Epidermal Polarity Genes in Health and Disease

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The epidermis of the skin is a highly polarized, metabolic tissue with important innate immune functions. The polarity of the epidermis is, for example, reflected in controlled changes in cell shape that accompany differentiation, oriented cell division, and the planar orientation of hair follicles and cilia. The establishment and maintenance of polarity is organized by a diverse set of polarity proteins that include transmembrane adhesion proteins, cytoskeletal scaffold proteins, and kinases. Although polarity proteins have been extensively studied in cell culture and in vivo in simple epithelia of lower organisms, their role in mammalian tissue biology is only slowly evolving. This article will address the importance of polarizing processes and their molecular regulators in epidermal morphogenesis and homeostasis and discuss how alterations in polarity may contribute to skin disease.

Polarity is a fundamental property of cells and tissues that results from the differential distribution of cellular components (proteins, lipids, RNA, organelles) to promote asymmetry in form and/or function. This is important in a range of physiologically relevant processes such as oriented cell division, directed migration, barrier function, and recognition and adhesion of cells. In general, polarity can be achieved at the cellular level, known as cell polarity, or at the tissue level, known as tissue polarity or planar cell polarity. Perhaps the best-characterized example for cell polarity is epithelial polarity, in which simple epithelia such as the intestine establish two different membrane domains, the apical and basolateral domain (Roignot et al. 2013). This apicobasolateral polarity is important for barrier function, vectorial transport, and sensory and signal perception. In

tissue polarity, cells or structures within cells orient in the plane of the tissue. This coordination of cell polarity in a tissue is crucial for proper tissue formation and function and regulates, for example, intercalation/convergence extension movements essential to shape the different body axes during development, the positioning of motile and sensory cilia as well as the polarization of the developing epidermis and hair follicles (Wang et al. 2006; Devenport et al. 2011; Wallingford 2012).

The most outer layer of the skin, the epidermis, is a multilayered stratifying epithelium and does not display the characteristic features of simple epithelial apicobasolateral polarity. The epidermis consists of the interfollicular epidermis (IFE) and epidermal appendages: hair follicles, sebaceous glands, and sweat glands. The continuous self-renewal of this tissue is driven

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F. Tellkamp et al.

by the existence of different stem and progenitor populations located in the basal layer of the IFE and in different locations in the hair follicle (Blanpain and Fuchs 2009; Watt and Jensen 2009). After exiting the cell cycle, basal keratinocytes undergo a terminal differentiation program to either form the stratum corneum, a dead, cornified, and water impermeable cell layer (Candi et al. 2005; Koster 2009), or another keratinized structure, the hair.

Many features within the epidermis are polarized (Fig. 1A) and, more importantly, this polarization is crucial for the formation and maintenance of the IFE and its appendages. For example, during stratification keratinocytes differentiate and undergo controlled cell shape changes until they reach the stratum corneum. This process requires intercellular rearrangements to allow cells to migrate through the layers. Another example is oriented cell division of basal cells in the IFE and in hair follicles. By orienting the mitotic spindle either parallel or perpendicular with respect to the underlying basement or hair follicle axis, stem and progenitor cells can control cell fate and differentiation while guaranteeing renewal. Wound closure is a highly polarized process that requires the coordinated secretion and deposition of the extracellular matrix to allow for directional migration of keratinocytes (Fig. 1B). Cilia are positioned in a polarized manner on keratinocytes and this is likely important for proper signal transduction. Not only individual cells or subcellular structures are highly polarized but the orientation of multicellular structures, such as sebaceous glands and hair follicles, are organized in the plane of the tissue. All of these processes depend on cell and tissue polarity and work in recent years has started to unravel how polarity genes contribute to these processes in the epidermis. In this article we will focus mostly on the role of cell polarity in the epidermis.

POLARITY PROTEIN SIGNALING NETWORKS

A highly conserved set of proteins, the so-called polarity proteins, orchestrates the setup, maintenance, and reorganization of polarity. These

polarity proteins integrate upstream signals of various kinds to instruct regulators of the cytoskeleton to control, for example, polarized membrane trafficking, adhesive interactions, and signal complex localization (Fig. 2). In this article, we will focus mostly on the role of cell polarity proteins in the epidermis.

Three main cell polarity complexes have been described that are implicated in different aspects of establishing and maintaining asymmetry: the Scribble/Dlg large (Dlg)/Lethal Giant Larvae (Lgl) complex, the atypical PKC (aPKC)/Par3/Par6 complex, and the Crumbs/Patj/Pals complex (Fig. 2). In addition, Par4, known as Lkb1 in mammals, and Par5 (14-3-3 proteins in mammals) engage with these complexes to regulate polarity. Several excellent reviews describe the structure and cell biological role of these proteins, which include adhesion, scaffold, kinase, and regulatory functions (Goldstein and Macara 2007; Hurov and Piwnicka-Worms 2007; Assemet et al. 2008). Initially predominantly identified in *Caenorhabditis elegans* and *Drosophila* (Bulgakova and Knust 2009; St Johnston and Ahringer 2010), it is now clear that the mammalian counterparts of these proteins play similar essential roles in morphogenesis and tissue homeostasis.

BARRIER FORMATION AND FUNCTION IN THE EPIDERMIS

A crucial function of the epidermis is the establishment and maintenance of a lifelong self-renewing barrier that does not only provide protection against water loss and mechanical insults, but also guards against UV-light, pathogens, and temperature changes. Keratinocytes must undergo a spatiotemporal highly controlled differentiation program to establish and maintain this barrier. Disturbance in this program resulting in an impaired barrier function has been implicated in a range of diseases (e.g., atopic dermatitis, psoriasis, and ichthyosis) (De Benedetto et al. 2012; Kubo et al. 2012) and can contribute to a cancer permissive microenvironment (Demehri et al. 2009).

Although the epidermis does not establish apicobasolateral polarity as observed in simple

Figure 1. The mammalian epidermis is a polarized stratified epithelium. (A) The interfollicular epidermis develops apicobasolateral polarity across the different layers. The last viable layer, the stratum granulosum, is forming the apical border. Polarization is reflected in the differential localization of integrin-based cell–matrix junctions and the cell–cell junctions desmosomes, adherens, and tight junctions (all in gray shades). Both the microtubule (blue) and actin (green) cytoskeleton show polarized distribution throughout the different layers. Microtubule-based cilia are positioned at the apical side of keratinocytes (blue protrusions) near the centrosome (red). (B) Wound healing requires the coordination of several polarized processes. After wounding, basal cells migrate in a directional manner into the wound bed on a provisional matrix that is secreted in a polarized manner by keratinocytes and fibroblasts. This migration required rearrangements of the actin cytoskeleton and formation of new contacts with the extracellular matrix (ECM).

F. Tellkamp et al.

Figure 2. Schematic overview of the interactions between the main cell polarity proteins and how they establish, maintain, and modify polarity.

epithelia, many processes in the stratifying IFE barrier resemble features of polarized simple epithelial cells (Fig. 1A): (1) Basal cells have a highly polarized appearance with asymmetric distribution of integrin cell matrix receptors and polarity proteins as well as a polarized positioning of the nucleus, mitochondria, and the apically localized centrosome. (2) Both the actin and microtubule cytoskeleton show a polarized distribution in the epidermis. In basal cells, microtubules are organized in a radial array around the centrosome but translocate to the cortex in suprabasal layers (Lechler and Fuchs 2007). Actin is most strongly organized at the cortex in the most upper (“apical”) viable layer of the epidermis, the stratum granulosum. (3) Barrier-forming tight junctions (TJs) are only present in the stratum granulosum. These junctions are essential for the epidermal water barrier (Furuse et al. 2002; Tunggal et al. 2005) and regulate immune responses as Langerhans cells use the TJ pore to take up external antigens (Kubo et al. 2009). (4) Formation of the stratum

corneum depends on the fusion of lamellar bodies (LBs) and keratohyalin granules with plasma membranes at the transition between the stratum granulosum and corneum layers (Lippens et al. 2009).

The stratum granulosum might thus be considered the viable apical boundary that contains TJs. As in simple epithelia these may serve as a landmark to separate the basolateral layers from the most apical layer and therefore control polarized targeting of LBs and keratohyalin granules toward the more apically localized stratum corneum.

The mechanisms that coordinate the polarization of the epidermis across the tissue are mostly unknown. As in simple epithelia, important cues are provided by adhesion and signaling from cell–matrix and cell–cell junctions. Loss of $\beta 1$ -integrin cell–matrix adhesion receptors or the integrin-linked kinase (ILK) interferes with proper polarization of basal cells and disturbs epidermal differentiation (Brakebusch et al. 2000; Raghavan et al. 2000; Lorenz et al. 2007). Epidermal loss of the AJ proteins E-cadherin or β -catenin results in a leaky TJ epidermal barrier (Tunggal et al. 2005; Ray et al. 2013). β -Catenin serves as a mechanosensor necessary to strengthen adhesion and TJs, likely by increasing their interaction with the actin cytoskeleton.

The desmosomal protein desmoplakin I (DPI) coordinates the organization of cortical microtubules in suprabasal layers by recruiting a subset of centrosomal proteins, such as Lis1, a protein implicated in the organization of microtubules. Epidermal loss of Lis1 did not only result in a lack of cortical microtubule recruitment to desmosomes in the suprabasal layers but, surprisingly, impaired desmosomal stability (Sumigra et al. 2011). The cortical localization of microtubules is also necessary to recruit myosin II that strengthens AJs, which in turn promotes TJs epidermal barrier function (Sumigra et al. 2012). Vice versa, AJs are necessary for desmosome assembly in the epidermis (Michels et al. 2009). Together these results indicate that the coordinated formation of junctions and their association with the different cytoskeletal networks are crucial for proper

epidermal differentiation and barrier formation.

Polarity protein signaling may orchestrate the interplay between epidermal junctions and the cytoskeleton. Loss of or interference with Par3 or aPKCs alter the microtubule and actin cytoskeleton, impair AJs, and inhibit TJ function (Helfrich et al. 2007; Iden et al. 2012). Similarly the small GTPase Rac regulates keratinocyte TJ barrier function through the aPKC/Par3 complex (Mertens et al. 2005). Cell adhesion itself may positively enforce polarity signaling as loss of E-cadherin or CD44 alters aPKC activity and localization associated with reduced TJs function (Tunggal et al. 2005; Kirschner et al. 2011). Given their important role in several key aspects of epidermal barrier function, assessing the contribution of polarity proteins to human skin barrier diseases will be an important avenue for the future.

PRIMARY CILIA: COORDINATION OF POLARITY AND GROWTH FACTOR SIGNALING?

Primary cilia are small microtubule-based cylindrical membrane organelles that project into the extracellular space. Through enrichment of receptors, for example, Wnt, Hedgehog (HH), and Notch, cilia function as signal centers in sensation, signal reception, and mechanical cues (Goetz and Anderson 2010). Cilia dysfunction is associated with a range of (developmental) disease syndromes, generally referred to as ciliopathies (Hildebrandt et al. 2011). Recently, a direct role for cilia dysfunction in human skin disease was suggested as mutations in core cilia proteins were found in rare cranioectodermal dysplasia syndromes (Ruiz-Perez and Goodship 2009; Walczak-Sztulpa et al. 2010). Moreover, the Birt–Hogg–Dubé syndrome, which among others is associated with an increased risk of skin cancer, was recently linked to alterations in ciliogenesis (Luijten et al. 2013).

Within the skin, primary cilia are found on most dermal and epidermal cell populations. By sensing Hedgehog signals, primary cilia on dermal cells are required for hair follicle morpho-

Epidermal Polarity Genes in Health and Disease

genesis (Lehman et al. 2009). Epidermal inactivation of cilia components has revealed different roles for cilia in the developing epidermis. On interfollicular keratinocytes cilia control Notch signaling to balance IFE proliferation and differentiation during morphogenesis. At a later stage, epidermal cilia are necessary for the transduction of HH signals to promote hair follicle morphogenesis (Ezratty et al. 2011). Cilia also control adult epidermal homeostasis perhaps by balancing HH, which promotes hair follicle identity, versus p63 signaling, which stimulates IFE fate (Croyle et al. 2011).

Epidermal-derived polarity cues provided by the extracellular matrix are important for the formation of dermal cilia. Epidermal loss of the extracellular matrix protein laminin-511 resulted in shortened and structurally altered cilia on dermal papilla cells and a block in hair follicle formation, likely as a result of altered HH signaling (Gao et al. 2008). Disturbed cell-matrix (loss of β 1-integrin) or cell–cell (loss of α -catenin) adhesion also impairs cilia formation (Ezratty et al. 2011), although the mechanism is unclear. As both of these adhesive junctions interact with actin, they may regulate ciliogenesis through the actin regulatory protein “missing in metastasis” (MIM). MIM controls HH signaling and dermal cilia formation through regulation of the actin cytoskeleton (Bershteyn et al. 2010).

Recent evidence indicates that cilia formation in simple epithelia requires the activity of cell polarity proteins. In these cells, the Par/aPKC complex can localize to cilia through interaction with Crb3 and down-regulation of Par3 or Crb3 interfered with cilia formation (Fan et al. 2004; Schermer et al. 2006; Sfakianos et al. 2007). The role of cell polarity proteins in the regulation of skin cilia is less clear. In different skin cells MIM forms a complex with aPKC- λ /Par3 at the basal body to regulate HH signaling (Atwood et al. 2013). However, loss of aPKC- λ only interfered with cilia formation in transformed (Atwood et al. 2013) but not in primary keratinocytes (own unpublished observations). These results suggest a cell context-dependent function for aPKC- λ polarity signaling in cilia formation.

F. Tellkamp et al.

POLARITY AND THE REGULATION OF EPIDERMAL CELL FATE

The epidermis is derived from a single layer of ectoderm that ultimately gives rise to the formation of different populations of keratinocytes that constitute the interfollicular epidermis, hair follicles, sebaceous-, sweat-, and mammary glands (Watt 2001; Fuchs 2007; Doucet et al. 2013). This implies that during morphogenesis these differential fates have to be specified. Lineage tracing analysis revealed that in the adult epidermis different populations of stem cell/progenitor cells exist that replenish the different lineages on turnover (Van Keymeulen and Blanpain 2012). In adult skin, mechanisms must thus exist by which epidermal progenitors self-renew while also generating the appropriate differentiated cell types. From bacteria to mammals oriented cell divisions are used to produce daughter cells with similar or differential cell fate and/or to partition more damaged or older versus newer components in one of the daughter cells (Inaba and Yamashita 2012; Li 2013). Symmetric cell divisions (SCD) generate two daughter cells of the same fate, whereas asymmetric cell divisions (ACD) generate two daughters with differential fate. During development or regeneration oriented division can also be coupled to the expansion and/or elongation of the embryo or tissue along a specific axis.

Polarity proteins are key regulators of oriented cell divisions. Although the detailed mechanisms vary within different systems (Knoblich 2008; Lu and Johnston 2013), polarity proteins establish a polarity axis at the cortex that is essential to couple the distribution of cell fate determinants to the orientation of the spindle (intrinsic mechanism). ACD can also result in differential positioning of the two daughters in the tissue, thereby exposing these cells to different niche signals that promote or inhibit differentiation and/or cell specification (extrinsic mechanism). Although these two mechanisms are not necessarily exclusive, thus far an ACD-mediated differential separation of cell fate determinants has not been shown in the epidermis. Evidence does exist for extrinsic regulation of differential epidermal fate (e.g., through Insu-

lin/IGF-1, Notch, or adhesive signals) (Lechler and Fuchs 2005; Williams et al. 2011; Günschmann et al. 2013).

Within the epidermis symmetric divisions are defined as parallel to the basement membrane or the long axis of the hair follicle, whereas ACDs are defined as perpendicular to these axes (Fig. 3A). A shift in the balance of SCD toward ACD drives the formation of a multilayered stratified interfollicular epidermis (Poulson and Lechler 2012). Asymmetric divisions also occur during the specification of sebaceous gland cell identity (Frances and Niemann 2012) and in the junctional zone (Niessen et al. 2013). In the hair follicle bulb, asymmetric and symmetric divisions may regulate the appropriate differentiation of the different hair follicle layers (Fig. 3A). Although ACDs do occur in the bulge (Niessen et al. 2013), lineage tracing analysis and life cell imaging indicates that bulge stem cells mostly rely on SCD for self-renewal (Zhang et al. 2009; Petersson et al. 2011), whereas on entry into anagen, the growth phase of the hair cycle, asymmetric divisions have been observed in the secondary hair germ (Rompolas et al. 2012), where activated progenitors reside (Fig. 3A), and in the proliferative zone of the outer root sheath (Rompolas et al. 2013).

First evidence that implicated polarity proteins in the regulation of epidermal-oriented cell division came from a seminal study by Lechler and Fuchs (2005), in which they showed that the onset of stratification coincided with a shift from symmetric toward asymmetric division in basal cells of the developing epidermis. Both Par3 and aPKC were distributed asymmetrically at the apical pole of basal cells. In mitosis, these proteins colocalized with Inscutable (Insc) and the spindle orientation complex consisting of Gai, LGN, NuMA, and dynactin (Dctn) (Lechler and Fuchs 2005; Williams et al. 2011). In *Drosophila* neuroblasts Insc couples polarity to spindle orientation by binding both Par3 and Partner of Inscutable, Pins, the *Drosophila* homolog of LGN (Knoblich 2008). A similar Par3-Insc-LGN complex was found in the developing epidermis (Lechler and Fuchs 2005), indicating that the aPKC/Par3 complex may also interact with the spindle orientation

Figure 3. Oriented cell divisions in the epidermis. (A) Schematic overview of asymmetric (ACD) and symmetric (SCD) cell divisions in interfollicular epidermis (IFE) and the hair follicle (HF). ACDs in the basal IFE keratinocytes give rise to one cell that remains in the basal layer and one differentiated cell. In contrast, symmetric cell divisions give rise to two basal cells. Both ACD and SCD were observed in the junctional zone (JZ, red) of telogen and anagen hair follicles. These divisions likely contribute to the renewal of these progenitors and also fuel the sebaceous gland and the IFE. SCD ensure the self-renewal of the HF stem cells in the bulge (green). In early anagen HFs, ACDs were observed at the border of the bulge and secondary hair germ (dark gray cells), where they may contribute to the expanding lower hair follicle population. ACDs have also been observed in the hair bulb, where they may drive the differentiation of outer root sheath cells (ORS) into the differentiated hair follicle layers: inner root sheath layers (IRS) and hair shaft layers. ACDs likely contribute to the formation of the sebaceous gland (SG) during epidermal morphogenesis. (B) Schematic overview of the polarized distribution of polarity proteins and spindle orientation machinery in symmetric and asymmetric dividing basal keratinocytes.

complex in the epidermis to drive asymmetric division (Fig. 3B).

Adhesive cues within the epidermis are likely crucial as loss of either $\beta 1$ -integrin-mediated adhesion or the adherens junction protein α -catenin resulted in a loss of apical localization of aPKC, LGN, and NuMA (Lechler and Fuchs 2005), coinciding with disturbed differentiation and hyperproliferation. On in vivo knockdown of *LGN*, *Numa1*, or *Dctn1* the spindle is biased toward SCD, resulting in impaired stratification and epidermal barrier formation (Williams et al. 2011). Similarly, in vivo overexpression of *Inscutable* is initially sufficient to promote ACDs, but the SCD/ACD ratio in these mice is restored later in development, suggesting the existence of a compensatory mechanism (Poulson and Lechler 2010).

A recent study implicated a direct role for polarity protein signaling in the regulation of

epidermal cell fate and oriented division. Epidermal inactivation of aPKC- λ , the predominant aPKC isoform expressed in the epidermis, resulted in a gradual loss of hair follicle bulge stem cells accompanied by a temporary increase in more committed progenitors located in the isthmus/junctional zone, the IFE, and lower HF. Loss of aPKC- λ induced a shift toward more ACDs in the IFE, bulge, and the junctional zone/isthmus region. Most importantly, lineage tracing of lower hair bulge and hair germ stem cells showed that, on loss of aPKC- λ , these cells no longer exclusively contributed to the lower hair follicle but also repopulated the upper junctional zone, the IFE, and on occasion even the sebaceous glands (Niessen et al. 2013). Thus, aPKC- λ regulates epidermal homeostasis and cell fate likely by balancing SCD and ACD (Fig. 4A). How aPKC- λ regulates this balance is not

F. Tellkamp et al.

Figure 4. The balance between ACD and SCD regulate epidermal homeostasis. (A) A schematic overview of the regulation of cell fate by aPKC-λ. Lineage tracing analysis using inducible Lgr5-Cre^{ERT2}:Rosa26LacZ mice. In telogen follicles Lgr5-positive cells (blue) reside in the lower bulge (green) and hair germ. During anagen, the Lgr5⁺ progeny exclusively contributes to the down-growing hair follicles. Lgr5⁺; aPKC⁻ progeny contribute not only to the lower newly forming hair follicle but also to the upper junctional zone (red) and the interfollicular epidermis, showing that aPKC-λ and thus polarity signaling determines cell fate in the epidermal lineage. (B) The ACD/SCD ratio balances differentiation and self-renewal to regulate epidermal homeostasis. (C) Model showing how an increase in ACD drives a gradual loss of quiescent stem cells and a transient increase in more committed proliferating progenitors that further differentiate over time. This is indeed observed upon loss of aPKC-λ, providing evidence for this model. Based on work in *Drosophila*, this model also predicts that an increase in ACD would suppress tumor formation and vice versa.

clear. Although aPKC is apically localized in both asymmetrically dividing *Drosophila* neuroblasts and basal keratinocytes, the fate of the future daughter cells that inherit this domain is opposite: inheritance of stem cell properties in case of the neuroblast, whereas the future apical epidermal daughter will differentiate. This is similar to the situation in *Drosophila* intestinal stem cells, where the aPKC/Par3 domain marks the future differentiated daughter. Interestingly, in these cells, integrin-mediated adhesion was essential for asymmetric distribution and differentiation similar to the developing IFE. Moreover, increased aPKC activity enhanced Notch/Delta signaling to promote differentiation (Goulas et al. 2012). Although the latter is in contrast to the finding that loss of aPKC-λ promotes ACD in the epidermis, overall these findings show a strong parallel to the epidermis where loss of integrins results in loss of oriented cell division and Notch/Delta signaling is downstream from ACD (Williams et al. 2011). Thus, unlike neuroblasts, oriented division in the *Drosophila* intestine and in the epidermis appears

to be regulated by both intrinsic and extrinsic signals.

Understanding how the balance between ACD and SCD is regulated is most likely crucial for skin diseases, as an imbalance toward SCD may promote overgrowth and expansion of stem cells, perhaps leading to inappropriate healing and ultimately cancer (see below). On the other hand, a shift toward ACD might promote premature differentiation, resulting in a hypomorphic epidermis and altered sebaceous gland, HF and sweat gland function (Fig. 4B).

POLARIZATION IN EPIDERMAL REGENERATION AND MIGRATION

Cutaneous wound healing is a complex process necessary to efficiently restore skin barrier function. This process requires a tightly orchestrated spatiotemporal response of different skin cell types (Gurtner et al. 2008). Several of these responses involve polarization of cells in the plane of the tissue and this is likely essential for restoration of tissue architecture and homeostasis.

Within the epidermis keratinocytes need to coordinate proliferation with cell migration. On wounding, leading edge keratinocytes migrate in a directional fashion to close the wound. This is accompanied by a polarized secretion of provisional matrix and the reorganization of intercellular and cell-matrix contacts (Fig. 1B). Polarity cues are derived from a combination of the provisional matrix deposited and remodeled by keratinocytes and fibroblasts, the absence of intercellular contacts at the leading edge as well as soluble signals. Polarized proliferation of keratinocytes occurs in the area directly after the leading edge (Fig. 4C) to provide sufficient new cells to restore surface coverage. This might involve a shift from ACD to SCD to promote divisions that expand the basal cell layer.

In vitro studies have shown that cell polarity proteins regulate front rear polarization and the reorientation of the nucleus and centrosome during directed migration in diverse cell types (Etienne-Manneville 2008). Epidermal deletion of the small GTPase Rac delayed in vivo wound healing likely as a combined result of a reduction in proliferation and migration. Rac activity has been implicated both upstream of and downstream from aPKC (Mertens et al. 2005; Scotti et al. 2010) and might thus regulate ACD/SCD decisions. In line, Rac inactivation is associated with epidermal stem cell loss (Benitah et al. 2005; Castilho et al. 2007), Rac mutant keratinocytes also manifested reduced persistence in lamella protrusion providing an explanation for the reduction in migration (Pegtel et al. 2007; Tscharncke et al. 2007). This may involve the Rac exchange factor TIAM1, which associates with Par3 and aPKC at the leading edge of keratinocytes to regulate persistent migration in vitro (Pegtel et al. 2007). Scribble may function as another coordinator of Rac activity in collective cell migration (Dow et al. 2007). Interestingly, Scribble may integrate cell and planar polarity signaling to regulate epidermal wound healing. In mice, mutations for Scribble genetically interact with mutations in different PCP genes resulting in strongly impaired embryonic wound healing (Caddy et al. 2010).

An important future research topic will be to examine whether altered polarity signaling

Epidermal Polarity Genes in Health and Disease

contributes to impaired wound healing, a major and increasing socioeconomic problem caused by the increase in obesity-related skin problems (e.g., “diabetic ulcers”) and the aging population.

ALTERED POLARITY SIGNALING: A DRIVER OF NONMELANOMA SKIN CANCER?

Cancer initiation and progression is characterized by changes in cell adhesion and in cell and tissue architecture. This may not only drive migration and invasion of cancer cells but may also contribute to a loss of proliferation control owing to, for example, changes in the microenvironment of stem/progenitor cells resulting in altered division orientation. As polarity proteins are key determinants of cell and tissue architecture, it is perhaps not surprising that altered polarity signaling can contribute to and has been implicated in a range of human cancers (Ellenbroek et al. 2012; Martin-Belmonte and Perez-Moreno 2012; Muthuswamy and Xue 2012).

Mutations in LKB1 result in Peutz–Jegher syndrome (PJS), a rare autosomal dominant syndrome characterized by the development of gastrointestinal polyps and mucocutaneous pigmentation abnormalities (Jansen et al. 2009). These patients are also more susceptible to a range of malignant epithelial tumors. In mice, either haploinsufficiency or epidermal inactivation of LKB1 strongly promotes DMBA-induced SCC not only in the skin but also in the lung (Gurumurthy et al. 2008). Interestingly, the SCCs did not originate from papillomas, as is usually the case in DMBA protocols. Moreover, haploinsufficient LKB1-derived SCCs showed loss of heterozygosity. LKB1-negative tumors were associated with increased Ras pathway activity, suggesting that loss of LKB1 promotes SCC formation at least in part through the Ras pathway.

In general, the Lgl/Scribble/Dlg polarity complex proteins show a reduced expression in human tumors and are considered potential tumor suppressors. In line, re-expression of Hg12, a human homolog for Lgl in melanoma cell lines inhibits migration, restored E-cadherin

F. Tellkamp et al.

expression, and decreases MMP expression (Kuphal et al. 2006). Loss of Lgl1 in mice induced brain hyperplasia (Klezovitch et al. 2004), similar to what has been observed in *Drosophila* Lgl mutants (Bilder 2004). A recent study in zebrafish epidermis provides a potential mechanism by which Lgls may serve as a tumor suppressor in the skin. Interestingly, loss of Lgl2 also induced epidermal overgrowth and epithelial to mesenchymal transition (EMT), which were both driven by enhanced ErbB2 signaling (Reischauer et al. 2009).

Two-stage DMBA/TPA nonmelanoma skin carcinogenesis mouse experiments revealed a dual role for Par3 in skin tumorigenesis (Iden et al. 2012). Epidermal loss of Par3 inhibited papilloma formation accompanied by increased apoptosis and a reduction in Ras-driven proliferation. The latter was dependent on intact cell–cell contacts. In contrast, loss of Par3 promoted the formation of keratoacanthomas (KA), a tumor type that is frequent in humans but rarely observed in mice. In agreement, Par3 is at sites of cell–cell contacts in human papillomas but is lost in human KA. Interestingly, Par3 is essential to localize its binding partner aPKC at the membrane (Iden et al. 2012). aPKC- λ is overexpressed in human cancer and shown to be a strong tumor promoter in a range of epithelial cancer models (Murray et al. 2011). It is thus tempting to speculate that in papilloma formation, aPKC exerts its tumor promoting activity at the membrane, whereas in KAs aPKC may drive tumor formation in the cytoplasm. Evidence for the latter was provided in a breast cancer model, in which loss of Par3 promoted tumor initiation and invasion likely as a result of cytoplasmic aPKC activation (McCaffrey et al. 2012). Par3 may thus function either as a tumor promoter or tumor suppressor in the skin, perhaps depending on the cell of origin within the epidermis.

In line with these observations is the recent finding that overactivation of the Par3 binding partner aPKC- λ promoted basal cell carcinoma (BCC). This study identified aPKC- λ as a direct target of HH signaling, a major driver of BCC (Atwood et al. 2013). In turn, aPKC- λ provides a positive-feedback loop by phosphorylating

Gli1, thereby promoting DNA binding of Gli and thus its transcriptional output. More importantly, chemical inhibition of aPKC blocked BCC tumor growth also in lines that were resistant to the inhibition of the HH receptor Smoothened (Atwood et al. 2013). This study thus identifies polarity signaling as a potential novel target in the treatment of BCC.

As Par3 can also have functions independent of aPKC/Par6 it will be important to dissect the role of Par3 in aPKC driven BCC skin cancer and vice versa to ask whether the Par3 tumor promoting and suppressive functions depend on aPKC. Loss of aPKC- λ promotes ACD, differentiation, and loss of stem cells (Niessen et al. 2013), whereas in *Drosophila*, constitutive aPKC membrane expression drives SCD and overgrowth of stem cells, resulting in tumor formation (Fig. 4B). It will thus be important to determine whether Par3 and aPKC- λ promote epidermal tumorigenesis through control of cell fate, differentiation status, and division orientation within the different epidermal compartments.

Overall, these data indicate that altered polarity protein signaling directly contributes to nonmelanoma skin carcinogenesis and that identification of the underlying mechanisms may provide potential novel targets for tumor therapy.

LINKING CELL POLARITY TO GROWTH, IMMUNITY, AND ENERGY METABOLISM

Cell polarity proteins not only regulate cell and tissue architecture but also are intermediates in pathways that control growth, metabolism, and inflammation, suggesting a direct link between these processes (Fig. 5).

The Hippo pathway is perhaps the best example how cytoarchitectural status controls growth. The Hippo tumor suppressor negatively regulates the activity of the transcription factor Yap to control cell proliferation and thus organ size. Several recent papers identified a role for polarity proteins and intercellular junctions in the regulation of Hippo signaling (Boggiano and Fehon 2012). In the epidermis, the AJs protein α -catenin binds Yap and regulates its subcellular localization. Epidermal loss of

Figure 5. Polarity proteins as central integrators of cell architecture, innate immunity, metabolism, and growth. Schematic overview that illustrates how polarity protein signaling may integrate upstream signals and serve as central coordinators of the epidermal response to restore tissue homeostasis on different epidermal insults.

α -catenin results in nuclear localization and transcriptional activation of Yap to promote overgrowth resulting in skin tumors (Schlegelmilch et al. 2011; Silvis et al. 2011). The exact mechanism by which α -catenin controls Yap is not clear. One potential mechanism might be through its interaction with merlin, a Ferm domain containing protein, which in *Drosophila* is an upstream regulator of Yap. Similar to α -catenin merlin mediates contact-mediated suppression of proliferation in cultured epithelial cells (Lallemand et al. 2003). In the epidermis, merlin connects α -catenin to Par3 and thus aPKC to regulate adherens junction maturation and spindle orientation (Gladden et al. 2010). Nevertheless, a direct link to regulation of Yap in the epidermis has not yet been reported.

Polarity may also directly link to the metabolic status of cells. The Par4/LKB1 serine/threonine kinase is a positive upstream regulator of at least 14 AMPK-related kinases, including the polarity protein Par1/MARK. These kinases thus couple LKB1 to a range of pathways that regulate diverse processes, such as cellular responses to metabolic stress, cell size, cell-cycle regulation, and cell polarity (Jansen et al. 2009). On low ATP conditions, LKB1 cooperated with the metabolic stress kinase AMPK to regulate epithelial polarization (Lee et al. 2007; Mirouse et al. 2007). LKB1 may thus directly couple energy status to the regulation of cell shape and cellular interactions.

The Par3/Par6/aPKC complex may also control metabolic signaling downstream from the insulin receptor as insulin treatment stimulated aPKC kinase activity (Kanzaki et al. 2004). In line, specific loss of aPKC- λ in classical insulin-sensitive tissues, such as pancreas or muscle, resulted in impaired insulin sensitivity (Hashimoto et al. 2005) and mimicked human metabolic syndrome (Farese et al. 2007). Interestingly, increased insulin sensitivity was observed on liver-specific loss of aPKC- λ , suggesting a cell-type-specific regulation of this pathway by aPKC- λ (Matsumoto et al. 2003). Finally, aPKCs have been implicated in the regulation of innate and adaptive immune signaling (Moscat et al. 2009). For example, inactivation of aPKC- ζ in all tissues of the mice results in impaired B-cell survival and altered NF- κ B signaling (Leitges et al. 2001). At present, it is unclear whether in the epidermis polarity signaling regulates metabolic activity and innate immunity.

CONCLUDING REMARKS

Polarity protein signaling is slowly emerging as a central pathway important for the regulation of diverse processes. In many skin diseases, impaired epidermal barrier function is associated with an inflammatory and hyperproliferative response (Kubo et al. 2012). Wounding also elicits a spatiotemporal coordinated inflammatory and proliferative response that is integrated with

F. Tellkamp et al.

changes in cell shape, adhesion, and migration. As polarity proteins have been implicated not only in the regulation of the cytoarchitecture but also in growth control, innate immunity, and metabolic signaling, these proteins may thus serve as central integrators of different upstream signals to coordinate the cell and tissue response to maintain and restore tissue homeostasis (Fig. 5). Key future questions will be whether these functions of polarity are indeed coupled and how altered polarity signaling disturbs skin homeostasis leading to disease.

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F. Tellkamp et al.

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