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SPOTLIGHT

The curious incident of epithelial polarity where there should be none

Madeleine L. Ball[1] and Katja Röper[1,2]

In this issue, Almasoud et al. (https://doi.org/10.1083/jcb.202504139) report a surprising finding that epithelial cell polarity is present in a tissue with no known polarized function, in a cell type that was assumed to show a distinct lack of such polarity—the mesenchymal cells of the *Drosophila* fat body. Exceptions such as this help to broaden our understanding of the use of regulators and pathways we thought we fully understood.

Although cell polarization is a particularly well-known hallmark of epithelial cells, it is by no means exclusive to them (Fig. 1 A). Across embryonic development, polarization of cells is a very common theme, even if not immediately obvious, and can be found in many different contexts, such as in asymmetrically dividing stem cells (1), migrating cells (2), or in neurons during early neural development (3). However, the cell polarity of epithelial cells is special, as it is intrinsically tied with required tissue function (Fig. 1 B). Epithelial cells have strong apical–basal polarity that can provide localized junctional complexes that, in the case of adherens junctions, build strong cell–cell adhesion, and in the case of tight junctions, provide a diffusion barrier and make the epithelium tightly connected (4).

Epithelial tissues cover both external and internal surfaces of the body and act as a semipermeable selective barrier between the body's internal space and the outside world. This blocks the ingress of toxins and pathogens from the outside and the loss of water and other essential components from the inside but also provides selective absorption and/or secretion of selected cargo. These core characteristics of epithelial tissues are key to many housekeeping functions and are also essential to developmental control (4). Apical–basal polarity enables the import and export of morphogens, such as Hedgehog and Wnt, thereby shaping signalling gradients that guide tissue patterning and ultimately morphogenesis (5). Maintaining tissue integrity is reliant on robust cell adhesion of epithelial cells. If lost during morphogenetic processes such as neural tube closure and branching morphogenesis, disruptions in core epithelial functions result in diseases such as spina bifida, polycystic kidney disease, and congenital heart defects (6–8). Mesenchymal cells, on the other hand, are usually associated with loose organization, weak connections to neighboring cells, and no apical–basal epithelial polarity, though they can display front-rear polarity during migration.

A conserved set of polarity proteins is key for the establishment and maintenance of apical–basal polarity in epithelial cells. These include atypical protein kinase C (aPKC) and Crumbs that are localized at the apical-most end of the lateral sides; the junctional complex contains Par-3 and E-cadherin at adherens junctions, and the basolateral complex contains Lethal giant larvae (Lgl), Discs large (Dlg), and Scribble located at the lateral and basal sides (4). The regulatory interplay between these polarity complexes patterns the cells into different membrane domains across the apical–basal axis that in turn patterns intracellular polarized organization. The polarity complexes are involved in many downstream signalling pathways and influence effectors that impact developing tissues. The case of the *Drosophila* fat body (Fig. 1 C) is surprising because there is currently no known polarized function for the organ. In addition to storing energy in the form of triacyl glycerides, the larval fat body is also an important source of antimicrobial peptides and endocrine hormones, but with an open circulatory system, a need for directional absorption or secretion is not immediately obvious (9, 10).

The exciting work presented by Almasoud et al. (11) demonstrates that despite not being epithelial, the fat body has apical–basal polarity—with familiar components of the classical epithelial polarity complexes localized in a polarized manner, with aPKC and Crumbs on an apical-like side and Lgl and Dlg on the opposing basal-like side (Fig. 1 D). Knockdowns of aPKC, Crumbs, Lgl, and Scribble in the fat body led to cell–cell adhesion defects, strengthening the idea that the classical apical–basal polarity proteins are also involved in the regulation of cell–cell adhesion in the fat body cells, similar to one of their key roles in true epithelia. One of the crucial differences between the fat body cells and typical epithelial cells is the lack of strong E-cadherin, which does not seem to be important for adhesion in the fat body. In contrast, E-cadherin is essential for epithelial cell–cell adhesion and function. In the fat body, it seems that cell–cell adhesion is instead primarily mediated by collagen IV–intercellular-concentrations (CIVICs), where integrins on the lateral sides of two

[1]Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK; [2]MRC Laboratory of Molecular Biology, Cambridge, UK.

Correspondence to Katja Röper: kr250@cam.ac.uk.

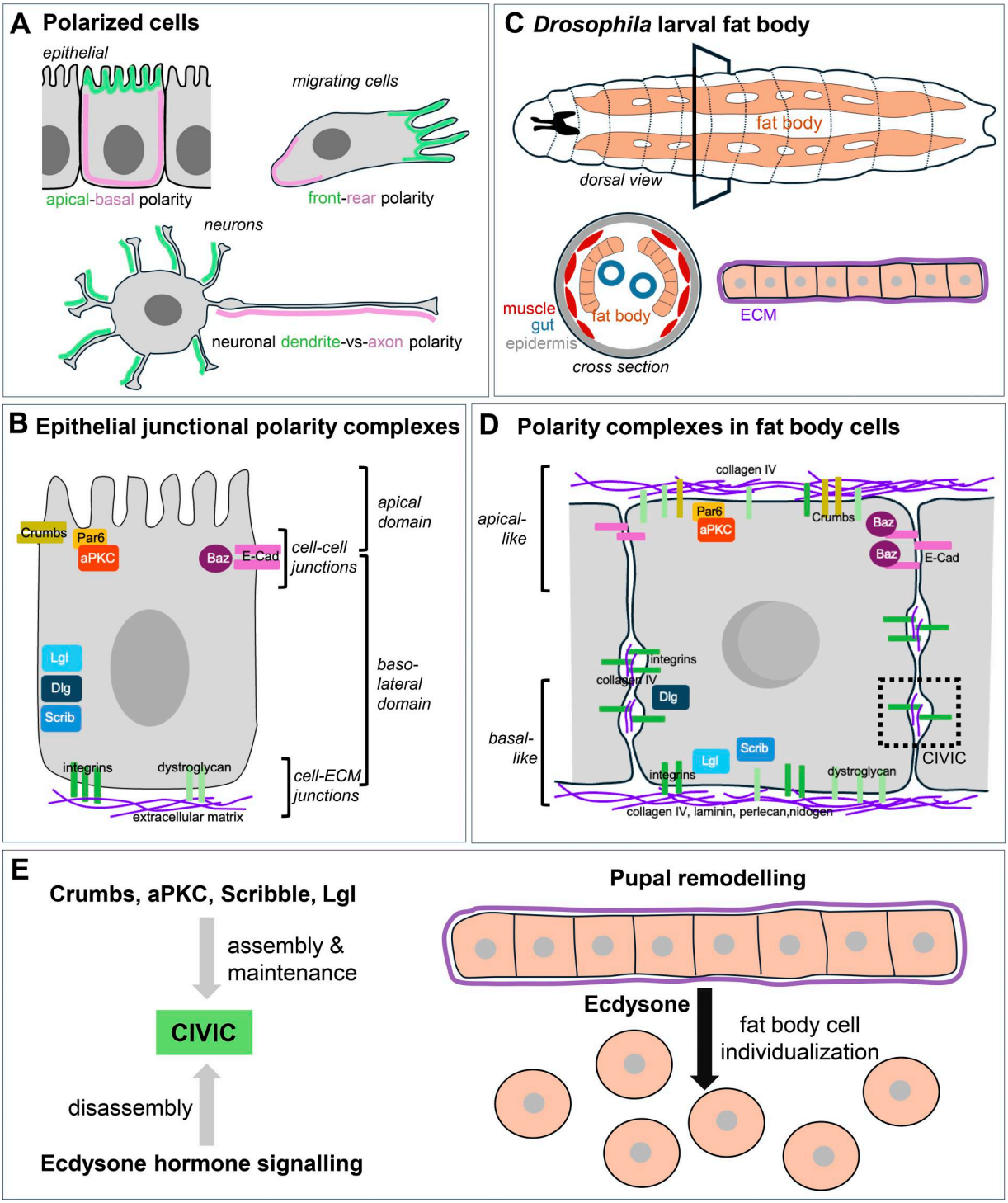

Figure 1. **Polarity systems and the fat body. (A)** Classical polarised cells: epithelial cells (apicobasal polarity), migrating cells (front-rear polarity) and neurons (dendrite-versus-axon polarity). **(B)** In a classical epithelial cell polarity and adhesion complexes define and maintain the polarity: Crumbs/aPKC/Par-6 at the apical side, E-Cadherin/Par-3 at the adherens junctions and Scribble/Dlg/Lgl the lateral side, with integrins and dystroglycans mediating adhesion to the extracellular matrix (ECM) at the lateral side. **(C)** The *Drosophila* larval fat body, as the equivalent of vertebrate adipocytes, comprises two single-layered sheets of cells surrounded by ECM sandwiched between body wall muscles and internal gastrointestinal organs. **(D)** In *Drosophila* larval fat body cells all complexes are localised to equivalent positions in an apical-like and basal-like region of the cells with two differences: cell–cell adhesion is mainly mediated via so-called CIVICs (collagen IV-intercellular concentrations). with only a small contribution from E-Cadherin, and the sheet of cells is surrounded by ECM, but with differing composition between apical-like and basal-like domains. **(E)** As in epithelial cells, Crumbs, aPKC, Scribble and Lgl a key to the assembly and maintenance of cell–cell adhesion in the larval fat body. The developmental disassembly of the fat body into individual cells at the beginning of pupal stages is triggered by ecdysone signalling leading to downregulation of polarity factors leading to loss of cell–cell adhesion via CIVICs.

neighboring cells adhere to a small patch of collagen IV located there. Such CIVICs are spread along lateral sides, but more concentrated near the basal-like side. In knockdowns of aPKC and Scribble, a near complete loss of CIVICs was seen (Fig. 1 E). In contrast, a knockdown of Crumbs redistributed CIVICs along the lateral domain, with higher numbers of CIVICs on the apical-like than on the basal-like region.

The loss of cell–cell adhesion in the fat body is a process that occurs as part of the developmental progression into pupal stages, in a process termed fat body remodelling, but the regulatory control of this remodelling was not known. Almasoud et al. now show that the hormone ecdysone that controls several step changes along the developmental timeline also controls fat body dissociation by directly affecting the localized distribution of polarity components in the fat body (Fig. 1 E).

The regulation of cell–cell adhesion is a simple conceptually, but its dynamic regulation is crucial for embryonic development—enabling cells to move, change shape, and form complex tissue shapes and organ systems. Cell polarity and cell adhesion are also two commonly mutated processes in diseases such as cancer, particularly resulting in cells losing their connection to neighboring cells and undergoing epithelial-to-mesenchymal transition (EMT) (12). EMT underlies the ability of cancer cells to disassociate from their point of origin to establish new tumors in other locations in the body (known as metastasis), with metastases commonly associated with a worse prognosis (13). The developmentally regulated dissociation of the fat body that Almasoud et al. now show to be controlled via polarity proteins controlling CIVIC-mediated cell—cell adhesion in the fat body is very reminiscent of an EMT-like process. The study of this unusual case of epithelial-like polarity might therefore allow us to gain a greater mechanistic insight into EMT regulation.

Whilst apical–basal cell polarity is a defining feature of epithelia, there are evolutionary more basal organisms that are assembled into multicellular structures without exhibiting strong cell polarity. Filamentous cyanobacteria such as *Anabaena* form long chains of largely symmetrical cells that are functionally equivalent and only show polarity upon differentiation into specialized cell types like heterocysts (14). Some multicellular algae, such as *Scenedesmus* or *Ulothrix*, form filaments or colonies containing cells that display minimal polarity that is often only transient or induced by environmental cues rather than being developmentally fixed (15). In slime molds such as *Dictyostelium*, identical amoebae aggregate into multicellular assemblies in which front-rear polarity arises dynamically during migration; however, once aggregation cues are removed, the individual cells do not maintain stable polarity (16). Together, these examples illustrate that apical–basal cell polarity is not necessarily required for multicellularity or multicellular organization. Changes in polarity, though, in the form of developmental MET (with mesenchymal-to-epithelial transition being the acquisition of epithelial polarity) or EMT processes form the basis of dynamic shaping of developmental changes, and the remodelling of the larval fat body in *Drosophila* is a curious one that will likely shed light onto other versions of nonclassical EMT.

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