzled proteins are as varied as the number of cell types that express them. In addition to Drosophila and C. elegans, frizzled mutants have also been described in mouse and humans, and interference with frizzled function using antisense or dominant-interfering constructs has been described in Xenopus and zebrafish. Some of the phenotypes associated with loss of function of Frizzleds in various organisms are listed in Table 1. Of particular note is the fact that mutations in human FZD4 are found in familial exudative vitreoretinopathy (FEVR), an inherited form of retinal degeneration with associated progressive hearing loss [25]; investigation into the related Norrie’s disease, which arises from mutations in a novel, secreted protein called Norrin, led to the exciting recent discovery that Norrin is a ligand for FZ4 that can activate canonical Wnt signaling and yet is distinct from the Wnt proteins [26].

Mechanism
Wnts bind to Frizzleds with high affinity (where tested) through the Frizzled CRD [5,15,27,28]. Furthermore, expression of the CRD alone antagonizes Wnt/ß-catenin signaling [19], as does expression of secreted Frizzled-like proteins, such as Frzb-1, which have sequence similarity to the extracellular CRD domain of Frizzleds [6]. The amino-terminal extracellular region, including the CRD, has also been proposed to play a role in dimerization of the receptor and activation of
canonical Wnt/β-catenin signaling; Carron et al. [29] reported that Xenopus Frizzled3 (Xfz3) dimerizes to activate canonical signaling and that Xfz3, which is monomeric, can activate Wnt/β-catenin signaling if artificially forced to dimerize but not when it is a monomer. In Drosophila, the CRD of Fz has an approximately ten-fold lower affinity for Wg protein than does the CRD of Dfz2, and ligand affinity is one determinant in the specificity of different Frizzled proteins for different pathways downstream of Wnt signaling [27].

The mechanism by which Frizzled proteins transduce signals once ligand has bound is largely unknown for any of the Frizzled-mediated signaling pathways. Screens for Drosophila mutations that disrupt canonical Wnt signaling in embryonic segments and in imaging disks identified a number of downstream components, including dishevelled, shaggy/zeste-white-3 (homologous to vertebrate glycogen synthase kinase 3), and armadillo (homologous to β-catenin), but none of the proteins encoded by these genes has been shown to interact directly with Frizzled proteins. Dishevelled is recruited to the membrane if Frizzleds are overexpressed (reviewed in [30,31], but the functional significance of these interactions is not yet known.

Table 1

| Species | Genotypes | Phenotypes | References |
|---------|------------|------------|------------|
| Drosophila | fz+/-- | Disruption of planar cell polarity in sensory bristles, dorsal epidermis, and ommatidia | [1,39] |
| Drosophila | Dfz2+/+4 | Viable | [22] (see also [40-42]) |
| Drosophila | Fz+/--; Dfz2+/+4 | Wg signal transduction is abolished in embryos and the wing imaginal disk | [22] |
| Drosophila | fz+/--; Dfz2 deficiency | Mimics loss of wg in embryonic epidermal patterning, neuroblast specification, midgut morphogenesis, and heart formation | [40-42] |
| Drosophila | fzRNAi, Dfz2RNAi | Defects in embryonic patterning that mimic wg loss of function | [43] |
| Drosophila | Dfz3+/+4 | Suppresses a hypomorphic wg mutation | [44] |
| C. elegans | mom-5+/-- | Embryos lack endoderm and overproduce pharyngeal tissue | [45] |
| C. elegans | mig-1+/-- | Abnormal migration of the Q neuroblast | [46] |
| C. elegans | Lin-17+/-- | Disruption of a variety of asymmetric cell divisions | [47] |
| Mouse | mfz4+/-- | Severe defects in major axon tracts within the forebrain | [48] |
| Mouse | mfz4+/-- | Defects in cell survival in the cerebellum; vascular defects in retina, cochlea, and cerebellum | [26,49] |
| Mouse | mfz5+/-- | Embryonic lethal (at day 10.75) because of defects in yolk-sac angiogenesis | [50] |
| Human | hFZD4+/- | Familial exudative vitreoretinopathy | [25] |
| Xenopus | Xfz3MO | Loss of neural crest induction | [51] |
| Xenopus | Xfz7MO | Depletion of maternal Xfz7 disrupts dorsal anterior development | [52] |
| Xenopus | Xfz7MO | Severe gastrulation defect arising from inability of involuted anterior mesoderm to separate from the ectoderm | [24] |

MO, morpholino oligos; AS, antisense oligos; RNAi, RNA interference. See also [6].

Xenopus Kermit, a PDZ domain protein of previously unknown function [31], interacts directly with the cytoplasmic domain of Frizzled proteins and is recruited to the cell surface specifically by Fz3. Kermit is required for Wnt1/Fz3-mediated induction of neural crest, but it is not yet known whether Kermit functions in other settings involving Wnt/Fz signaling, and corresponding Kermit-like molecules for Frizzleds other than Fz3 have not yet been identified. PSD-95, a mouse PDZ-domain protein, can interact with mouse Fz1, Fz2, Fz4, and Fz7 [32], and the fly PDZ-domain protein GOPC interacts with the carboxyl terminus of Drosophila fz [33], but the functional significance of these interactions is not yet known.

The arrow gene of Drosophila, which is required for canonical Wnt signaling, was recently found to encode a type-1 membrane receptor similar to low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and LRP6; [34]). Disruption of LRP6 in mouse causes multiple phenotypes consistent with loss of Wnt signaling [9]. A dominant negative form of LRP6 inhibits Wnt signaling in Xenopus, and human LRP6 protein co-immunoprecipitates with the Fz8 CRD in a Wnt-dependent manner, suggesting that binding of Wnt to Frizzleds generates a ternary signaling complex of ligand (Wnt), receptor (Frizzled), and coreceptor (LRP) [9]. Co-immunoprecipitation of Wnts with LRP6s has also been
described by others using vertebrate proteins [9], but not with Drosophila Frizzled, Arrow, and Wg proteins [6]. Expression of a chimeric molecule in which the carboxyl terminus of Arrow has been fused to Dfz2 robustly activates canonical Wnt signaling in the wing, supporting the hypothesis that binding of Wnts to Frizzleds somehow leads to interaction with and activation of Arrow/LRPs [35]. In addition, LRP5 and Arrow interact directly with Axin, a cytoplasmic scaffold protein that is the hub of cytoplasmic regulation of Wnt signaling, recruiting Axin to the membrane [35,36]. These observations are consistent with the idea that the Wnt signal is transduced through Frizzled proteins to Arrow/LRP, which then modulates cytoplasmic signaling through recruitment of the Axin complex. Arrow is not apparently required for PCP signaling [34].

In Drosophila, no ligand has been identified for activation of the PCP pathway. As discussed above, a number of components have been shown to be required for PCP signaling, and many localize at either the posterior region of the cell (Frizzled and Dishevelled) or in the anterior of the adjacent cell (for example, Strabismus, a novel transmembrane protein, and Prickle, a LIM-domain protein). Many of these components have been implicated in the regulation of convergent-extension movements in vertebrate embryos, and a role for Wnts, including Wnt11 and Wnt5a, is supported by genetic evidence in zebrafish and by the use of dominant-negative ligands in Xenopus [5]. The mechanism by which Frizzleds communicate with other components of the PCP pathway remains an intriguing mystery, however.

Regarding Wnt/calcium signaling, overexpression of rat Fz2 by injection of mRNA causes an increase in intracellular calcium in zebrafish embryos, and overexpression of Frizzleds in Xenopus can lead to activation of protein kinase C (PKC) [23]; these effects are sensitive to pertussis toxin and other G-protein antagonists [37]. In addition, a complex chimeric molecule that incorporates the extracellular and ligand binding domains of the β-adrenergic receptor and the intracellular sequence of rat Fz2 was shown to cause intracellular calcium release within minutes after addition of adrenergic agonists [37]. Although this chimeric receptor is artificial, this was an important experiment because purified Wnts were not available until recently and the chimera provided a clever and novel approach to activate the pathway rapidly.

A similar chimeric receptor involving rat Fz1 and the β-adrenergic receptor has also been used to support a role for G proteins in canonical Wnt signaling [37]; additional support for a role of G proteins was provided by the observation that overexpressed RGS4, a G-protein antagonist, appears to block canonical Wnt signaling in Xenopus axis-duplication assays. These indirect assays support a potential role of G proteins in mediating the canonical and Wnt/calcium pathways, although a requirement for G proteins has not yet been established by loss-of-function experiments [7]. A new, noncanonical pathway involving Dvnt4, Frizzleds, and PKC has also recently been described in Drosophila in the developing ovary [38].

Frontiers

An important remaining question is how Frizzleds transduce a signal upon binding of the ligand. For the canonical Wnt pathway, as discussed above, ligand binding may initiate interaction with Arrow/LRPs, but the nature of the interaction is not known. Arrow/LRP does not appear to be involved in the PCP pathway, and other potential coreceptors have not been identified for this pathway. Whether Frizzleds are regulated by a secreted ligand in the PCP pathway also remains an open question, at least in Drosophila. The mechanism of signal transduction in the Wnt/calcium pathway is also an area of intense research, and the exciting possibility that Frizzleds couple directly to G proteins is still a controversial area, perhaps in part because of the lack of genetic data to support the idea of this interaction.

Information on the specificity of ligand-receptor interaction is also limited. Direct binding assays have been performed for a limited number of ligands, although this is likely to change now that a purification protocol has been established for Wnt proteins [6]. A classification of Wnt proteins has suggested that some ligands, such as Wg, Wnt1, and Wnt3a, function as ligands that activate the canonical pathway, whereas others, such as Wnt5a, Wnt11, and Dvnt4, function in noncanonical pathways. Whether this distinction applies to Frizzleds remains to be resolved. In Drosophila, Fz functions in both pathways but Dfz2 functions only in canonical signaling; in vertebrates, this distinction is less clear (compare [23] with [12]).

Frizzled proteins are asymmetrically distributed in tissues that exhibit planar polarity in the fly, and PCP signaling has been proposed to regulate oriented cell movements in vertebrate gastrulation; so far, however, an asymmetric subcellular distribution of vertebrate Frizzled proteins has not been demonstrated, largely because of the difficulty in generating antibodies sensitive enough to detect the endogenous protein. In addition, the biochemistry of PCP signaling is in its early stages, mainly because a biochemical readout for this pathway has not been clearly established, and it remains unclear whether PCP is regulated by a ligand-receptor interaction.

Finally, Wnt/Frizzled signaling clearly plays important roles in adult tissues as well as embryonic development. The limited number of human diseases found so far to be linked to mutations in frizzled genes is likely to expand in the near future.

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