Forced back into shape: Mechanics of epithelial wound repair

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Abstract

Wound repair, the closing of a hole, is inherently a physical process that requires the change of shape of materials, in this case, cells and tissues. Not only is efficient and accurate wound repair critical for restoring barrier function and reducing infection, but it is also critical for restoring the complex three-dimensional architecture of an organ. This re-sculpting of tissues requires the complex coordination of cell behaviours in multiple dimensions, in space and time, to ensure that the repaired structure can continue functioning optimally. Recent evidence highlights the importance of cell and tissue mechanics in 2D and 3D to achieve such seamless wound repair.

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Introduction

During organ development and homeostasis, a continuous epithelium is required for precise morphogenesis and subsequent organ function. Epithelial wounds must be repaired quickly and accurately to maintain tissue patterning and preserve structural integrity. Epithelial cells range from flat squamous to tall columnar cells, which organise into a plethora of single or multilayered sheets, curved tubes, or folds. Through repair, the movements of individual cells must coordinate to restore their tissue's original morphology, a process highly dependent on the original architecture of the unwounded three-dimensional (3D) tissue.

The mechanical properties of cells and tissues play a key role in shaping cells and regulating biochemical signalling during wound repair [1–6]. Remarkably, there are many epithelia that repair rapidly using only cell shape changes and cell topological rearrangements [7,8]. These epithelial models are useful in studying the mechanics of re-epithelialization independently of proliferation and inflammation, where many different cell types and signalling molecules interact. Furthermore, theoretical (computational) models have helped us to simplify epithelial systems further to test possible physical mechanisms driving repair.

In this review, we discuss recent findings of physical mechanisms that contribute to minor wound repair and gap closure without the need for compensatory proliferation. In particular, we will highlight and speculate on how seemingly non-physical cell behaviours may also contribute towards physical mechanisms of wound repair. We will highlight the importance of cell and tissue mechanics beyond two dimensions (2D) and towards three dimensions (3D). Furthermore, we introduce the role of the basement membrane as an essential constituent of wound healing models, both *in vivo* and *in silico*.

Two dimensional physical repair mechanisms

Physical wound repair mechanisms have been extensively described in 2D, where supracellular actomyosin cables [9,10] and crawling cell migration drive closure [11,12] (Figure 1A). The choice of mechanism depends on the system, type of damage, and wound size, which is thoroughly summarised by Begnaud et al. [13]. Actomyosin-driven mechanisms are highly conserved throughout evolution, as indicated by recent studies in cnidarians [10,14] and sponges [9]. They are also used in a wide range of gap-closing morphogenetic processes, such as dorsal closure and gastrulation [15]. Accordingly, there are a plethora of molecules that ensure correct spatiotemporal regulation of actomyosin structures [12].

To execute these distinct behaviours, cells use branched and linear actomyosin substructures coordinated via different actin nucleators. When the removal of either

Figure 1
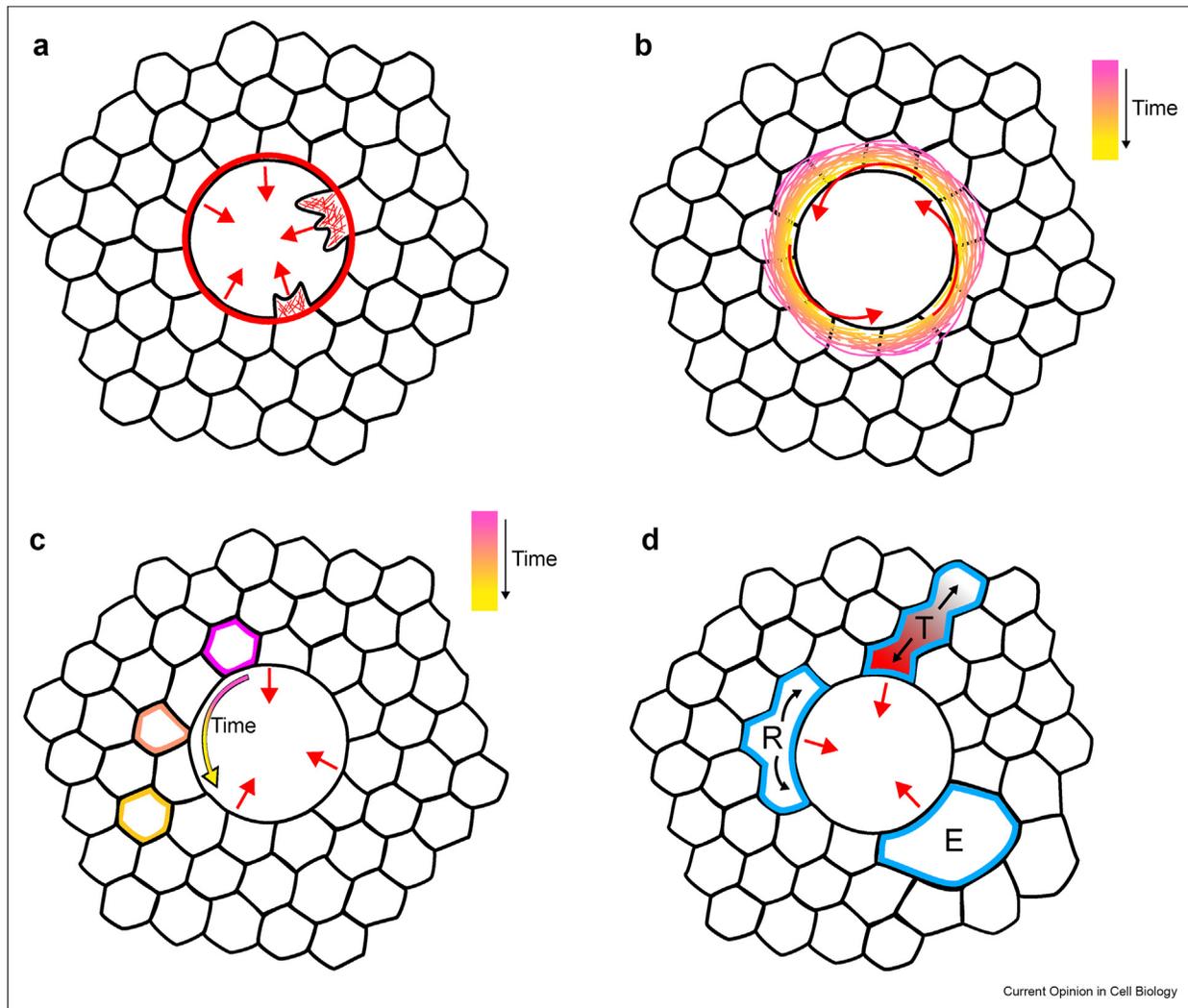
Two-dimensional physical wound healing mechanisms. **a)** There are two major physical mechanisms involved in wound healing: the purse-string and lamellipodia, with actomyosin machinery in red. **b)** Swirling mechanism, where the cells become softer. Linear actin assembles into a swirling mechanism. **c)** Cells intercalating away from the wound edge, with the pink to yellow gradient indicating time. The cell begins at the wound edge (pink) and then moves away from the wound edge (yellow). **d)** Blue cells undergo either endoreplication (cell 'E') or fusion (tangentially as 'T' or radially as 'R'). The red gradient in cell 'T' indicates that resources are moving towards the wound edge cell after tangential fusion. In all panels, red arrows indicate the direction in which the cells are being pulled.

substructure cannot be compensated for, wound healing defects occur. For instance, when linear actin nucleators, like Diaphanous and Dishevelled-associated activator of morphogenesis (Daam), are removed, the intensity of the actin ring is reduced, causing premature ring disassembly and defects in tissue repair in Drosophila embryos [16]. In contrast, the removal of branched actomyosin with Arp2/3 RNAi is compensated for by a novel chiral swirling mechanism generated by parallel linear actin filaments [16] (Figure 1B). Removing branched actomyosin might make cells softer, allowing them to move more freely. As a result, a swirling mechanism is now able to generate enough force to move cells inward and close the wound, eliminating the need for a purse string.

Decreasing myosin II activity has been shown to decrease tissue tension in the *Drosophila* wing disc, allowing cells to intercalate more [7,17]. This increase in tissue fluidity, similar to the previously described swirling mechanism, reduces the need for a purse string and allows cells to intercalate away from the wound gap [7,17] (Figure 1C). This prevents cells from becoming tightly packed together, or "jammed". As cells intercalate away, the number of cells at the wound edge decreases, which reduces cell jamming at the wound edge, enabling a less strained and more favourable cell packing configuration [7]. Without intercalations, wound edge cells must elongate into a highly strained shape to pack into a multicellular

rosette structure when the gap is closed [18]. In developing tissues, it is vital to unjam the highly jammed rosette to allow cell and tissue movements required for morphogenesis and to restore normal cell patterning, critical for cell—cell communication.

An alternative non-actomyosin-driven mechanism of wound closure is the expansion of cells to 'plug' the wound gap with cellular material. Multinucleate syncytia, or swollen cells, are formed by fusing with neighbouring cells or by undergoing endoreplication [6,19—21] (Figure 1D). The size of polyploid cells is often proportional to the wound size [22]. Endoreplication allows cells to grow exponentially without dividing to replace lost tissue mass, whereas cell fusion maintains the mass and volume of the tissue whilst decreasing cell number. Using the *Drosophila* pupal epidermis, White et al. found that cells can fuse radially or tangentially to the wound (Figure 1D). Radial fusion accelerates closure by reducing the need for intercalation, often the slowest step of healing [7]. This fusion-induced reduction in cell number at the wound edge effectively reduces jamming at the wound edge as the purse string contracts, enabling faster closure. Tangential fusion, on the other hand, allows distal cells to quickly pool resources such as actin to the wound margin, enabling syncytia to move faster than smaller cells [20]. Autophagy is required for the formation of multinucleate syncytia in post-embryonic wound healing [23], but in embryonic *Drosophila* wounds, autophagy prevents cell swelling, which slowed wound repair [24]. Wound-induced polyploidy also has implications for tissue mechanics and homeostasis post-repair. This was demonstrated in the *Drosophila* abdomen where myosin II upregulation in polyploid cells increases epithelial tension to compensate for severed muscle fibres necessary for abdominal bending [6]. Other mechanisms may arise when the mechanical properties of the environment constrict movement. For instance, *Caenorhabditis elegans* have a collagen-rich cuticle encasing their epidermis and during wound repair, microtubule dynamics are required for actin ring recruitment [25].

The behaviours described in these studies have focussed on the apical plane. While this may be representative of flatter epithelia consisting of squamous or cuboidal cells, many tissues are curved or formed of taller columnar cells with complex morphologies [26,27], and therefore more complex mechanisms may be required for wound closure and to restore original tissue morphologies.

Two dimensional computational models

Many theoretical (computational) models have been used to test potential biophysical mechanisms of wound repair, offering valuable insights. So far, most theoretical models have simplified the problem to 2D, focussing on either the apical or the basal domain [28—34]. A common theoretical framework to model wounded epithelia is the vertex model, where cells are represented as polygons and their vertices move according to different energy contributions. These vertex models have been used to infer how the mechanical properties of wing disc cells change in response to small wounds [7,35]. Simulations have suggested that, depending on the initial geometry of the cells and the mechanical properties of the tissue, different mechanisms may emerge to seal the wound [7,35]. For example, if the tissue is more "fluid," cells can intercalate more easily and flow away from the wound, reducing the need for an actomyosin purse-string to a minimum, as others have suggested in the *Drosophila* embryo during dorsal closure [36]. However, if cells cannot easily remodel their junctions and intercalate, i.e., they are in a more "solid" state, then cell shape changes, such as cell elongations to form a multicellular rosette around the wound, might be more physically favourable.

Other biophysical models have been used to study tissue repair, such as Cellular Pots Models (CPM), where each cell is a subset of lattice regions moving within a bigger rectangular space depending on some set of defined rules. For instance, Hirway, Lemmon and Weinberg developed a hybrid cellular pots model (hCPM) to study cells undergoing epithelial-mesenchymal transition (EMT) during wound healing [29]. Interestingly, by coupling intracellular and extracellular signalling with migration and mechanical forces, they discovered that, even though EMT is initiated at the wound edge, it is propagated to neighbouring cells towards the tissue interior due to mechanical coupling. Overall, they suggested a tight coupling between mechanochemical signalling, the extracellular matrix (ECM), and EMT [29].

Three dimensional wound repair mechanisms

Although wound repair experiments and theoretical models have been simplified to 2D, cells, tissues, and wounds are inherently 3D structures. 3D cell shape is governed by surface tension. Surface tension, in turn, is controlled by cortical tension, cell—cell contacts, and cell-ECM contacts, which are all altered during tissue repair. Despite advances in 3D computational modelling, investigating 3D cell behaviours experimentally is technologically and computationally challenging, especially in *in vivo* multicellular crowded tissues. For example, in pseudostratified epithelia, nuclei are staggered across the apicobasal axis, and as a result, cells are scutoids [27]. In many epithelia, apical and basal cell surfaces can intercalate independently [37] (Figure 2A). Therefore, it may be incorrect to assume that the behaviour of the apical surface approximates that of the

Figure 2
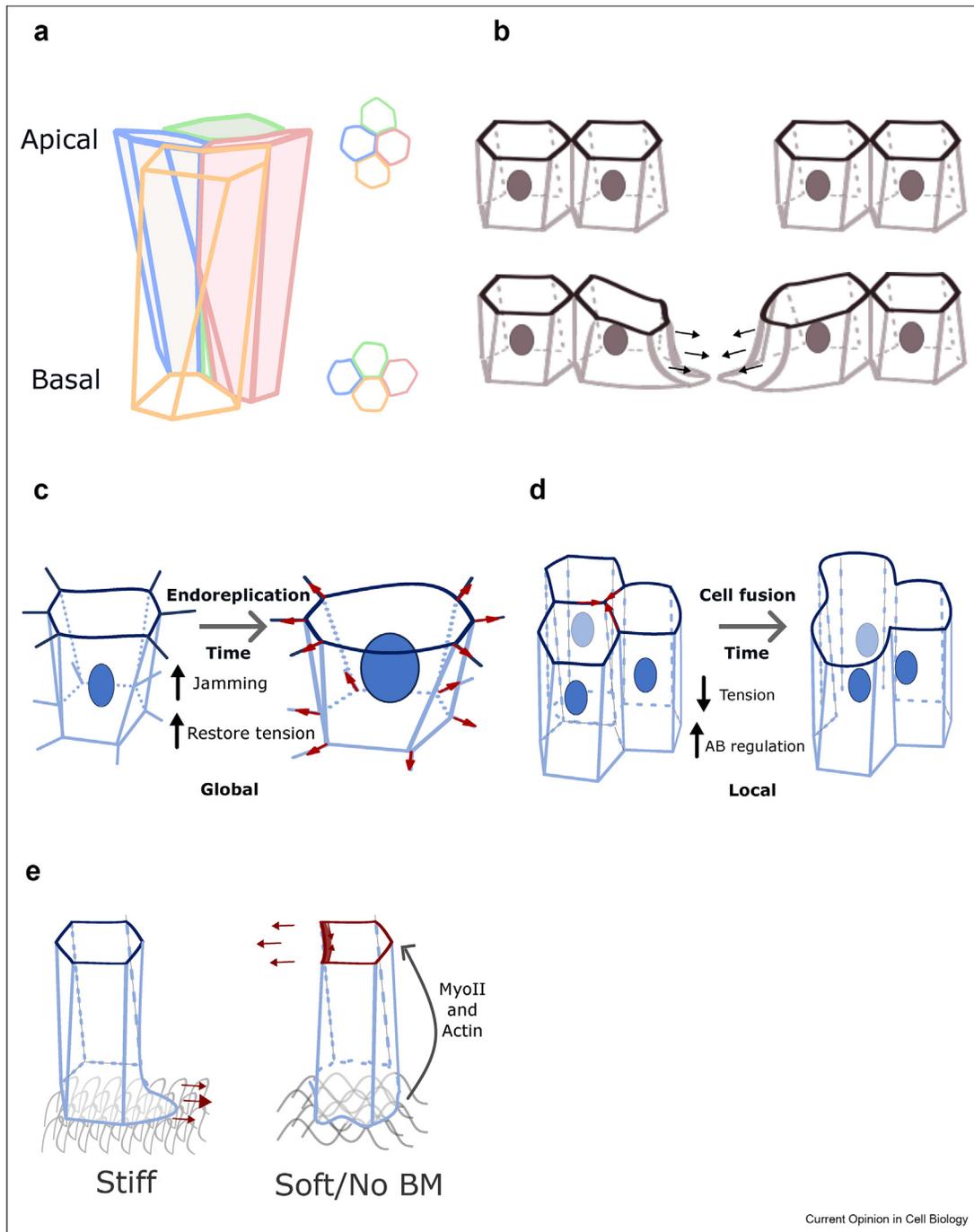
Physical mechanisms in three dimensions. **a)** 3D coordination between the apical and basal domain, emphasising the importance of considering apical and basal differences. Four cells with a scutoidal shape are displayed in red, blue, green, and yellow. Note that red and blue are neighbours apically, but not basally. **b)** Top: four cells with a gap or wound as the empty space. Bottom: Cells at the wound edge start to change shape to close the wound gap while maintaining their original cell volume. **c)** The left cell undergoes endoreplication, and the result is the cell on the right. The cell has grown in volume but not in height, increasing the jamming of tissue and restoring its global tensile state. **d)** Three cells fuse into one (left to right), resulting in a decrease in tension locally. It will also be energetically beneficial since apico-basal coordination is no longer required, nor are intercalations amongst these three cells. **e)** The cell (blue) on the left has a stiffer substrate (grey waves), which enables it to move as if it were on a solid surface. Cell on the right has a softer or no substrate, which prevents it to engage and move on the substrate. In turn, Myosin II and Actin can be recruited apically which allows the cell to create a contractile purse-string. Note that, overall, red arrows suggest the direction of the forces being applied. Grey arrows indicate time.

whole cell. Live imaging of these complex 3D tissues requires high spatial and temporal resolution, together with the time-intensive and often manual segmentation of multiple cells to extract 3D morphological quantifications. As such, little is known about the lateral and basal behaviours of cells during wound healing.

In limited *in vitro* cell culture studies where cells are relatively flat, myosin accumulations appear to move from the apicolateral membrane to the basolateral membrane, showing spatially distinct behaviours in 3D [38]. Xu et al. measure an approximately 40% decrease in monolayer height at the wound edge compared to the regular monolayer [8] (Figure 2B). This supports the hypothesis proposed by Ioannou et al. where cells must shorten to preserve their volume in their 3D model [4]. Combining cell shape changes with an increase in wound edge cell volume would increase the efficiency of healing as they 'fill up' the gap. If cells undergo endoreplication to increase their volume, global tissue tension would also likely change as surrounding cells become compressed to accommodate the growing cell (Figure 2C). Since endoreplication also triggers the upregulation of myosin II [6], it increases the contractile behaviour of the cell, providing a way to restore tension to its original state (Figure 2C). Alternatively, fusing with neighbouring cells dissipates tension at tricellular junctions by removing them where needed, thus reducing local tissue tension (Figure 2D). A single large cell may be more beneficial than the equivalent volume distributed across several smaller cells, as fewer junctions must be remodelled. Furthermore, the need to coordinate the movement of multiple apical and basal surfaces is eliminated as several cell faces are reduced to only one (Figure 2D). Overall, these mechanisms change the tissue tension either locally or globally as needed, which will vary according to its stage in development or homeostatic function [7,19,39].

Three dimensional computational models

To quantitatively study the coordination of complex 3D cell shape changes in driving tissue morphogenesis and the physical benefits of, for example, cell fusion for tissue repair, we must develop 3D models of wound repair [40]. Ioannou et al. highlighted the importance of cell shape changes not only on the apical side but also in 3D for wound closure [4]. They developed a 3D vertex model to analyse the mechanical forces during tissue repair in the *Drosophila* imaginal wing disc. Remarkably, they predicted that cells at the wound edge should change height if their volume must be preserved. Considering that the apical and basal domains have different mechanical forces, where the apical forces dominate, tilted cells appear at the wound edge. Tilted cells have been linked to a greater number of intercalations [26] which could explain the onset of intercalations measured by Tetley et al. towards the end of wound healing [7].

Recently, the field has been shifting towards understanding the role of cell substrates (modelled as the basement membrane or ECM) during gap closure [41,42]. Of particular interest is Bai and Zeng's work, where they developed a finite element model with an epithelial monolayer sheet and a thicker layer of ECM substrate. They predicted that wound closure efficiency correlates to lamellipodia protrusion strength [41]. Altogether, these models show an increasing importance in the role of cell geometry, wound geometry, and the surrounding substrate in regulating wound closure mechanisms.

The basement membrane

An important component affecting 3D tissue morphology is its underlying substrate, the extracellular matrix (ECM), known as the basement membrane (BM) in epithelial tissues [43,44]. The role of ECM mechanical properties such as stiffness and alignment is well established in cell migration [43]. Substrate stiffness can provide feedback on the cell's mechanical state, with Sonam et al. finding that Madin-Darby Canine kidney (MDCK) monolayers switch from compressive stress on stiff substrates to highly tensile on soft substrates [45]. Similarly, Ajeti et al. found that on stiff substrates, monolayer elasticity increases and lamellipodia-driven wound closure is favoured, whilst on softer substrates, monolayer elasticity decreases and the purse-string mechanism is favoured instead [32]. The rate of wound closure seems to be independent of substrate rigidity [32]. This choice in strategy may be explained by the localisation of actin machinery dependent on the substrate stiffness. On a stiff substrate, the cell is able to attach to the substrate, allowing lamellipodia to stably form, but on soft or completely damaged substrates, it would be harder for the cells to attach. Instead, actin concentrates on the apical surface of the cell to generate tension by forming cables (Figure 2E).

The exact role of the BM during *in vivo* wound repair will depend on whether the BM is itself damaged or not during wounding. To date, relatively little *in vivo* work has explicitly addressed this; however, if one likens *in vitro* findings of cell migration on soft substrates to damaged BM scenarios, one may be able to extend *in vitro* mechanisms into *in vivo* settings. For example, similar to the above MDCK studies, Kamran et al. found that removing BM from *Clytia hemisphaerica* wounds causes a rapid switch from lamellipodia-dependent cell crawling to purse string-mediated closure [10,14], reinforcing the idea of the BM as a key participant in the mechanical environment and in defining wound closure mechanisms. Although the role of the BM on 3D cell shape during tissue morphogenesis is clear, little is known during wound healing [44], although there is clear evidence of crosstalk and transmission of forces between the ECM and epithelia during repair [46]. Ly

et al. recently found that the cell-matrix protein Talin is polarised at wound edge cells in *Drosophila* embryos. When Integrin was knocked down, E-cadherin at tricellular junctions and the actin purse string were reduced [47]. During mouse neural tube closure, there is also an integrin-mediated zippering mechanism driving closure, in addition to actomyosin purse-string and cell crawling [48]. However, little work has focussed on the role of the cell-BM adhesions and the BM itself in the modulation of 3D cell shape during wound healing in *in vivo* tissues.

Conclusions and future perspectives

It is evident from tissue morphogenesis that it is important to consider the 3D geometry of cells; tissue repair is no exception. Understanding how the apical, lateral, and basal domains of cells interact together with their surrounding micro-environment is key to having a complete picture of the mechanical landscape of tissue repair. Even revisiting previously described wound healing mechanisms in 3D will yield new insights with the latest developments in microscopy. To overcome the bottleneck of image analysis, advances in artificial intelligence and segmentation are needed [49,50].

It is also important to consider how we define a perfectly healed system. Is the 'simple' restoration of size, shape, and cell types sufficient? Or should we also assess the function, such as the ability to withstand the same mechanical load? Clearly, it is important to repair without a scar, to stop inflammation, and to prevent 'over-healing'. All of this requires consideration of the microenvironment, with the BM being the immediate non-cellular structure surrounding epithelia. BM defects in wound repair may have wider disease implications, such as in epithelial polarity, EMT, cancer progression, and fibrosis [51]. A deeper understanding of the role of the basement membrane, as well as how this is coordinated with 3D cell dynamics, will be essential for a complete understanding of efficient and accurate wound repair.

Author contributions

S.E.L., P.V.M., and Y.M. conceptualised the content together; S.E.L. and P.V.M. wrote the first draft; S.E.L., P.V.M., and Y.M. reviewed and edited the text.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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