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Review

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Cell proliferation and differentiation during epidermis renewal

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Abstract: Residing at the outermost layer of the skin, the epidermis is composed of stratified squamous epithelial cells. Regular renewal of the epidermis is essential for maintaining its barrier function, which is dependent on the orchestrated proliferation and differentiation of stem cells located in the basal epidermis. This process necessitates precise dual regulation through the intrinsic control of cell division orientation and external microenvironmental influences. In this comprehensive review, we delve into the critical processes underlying epidermis renewal, emphasizing the balance between symmetric and asymmetric cell fate and the integration of differentiated cells into the suprabasal layer. Our paper highlights the pivotal roles of single-cell omics, live imaging and artificial intelligence (AI)-driven modeling techniques in elucidating the molecular mechanisms governing cell proliferation and differentiation during epidermis renewal.

Key words: Epidermis renewal; Stem cell proliferation; Asymmetric cell division; Basement membrane dynamics; Single-cell omics; Mechanotransduction

1 Introduction

The outermost layer of the skin is primarily composed of the interfollicular epidermis, which is the stratified epithelium located between pilosebaceous units (Banjac et al., 2023). The epidermis serves as a crucial interface, establishing a formidable barrier that separates the internal milieu of the body from the external environment and protects organisms from dehydration, physical trauma, chemical erosion, and pathogen invasion (Feng et al., 2024; Schmuth et al., 2024). To comprehend the barrier function of the epidermis, it is essential to understand how it evolves from its initial state during development to its mature form. The epidermis initially develops from a monolayer of epithelial cells originating from the ectoderm (Smart, 1970). During embryonic and postnatal development, stem cells produce two equally proliferative daughter cells through symmetric division to accommodate growth, a process that continues throughout life with a decreasing proliferation rate after birth (Dekoninck et al., 2020). Around embryonic day (E) 9.5, upon induction by p63, progenitor cells begin to downregulate the expression of keratin-8 (K8) and upregulate the expression of K5 and K14 (Koster and Roop, 2004), giving rise to two cells with different fates by asymmetric division perpendicular to the basement membrane, one of which is committed to differentiation. The process of differentiation is irreversible and gradually leads to the formation of the stratum spinosum, stratum granulosum and stratum

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corneum, establishing the epidermal barrier with tighter cell connections to withstand post-embryonic environmental conditions (Hardman et al., 1998).

In the human epidermis, it typically takes 14 to 18 days for a newly produced cell to transition into a cornified cell (Christophers and Laurence, 1976). This cycle of cell renewal is primarily controlled by stem cells located in the basal epidermis. However, in adulthood, most progenitor cells produce offspring through asymmetric division, half of which preserve the progenitor's proliferative potential while the other half, regulated by internal and external environmental factors, are committed to differentiation (Gola and Fuchs, 2021; Bansaccal et al., 2023; Eyermann et al., 2024; Roig-Rosello et al., 2024). The traditional view is that fast-cycling progenitor cells originate from slow-cycling stem cells in the epidermis (Mascre et al., 2012). However, recent studies have proposed an alternative perspective, suggesting that there are two independent cell populations with different cell cycle kinetics, both of which containing stem cells (Sada et al., 2016). In either case, this process of differentiation is irreversible as cells gradually migrate upward and replace shed stratum corneum cells, thereby maintaining the barrier function of the skin (Rompolas et al., 2016).

The disruption of balance between proliferation and differentiation can result in structural damage to the epidermis and the formation of tumors (Blanpain and Simons, 2013). A fundamental aspect of skin homeostasis is understanding how basal stem cells achieve dynamic equilibrium between symmetric divisions for proliferation and asymmetric divisions for differentiation. The mechanisms by which stem cell pools remain stable and how daughter cells differentiate to replace shed cells are critical but not fully understood aspects of epidermis renewal.

2 Development and structure of the epidermis

The stratified epidermis of the skin is derived from the monolayer epithelium that surrounds the embryonic ectoderm (Matsui, 2023; Holthaus and Eckhart, 2024). Prior to the establishment of a fully functional barrier, a transitional structure called periderm is formed. A subset of cuboidal ectodermal cells expresses keratin-17, they detach from the basement membrane, and migrate over the basal layer to form a temporary barrier structure (Visscher et al., 2022; Jacob et al., 2023). Unlike the human single layer periderm, the mouse periderm consists of two layers, an outer layer that is presumed to be absorptive and an inner layer packed with specific granules. The periderm disintegrates due to loss of contact with terminally-differentiated keratinocytes and is replaced by stratified epithelium (Panteleyev, 2022). At around E8.5, p63 expression initiates the process of epidermal stratification. During this phase, progenitor cells undergo the downregulation of simple keratin intermediate filaments such as K8 and begin to express early differentiation markers K5 and K14 (Koster and Roop, 2004; Baba et al., 2020). At E13.5, epidermal stratification initiates with the emergence of intermediate cells expressing K1/K10. During this phase, robust proliferative activity is observed, and mitotic cells are detectable even within suprabasal layers. At E15.5, a fully differentiated stratum spinosum is established (Fuchs and Green, 1980; Liu et al., 2013; Damen et al., 2021). As epidermal development progresses, spinous cells undergo differentiation to become granular cells that express loricrin and pro-filaggrin at E16.5 (Mehrel et al., 1990; Joost et al., 2016). Ultimately, the formation of a rigid scaffold through the cross-linking of proteins and the covalent attachment of lipids on their outer surface results in the development of the cornified cell envelope, thereby establishing the barrier function of the skin at E18.5 (Liu, et al., 2013; Rinnerthaler et al., 2015). Prior to birth, a fully developed epidermis comprising the stratum basale, stratum spinosum, stratum granulosum and stratum corneum has already been established (Yin et al., 2023) (Fig. 1). Notably, the current stratification method of epidermal layers primarily relies on intermediate filament protein profiling. However, under specific pathological conditions, particularly in cases of abnormal cellular thickening, it remains challenging to discern whether this phenomenon results from the hyperproliferation of basal cells that mechanically displace a subset of cells into the suprabasal compartment, or microenvironmental alterations in the suprabasal niche enable vertically-divided daughter cells (presumably destined for differentiation) to retain partial basal progenitor

properties, and evidenced by persistent K5/K14 immunoreactivity. This diagnostic ambiguity necessitates the integration of complementary detection modalities to accurately characterize aberrant cell populations. Such multidimensional analysis could significantly enhance diagnostic specificity and therapeutic targeting in epidermal pathologies.

3 Contribution of the basement membrane to epidermis renewal

The basement membrane is a highly organized extracellular matrix network located at the epithelial-mesenchymal interface of tissue. It comprises two independent networks of polymerized laminin and cross-linked collagens (Piperigkou et al., 2018), providing structural support for cells and influencing their fate (Bergman et al., 1992; Koster and Roop, 2007). Between the epidermis and dermis, the basement membrane provides adhesion and controls cell fate via integrin-mediated focal adhesions and hemidesmosomes (Rousselle et al., 2022). The integrin- and laminin-dependent contact on the basement membrane during cell division appears to contribute to polarity formation and influence the proliferation/differentiation decisions of basal keratinocytes (Haake et al., 2024; Villeneuve et al., 2024). Integrins are thought to crosstalk with receptors such as EGFR, triggering the signaling cascade of mitogen-activated protein kinase, janus kinase/signal transducer and activator of transcription and phosphatidylinositol-3 kinase, which in turn promote the maintenance of the stem cell population in basal cells (Simpson et al., 2011; Te Molder et al., 2021; Arnaud et al., 2023). With aging, the loss of hemidesmosomes on the basement membrane triggers mechanical signals that alter its structure and reduce the anchoring of basal keratinocytes, one of the main reasons that ultimately forces them to differentiate (Khalilgharibi and Mao, 2021; Roig-Rosello, et al., 2024). The basement membrane contains a variety of growth factors, morphogens, and other regulatory macromolecules that play a role in orchestrating the various processes necessary for the proper functioning of keratinocytes (Pozzi et al., 2017; Randles et al., 2017). Additionally, as the epidermis extends into the dermis and embeds between dermal papillae, the unique structure of the basement membrane reinforces connectivity between the dermis and epidermis, imposing mechanical constraints on keratinocytes that may affect their fate (Lawlor and Kaur, 2015) (Fig. 2).

The basement membrane, functioning as both a biomechanical scaffold that preserves tissue architecture and transduces essential mechanotransduction cues, simultaneously orchestrates stem cell differentiation and maintains tissue-specific progenitor niches through the spatial presentation of growth factors (e.g., FGFs, TGF-β). This dual regulatory network endows the basement membrane with spatiotemporal regulatory precision, enabling robust defense against homeostatic imbalances caused by extrinsic environmental perturbations or intrinsic cellular dysregulation. Advances in understanding the composition of basement membrane and its roles in epidermis renewal are driving innovations in wound healing and disease treatment. In recent years, several studies in this field have been conducted. For example, the topical application of recombinant type VII collagen promoted wound healing (Wang et al., 2013); the development of decellularized matrix-based bioinks incorporating basement membrane components (collagen IV, laminin) enhanced artificial skin mechanics and cytocompatibility (Kim et al., 2020); base-editing technologies correcting basement membrane-associated genes in progeria models recovered regenerative capacity (Koblan et al., 2021), etc. However, epidermis renewal involves complex basement membrane dynamics that serve not only as a physical scaffold but as an information processor directing stem cell fate. While tissue engineering has progressed from component replication to dynamic biomimicry, cross-scale regulation (molecular-cellular-tissue) remains a challenging task. Programmable basement membrane reconstruction will be enabled by the future integration of synthetic biology, single-cell mechanophenotyping (e.g., atomic force microscopy), and AI-driven scaffold design.

4 Cell division during epidermis renewal

The skin epidermis generates approximately 10^7 new cells every day to replace continuously shed stratum corneum cells (Sender and Milo, 2021). The core of maintaining a stem cell pool lies in balancing self-renewal and differentiation to generate a sufficient number of specialized cells to execute basic tissue functions. To accommodate rapid growth during embryonic development, epidermal basal cells need to undergo symmetric divisions to generate a large number of daughter cells with equivalent proliferative potential. Even from E13.5 to E15.5, suprabasal layer cells can proliferate symmetrically to expand the cell population (Damen, et al., 2021). From this point onward, certain cells are stimulated by signals to undergo asymmetric divisions in order to produce differentiated cells (Lechler and Fuchs, 2005; Williams et al., 2011)(Lechler and Fuchs, 2005; Williams, et al., 2011). There is also evidence indicating that some basal cells participate in epidermis renewal by directly delaminating from the basement membrane rather than undergoing division (Damen, et al., 2021). Upon reaching adulthood, it is no longer necessary for the epidermis to have a rapid proliferation rate but instead it transitions toward a balance that maintains the number of cells with proliferative potential and those destined for differentiation (Morrison and Kimble, 2006; Gola and Fuchs, 2021). Cell division plays a critical role in determining the fate of hair follicle and interfollicle epidermal stem cells (Niessen et al., 2013), as well as in regulating hair follicle formation and epidermis hyperproliferation (Ouspenskaia et al., 2016; Seldin et al., 2016). The pattern of cell division is closely associated with the orientation of the mitotic spindle apparatus (Bergstralh et al., 2017; Seldin and Macara, 2017). It is important to note that "oriented cell division" does not necessarily mean "asymmetric" or "symmetric" cell division, with the former referring to the alignment of directions along a particular axis during division, and the latter referring to whether the distribution of materials within the cell and the fate of the daughter cells are equal (Williams and Fuchs, 2013). Even when cells divide symmetrically, the daughter cells may have different fates under different environmental stimuli. In the epidermis, cell divisions oriented perpendicular to the basement membrane typically result in asymmetric cell fate allocation under homeostatic conditions. This outcome is determined by both the heterogeneous distribution of intrinsic signaling molecules between daughter cells and the biomechanical heterogeneity of the microenvironment, as discussed in detail below. Epidermal stem cells and progenitors regulate their number and stemness during homeostasis in two main ways: 1) In wound healing, most daughter cells from symmetrical divisions parallel to the basal membrane still maintain their proliferation ability due to basement membrane contact, increasing the stem cell pool; 2) During normal renewal, one daughter cell from asymmetric divisions perpendicular to the basal membrane remains adherent, maintaining stem cell numbers. There is a "self-renewal checkpoint" that restricts the self-renewal of stem cells in response to genotoxic stress (Matsumura et al., 2016). It has been shown that stress-induced collagen type XVII alpha 1 Chain (COL17A1) proteolysis plays a role in mediating the checkpoint function of stem cells, leading to the natural selection of eligible stem cells for organ homeostasis over their lifespan (Liu et al., 2019). Furthermore, self-renewal can also be promoted by neighboring differentiation events (Mesa et al., 2018). Aberrant proliferation kinetics in basal layer cells, such as excessive mitotic activity may lead to pathological hyperplasia or carcinogenesis, while insufficient proliferation could compromise epidermal barrier integrity. Maintaining this homeostatic equilibrium requires a sophisticated regulatory network, the elucidation of which holds critical implications for understanding disease pathogenesis and developing therapeutic interventions.

5 Spindle orientation during cell division

In the basal epidermis, approximately 60%-80% of the cells undergo asymmetric division to produce one basal cell and one differentiated cell (Rompolas, et al., 2016). The polarity of asymmetric division in epidermal basal cells is determined by both external and internal factors. External factors such as β1, β4 integrins, and the β1-integrin-binding protein kindlin-1 on the basement membrane play significant roles in cell division

polarity (Weaver et al., 2002; Ussar et al., 2006). The intrinsic molecular mechanism of asymmetric division has been highly conserved during evolution (Betschinger and Knoblich, 2004). It has been observed that the basal cells do not establish a division axis before mitosis, and the spindles are randomly distributed even in the prophase until the direction of division is finally determined by the movement of centrosomes in the prometaphase and late metaphase (Poulson and Lechler, 2010). Spindle orientation involves two steps mediated by the apical polarity complex and the spindle position complex. During junctional maturation, Merlin associates directly with α-catenin and links it to Par3, thereby providing an essential link between the adhesion junction and Par3. It is also possible that Par3 localizes to the apical cortex in the same way as it does during asymmetric division (Gladden et al., 2010). The apical polarity complex composed of Par3, atypical protein kinase C (aPKC) and partitioning-defective 6 (Par6) locates on the cortical crescents, and then recruits the Leu-Gly-Asn repeat-enriched protein (LGN)–Gα(i)–nuclear mitotic apparatus protein (NuMA)–dynein–dynactin complex to the apical cortex through Insc (Poulson and Lechler, 2010; Williams, et al., 2011; Niessen, et al., 2013; Ali et al., 2016; Seldin, et al., 2016; Ma et al., 2022; Yan et al., 2022). CDC42 may also play a role in this process (Prado-Mantilla and Lechler, 2023). In Drosophila, neuroblasts lacking Insc fail to properly orient their spindle position complex. Conversely, in the neuroectoderm, the overexpression of Insc can reorient the spindle (Kraut et al., 1996), demonstrating that Insc is both necessary and sufficient for the initiation of asymmetric division. This notion is further supported by the upregulation of Insc at E13.5 coinciding with the stratification of the epidermis (Poulson and Lechler, 2010). During mitosis, Insc assists in recruiting LGN to the cell cortex through GPI-linked Gα(i), which binds LGN C-terminal GoLoco motifs. The stability of this complex structure is enhanced when all three components are present (Williams, et al., 2011). Recent structural studies on LGN indicate its inability to bind both Insc and NuMA simultaneously, with a higher affinity for Insc than NuMA (Zhu et al., 2011). This discovery is consistent with the model proposing that Par3-Insc and Gαi3 facilitate the apical recruitment of LGN during early mitosis, thereby promoting its transfer to NuMA. LGN-NuMA plays a crucial role in redirecting the mitotic spindle (Williams et al., 2014), and a variety of proteins collaborate to finalize the process of mitosis (Zhong et al., 2022; Yang et al., 2023; Yu et al., 2023) (Fig. 3). Interestingly, in K14-Cre^{+}, Sas-4$^{f/f}$ and p53$^{f/f}$ conditional double-knockout mice, the proliferation and differentiation of progenitor cells in the late epidermal development stage are not coordinated with the direction of division. This suggests that, aside from spindle orientation, there may be other mechanisms regulating cell differentiation at this stage (Damen, et al., 2021). Stimulated by internal and external signals, cells begin to differentiate and replace the shed cells through asymmetric division.

Despite that our knowledge of cell division in the epidermis has significantly improved in recent years, the mechanisms by which cells determine their specific division orientation with spatiotemporal precision remain unclear. Elucidating the molecular basis of this process holds significant value in understanding epidermal development and homeostasis maintenance. As mentioned above, a critical question persists: whether the basement membrane dictates stem cell division patterns by mechanical signaling changes that subsequently influence daughter cell fate, or stem cells sense the local cellular density and autonomously regulate their division orientation and utilize the basement membrane to determine progeny cell destiny. Determining which component plays the predominant regulatory role in this process, or whether it results from coordinated interactions between both elements, crucially requires clarifying the underlying molecular mechanisms; resolving these questions can substantially improve our comprehension of epithelial tissue dynamics.

6 Cellular lineage and cell differentiation commitment

The epidermis at different locations may exhibit distinct patterns of cell lineages. Classical models of adult epidermal homeostasis suggest that cells with infrequent division are long-lived stem cells (SCs) that give rise to rapidly dividing short-lived progenitor cells (Clayton et al., 2007; Sada and Tumbar, 2013). Consistent with this model, the adult mouse skin epidermis has two types of cells with proliferative potential: slow-cycling stem cells and more rapidly cycling committed progenitor cells, each performing different functions during homeostasis and interfollicular epidermis repair (Shin and Peterson, 2013; Aragona et al., 2020; Lotti et al., 2022). The basal layer of the mouse ear and paw epidermis comprises of a single equipotent stem cell population, where daughter cells are generated with either independent fate in the ear or positively correlated fate in the paw,

indicating non-hierarchical or asymmetric division (Rompolas, et al., 2016). However, in the mouse tail epidermis, these two populations, identified by the two markers of distal-less homeobox 1 (Dlx1) and solute carrier family 1 member 3 (Slc1a3), respectively, inhabit distinct territories and exhibit different rates of proliferation and upward cellular transport (Sada, et al., 2016). Another study indicated that, in the mouse tail epidermis, cells of the basal layer house a distinct slow-cycling epidermal stem cell population distinguished by thymocyte cell surface antigen 1 (Thy1) expression, which coexists with transient amplifying progenitors (Koren et al., 2022). This dual population theory appears to be more appropriate than the single stem cell theory for explaining the differential proliferation rate within the scale and interscale during adult mouse tail epidermis homeostasis (Dekoninck, et al., 2020).

Although epidermal stem cells display regional heterogeneity in molecular signatures and subpopulation compositions across anatomical sites, their progeny differentiation processes often share common features. Cell fate asymmetry originates from mitotic polarity establishment in the mother cell during cytokinesis, driving the asymmetric segregation of fate-specifying signaling complexes between daughter cells. Daughter cells containing EGFR exhibit increased cycling activity (74), and overexpression of EGFR in the basal layer contributes to epidermal hyperproliferation and delays differentiation (38). In contrast, Notch signaling has an opposing function to that of EGFR. Notch acts to repress proliferation and induce terminal differentiation (75). EGFR overrides Notch at the basal layer, inhibiting Notch activity. In the suprabasal layer where EGFR is absent, Notch promotes differentiation (76) (Fig. 3). Nevertheless, once daughter cells commit to differentiation from stem cells or progenitor cells, there is a general consensus on the model for how cells migrate from the basal layer of the epidermis to the outermost layer. The epidermal differentiation unit, a three-dimensional organization of columns modified by the epidermal proliferation unit (Ghazizadeh and Taichman, 2001), is defined by the perimeter of the most external terminally differentiated cells. Approximately 90% of the cells in the unit align into a vertical column and move upward to recycle the same space occupied by preceding cells, while a minority of cells inhabiting the basal and spinous layers can switch to neighboring EDUs. Additionally, the inhibition of Wnt signaling promotes differentiation in interfollicular epidermis and sebaceous gland lineages (77). When cells arrive in the granular layer, their fate becomes vertically fixed. Following departure from the basal layer, the granular layer serves as a buffer zone, spatially coordinating the transition to cornified tissue (Rompolas, et al., 2016) (Fig. 4).

The evolution of epidermis renewal models – from the classical unipotent stem-progenitor paradigm to the recently proposed dual stem cell paradigm – has significantly advanced our understanding of epidermal homeostasis. However, this progression raises the critical questions of (1) whether there exists a definitive demarcation between stem and progenitor cells, and whether distinct biomarkers or functional criteria could reliably discriminate these populations; (2) beyond the tail epidermis demonstrating dual stem cell populations, whether other regions harbor heterogeneous stem cell subpopulations whose identification has been hindered by technical limitations in single-cell omics resolution; (3) given the murine tail's developmental expansion requiring orthogonal growth axes maintained by discrete stem cell subsets, whether analogous functional heterogeneity emerges during human morphogenesis to coordinate differential growth rates across body regions. These considerations suggest an intriguing research frontier in developmental biology.

7 Conclusions

The skin's ability to maintain structural integrity through continuous epidermis renewal involves complex interactions between basal stem cells, microenvironmental cues, and molecular signaling networks. While recent advances have elucidated mechanisms governing stem cell division patterns and basement membrane dynamics, key questions remain regarding the spatiotemporal regulation of cellular heterogeneity and fate determination. Future research should prioritize mapping functional stem cell subpopulations across anatomical regions using spatial multi-omics, particularly the investigation of how mechanical forces and matrix remodeling influence division axis orientation during aging or injury. Concurrently, deciphering feedback mechanisms that adjust symmetric/asymmetric division ratios via mechanosensitive pathways (e.g., integrin-EGFR crosstalk) could revolutionize therapeutic strategies. Clinically, these insights enable the application of targeted approaches: modulating Notch signaling for psoriatic hyperplasia, bioengineering laminin-rich scaffolds for chronic wounds, or preserving COL17A1-mediated stem cell competition in aging

skin. Technological integration proves that live imaging of 3D organoids by AI modeling can predict division outcomes under varying biomechanical stresses, while base editing offers the precision correction of basement membrane gene defects. Emerging synthetic matrices with tunable stiffness gradients may recreate niche-specific signals for *in vitro* epidermal expansion. Ultimately, converging single-cell resolution datasets with dynamic microenvironmental profiling will be able to unravel the four-dimensional control of epidermal homeostasis, bridging molecular mechanisms with clinical translation. This systems-level understanding promises to transform regenerative dermatology through personalized interventions that restore tissue architecture in genetic disorders, chronic ulcers and degenerative conditions, while informing broader paradigms of epithelial tissue engineering.

Data availability statement

All data generated or analyzed in this study are available from the corresponding author upon reasonable request.

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Author contributions

Kai LIU and Dengwen LI conceptualized and wrote the manuscript and created the figures. Kai LIU, Kaidi REN, and Yang YANG contributed to the writing of the manuscript. Dengwen LI reviewed and modified the manuscript. All authors approved the final version of the manuscript..

Conflict of interest statement

All authors disclosed no relevant relationships.

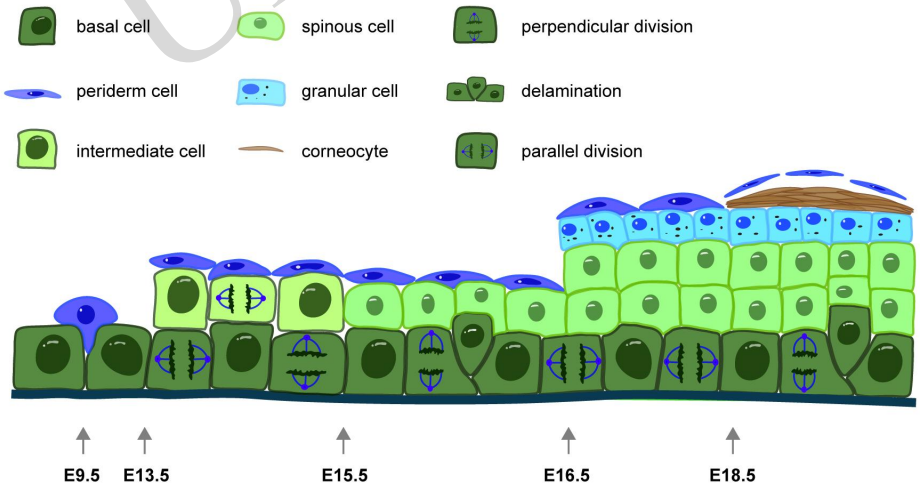

Fig. 1 Development and structure of the epidermis

At E9.5, the periderm cells detach from the basement membrane to form a temporary barrier structure, and are eventually shed alongside terminally differentiated corneocytes. By E13.5, a subset of basal progenitor cells undergoes planar-to-apical division reorientation, initiating terminal differentiation programs that drive the emergence of K1/K10-positive intermediate cells within suprabasal compartments. The formation of the stratum spinosum occurs at E15.5, followed by the stratum granulosum at E16.5, and finally the stratum corneum at E18.5.

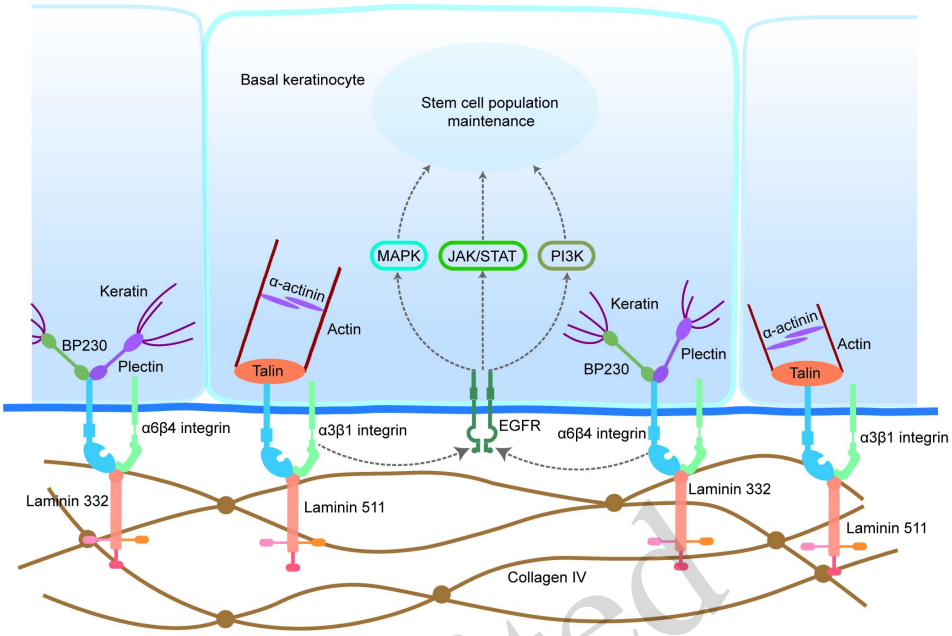

Fig. 2 Contribution of the basement membrane to epidermis renewal

The basement membrane (BM) is a highly organized extracellular matrix network located at the epithelial-mesenchymal interface of tissue, which comprises two independent networks of polymerized laminins and cross-linked collagens. Hemidesmosomes connect to the basement membrane through α6β4 integrins and bullous pemphigoid antigen (BP)180, and are tethered to intermediate filaments by plectin and BP230. Focal adhesions are mediated through the interaction between integrin α3β1 and LM-511, and are linked to the actin cytoskeleton through Talin and Kindlin. Integrins are thought to crosstalk with receptors such as epidermal growth factor receptor (EGFR) to induce proliferation of cells via the signaling cascade of mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K). As cells undergo stratification, the decreased density of integrins allows for differentiation.

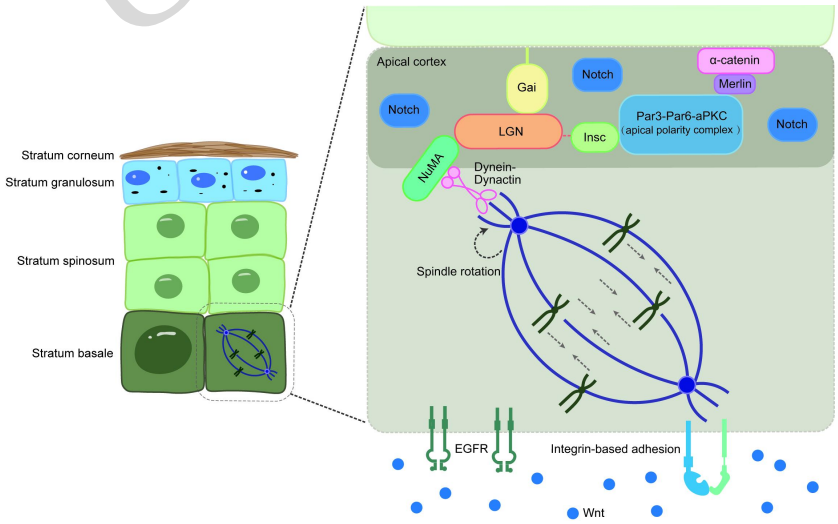

Fig. 3 Spindle orientation and cell differentiation commitment

During prometaphase, the apical polarity complex composed of aPKC, Par3 and Par6 localizes on the cortical crescents. This may be facilitated by the interaction of this complex with α-catenin via Merlin. Subsequently, the apical complex recruits the LGN–Gα(i)–NuMA–dynein–dynactin complex to the apical cortex, leading to spindle rotation. The β1, β4 integrins and β1-integrin-binding protein kindlin-1 located on the basement membrane also play a vital role in establishing and maintaining cell division polarity. After the establishment of cell division polarity, certain signaling molecules such as Notch and EGFR become asymmetrically distributed, thereby determining the fate of daughter cells.

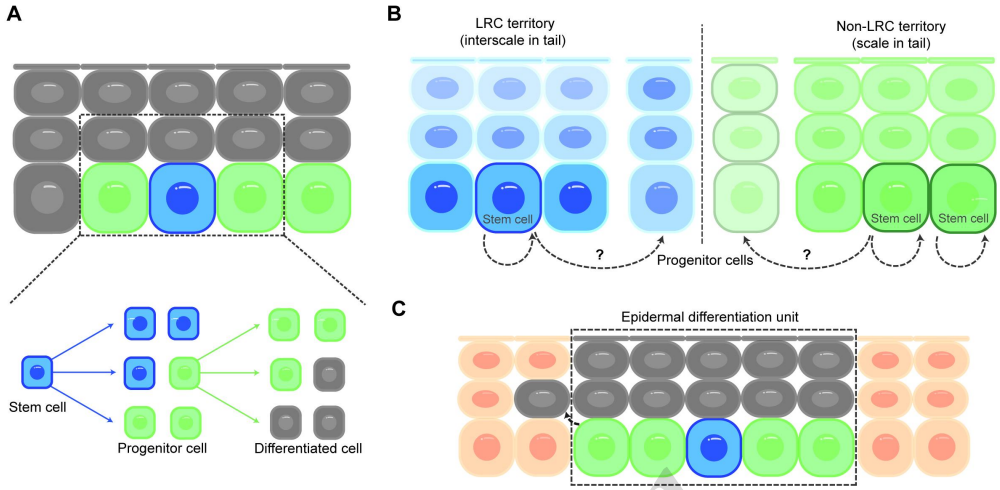

Fig. 4 Cellular lineage and cell differentiation commitment

A. The cellular lineage hierarchy consists of long-lived stem cells that give rise to short-lived progenitors, which in turn generate differentiated cells via asymmetric division. B. Utilizing the H2B–GFP pulse-chase system, two territories (LCR and Non-LCR) have been identified in the mouse tail epidermis. These territories are composed of distinct stem cells exhibiting different patterns of proliferation, differentiation and upward cellular transport. It is currently unknown whether these stem cells have the capacity to give rise to progenitor cells. C. Basal stem cells stochastically commit to differentiation and transition through the suprabasal layers predominantly via existing epidermal differentiation units. A small percentage of cells switch to another unit to complete this process.

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