inner leaflet. This is thought to facilitate the invagination of membrane pits or vesicle scission.

Rigorous proof that membrane bending by a Cbl–endophilin complex helps to dispatch ubiquitin-tagged RTKs on their long intracellular journey will require analysis by electron microscopy and precise definition of endophilin's catalytic site. Moreover, endophilin's enzymatic activity in solution is very weak (it converts just one molecule of LPA per minute); if it is important in receptor endocytosis, it has to work much more quickly in cells. Alternatively, endophilin might bend the membrane by forming a complex with other endophilin molecules and directly invaginating lipid bilayers[8].

On the ubiquitination side, a major unanswered question is how the clathrin coat identifies ubiquitin-tagged RTKs. A ubiquitin-interacting amino-acid motif, found in both endosomal and proteasomal proteins, could provide the link, but firm evidence is lacking. More generally, because receptor sorting occurs in other endocytic compartments, as well as in the cellular pathway for protein synthesis and sorting, the newly discovered ability[1,2] of Cbl to couple sorting events to membrane bending may become a prototype mechanism in vesicular transport. ■

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Oceanography

An extra dimension to mixing

Chris W. Hughes

According to a new theory, stratification of the oceans is controlled by a balance between heat input at the surface and heat redistribution by eddies. But it is early days for this sea-change in thinking.

In the oceans, buoyant surface water lies above denser deep water. In most parts of the world there is a well-defined boundary between the two in which, at depths typically between 100 m and 1,000 m, the temperature changes rapidly between surface and deep values. This sharp temperature gradient is known as the permanent thermocline. Its depth and sharpness vary around the world, and control the speed at which the ocean circulation adapts, for example, to winds, and to the currents that result from these and other 'forcing' phenomena. Understanding what sets the depth and form of the

Neurobiology

The bitter-sweet taste of amino acids

Amino acids are essential for life: they form the building blocks of the proteins that our genetic code encrypts. And thanks to nature's ingenuity, mammals have evolved a partiality for the flavour of these crucial components; some taste bitter, others sweet and some simply delicious, or 'umami' — a taste that is associated in Western countries with Chinese takeaway meals. But what are the molecular players that underlie this perceptual diversity?

In this issue (*Nature* **416,** 199–202; 2002), Greg Nelson and colleagues begin to solve the conundrum. They have characterized a mammalian amino-acid taste receptor and find that, surprisingly, this one receptor responds to several of the 20 L-amino acids that are commonly found in proteins. In another clever move by nature, the receptor is entirely unresponsive to their mirror images — the biologically less significant D-amino acids.

The amino-acid receptor is located on the surface of taste cells and is coupled to well-known molecular switches called G proteins. In fact, it consists of two different, taste-specific G-protein-coupled receptors (GPCRs), T1R1 and T1R3. Nelson *et al.* developed a cell-based assay to identify candidate taste receptors, and found that cells expressing both T1R1 and T1R3, together with a 'promiscuous' G protein that causes the release of calcium from internal cellular stores, responded to the application of different L-amino acids with an increase in intracellular calcium concentration. Moreover, a substance that enhances the tongue's response to L-amino acids — inosine monophosphate — increased the response of the T1R1+3 receptor *in vitro* and *in vivo*.

Interestingly, when T1R3 is combined with a different taste-specific GPCR protein called T1R2, it forms a functional 'sweet receptor' (G. Nelson *et al. Cell* **106,** 381–390; 2000). The authors now show that this receptor is activated by a range of sweet-tasting D-amino acids. So, depending on the identity of its partner protein, T1R3 may contribute to the sensation of different tastes.

While carrying out this work, Nelson *et al.* also found a molecular explanation for the taste preferences of different species. For example, the human T1R2+3 sweet receptor is much more responsive than its rodent equivalent to artificial sweeteners such as aspartame and cyclamate. And the human T1R1+3 amino-acid receptor is more sensitive to monosodium glutamate than to any of the amino acids. This suggests that activation of the human T1R1+3 receptor gives rise to the sensation of umami, perhaps in concert with another candidate receptor for monosodium glutamate that was described two years ago by N. Chaudhari and colleagues (*Nature Neurosci.* **3,** 113–119; 2000).

But the mystery of how different amino acids can activate just one receptor, yet give rise to a whole spectrum of taste sensations, remains to be solved. If our sense of smell is any precedent, the answer will emerge not only by working out which tastes are detected by which receptors, but also by understanding the complex network of nerves that sends these signals to the brain.

Lesley Anson

thermocline is therefore one of the fundamental aims in oceanography.

The short answer is heating and cooling, as warmer water is less dense. But two papers by Marshall and colleagues, published in the *Journal of Physical Oceanography*[1,2], provide a challenge to the usual textbook answers. The authors suggest that the limiting term in the ocean budget for water buoyancy, and therefore the factor that determines the steady state for the thermocline, is the rate at which eddies are formed and transfer heat.

In one model, known as the ventilated thermocline[3], wind action causes surface water to circulate to intermediate depths, resulting in vertical temperature transfer. The variation of temperature with depth, which defines the thermocline, arises as horizontal temperature variations at the surface are 'mapped' onto the vertical plane by this circulation. When the influence of these 'ventilated' waters on water that circulates without reaching the surface is taken into account[4], the theory is quite successful in explaining many observed features of the ocean.

But the ventilated thermocline model nonetheless remains incomplete. It describes a wind-driven circulation only, and does not account for the processes that actually set up the large-scale temperature gradients in the ocean. These processes include the greater heating from the Sun in the tropics than at the poles, and the effect that this has on water movement. Certain issues of water dynamics are also swept under the carpet by assuming the existence of 'passive western boundary currents', such as the Gulf Stream, which flow near to the western edges of ocean basins. These currents are needed to 'close' the circulation, making it hard to talk about such things as heat budgets when a part of the closed circulation lies outside the theory.

An alternative to the ventilated thermocline is the 'diffusive thermocline' model[5], in which the maintenance of large-scale temperature differences is explicitly taken into account. This is essentially a one-dimensional theory. The deep waters of the ocean are formed at only a few sites in the North Atlantic and near to Antarctica, where surface water cools, becomes denser and less buoyant, sinks to the bottom, and spreads around the world by flowing at great depth. The denser water is formed mostly by cooling, although salinity also determines density and can be important in the formation of these deep waters.

To complete the circuit, the deep water must upwell, becoming less dense as it does so. The diffusive thermocline theory assumes that downward diffusion of heat counteracts the upward movement of dense water to maintain stratification in the ocean. In subtropical regions, the wind pumps water downwards near the surface, resulting in a confluence of shallow and deep water at a certain depth. The resulting temperature discontinuity, which is smoothed by diffusion, gives rise to the thermocline.

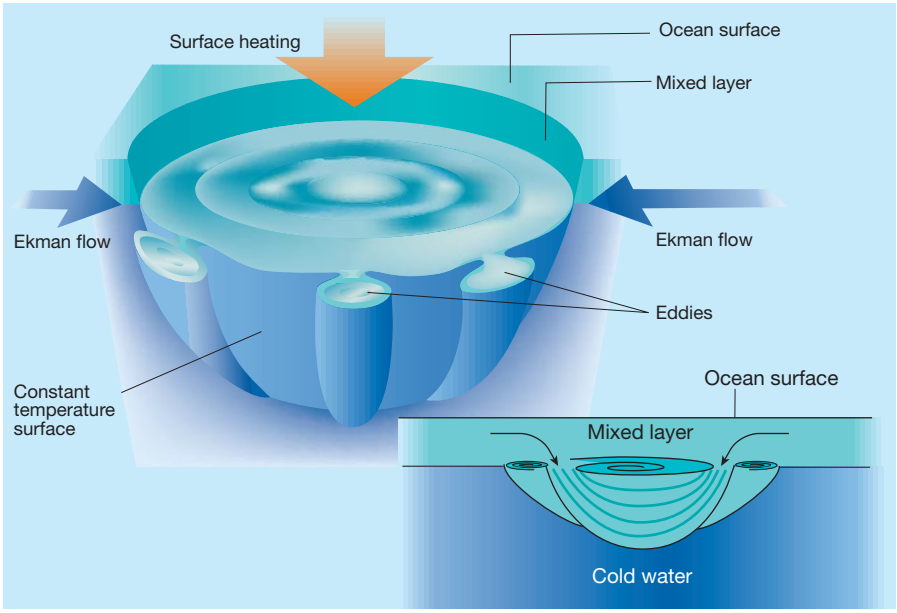

Figure 1 **An oceanographic mixing bowl. The bowl shape represents a surface on which the temperature is constant, capped by an Ekman layer in which the wind directly drives water flow and mixing. The sum of the heat input due to direct surface heating and to Ekman flow must be balanced by heat transport out of the bowl's sides below the mixed layer. Marshall and colleagues[1,2] propose that eddies breaking away from the bowl transport this heat at a rate that is determined by the bowl's shape. Applying this heat budget to a series of bowls nested inside one another (inset) results in a temperature pattern involving a region where temperature varies with depth: the thermocline.**

The principal shortcoming of the diffusive thermocline model is in reconciling the observed sharpness of the thermocline with measurements of turbulent diffusion (molecular diffusion is on a much smaller scale and can be neglected in the absence of small-scale turbulence). Measured diffusion rates[6–8] are ten times too small to match thermocline structure, except in a few regions where the topography of the ocean floor is rough or currents are particularly strong, enhancing the turbulence.

The new theory proposed by Marshall and colleagues[1] offers a variation on the 'closed heat budget' idea of the diffusive thermocline. It extends the one-dimensional idea of vertical diffusion to three dimensions by describing how large, horizontal eddies can transport heat across a mean temperature surface. The key to this theory is to consider the heat budget of a bowl of water, bounded by a surface on which the temperature is constant (Fig. 1). In a long-term steady state, the surface heating must be balanced by a combination of diffusion and advection of heat across the bowl. Assuming the diffusion by small-scale turbulence to be negligible outside a shallow, surface mixed layer where the flow is directly driven by wind (the Ekman layer), a three-way balance results. The heat drawn into the bowl by surface heating and advection in the Ekman layer must be balanced by loss of heat in eddies breaking off from the bowl. Although small-scale turbulence or diffusion is then required to dissipate the eddies, the factor that controls the heat budget is the rate of formation of large eddies which carry heat away from the bowl.

To estimate this rate, Marshall and colleagues assume that eddy heat flux is proportional to the temperature gradient, and to the tangential flow speed of the eddies. The tangential flow results from the pressure gradient associated with the temperature anomaly inside the bowl. The flow that arises from this radial pressure is deflected by the Coriolis force, which is due to the Earth's rotation and here creates a circulation around the bowl, so the flow speed can also be described in terms of temperature. By calculating the heat budgets of the water inside the bowl and of the surface mixed layer, a complete theory can be derived which determines the stratification that results from the imposed heating and Ekman flow — laboratory experiments show that it works. Interestingly, Ekman flow turns out to be a more important heat source for the deep ocean than direct surface heating.

The laboratory is one thing, but the real ocean is quite another. The laboratory experiments mimic a flat Earth, but the Earth's curvature and the topography of the ocean floor can both have a large impact on eddy generation, and ocean-floor topography can produce strong, narrow currents, effectively turning the neat bowl of Fig. 1 into something more like a squid with long, convoluted tentacles. Nonetheless, as Marshall and colleagues describe in their second paper[2], this

simple approach gives a reasonable scaling for stratification in the Southern Ocean and the resulting strength of the Antarctic Circumpolar Current (in which it is generally thought that eddy fluxes are indeed a significant factor[9]). Moreover, predictions for other ocean basins give reasonable thermocline structures, hinting that this concept has much wider applicability than in just the Southern Ocean, and that a complete thermocline theory must consider the role of eddies.

It is early days for an idea that has not yet been adapted to realistic ocean conditions. But the first signs are encouraging: it may be large, horizontal eddies — rather than small, vertical ones — that control the ocean. ■

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Cell biology

A new view of photoreceptors

Franck Pichaud and Claude Desplan

The light-gathering structures in our eyes are specialized membranes found on cells known as photoreceptors. Two studies show that a protein called Crumbs is crucial for the development of these membranes.

The striking conservation of gene function from fruitflies to humans is under the spotlight again. On pages 143 and 178 of this issue, Pellikka and colleagues[1] and Izaddoost and co-workers[2] describe the role of the Crumbs protein in controlling the development of photoreceptors — the light-detecting cells in the eye — in fruitflies. The story is fascinating in itself, but also has implications for our understanding of the forms of two inherited human eye disorders, retinitis pigmentosa and Leber congenital amaurosis[3,4], in which CRB1, the human counterpart of Crumbs, is mutated. Indeed, much of what is already known about the CRB1 protein is based on its physical and functional similarity to the fruitfly Crumbs.

The study of developmental genes in fruitflies (*Drosophila melanogaster*) has provided deep insights into complex cellular processes that do not exist in simpler model systems such as yeast. One such process is that by which the 'top' and 'bottom' of an epithelial cell become distinct — a feature that ensures that epithelial tissues, such as those that cover the skin and line the gut, retain their highly polarized architecture. At the cellular level, this polarity relies on the vectorial segregation of different proteins to specific regions of the plasma membrane, thereby allowing a cell to distinguish top from bottom[5].

For instance, a complex consisting of the proteins Crumbs, Discs lost and Stardust, together with another complex involving Bazooka, specifies the apical membrane (that at the top) of *Drosophila* epithelial cells[6–9]. The basolateral membrane (that at the bottom) is characterized by a complex comprising Lethal giant larvae, Discs large and Scribble[10,11] (Fig. 1a). Two narrow circumferential membrane domains form at the boundary between apical and basolateral membranes; these domains are needed to allow neighbouring epithelial cells to interact. One of the domains, the zonula adherens, is enriched in the cadherin–catenin protein complex. The other, the marginal zone, is found just apical to the zonula adherens and is enriched in apical determinants such as Crumbs.

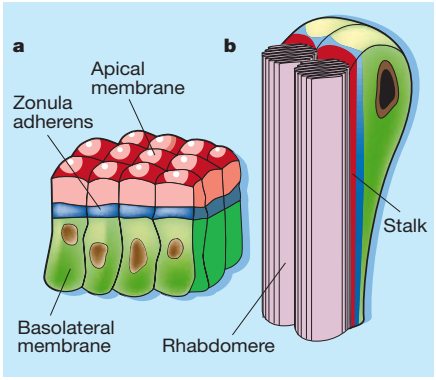

Figure 1 **Determinants of cellular polarity.** a, **Epithelial cells in the fly embryo. The apical part of the cell is in red, the zonula adherens is blue, and the basolateral part is green. The proteins Crumbs, Stardust, Discs lost, β_h-spectrin, Bazooka, protein kinase C and DPA-6 are present in the red areas; Armadillo/β-catenin, Canoe, Pyd and spectrins in the blue areas; and Lethal giant larvae, Discs large, Scribble and myosin II in the green areas.** b, **The same colour code is used for photoreceptors. The photoreceptor could be viewed as the equivalent of epithelial cells, but turned by 90°. The rhabdomere (light-gathering structure) is shown in purple; although the most apical membrane, it lacks Crumbs.**

Photoreceptors are a type of epithelial cell that undergoes a massive change in shape during development: their apical–basal axis rotates by 90° and the apical membranes elongate to form a long, densely packed array of light-sensitive membranes (Fig. 1b). These specialized membranes are called outer segments in vertebrates and rhabdomeres in flies. They originate from different apical extensions in vertebrates and invertebrates (from 'cilia' or 'microvilli', respectively[12]) and have different mechanisms for transducing light. Nevertheless, the final morphology is quite similar: both structures consist of packed apical membranes with high concentrations of a light-detecting pigment. The rhabdomere is supported by a specialized membrane, the stalk (Fig. 1b), which connects it to the zonula adherens; the vertebrate outer segment is similarly supported by the inner segment.

Knowing that Crumbs is involved in specifying apical membranes in *Drosophila* epithelial cells during development, Pellikka *et al.*[1] and Izaddoost *et al.*[2] wanted to find out whether this protein is also required for the massive changes that take place in the apical membranes of photoreceptors. Using the full range of tools available to *Drosophila* geneticists, including disrupting the function of the Crumbs gene in fly eyes, both groups discover a role for Crumbs in maintaining the integrity of the zonula adherens during photoreceptor development. In other epithelial cells, Crumbs is likewise involved in maintaining the zonula adherens, in order to specify the apical and basolateral membranes. But in photoreceptors this role is adapted to enable the rhabdomeres to elongate substantially. In addition, Pellikka *et al.* show that Crumbs has yet another function — to modulate the length of the stalk, recruiting new membrane as necessary to extend the stalk.

Interestingly, these two distinct processes — rhabdomere elongation and stalk extension — are mediated by two distinct regions within the Crumbs protein[1,2]. Crumbs is a transmembrane protein containing a sequence of amino acids known as a PDZ-binding motif (a protein-interaction motif) within its short intracellular region. The intracellular portion of Crumbs seems to be the only part needed for the integrity of the zonula adherens, and to specify apical membranes and facilitate rhabdomere elongation[1,2]. The very end of the intracellular domain recruits the Stardust protein, with the PDZ-binding motif recruiting Discs lost[6–8].

The extracellular part of Crumbs, on