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LETTER TO THE EDITOR

Why does epithelia display heterogeneity? Bridging physical and biological concepts

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Epithelial cells construct inner and outer linings of our organs and function as physical barriers, thus, protecting the underlying tissue from infections, dehydration, and also aiding in efficient absorption of nutrients and gases (Alberts 2008). Cells within the epithelia perform these tasks, being jammed at their place while also making sure that epithelial homeostasis is maintained, failing in which can be potentially fatal for the tissue (Macara et al. 2014). Interestingly, the same cells can unjam and flow almost like a fluid during physiological and pathological situations such as organ development, wound healing and cancer metastasis (Friedl and Gilmour 2009; Mongera et al. 2018; Park et al. 2016; Sadati et al. 2013; Scarpa and Mayor 2016). In such situations, cells, rather than moving individually, migrate as a group in various patterns (Haeger et al. 2015; Petitjean et al. 2010; Poujade et al. 2007; Rorth 2012; Tarle et al. 2015). Reductionist view holds that such cooperative cellular events are mediated at the level of cell-cell interactions where local signals are translated into physical forces (such as those generated in the cellular cytoskeleton and those exerted across cell-cell junctions), which are then translated into cell motility (Das et al. 2015; Keller 2012; Ladoux and Mège 2017; Trepat et al. 2009). Such physical forces are believed to be fundamental to biological form and function but have remained hidden until recently when experimental methods are finally making them visible (Angelini et al. 2010; Angelini et al. 2011; Edwards and Schwarz 2011; Malinverno et al. 2017; Sabass et al. 2008; Schwarz and Soine 2015; Sunyer et al. 2016; Tambe et al. 2011; Trepat and Fredberg 2011). Furthermore, recent advances in mathematical biology have also led to the development of models that can predict various parameters of epithelial behaviour in both jammed and unjammed states (Edwards and Schwarz 2011; Garcia et al. 2015; Henkes et al. 2011; Mark et al. 2010; Mehes and Vicsek 2014; Sepulveda et al. 2013; Steinberg 2007). Together, these studies have revealed unpredicted behaviour of epithelial tissues and are beginning to explain why cells jam and unjam, and how collective cell behaviour is orchestrated. Since many excellent reviews have been written on the topic (Friedl and Gilmour 2009; Haeger et al. 2015; Merkel and Manning 2017; Park et al. 2016; Park and Fredberg 2016; Pegoraro et al. 2016; Sadati et al. 2013), here, we will only briefly describe the heterogeneous nature of the jamming transition from the physical perspective and focus mainly on its implications in regulating epithelial functionality while also taking into account the inherent biological heterogeneity present within the epithelium.

Jamming transition and dynamic heterogeneity

Ongoing cell divisions, apoptosis and cell mingling make the epithelia a highly dynamic place (Al-Hussaini et al. 2016; Christ et al. 1990; Gardner 1986; Macara et al. 2014). Interestingly, monolayer stress profiles of such epithelial layers reveal dynamic heterogeneity, with intercellular stress displaying stochasticity in space and time, meaning that stress is tied neither to any particular position nor to any particular cell within the monolayer (Angelini et al. 2010, 2011; Garrahan 2011; Tambe et al. 2011). Topography of these intercellular forces, at any given instant, can be compared with a rugged landscape, similar to that of a mountain range, where peaks arise from cooperation between tens of cells pulling together (Tambe et al. 2011) (Fig. 1a). Interestingly, cell

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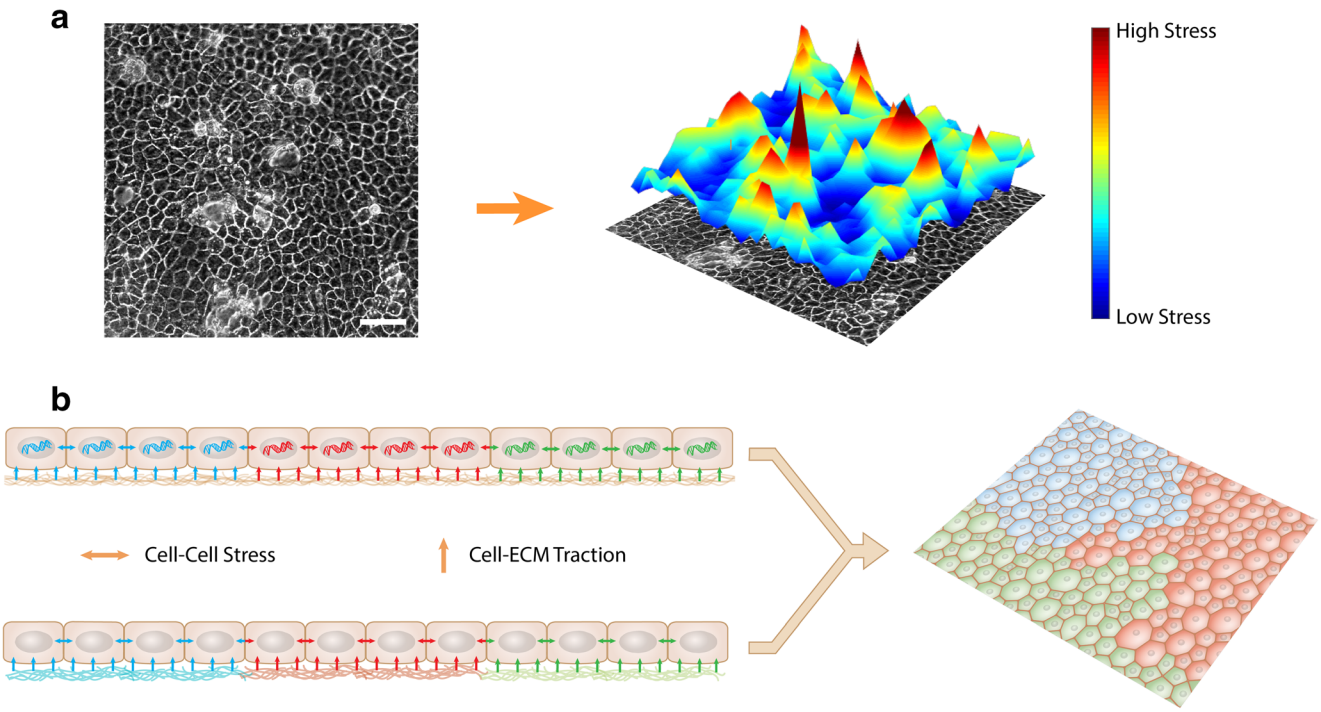

Fig. 1 **a** The intercellular stress profile in a confluent epithelial monolayer of canine kidney epithelial cells (MDCK) reveal a rugged stress profile at a given time point. Scale bar is 50 μm. **b** Cellular heterogeneities can arise from genetic differences or differential regulation of protein expression which are also influenced by external cues such as ECM components. In addition, heterogenous clones in epithelia might differ in their mechanical properties, having different levels of adhesion forces (cell-cell stresses and cell-ECM tractions), thus impacting on physical nature of epithelia

density also plays a key role in regulating dynamic heterogeneity; i.e. when cells start to crowd, their movement becomes arrested and zones of cooperativity grow bigger (Angelini et al. 2011). Such a scenario is intriguingly analogous to glass transition within a supercooled fluid or dense particulate matter in which a non-equilibrium jammed state is reached by cooling, crowding or by decreasing applied load (Debenedetti and Stillinger 2001; Mattsson et al. 2009; Mayer et al. 2008; Nagel 1998; Trappe et al. 2001). Hallmarks similar to glass transition (spontaneous intermittent fluctuations, dynamic heterogeneity, cooperativity and kinetic arrest) are observed by epithelial cell monolayer, wherein the dynamical arrest is caused upon crowding and depends upon parameters such as active motility, cellular forces, cell shape and applied stress. When these parameters are comprehended in a jamming phase diagram (Nagel 1998; Sadati et al. 2013; Trappe et al. 2001), predictions on epithelial physical behaviour can be made. For instance, as intercellular adhesion or crowding progressively increases, cell motility and rearrangement would become rare and therefore, cooperativity would increase, leading to a topologically frozen epithelium (Sadati et al. 2013). Subsequently, then, the question is what the extension of jamming at homeostasis should be that allows the epithelia to achieve their vital physiological functions such as regulating homeostasis and orchestrating collective cell migration.

Physiological relevance of heterogeneity

The ability of epithelial cells to dynamically remodel their surroundings as well as their own cytoskeleton in response to external cues such as damage or mechanical stresses is known to provide a mechanical resilience to epithelial tissues (Khalilgharibi et al. 2019; Trepat and Sahai 2018). Recent studies are suggestive of the hypothesis that, by maintaining a striking balance between jammed and unjammed phases, the epithelial monolayer might have evolved to attain such resilience, by virtue of which, it can efficiently undergo switch-like changes required for physiological functions (Park et al. 2015; Sadati et al. 2014; Saw et al. 2017; Vishwakarma et al. 2018). For instance, a recent study demonstrates that cooperative forces owing to dynamic heterogeneity control the selection as well as frequency of leader cells which guide collective migration during wound healing (Vishwakarma et al. 2018). Another study demonstrates that hot spots of compressive stresses within the epithelial monolayer induce topological defects that subsequently lead to local cell extrusion (Saw et al. 2017). Since hot spots of compressive stresses build up regions of multicellular cooperation (Tambe et al. 2011) which show density dependence (Angelini et al. 2011), efficient cell extrusion for regulating tissue homeostasis would intuitively require the right extent of cell packing. Such extrusion events are important, due to their relevance not only in regulating cell

density during epithelial homeostasis (Fadul and Rosenblatt 2018; Gudipaty et al. 2018) but also in removing aberrant or tumour cells via a mechanism described as cell competition, by virtue of which, epithelia gain the ability to defend itself against cancer (Kajita and Fujita 2015; Wagstaff et al. 2013). Understanding physiological relevance and extent of jamming in epithelia becomes even more important in tissues that are naturally subjected to elevated levels of stress, such as lung epithelium which goes through cyclic breathing stress and, therefore, tissue plasticity plays an important role in maintaining its integrity, especially during lung injury (Frank and Matthay 2003).

The physical heterogeneity described above is most likely to be influenced by the existing innate biological heterogeneities in the epithelia which are associated with variations in genome or protein expression patterns (Fig. 1b). A known outcome of this genetic variability is the somatic mosaicism that leads to the presence of multiple cell clones within an adult tissue. Somatic mosaicism can originate from epigenetics events (Rakyan et al. 2002; Sutherland et al. 2000) such as, for instance, the inactivation of one of the X-chromosomes in females (Rakyan et al. 2002) or from mobile DNA elements such as retrotransposons (Beck et al. 2011; De 2011). A classic example of somatic mosaicism can be observed in the skin with the presence of mosaicisms in the pigmentation known as *café-au-lait* spots (De 2011; Rawles 1947). In addition to these genetic differences, differential regulation of proteins expression induced by external cues, such as extracellular matrix (ECM), can also create cellular heterogeneity within the epithelial layer (Fig. 1b). The importance of such heterogeneity in regulating tissue homeostasis has been shown in the basal layer of esophageal epithelium containing stem cells responsible for tissue renewal (DeWard et al. 2014). It has been shown that, in this layer, population of stem cells has heterogenous proliferation rates which are distinguishable by the expression of specific cell-surface markers such as the laminin receptor integrin $\alpha 6\beta 4$. Here, the involvement of laminins, major components of extracellular matrix, suggests the importance of cell-ECM adhesion in maintaining cellular heterogeneity and, subsequently, in regulating tissue homeostasis (DeWard et al. 2014). Interestingly, cellular heterogeneity dictated by differential laminin expression has also been shown to be involved in regulating functionality of endothelial cells. For example, the extracellular matrix of endothelium in postcapillary venules consists of areas of high and low expression of the laminin 511 isoform compared with the capillaries where the expression of laminin 511 is homogeneous (Di Russo et al. 2017; Sixt et al. 2001). Such differential distribution of laminin controls endothelial cell junction tightness, thereby dictating the location of leucocytes extravasation through the blood-brain barrier which occurs only in low laminin 511 regions (Sixt et al. 2001; Song et al. 2017). In addition to the biochemical composition of ECM, its topography has also been shown to control the heterogeneity of epithelial cells. Recently, an elegant experimental setting using undulated elastomer surfaces revealed the effect of ECM topography on heterogeneity of keratinocytes (Mobasseri et al. 2019). After seeding primary keratinocyte on the surfaces, the monolayer assembled within a range of cellular stiffness, cell-cell adhesion forces and acto-myosin contractility levels. The results provided new insights into the possible heterogenous control of keratinocytes proliferation rates by the topography of the dermal ECM during ageing and inflammation (Mobasseri et al. 2019). Differential ECM expression also impacts on the aetiology of retinal degenerative disease, i.e. age-related macular degeneration. The early stage of the disease is characterized by high level of ECM accumulation known as *drusen* that occurs between the retinal pigment epithelium and the underlying Bruch's membrane (Coleman et al. 2008). Drusen formation is a common age effect, but only the accumulation of high number of large drusen (> 63 μm in diameter) correlates with epithelium degeneration and photoreceptor detachment (Coleman et al. 2008). Since the retina pigment epithelium presents a very high heterogeneity in cell shape (Fig. 2), protein synthesis and granule accumulation, it is tempting to speculate that this diversity of cell shape might also correspond to high heterogeneity in monolayer tensions and, therefore, might control drusen formation and their growth.

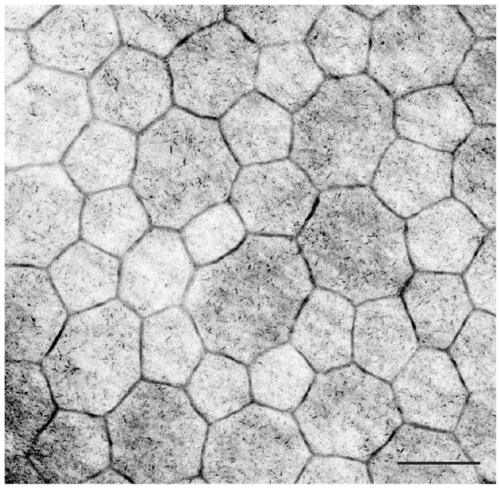

Fig. 2 Immunofluorescent staining of *en face* preparation of murine retinal pigment epithelium for filamentous actin reveals highly heterogenous character of this epithelium. To be noted is the postmitotic nature of these epithelial cells that exclude correlation of cell size with the cell cycle. Scale bar is 20 μm

Conclusion

Even though physical and biological heterogeneities are currently known to be distinct, they are likely to be interactive and interdependent. Local cellular heterogeneity might

influence the mechanical properties of epithelia, its ability to transduce forces and, hence, the nature of physical heterogeneity. Recent technological advancements in biophysics, cell biology and mathematical biology have now made it possible to analyse the physics and biology of the epithelia within the same framework. Such approaches allow us to attain a more comprehensive understanding on epithelial physiology and would subsequently require devising new treatment strategies for epithelial degenerative diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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