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SPOTLIGHT

Morphological control of gut lumen access shapes enteroendoceine cell function

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In this issue, Yu et al. (https://doi.org/10.1083/jcb.202506084) uncover a genetic mechanism that determines whether enteroendocrine cells access the gut lumen. Their findings link regional transcriptional control to epithelial integration of enteroendocrine cells, revealing how cell morphology shapes nutrient sensing in the intestinal epithelium.

Cell morphology and function are tightly coordinated in many biological systems, with cell shape often accompanying functional specialization (1). In the intestinal epithelium, this relationship is exemplified by two distinct morphologies of hormone-producing enteroendocrine cells (EEs), referred to as "open" and "closed" types. Open-type EEs extend an apical protrusion into the gut lumen and act as chemosensors of luminal contents, signaling through peptide hormone secretion (2). In contrast, closed-type EEs lack such protrusions and reside closer to the basal side of the epithelium, where they are thought to be activated indirectly via humoral or neural inputs (2). Although these morphologies have long been recognized in the mammalian intestine and linked to distinct functions, how they are generated and how they influence EE function have remained largely unresolved.

Using the adult *Drosophila* midgut as a model, Yu et al. show that EEs adopt these two morphologies—open and closed types—revealing that EE morphological diversity is conserved in the fly intestine. Open-type cells extend apical tips into the lumen, whereas closed-type cells remain embedded basally within the epithelium (Fig. 1 A) (3). Notably, these cell types show distinct regional distribution. Closed-type EEs are enriched in the middle gastric region (R3), whereas open-type EEs dominate throughout the rest of the midgut. This regional bias suggests that spatial cues along the gut axis govern EE morphology.

To uncover the molecular basis of this regional control, the authors reanalyzed existing single-cell RNA-sequencing datasets of *Drosophila* EEs (4). In prior work, EE subtypes, defined by hormone expression and transcription factors, had been mapped to specific gut regions. Using this spatial annotation, the authors inferred the likely distribution of open- and closed-type EEs and compared their gene expression profiles. Among these, genes encoding smooth septate junction (sSJ) components, such as *mesh*, *ssk*, and *Tsp2A*, are highly enriched in open-type EEs but largely absent from closed-type EEs. As septate junctions are the invertebrate counterparts of vertebrate tight junctions and are essential for epithelial barrier formation (5), this finding suggests that differential epithelial integration may underlie EE morphology.

Genetic experiments confirmed this hypothesis. Loss of sSJ components prevented open-type EEs from establishing apical access to the lumen, resulting in a shift toward closed-type morphology. Imaging analyses further revealed a stepwise integration process in which newly differentiated EEs extend their apical domain toward the lumen, assemble sSJs at their apical tip, and subsequently reposition these junctions to establish apical–basal polarity and luminal access. This integration resembles that of postmitotic enteroblasts, which remodel their junctions and incorporate into the epithelium as they differentiate into absorptive enterocytes (6, 7).

What regulates the expression of sSJ genes that underlie EE morphology? Yu et al. identified a transcriptional cascade that links regional patterning to epithelial integration. In the R3 region, the homeobox transcription factor Ptx1 maintains the expression of the Snail-family transcription factor *escargot* (*esg*) in newly differentiated EEs. Esg in turn represses sSJ gene expression, thereby preventing epithelial integration and enforcing the closed-type morphology. In the non-R3 region, where *Ptx1* expression is low, sSJ genes are expressed and EEs integrate into the epithelium to form open-type cells. These findings establish a simple yet elegant model by which regional transcriptional programs determine whether differentiating EEs assemble junctional complexes and acquire luminal access.

Importantly, this morphological distinction has direct functional consequences. Because open-type EEs extend into the gut lumen, they can directly detect dietary components. Converting open-type EEs into closed-type cells impairs their ability to respond to amino acids (Fig. 1 B), as measured by intracellular calcium signaling and hormone secretion (8, 9). These findings indicate that epithelial integration, and hence

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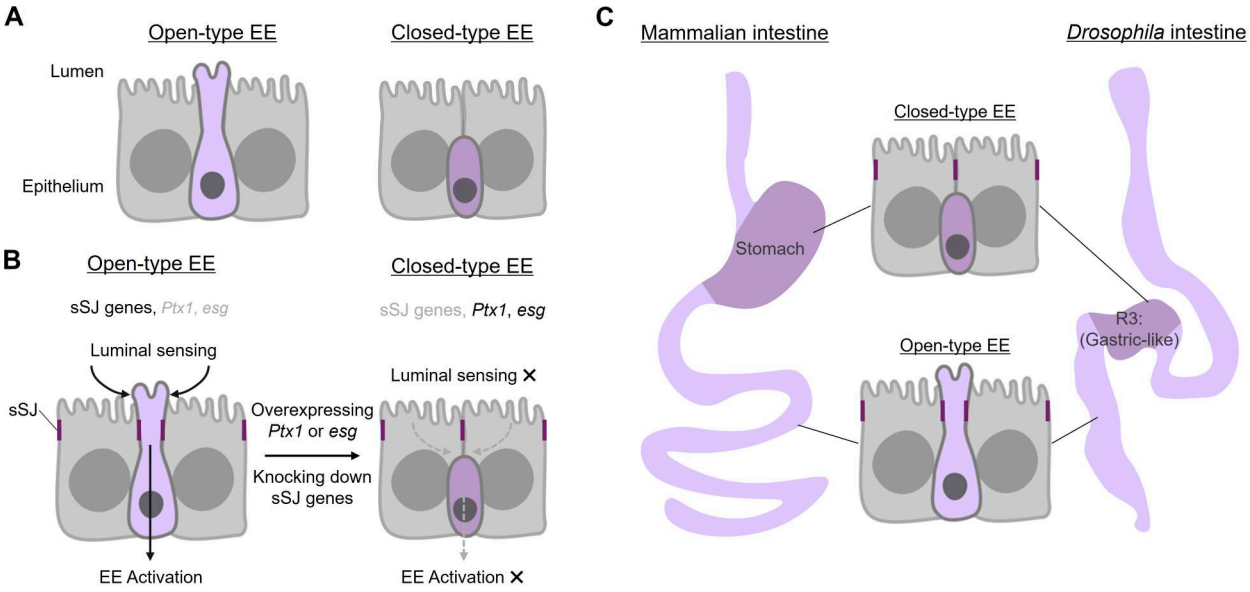

Figure 1. **EE morphology is genetically controlled, functionally relevant, and conserved across species. (A)** Open-type EEs extend an apical protrusion into the gut lumen, whereas closed-type EEs are embedded within the epithelium without luminal access. **(B)** Open-type EEs highly express sSJ genes, while closed-type EEs highly express transcription factors, *Ptx1* and *esg*. Overexpression of *Ptx1* or *esg*, or knockdown of sSJ genes, converts open-type EEs into closed-type ones, thereby impairing luminal sensing and peptide secretion. **(C)** Similar open- and closed-type EE configurations are observed in both mammalian and *Drosophila* intestines, suggesting that EE morphology and epithelial positioning are evolutionarily conserved.

luminal access, is a prerequisite for the nutrient-sensing function of EEs.

This study places EE morphology within an evolutionary context. While open- and closed-type EEs have been described in the mammalian intestine (2), the authors showed that comparable morphologies exist in the *Drosophila* midgut. Closed-type EEs are enriched in the R3 region in the *Drosophila* midgut, a gastric-like region reminiscent of the mammalian stomach, where closed-type EEs are also more prevalent (Fig. 1 C) (2). Consistent with this conserved regional organization, the conserved role of Snail-family transcription factors in regulating epithelial junctions across species (10) further suggests that the mechanism controlling EE morphology may be broadly conserved.

In addition to conservation, this study suggests that EE morphology may represent a tunable cellular state rather than a fixed cell identity. Indeed, manipulation of the Ptx1-Esg-sSJ axis alters morphology without major changes in peptide hormone expression, indicating that morphology can be controlled independently of endocrine differentiation state. Together with the functional consequence of altering morphology, these observations imply that EE morphology modulates sensory capacity without requiring lineage respecification, acting as an adjustable interface with the environment.

If EE morphology is flexible, it may also change during tissue adaptation. Differentiated EEs can revert to progenitor-like states under environmental challenges such as nutrient fluctuations or irradiation (11, 12). While EE dedifferentiation is accompanied by morphological remodeling (11), whether a transition between open and closed morphologies is involved remains unknown. The identification of intermediate "pre-open" EEs raises the possibility that such a transition may occur during this process before acquiring progenitor-like features.

At the cellular level, however, the mechanism of epithelial integration remains incompletely understood. While the authors proposed a stepwise integration process, it remains unclear whether EEs utilize structures analogous to the pre-apical compartment described in enteroblasts (6, 7). Resolving whether similar or distinct integration mechanisms operate across epithelial cell types in different species will provide insights into how epithelial barrier integrity is maintained during differentiation.

A second unresolved question concerns how regional specificity is achieved despite broader expression of upstream regulators. Ptx1 is not restricted to R3 EEs, yet its ability to sustain *esg* expression and enforce closed morphology appears regionally confined. Consistent with this, although Esg is a stemness factor, its ectopic expression only partially converts EE morphology without fully inducing a progenitor-like state. These results imply a dose- or context-dependent regulatory mechanism, in which differences in transcription factor levels produce discrete morphologies. Understanding how such graded inputs are converted into distinct outcomes will be essential for elucidating how regional information is implemented at the cellular level.

Finally, the physiological role of closed-type EEs remains to be characterized. Unlike open-type EEs, which directly access luminal contents, closed-type EEs may respond to alternative inputs such as mechanical cues, circulating factors, or neural signals. Defining the inputs and outputs of these cells will be critical for understanding how regionally specialized EEs contribute to gut–brain and gut–systemic communication.

Taken together, Yu et al. uncover a transcriptionally controlled mechanism that links regional identity to epithelial integration and cell morphology. Their work reveals how the positioning of EEs within the epithelium determines their access to the gut lumen and, consequently, their ability to sense environmental cues. These findings highlight EE morphology as a key regulator of EE sensory functions, which may ultimately influence organismal physiology.

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