This important observation inspired further studies using other viruses, and soon it was demonstrated that both influenza virus and vesicular stomatitis virus could mediate cell-cell fusion to create multinuclear bodies called syncytia, but only in acidified cultures[2]. Combining this finding with studies on the influenza fusion protein, hemagglutinin (HA), it became clear that at acidic pH, HA undergoes a dramatic conformational change that exposes a conserved hydrophobic region called the fusion peptide that could insert into the host cell membranes.

With atomic resolution structures of HA fragments under both neutral and acidic conditions[3,4], we now know a great deal about the conformational change in HA; however, exactly how the fusion peptide promotes membrane fusion is still unclear. On page 715 of this issue of *Nature Structural Biology*, Lukas Tamm and colleagues report conformations of a synthetic fusion peptide inserted in a membrane. These new structures are beginning to fill a gap in our understanding of viral membrane fusion.

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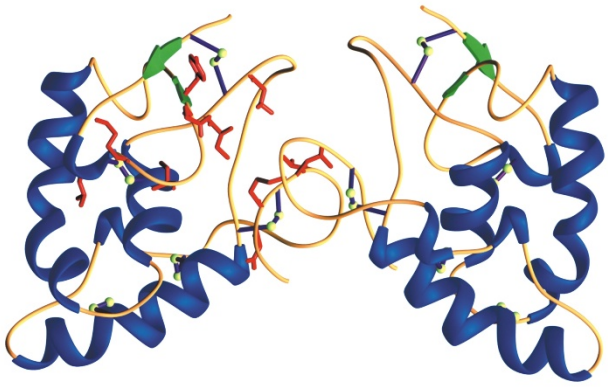
Frizzled proteins pair up

Several types of human cancer, particularly colon cancer, have been linked to the Wnt signaling pathway. This pathway is involved in a variety of normal growth and developmental processes, and like many such pathways, turning it on at the wrong time or in the wrong place can have drastic effects. The Wnt proteins are conserved, secreted glycoproteins that act as cell-to-cell signaling molecules, and the genes encoding them have been classified as oncogenes. While many of the critical effector molecules in the Wnt pathway have been identified, exactly how the signal gets transduced from the cell surface is not understood.



The identities of the receptors for the Wnt family were completely unknown until five years ago, when the seven-transmembrane Frizzled proteins were found to serve this function in *Drosophila*. The Wnt binding activity of these proteins resides in their N-terminal cysteine-rich domains (CRD), which are both necessary and sufficient for conferring Wnt binding to transfected cells. The first structure of a CRD from a member of this large family of receptors has been published recently by Dann *et al.* (*Nature* **412**, 86–90; 2001) The authors determined the structure of the CRD from mouse Frizzled 8 (shown here in the dimeric form seen in the crystal) as well as the homologous domain from the secreted Frizzled-related protein 3, which functions as a Wnt-signaling antagonist. The structures reveal a novel fold consisting of several helices (blue), a minimal two-stranded β-sheet (green), and five disulfide bonds (purple; sulfur atoms are in yellow) per monomer.

The two structures point to a new potential feature of the Wnt signaling pathway. Although the CRD domains are monomeric in solution, they form dimers in the crystals. The fact that the dimer interfaces are highly complementary and are conserved between the two proteins suggests that dimerization may have a role in the function of these proteins.

Mutagenesis studies further suggest that this may be the case. Using three different mutagenesis strategies coupled with a cell-surface binding assay, the authors identified a number of residues in the Frizzled 8 CRD that, when mutated, disrupt Wnt binding (shown in red for one of the monomers). Interestingly, this putative binding surface partially overlaps with the dimer interface, suggesting that some of the mutations that disrupt Wnt binding may do so by disrupting dimerization on the cell surface.

Confirmation of this hypothesis awaits further investigation, but the structure determined by Dann *et al.* provides the first hint that the Wnt pathway could join the ranks of the many other signaling pathways that involve receptor oligomerization.

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