responsible (Fig. 1b). Strain is an established means by which to achieve magnetoelectric coupling between two suitable materials that are intimately connected[12,13].

Even in an experiment in which it was clear that exchange bias (from yttrium manganite, $YMnO_3$, rather than $BiFeO_3$) could be electrically controlled[14], it was not clear whether the observed suppression in exchange bias was due to magnetoelectric coupling, strain, heating or a combination of all three. Experiments without strain and heating would permit the mechanism shown in Figure 1a to be unambiguously identified. Strain and heating are also potentially detrimental to device performance. Strain could be abolished either by clamping active regions by their surrounds, or by using a ferroelectric that is not ferroelastic and therefore does not change shape when electrically switched. Heating could be measured by monitoring leakage currents though the material.

The control of magnetic domains in a ferromagnetic film through an adjacent voltage-driven multiferroic promises to combine the best features of FeRAM and MRAM. But this promise is very distant, with many challenges beyond the unequivocal identification of the mechanism at buried and imperfect interfaces. One initial challenge would be to vary the crystallographic orientation of the $BiFeO_3$ with respect to the applied electric field.

The clear link established by Lebeugle *et al.*[1] between the structural, electronic and magnetic properties of a complex oxide is refreshing. Furthermore, their approach of starting with a single bulk domain relied strongly on the frequently under-appreciated activity of sample preparation. Unexpectedly, the cycloid seems to be good for magnetoelectric coupling, and $BiFeO_3$ may yet provide further surprises given its many phase transitions at both high[15] and low[16] temperatures. ■

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DEVELOPMENTAL BIOLOGY

Our fly cousins' gut

Chrysoula Pitsouli and Norbert Perrimon

What do we humans have in common with flies? Quite a lot, at least at the cellular and molecular levels. Our intestine, for instance, is similar to that of the fly, not only in function but also in its development and maintenance.

Epithelial cells lining the intestine become damaged by ingested food, pathogens and toxins, and so must be constantly renewed. Intestinal stem cells compensate for the loss of these cells by producing all of the mature intestinal epithelial cell types[1], and an imbalance in this process can lead to diseases such as cancer[2]. Our knowledge about intestinal homeostasis comes mainly from studies in mice. But the fact that flies are so amenable to genetic dissection — a task more difficult to carry out in mammals — has also allowed fascinating insights[3–5] into this process. The latest offering comes from a study by Takashima *et al.*[6] (page 651 in this issue), who highlight a remarkable similarity between mammals and the fruitfly *Drosophila melanogaster* in intestinal stem-cell renewal and differentiation, and the underlying molecular signalling pathways.

In mice and humans, intestinal stem cells are located in the numerous invaginations of the gut epithelium called crypts. The mesenchyme tissue surrounding the crypts acts as a niche for these cells, and guides their decision to self-renew or differentiate. At the bottom of each crypt, stem cells self-renew and produce progeny known as transit-amplifying cells, which divide several times before differentiating into the various mature intestinal cell types. During this process, the cells are continually migrating from the bottom of the crypts towards the gut lumen. There, the mature intestinal cells are exposed to the gut content and are finally shed from the epithelium[1].

The digestive system of adult *Drosophila* is a tube composed of epithelial cells with absorptive and secretory functions similar to those of the mammalian intestine[7]. A population of stem cells interspersed among the epithelial cells in the insect's midgut maintains homeostasis there[3–5], dividing to replenish epithelial cells lost through apoptosis (programmed cell death)[4]. Takashima *et al.*[6] now identify a different population of cells that they propose represents stem cells responsible for the development and maintenance of the insect's hindgut.

The authors show that the way in which homeostasis is achieved in the hindgut of adult *Drosophila* is strikingly similar to the related process in a mammalian crypt. By studying cell morphology in the hindgut epithelium and monitoring the kinetics of cell proliferation, they find that the anterior part of the hindgut (that nearest to the midgut) corresponds to a proliferation zone. This zone consists of anteriorly located, slowly proliferating cells, which give rise to fast-proliferating progeny (reminiscent of transit-amplifying cells in mammals) towards the posterior. These cells in turn produce differentiated hindgut cells, which lie even more posteriorly. Lineage analysis of the adult hindgut led the authors to propose that the slowly proliferating cells behave as stem cells (they self-renew and produce differentiated progeny).

Furthermore, this proliferation zone seems to have a crucial role in the development of the hindgut. Takashima *et al.*[6] traced hindgut cells from their development in larvae, through metamorphosis to adult flies. They find that, in the larva, these cells proliferate to generate adult tissue by replacing the dying larval cells. But they differ from other types of adult fly progenitor cell in that they persist in the adult insect, proliferating and constitutively

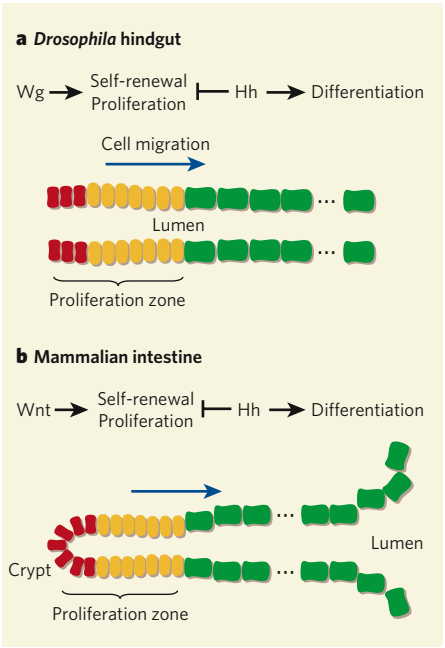

Figure 1 | Similarities between the fly hindgut and a mammalian intestinal crypt. Takashima *et al.*[6] propose that, in the *Drosophila* hindgut (**a**), stem cells (red), proliferating progenitor cells (yellow) and differentiated intestinal cells (green) are arrayed similarly to those in a crypt of the mammalian intestine (**b**). In both settings, the Wnt/Wg and Hedgehog (Hh) signals seem to be responsible for self-renewal/proliferation and differentiation, respectively. Self-renewal and differentiation of cells in adult *Drosophila* hindgut seem to be reminiscent of a process that occurs during the larval development of this organism.

producing new hindgut cells, albeit more slowly than during metamorphosis. The signal that triggers proliferation of the hindgut cells is not known. It is possible that dying larval cells send a signal to these cells instructing them to replenish hindgut cells during metamorphosis, in a process similar to the apoptotic mechanism that triggers homeostasis in the fly midgut[4] and the mammalian intestine[8].

The concerted action of signalling molecules that regulate communication between the niche and the gut epithelium is crucial for maintaining the balance between cell renewal and differentiation. In the mouse gut, interplay between the signalling molecules Wnt, Hedgehog, BMP and Notch determines whether stem cells self-renew or differentiate. Wnt signalling is activated in the crypt and maintains cells in a proliferative state; increased activity of the Wnt pathway leads to enlarged crypts — often causing intestinal tumours[2] — whereas on its inhibition, crypts disappear. The signalling pathway mediated by Notch acts jointly with Wnt to sustain stem-cell proliferation, and is essential for the differentiation of specific cell types. Hedgehog signalling promotes differentiation and restricts crypt formation. This is accomplished, at least in part, through its effect on BMP signalling[1].

It is fascinating to discover that the same pathways regulate cell proliferation in the fly hindgut. Takashima *et al.*[6] find that Wingless (Wg) — the fly protein related to Wnt — is expressed in a narrow stripe of cells at the anterior of the hindgut proliferation zone (Fig. 1). The outcome of perturbing Wg signalling is remarkably similar to that observed following perturbations of the Wnt signal in the mammalian intestine: whereas increased expression of the *wg* gene leads to expansion of the proliferation zone (reminiscent of crypt enlargement), blocking this gene's expression shrinks the pool of dividing cells (reminiscent of crypt disappearance). Furthermore, the Hedgehog pathway regulates the proliferative behaviour of these cells in *Drosophila* as it does in mammals; when this pathway is blocked, cells do not differentiate, remaining in a proliferative state.

Takashima and colleagues' work clearly demonstrates that the mechanism of cell proliferation in the adult fly hindgut follows on from that at work during development of this tissue. Whether the process in adults corresponds to a distinct homeostatic mechanism or is a continuation of development remains to be determined. Another question is why there is a need for fresh adult hindgut cells. In the case of the adult fly, midgut stem cells are required to replenish dying intestinal cells[4], and the same is true for the mammalian intestine[1,8]. What is the mechanism of cell loss in the hindgut? Does shedding or apoptosis also occur there? In *Drosophila* we have an ideal model to address these questions, thus furthering our understanding of intestinal homeostasis. ■

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STRUCTURAL BIOLOGY

It's not all in the family

Baruch I. Kanner

There are no sequential snapshots of a transporter protein as it mediates the simultaneous passage of ions and solutes into a cell. Comparing different snapshots of structurally related transporters offers fascinating insights.

Ion-coupled transporters are molecular machines that allow the passage of specific solutes, such as nutrients and neurotransmitters, across the cell membrane by transferring them together with one or more cations, often sodium ions. The energy released as these cations move into the cell down their concentration gradient is used to power the 'uphill' movement of the solute. For proper function, the transporter, which is embedded in the cell membrane, must alternately expose a binding site at either side of the membrane, capturing its cargo on one side and releasing it on the other — a principle called alternating access. In recent years, the structures of several ion-coupled transporters have been resolved, but in only a single conformation during transport. If we are to understand the molecular mechanism underlying transport, we need to know the structure of the transporter in different conformations. Faham *et al.*[1] take an initial, rather unexpected, step towards this goal by documenting in *Science* the first crystal structure of the sodium-coupled galactose transporter vSGLT.

A bacterial protein, vSGLT is a member of the family of solute sodium symporters (SSS). Members of this family have crucial roles in human health, and mutations in glucose and iodide symporters result in metabolic disorders. These symporters share no significant similarity in amino-acid sequence to members of another family — neurotransmitter sodium symporters (NSS). Yet Faham and colleagues find that there is an unexpected structural resemblance between vSGLT and LeuT (ref. 2), a bacterial member of the NSS family.

Although both vSGLT and LeuT crystallize as dimers[1,2], in each case the monomers seem to be the functional units. Each monomer has a single binding pocket located at the interface of two inverted structural repeats (transmembrane α-helices TM2–TM6 and TM7–TM11 in vSGLT, and TM1–TM5 and TM6–TM10 in LeuT). Another striking feature common to the two transporters is that, in each structure, two transmembrane domains — TM2 and TM7 in vSGLT, and TM1 and TM6 in LeuT — have an interruption in the α-helix. Such interruptions, which were first observed in the transmembrane domains of the calcium pump[3], expose oxygen and nitrogen atoms in the peptide bonds of the amino-acid chain, for direct interaction with the solute and its co-transported cations.

Numerous functional studies on different types of transporter have found indirect evidence for alternating access, one of the most suggestive analyses being that of lactose permease of the bacterium *Escherichia coli*[4]. But what is particularly exciting about the structure of LeuT, and now Faham and colleagues' structure of vSGLT, is that whereas the former captures LeuT with its binding site facing the extracellular milieu, the opposite is true for vSGLT. So a comparison of these two structures allowed the authors[1] to provide the first direct clue for alternating access in membrane transporters. The two structures apparently result from structural rearrangements of several transmembrane α-helices (Fig. 1, overleaf).

Unlike the vSGLT structure, that of LeuT is of high enough resolution to allow the identification of bound sodium ions (Na^+). Nevertheless, Faham *et al.*[1] predict the existence of such a Na^+-binding site in vSGLT — and in other members of the SSS family — at a similar position to one of the Na^+-binding sites of LeuT (referred to as Na2). They obtain experimental support for this by studying the effects of mutations in an evolutionarily conserved serine amino-acid residue on TM9. Although the conservation of a Na^+-binding site gives extra confidence that the two structures can be compared for mechanistic purposes, it will be essential to obtain structures of the outward- and inward-facing conformations of a single transporter.

As for the position of galactose in the binding pocket of vSGLT, the authors could identify it unambiguously. This sugar seems to be sandwiched between groups of hydrophobic residues. The intracellular-exit pathway appears