because MoS_2 is rougher at atomic scales than is graphite (and h-BN). Through computational modelling, the authors found that MoS_2 surfaces have bumps around 1 Å in height, which is comparable to the diameter and the de Broglie wavelength of helium molecules (all matter can exhibit wave-like behaviour, and the de Broglie wavelength is the wavelength associated with that behaviour). In other words, the MoS_2 nanochannels are too bumpy for specular reflection.

Keerthi and colleagues' findings prove that complete specular reflection and frictionless gas transport can occur in nanochannels that have perfectly flat surfaces. This is an exciting discovery, because previous studies[5,6] have reported only partial specular reflection. Even more intriguingly, the authors make several unexpected observations, some of which cannot be explained by classical physics.

The first and most important of these observations is that frictionless gas transport is affected by the matter waves of the gas molecules. The authors found that the permeability of deuterium (D_2) in graphite nanochannels is much lower than that of hydrogen (H_2), its lighter isotopic counterpart, even though Knudsen theory predicts the opposite. This is because deuterium molecules have a smaller de Broglie wavelength than do hydrogen molecules, and therefore 'see' the channel walls as being rougher, even though the two types of molecule have the same diameter and interact in the same way with the channel walls. The authors also showed that computational simulations of gases that represent classical molecule–wall interactions, but not quantum effects (that is, the effects of matter waves), predict only partial, rather than complete, specular reflection in graphite and h-BN nanochannels. This suggests that quantum effects must contribute to specular reflection.

The other interesting observation is that the permeability of helium in graphite and h-BN channels varies unexpectedly with channel height: it initially increases, then decreases as the channel height increases, reaching a maximum value for heights of four atom layers. This behaviour is at odds with conventional thinking that complete specular reflection is not affected by channel height. Keerthi *et al.* speculate that the height dependence results from the interplay between two effects: small channels have relatively small 'capture zones' for incident gas molecules at their entrances, whereas hydrocarbons from the surrounding air can be adsorbed to larger channels during channel fabrication, roughening the atomically flat surface. Neither of these effects is included in existing models of gas flow, but they seem to have key roles in determining permeability in the real world.

The new findings call for a re-examination of the classical physics of gas dynamics at low pressure and its correlation with quantum mechanics. However, more experiments with other gases in graphite and h-BN nanochannels are needed to further unravel the influence of molecular diameter and de Broglie wavelength on specular reflection, given that larger diameters typically correspond to smaller de Broglie wavelengths. Moreover, a quantitative comparison of gas transport through rectangular nanochannels and through circular nanotubes made of the same material is needed to evaluate the effect of channel curvature.

In addition, the factors that cause the degradation of specular reflection should be investigated, such as the affinity of gas molecules for channel walls. The variation of gas permeability as a function of confinement and temperature should also be measured for both specular and diffuse reflection. In parallel with the experimental work, more simulations or theoretical work that consider quantum effects are needed, to quantitatively understand and predict the properties of frictionless gas transport.

Such research potentially offers comprehensive insight into the nature of gas transport through channels and at low pressures. Knowledge of such gas transport has found extensive application in studies of the aerodynamics of space vehicles, in micro-electromechanical systems, and in shale-gas extraction[7,8]. Further research might also shed light on how laminar membranes can be made from 2D materials for separating mixtures of gases, thereby improving separation efficiency while reducing energy consumption[9]. Finally, frictionless gas transport through channels that are asymmetrically constricted[10] could enable gas-flow rectification[11], a process that might allow the development of new pumps, valves and other devices for controlling gas flow. ■

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STEM CELLS

Intestinal-niche conundrum solved

The cellular microenvironment required to sustain adult intestinal stem cells has long been controversial. Cells that release proteins needed for intestinal-tissue renewal have now been defined. SEE LETTER P.449

LINDA C. SAMUELSON

The human small intestine and colon are maintained throughout life by tissue-resident stem cells, which renew the gut lining at an astounding rate by generating billions of cells every day. The self-renewal, proliferation and differentiation of these intestinal stem cells are prompted by molecular signals from nearby cells called niche cells. Over the past decade, stem-cell biologists have debated the identity of the intestinal niche cells[1]. Two papers in *Nature* (one by Shoshkes-Carmel *et al.*[2] published earlier this year, and the other by Degirmenci *et al.*[3] on page 449) now identify a niche-cell population that provides a signal essential for stem-cell renewal.

Intestinal cells are arranged in a strict spatial layout. Stem cells are found at the base of pit-like structures in the gut wall, called crypts (Fig. 1). They produce highly proliferative progenitor cells, which differentiate into the various mature epithelial-cell types that make up the gut lining as they move away from the crypt base.

By contrast, Paneth cells are differentiated epithelial cells that move down from the progenitor zone to the crypt base. The close physical association between Paneth cells and stem cells has led to the proposal that Paneth cells have niche function, promoting stem-cell self-renewal. Providing support for this idea, a study has shown that Paneth cells enhance intestinal stem-cell growth in culture, and that intestinal stem-cell numbers are reduced in mice in which Paneth-cell numbers are artificially depleted[4]. However, other studies have come to the opposite conclusion, showing normal stem-cell function after Paneth-cell loss[5,6]. Furthermore, Paneth cells are not normally found in colonic crypts. Thus, the status of Paneth cells as niche cells is controversial.

Searching for cells that produce the telltale proteins that promote stem-cell self-renewal is one way of identifying the niche-cell population. The main signalling pathways for

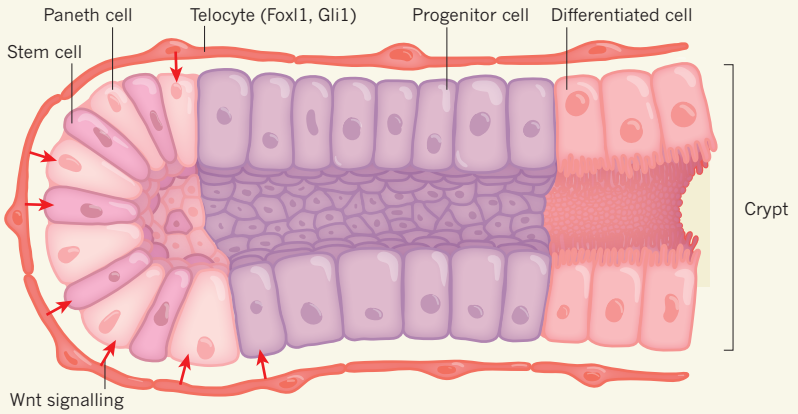

Figure 1 | The intestinal stem-cell niche. Intestinal stem cells generate highly proliferative progenitor cells that differentiate into the various epithelial-cell types that make up the gut lining. The stem cells are located in the base of structures called crypts, and are interspersed with differentiated epithelial cells called Paneth cells. Wnt proteins secreted from a previously unknown cell type trigger Wnt signalling at the crypt base, and these proteins are essential for stem-cell maintenance. Two studies[2,3] provide evidence that a specialized non-epithelial cell called a telocyte emits Wnts. The telocytes are characterized by production of the proteins Foxl1 and Gli1, and have long extensions that form a sub-epithelial network to support tissue renewal.

stem-cell maintenance are Notch[7] and Wnt[8]. The Wnt signalling pathway is of particular interest, because elevated signalling in stem cells leads to unchecked proliferation and tumour formation[8]. Indeed, mutations that activate the Wnt signalling pathway are associated with most human colon cancers[9].

Wnts are secreted proteins that bind to cell-surface receptors to activate the Wnt signalling pathway in neighbouring cells. They are produced by many different intestinal cells, including Paneth cells. However, genetic depletion of Wnts in all intestinal epithelial cells does not alter stem-cell function or crypt structure[10]. Therefore, intestinal epithelial cells are not an essential source of Wnt. This implies that there must be an alternative, non-epithelial-cell source for this niche factor. But what is that source?

An intestinal population of connective-tissue cells called stromal cells, which produce the protein Foxl1, is required for crypt-cell proliferation in adult mice[11]. Shoshkes-Carmel *et al.* took advantage of this fact to identify a Wnt source. They used genetic engineering to delete the gene *Porcn*, which encodes a protein required for Wnt secretion, in Foxl1-producing cells in mice. This resulted in rapid, catastrophic crypt collapse, a decrease in the number of intestinal stem cells, and defects in epithelial-cell proliferation. Extensive epithelial degradation was apparent in both the small intestine and colon three days after *Porcn* deletion. Thus, the Foxl1-producing stromal cells are the elusive Wnt-producing niche cells.

Degirmenci *et al.* took a similar approach, but analysed stromal cells that produced a different protein, Gli1. The same research group previously demonstrated that this cell population expressed Wnts[12]. The authors deleted the gene *Wls*, which (like *Porcn*) encodes a protein required for Wnt secretion, in Gli1-producing cells in mice. This led to crypt collapse in the colon. No effects on the small intestine became apparent until the researchers deleted *Wls* in both epithelial cells and Gli1-producing stromal cells. Surprisingly, the response was relatively slow in both cases — stem-cell loss and crypt collapse took two to three weeks.

Wnt depletion has a more limited, slower effect in Gli1-producing cells than in Foxl1-producing cells, but the reason for this is unclear. Perhaps Wnt secretion was not completely blocked in the Gli1-producing cells in the small intestine, and the slower effect was due to the long half-life of the Wls protein[12]. Regardless of the differences, the fact that blocking Wnts in each cell population leads to stem-cell loss suggests that these stromal cells are the elusive Wnt-producing niche cells. The authors of the two papers have shown that there is physical overlap between the Foxl1-producing and Gli1-producing stromal cells, suggesting that each study identified the same cell population. However, single-cell analyses revealed subpopulations within each of these stromal-cell types. Whether only certain subpopulations have niche function remains to be defined.

Both groups found that the Wnt-expressing niche cells were positioned close to intestinal epithelial cells, in a prime location to affect stem-cell function. Shoshkes-Carmel *et al.* performed high-resolution microscopy, which revealed that these cells are telocytes — thin cells with long protrusions called telopodes, which form a 3D network underlying the epithelial cells throughout the gut. Both groups showed that these telocytes might be signalling hubs, because they express, in addition to Wnts, several other niche factors involved in stem-cell function and tissue renewal. Moreover, telopodes have the potential to interact with immune cells, blood vessels and nerves[13]. Telocytes might therefore be central coordinators of intestinal renewal beyond their role in Wnt signalling.

Wnt signalling is highest at the base of the crypts, where stem cells reside[1]. Shoshkes-Carmel *et al.* showed that telocytes express different levels of Wnts and Wnt inhibitors along the length of the crypt, with higher levels of Wnt protein at the crypt base enabling localized activation of Wnt signalling in stem cells. Whether this compartmentalization reflects reciprocal signalling interactions between stem cells and telocytes is an interesting question — if so, it could indicate that telocytes are responsive to stem-cell status. In support of this idea, Degirmenci *et al.* showed that the numbers of Gli1-producing cells increased after colon damage, suggesting that this stromal population might adapt to restore homeostasis after damage.

Along with another recent report of a stromal-cell source for Wnts[14], the groups' identification of telocytes as Wnt niche cells has resolved the controversy over which Wnt source regulates intestinal maintenance. A key next step will be to characterize the telocytes' role in intestinal regeneration after injury, or in diseases that affect stem-cell proliferation, such as colon cancer. Further analysis will also be needed to determine whether a single telocyte population is responsible for niche function, or if different populations orchestrate the many stromal growth factors and inhibitors that regulate intestinal stem-cell function. A deeper understanding of how telocytes regulate intestinal stem cells is likely to provide insights into mechanisms of normal intestinal-tissue renewal and regeneration, and dysfunction associated with intestinal disease. ■

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CORRECTION

The News & Views article 'Intestinal-niche conundrum solved' (*Nature* **558**, 380–381; 2018) indicated that two papers (M. Shoshkes-Carmel *et al. Nature* **557**, 242–246; 2018, and B. Degirmenci *et al. Nature* **558**, 449–253; 2018) solved an outstanding debate — the identify of a stromal-cell population that sends Wnt signals to intestinal stem cells. However, a paper published earlier this year (G. Greicius *et al. Proc. Natl Acad. Sci. USA* **115**, E3173–E3181; 2018) also identified a stromal-cell source for Wnt signals.