conclusions about the agonist-binding site. First, it is defined by several discontinuous regions of amino-acid sequence, known as loops. The main loops are A–C on the α-subunit and D on the γ- or δ-subunit, so the agonist-binding site spans an interface between subunits. Loops E and F are less important. Second, the agonist-binding site does not appear to contain a negatively charged amino acid to bind the positive acetylcholine, but instead is rich in aromatic residues (tyrosine and tryptophan). Apparently, acetylcholine binds the receptor through an interaction with aromatic residues, especially tryptophan 149 in the α-subunit (residue 143 in the acetylcholine-binding protein).

When the earlier results are mapped onto the new structure of the acetylcholine-binding protein, the remarkable image shown in Fig. 1c emerges. Loops A–D do indeed form a binding site, with loops E and F more remote. The disulphide bond is right in the middle of the action. The binding site is shaped by the five key aromatic residues, and resembles a box that is open at one end to allow the agonist to enter. Loop C contains the signature loop, which lies at the top of the binding domain — that is, at the top of the box. This is surprising. It means that, in the full receptor, the signature loop is positioned to interact directly with the membrane, or possibly with the transmembrane regions (or the short sequence connecting two of them) of the receptor. The implication is that the signature loop might be involved in ‘gating’ — the coupling of agonist binding to the opening of the ion-channel portion of the receptor. Intriguingly, the residues of the signature loop in the acetylcholine-binding protein interact more favourably with water than do those of the nicotinic receptors. This may be why this protein could be more easily overexpressed in soluble form for crystallization.

In the wake of these papers, computational models of the agonist-binding region of the acetylcholine receptor, as well as of those of other members of the group (the serotonin, γ-aminobutyric acid, glycine and glutamate receptors), will no doubt appear soon. Molecules that stimulate or block these receptors are useful in treating several ailments (Fig. 2), and structural information on the binding region will aid the design of even better treatments. Also, the structure of the transmembrane domain and, crucially, the mechanism of gating must be worked out. And it remains to be seen whether the snail acetylcholine-binding protein has counterparts in mammals.

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Making head or tail of Dickkopf
Roel Nusse

Signals that guide embryonic cells through development are often under the control of inhibitors. It now seems that one such inhibitor does not bind to the signal itself, but rather to the receptor that detects the signal.

A typical cell’s network of signal-transduction pathways has so many molecular interactions that it looks like a complex wiring diagram. Recently, it has become clear that signalling events outside the cell can be equally elaborate, with many different components that bind to each other and act as positive or negative regulators of binding. This is particularly true for proteins with key functions in development, such as bone morphogenetic protein; Hedgehog and Wnt. Various factors can interact with these proteins outside the cell, modulating their activity or altering their structure. On page 321 of this issue, Mao and colleagues describe an interesting twist to the regulation of extracellular signalling through Wnt proteins. Wnt proteins, which are found in animals from Hydra to insects, worms and vertebrates, have a wide range of activities during animal development; for example, they are involved in the formation of the head-to-tail axis of the embryo. Extracellular Wnt proteins trigger signalling pathways inside cells that proceed through several protein complexes that interact dynamically with each other. One protein in these pathways is the
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β-catenin molecule. Normally, β-catenin is kept in check by a large complex of several proteins (including one called Axin6, Fig. 1a). This complex promotes the addition of phosphate groups to β-catenin, enabling it to be detected by the cellular protein-degradation machinery. Signalling from Wnt releases β-catenin from its guard, allowing it to move to the nucleus, where it combines with a protein called TCF to activate the expression of target genes (including some that are involved in cancer).

At the surface of cells, two kinds of protein are involved in receiving the Wnt signal. Members of the Frizzled receptor family consist of amino-acid chains that snake back and forth through the outer membrane of the cell. They use an extended amino-terminal region (called the cysteine-rich domain) to bind the Wnt protein8 (Fig. 1b). There are many genes encoding Frizzled proteins (ten in the human genome), and different Frizzled proteins probably have different affinities for various types of Wnt protein.

Genetic evidence from studies of fruitflies (Drosophila melanogaster) and mice suggested that the second receptor for Wnt is LRP5/6 (refs 9, 10). LRP5/6 is a long protein with a single transmembrane domain (Fig. 1b). Wnt proteins can form a complex with the cysteine-rich domain of Frizzled and with LRP5/6 (ref. 11), leading to a picture of a dual-receptor complex, which might form as the consequence of binding to Wnt. The intracellular parts of the receptors pass on this information, turning on the pathways that feed through β-catenin inside the cell.

It now appears that LRP5/6 has a second function: it binds to a molecule that counteracts Wnt. That molecule is called Dickkopf (Dkk), meaning ‘fat head’, because it has the remarkable activity of promoting head formation in vertebrates. Active Wnt signalling can actually inhibit the development of anterior structures and the head13, and Dkk does not act as a competitive inhibitor by binding to Frizzled or LRP5/6 in Wnt’s place. In fact, it does not bind to Wnt or to Frizzled at all. Following O’Cann’s razor reasoning, Mao et al.12 tested whether Dkk binds to LRP5/6, and found that it does — through a part of LRP5/6 that is not needed for interactions with either Wnt or Frizzled. Similar results were obtained by Bafico et al.14. Binding to Dkk might alter the conformation of LRP5/6, so that it can no longer interact with Wnt and Frizzled (Fig. 1c). That would then halt the intracellular signalling pathways. But tests of this idea have been inconclusive so far.

Another study has also placed LRP5/6 centre stage in Wnt signalling. Reporting in Molecular Cell, Mao et al.15 show that the intracellular tail of LRP5/6 can bind to Axin (one of the proteins mentioned above that controls β-catenin in a Wnt-dependent manner). This observation provides a new link between the Wnt-receptor complex and intracellular components of these signalling pathways. Perhaps LRP5/6, once it has bound to Frizzled and Wnt, recruits and inactivates Axin, thereby releasing β-catenin (Fig. 1b). It will be interesting to see how the binding of Dkk to LRP5/6 influences the interaction between LRP5/6 and Axin. In general it is intriguing to find out whether the binding of different molecules to one receptor causes different events inside the cell.

These findings have several ramifications. For example, they may tell us something about the role of Frizzled in setting up the polarity of cells in a planar field16. Such planar polarity has been well studied in the outer layers of Drosophila tissues. Mutations in the Drosophila LRP5/6-encoding gene arrow or in the gene encoding Axin17 have no effect on planar polarity, so this process may not involve the binding of Wnt to the same dual-receptor complex. How can Frizzled have two separate tasks? The difference may lie in whether, once Wnt has bound to Frizzled, the complex then recruits LRP5/6 and Axin to signal to β-catenin rather than to set up polarity. Another question is whether Dkk is involved in Wnt signalling in Drosophila. There is no recognizable Dkk gene in the Drosophila genome18, but there could be unrelated proteins doing similar things. In fact, three other secreted factors inhibit Wnt in vertebrates, but none of these is detectable in the fly genome19.

Ironically, the most mysterious player in this theatre is Wnt itself, as the protein has yet to be purified in an active form. But irrespective of these and other questions, it is clear that developmental signals are more complex than most secreted molecules that affect cellular function — probably because they have so many different jobs to do.

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**Daedalus**

**Watching the wind**

The solar wind, says Daedalus, is a stream of electrons and positive particles emitted from the surface of the Sun at over 10 km per second. Modern electron optics is highly advanced these days, so it should be possible to obtain an image of the Sun’s surface from its emitted electronic wind.

So Daedalus is devising a satellite with a primary electron-coil a few hundred metres across, with a plane on which solar electrons can be focused. They will then emit light for photographic recording. Positive particles, repelled by the coil, should not interfere. In any case, Daedalus calculates that the Sun need only be a volt or so negative to emit electrons, whereas it must be about 2,000 volts positive to emit protons. He expects the solar wind to be biased in favour of the lighter particle.

Daedalus also likes the idea of placing the satellite at the quasi-stable 1 L 12 Lagrangian point, between the Earth and the Sun, where it can study the Sun continuously and relay its findings back to Earth.

The results, says Daedalus, should complement visual studies nicely. In normal times, the picture of the Sun by electron emission should match the visual one fairly well, although sunspots may appear anomalously dark (or bright), and emission near the poles may be dark as most of their electrons leave in other directions. The Sun is about 200 solar radii from the Earth. Assuming that the solar wind expands radially, the system has a fundamental magnification of about 200, which should enable fine detail of the Sun’s surface to be resolved.

But the real value of the system will be in detecting magnetic storms and other unusual conditions. High-velocity streams in the wind may need special servo control of the electron-optic coil voltage to bring them to a proper focus; corresponding low velocities will need an opposite correction.

A portrait of a magnetic storm will be most intriguing. Will it be local or global? Good predictions should be possible. It may even turn out that fine resolution of the solar surface holds the key. But Daedalus’s real goal is the electronic imaging of ‘active’ planets, such as Jupiter and Saturn, and even of detecting stellar winds from close stars. His satellite would have to be boosted to high velocity, of course, and its signal would be hard to detect. Daedalus reckons that stellar emission is much more intense at the poles, and some signal might even be received from the nearer stars this way.

David Jones