Organogenesis 7:3, 202-208; July/August/September 2011; © 2011 Landes Bioscience

Planar cell polarity pathway in vertebrate epidermal development, homeostasis and repair

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Key words: planar cell polarity, skin, wound repair, grainyhead-like, Drosophila, vertebrates, mammals, disease

Abbreviations: PCP, planar cell polarity; grh, grainyhead; grhl, grainyhead-like; fz, frizzled; cthrc1, collagen triple helix repeat containing 1; wnt, wg and int hybrid (wingless-type MMTV integration site); kny, knypek; gpc, glypican; rack, receptor of activated protein kinase C1; ror2, receptor tyrosine kinase-like orphan receptor 2; dvl, disheveled; pk, prickle; vangl, Van gogh-like; celsr, cadherin EGF LAG seven pass G-type receptor; ankrd6, ankyrin repeat domain 6 diversin; in, inturned; frtz, fritz; fy/fuz, fuzzy; lgl, lethal giant larvae; JNK, c-jun N-terminal kinase; RhoGEF, Rho guanine nucleotide exchange factor; WGEF, weak-similarity GEF; dlg, disc large; PTK7, protein tyrosine kinase 7; Stit, Stitcher; RTK, receptor tyrosine kinase; CE, convergence-extension; NNSE, non-neural surface ectoderm; Scrib, scribble; Rok, Rho-associated kinase; Ddc, Dopa decarboxylase; Ple, pale; shRNA, small hairpin ribonucleic acid; ERK, extracellular regulated kinase; MAPK, mitogen-activated protein kinase; UV, ultraviolet; ECM, extracellular matrix; cdc42, cell division control protein 42; Shh, sonic hedgehog

The planar cell polarity (PCP) pathway plays a critical role in diverse developmental processes that require coordinated cellular movement, including neural tube closure and renal tubulogenesis. Recent studies have demonstrated that this pathway also has emerging relevance to the epidermis, as PCP signaling underpins many aspects of skin biology and pathology, including epidermal development, hair orientation, stem cell division and cancer. Coordinated cellular movement required for epidermal repair in mammals is also regulated by PCP signaling, and in this context, a new PCP gene encoding the developmental transcription factor *Grainyhead-like 3* (*Grhl3*) is critical. This review focuses on the role that PCP signaling plays in the skin across a variety of epidermal functions and highlights perturbations that induce epidermal pathologies.

Introduction

Epithelial cells within a planar "sheet," such as the epidermis, display both apical-basolateral polarity at a single cell level and planar polarization extending broadly across the entire tissue. Whereas apical-basolateral polarity is often established simply through local extracellular cues, such as basal extracellular matrix or cell adhesion properties, planar cell polarity (PCP) establishment requires far-reaching, complex signal propagation to ensure that all cells in a tissue are precisely oriented. Diverse physiological processes, including many aspects of embryogenesis and patterning, chemotaxis, immune function and inflammatory response as well as wound healing, require polarized cell migration.[1-3] Well-defined signaling pathways control these processes to polarize the cell within the plane of the epithelium. The identification of the *frizzled* (*fz*) serpentine receptor, its ligand *wingless* and the associated PCP signaling pathway in Drosophila highlighted the importance of the cell orientation and movement in many developmental events.[4] Several ligands, receptors and cofactors have since been identified in vertebrates to regulate PCP, including the secreted glycoprotein *cthrc1*,[5] secreted *wnt5* [6] and *wnt11*,[7] the membrane-associated heparin sulfate proteoglycans *knypek* (*kny*) and *glypican 4* (*gpc4*),[8,9] the receptor for activated protein kinase C1 *rack1*[10] and the tyrosine kinase receptor *ror2*.[11] PCP signaling requires activation of the cytoplasmic factors *dishevelled* (*dvl1, dvl2, dvl3*) [12,13] and *prickle* (*pk1, pk2*),[14] the transmembrane protein *Van Gogh*/*Strabismus* (*vangl1, vangl2*),[15,16] homologs of *cadherin starry night*/*flamingo* (*celsr1, celsr2, celsr3*)[17] and the gene coding for cytoplasmic ankyrin repeat domain 6 *diversin* (*Ankrd6*),[18] a homolog of Drosophila *diego*, which collectively are recognized as the core PCP genes.[19]

The list of ancillary factors which cooperate with these core genes to regulate PCP is continually expanding and includes *inturned* (*in*),[20] *fritz* (*frtz*),[21] *fuzzy* (*fy*/*fuz*),[22] *scrib1*,[15] *lethal giant larvae* (*lgl*) [23,24] and *Grainyhead-like 3* (*Grhl3*).[3,25-27] Although some of the instructive cues operating in parallel to the core PCP genes are known and broadly include *fat, dachsous, four-jointed* as well as other potential regulators, such as *Hedgehog*,[28,29] this review will limit itself primarily to core PCP genes and downstream effectors of PCP signaling. The effector proteins in this pathway include *Daam1*, *JNK*, *Profilin*,[30] the small GTPases of the Rho subfamily RhoA, Rac1 and cdc42 and the Rho-associated kinase (Rok), all of which are largely involved in re-modeling of the actin cytoskeleton.[27,31,32] Disruption of any of the core PCP genes or their effector pathways results in polarity-related defects.

Consequences of PCP Defects

In the fly, polarity has been mainly studied in the context of tissue organization.[33,34] Disrupted PCP signaling in Drosophila

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Submitted: 08/25/11; Revised: 10/10/11; Accepted: 10/15/11
http://dx.doi.org/10.4161/org.7.3.18431

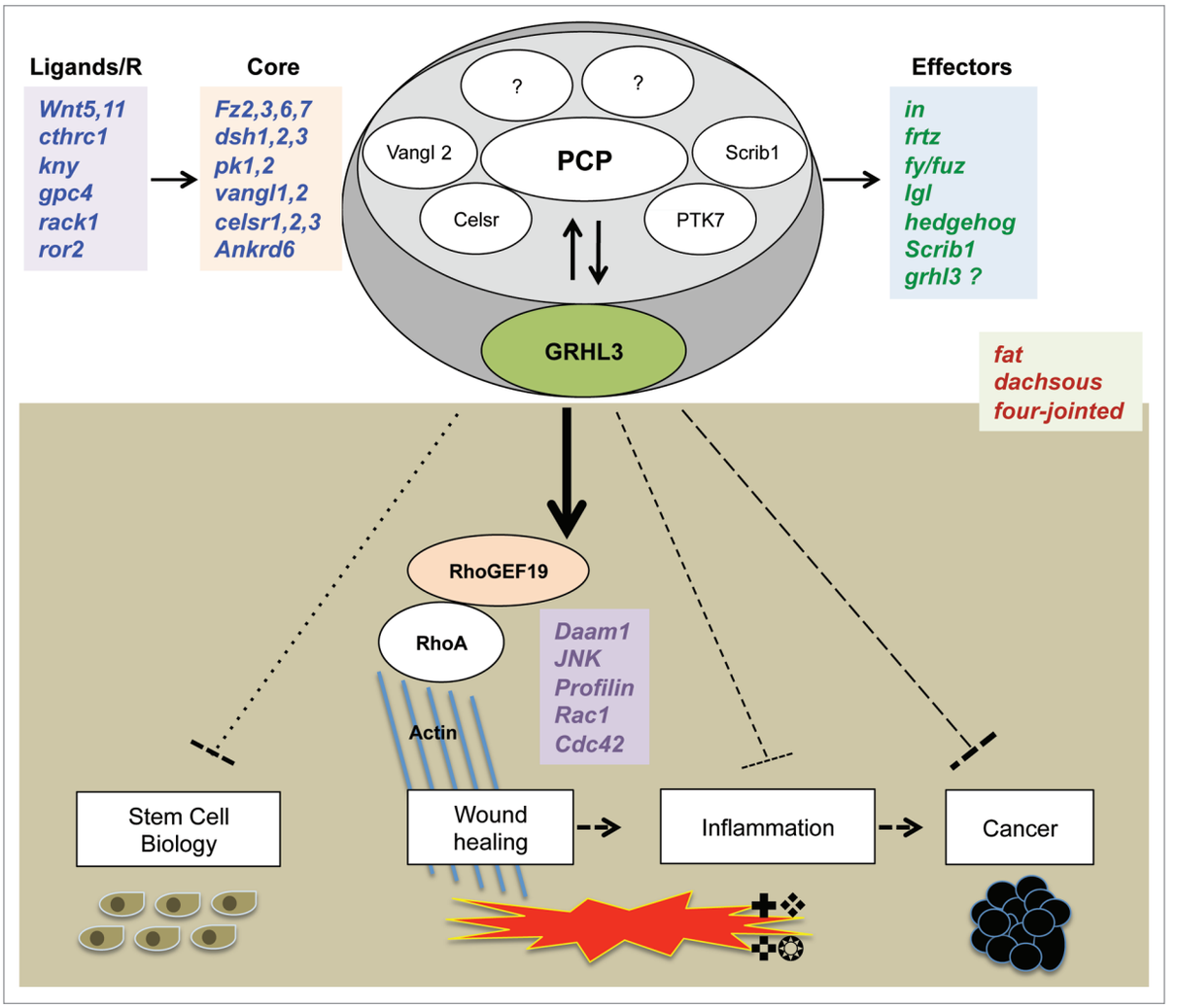

Figure 1. Regulation of epidermal homeostasis by PCP signaling. As a part of this pathway, GRHL3 is known to positively induce wound healing via activation of RhoGEF/RhoA axis. Furthermore, we hypothesize its involvement as a negative regulator of skin biology and pathology, including stem cell proliferation, inflammation and cancer.

leads to defects in wing hair polarity and disorganized ommatidia in the eye. Flies with disrupted expression of either the core PCP genes[33] or downstream effectors[26,35,36] present with misaligned wing hair orientation due to perturbed distribution of the actin pre-hair precursor.[22] The polarized distribution of core PCP genes is also essential for development of the denticle belts of Drosophila larval cuticles[37] as well as for dorsal closure,[38] which is an invertebrate paradigm of neural tube closure. In vertebrates, PCP-related defects include aberrant convergence extension (CE)-mediated axial elongation resulting in defective neural tube closure (including exencephaly, spina bifida and cranioraschischisis),[39] misaligned stereocilliary bundles of cochlear hair cells,[15] disorganized body hair orientation,[40] impaired ciliogenesis of primary and motile cilia[41] and renal tubular disorganization.[42,43]

More recently, putative roles for individual members of the PCP signaling pathway have emerged in many aspects of epidermal development (**Fig. 1**). From the early establishment of a protective barrier during embryogenesis to stem cell biology, aging, hair development and newly discovered roles in epidermal cancers and wound repair, PCP signaling regulates many of the core elements of epidermal function. Here, we highlight the influences of PCP signaling in skin morphogenesis, where hair follicle orientation, eyelid closure and wound healing require this pathway,[3,44] and review the growing body of literature implicating the *grainyhead* family as key players in skin homeostasis within many pathways related to epidermal PCP.

PCP in Epidermal Development during Embryogenesis

Much of our knowledge of PCP signaling in the epidermis comes from Drosophila. Alignment of the cells within the epidermal epithelium appears to require actomyosin-mediated contractility,[45] and this feature also appears crucial for allowing at least some epidermal cells to withstand mechanical stress and preserve

their shape and integrity.[46] Furthermore, core PCP genes are distributed in specific cellular compartments to maintain the polarized status during epidermal development.[38] Interestingly, although the gross defects in Drosophila cuticle formation are relatively mild following disruption of the core PCP genes, when one examines their function in higher vertebrates, severe ectodermal defects are seen. These include impaired skin barrier formation,[40] defective wound healing[3] and neural tube defects.[47-49]

Classically, the loss of vertebrate core PCP genes leads to neural tube defects, although it is important to note that not all PCP-mutants, such as mice deficient in *Fzd6*,[40] display this particular phenotype. The role that the embryonic precursor of adult skin, the non-neural surface ectoderm (NNSE), plays in neural plate folding, elevation and eventual closure is a subject of intense speculation. Although PCP factors are expressed within the neuroepithelium of the neural plate, an intriguing hypothesis is that PCP signaling is crucial in polarizing the NNSE abutting the lateral edges of the neural plate. This NNSE would then provide instructive signaling cues for PCP-mediated neurulation to occur.[50] It seems incongruous that the NNSE, which is both necessary and sufficient for neurulation to proceed (at least in the avian model),[51,52] would not have an instructive role in neurulation, and future studies will focus on the role of PCP in this context.

A further PCP event hypothesized to occur in vertebrate development, which does not exist in the fly, is the formation of motile cilia. Cilia are found on a variety of epithelial cells, where their function ranges from ensuring smooth circulation of cerebro-spinal fluid in the brain[53] to receiving and transmitting soluble signaling factors, such as Shh[54,55] or Notch.[56] PCP-mediated regulation of ciliogenesis in the epidermis has been suggested in Xenopus,[57,58] although the relationship between PCP signaling and ciliogenesis remains controversial. Athough PCP proteins themselves are undoubtedly involved in ciliogenesis,[20] the requirement for Wnt-mediated PCP signaling in ciliary polarity is less clear (elegantly reviewed by Wallingford and Mitchell, 2011).[55] For example, ciliogenesis and planar cell polarity were disrupted in the cochlea of a mouse model lacking the cilia gene *Polaris* even though core components of the PCP pathway were correctly distributed intracellularly, suggesting that cilia themselves may contribute to epithelial polarity in this model[59] or in other epithelial sheets, such as ependymal cells of the brain.[60] Work by Ezratty and colleagues suggests that ciliogenesis during embryonic development occurs only after the epidermis has been polarized.[56] Within the Xenopus epidermis, loss of cilia occurs through loss of *Dvl, Inturned* or *fuzzy*, but whether this is a PCP-mediated mechanism is unclear,[13,29] particularly as defective Dvl signaling causes cell autonomous defects without disturbing planar polarity.[58] Moreover, mice lacking PCP effector proteins, such as Fuzzy, display disturbed ciliogenesis but none of the disturbances in hair polarity (see below) associated with loss of core PCP genes.[61] Lastly, although early polarized distribution of cilia may be influenced by PCP signaling,[58] refinement of ciliary polarity occurs largely through mechanical sensing of fluid flow.[62] Further work appears necessary to confirm that orientation of cilia in the epidermis is, indeed, a PCP-mediated event.

PCP in Hair Orientation

PCP signaling in the regulation of hair orientation may refer either to sensory hair cells on the cochlear epithelium of the inner ear[15] or to the body hair covering (fur) appearing on the skin of terrestrial mammals. Although fur orientation in mammals is governed by many of the same PCP signals as the orientation of bristles in the Drosophila wing, it is important to note that the Drosophila wing bristles are simple, actin-based extensions (one bristle arising per cell), whereas fur in mammals results from the development and differentiation of multicellular complexes in the dermis.[63] Although disruption of PCP signaling has been shown to regulate both sensory hair cell and fur polarity, this section will only focus on polarized orientation of body hair on the skin.

Most of our knowledge regarding mammalian body hair orientation comes from the mouse. Wild-type mice display an organized coat of hair, with individual hairs orientated caudally. Mice lacking core PCP proteins, including Frizzled6 [40] or Celsr1,[64] display abnormal whorl-like patterns centering around localized areas on the body, head and limbs.[64] However, a certain degree of localized organization is apparent, as the hairs are still aligned in patterns and not randomly, as may be predicted from a loss of PCP-signaling. Localized interactions with adjacent cells presumably provide some instructive polarity signals, although these do not extend across the entire epithelial sheet. Importantly, the cellular structure of individual hairs or hair follicles is not disrupted, although the localization and distribution of hair follicles in the dermis is severely disorganized.[64] Interestingly, mutants lacking *Fzd6* are healthy and viable and, despite their hair polarity defects, display no defects in other PCP-related mechanisms, such as convergence extension movements or neural tube closure,[40] suggesting localized tissue-specific roles for certain PCP factors in vertebrates.

PCP in Stem Cell Biology of the Skin

Polarized intracellular protein segregation is particularly relevant to the processes of asymmetric cell division and self-renewal in stem cells. The stem cell divides to produce two cells, one of which is an identical clone of itself, whereas the other is a more differentiated, committed progenitor. Just how external PCP signaling can regulate stem cell division in the epidermis is a key question of epidermogenesis. Wnt signaling through β-catenin is already a known major regulator of epidermal stem cell function. Mice expressing stabilized β-catenin in the skin show epidermal hyperplasia, hair follicle tumor-like outgrowth and precocious transition from telogen to anagen phase via activation of stem cells.[65] It remains to be seen, however, whether Wnt signaling may also regulate PCP in this context independently of β-catenin.

Although not traditionally thought of as a PCP signal, asymmetric Notch signaling is involved in cell fate specification and pattern formation.[66] Recent results suggest that asymmetric stem cell divisions promote Notch-dependent epidermal differentiation, as compromising asymmetric cell divisions induces defects in epidermal stratification, terminal differentiation and barrier

formation.[67] In the epidermis, recent work has shown that ciliial defects lead to defective differentiation, putatively through altered Notch signaling,[56] and Notch is also a known tumor suppressor in the skin of adult mice.[68] Importantly, PCP signaling has been shown to directly regulate Notch pathway activation, for example, in regulating R3/R4 photoreceptors in the ommatidia of the Drosophila eye.[66,69] Loss of Notch-mediated polarity regulation of unipotent hair cell progenitors in zebrafish also leads to defective planar polarization of the neuromast epithelium,[70] raising the novel hypothesis that PCP-mediated regulation of the Notch pathway may be a crucial component in vertebrate epidermal stem cell biology.

In the mammalian epidermis, PCP proteins are asymmetrically localized in cells of the proliferative basal layer.[71,72] Asymmetric division of stem cells in this layer gives rise to a mitotically active progenitor cell that retains polarized distribution of core PCP proteins.[72] These cells are not only able to replenish the stratified, multi-layered epidermis, but can also regenerate dermal hair follicle precursors. A proposed mechanism by which epidermal stem cell and PCP fidelity is preserved is via "mitotic internalization," whereby membrane-bound PCP proteins are endocytosed during division and are correctly redistributed in daughter progeny to maintain planar polarity.[72] Mutants that were unable to internalize a core PCP gene, *celsr1*, exhibited misoriented hair follicles following mitosis, indicating that this internalization and resorting step is a key mechanism for maintaining planar polarity in the epidermis.

Work from our laboratory has identified a novel vertebrate mediator of PCP, *Grainyhead-like 3 (Grhl3)*, in the context of several processes, including neural tube closure, skin barrier formation, orientation of cochlear hair cells and epidermal wound healing. *Grhl3* is a vertebrate ortholog of the Drosophila PCP factor *grainyhead*, which, among other functions, regulates wing hair polarity,[26] cuticle formation,[25] expression of epidermis-specific genes,[73] wound healing[74,75] and the mitotic activity of neuroblasts.[76,77] In the context of epidermogenesis in mice, *Grhl3* regulates differentiation,[78] wound healing[3] and proliferation,[78,100] suggesting that *Grhl3* is a key determinant in the fine-tuning of cellular turnover in skin homeostasis.

PCP and *Grhl3* in wound healing. Wound healing requires both cell number regulation and cell migration. During development of the Drosophila ectoderm, PCP components contribute to maintain morphology through regulation of oriented cell division, as dividing cells develop tissues and organs.[79] In wound healing, replacement of damaged cells necessitates cell rearrangement to reconstitute organ shape in addition to cell number regulation, which occurs by mitotic reorientation. Recently, PCP genes have been shown to preserve tissue polarity during proliferation of the mammalian epidermal basal cells. *Celsr1, Vangl2* and *Fzd6* were inherited equally by progeny following mitosis and were able to properly re-localize and reorient themselves to keep a collective cell polarization across the epidermis.[72] In addition, the healing process represents an ideal model to study polarized cell migration, a fundamental element in this process. Despite this, the links between cellular migration in wound repair and PCP signaling have only recently been established.[3] Much like embryonic closure events mediated by PCP-CE signaling, spatial restriction of PCP components at the membrane of leading edge cells with receptor tyrosine kinase (RTK) activation transforms the extracellular gradient into a robust intracellular polarity, leading to polarized intracellular distribution of members of the Rho family of GTPases.[3,27,80]

Work from our laboratory has implicated many of the core and effector PCP genes (*Vangl2, PTK7, Scrib1* and *Celsr1*) in epidermal repair and has led to the identification of *Grhl3* as an important contributor to the PCP pathway.[3] *Grhl3* interacts genetically with these core PCP genes during epidermal healing and also in other PCP-mediated developmental events, including neural tube closure and stereociliary orientation in the cochlea. Like mutants harboring deletions in the other PCP genes, *Grhl3*$^{-/-}$ mice also present with severe neural tube defects, suggesting that *Grhl3* is a key novel regulator of the PCP pathway in mammalian epidermis.

The identification of *Grhl3* as a mammalian PCP determinant closely mirrors the function of the antecedent member of the family, Drosophila *grainyhead* (*grh*). *grh* genetically interacts with the core PCP genes in maintaining wing hair polarity,[26] and *grh* is also directly involved in cuticle repair.[74] Stitcher (*Stit*) induces *grh* expression in wound closure,[81] and extracellular-regulated kinase (ERK) signaling has been shown to be essential for *grh* activation in this context.[75] This pathway directly leads to the expression of *grh* target genes involved in wound healing, including *Dopa decarboxylase* (*Ddc*) and *pale* (*ple*). Independent of its role in wound healing, *grh* also regulates several genes involved in epidermal development, namely *ultrabithorax, engrailed* and *fushi tarazu*.[73] Thus, *grh* in the fly, as per *Grhl3* in the mouse, clearly has a significant role in both homeostatic epidermal development and the polarity-mediated processes of wound healing.

In mammals, both PCP core and effector genes contribute to epidermal development, particularly in regulating hair orientation and maintaining skin homeostasis.[3,61] In response to wounding, *Grhl3* expression is required for cells at the wound margin to establish directional polarity of the leading edge. This is achieved through direct transcriptional activation of the PCP effector molecule, *RhoGEF19* by *Grhl3*.[3] *RhoGEF19*, a member of the small GTPase family, functions as a direct activator of RhoA, leading to actin polymerization, cytoskeletal arrangement and directed migration in wound healing.[3] The Xenopus ortholog of this factor, *WGEF*, is critical for CE and neural tube closure.[82] *WGEF* has been shown to bind Dishevelled and Daam-1 and to connect the PCP pathway to Rho activation in the frog, and preliminary studies from our laboratory indicate that it also plays a role in these processes in zebrafish (Dworkin, unpublished). Loss of *RhoGEF19* function induced by shRNA in a human epidermal cell line, HaCaT, leads to defective cellular migration across a scratch wound. This is accompanied by disruption of Golgi structure and Golgi pericentrosomal positioning, which impairs polarized secretion and directional cell migration.[83] Cells lacking *RhoGEF19* also fail to activate RhoA, resulting in loss of the coordinated actin polymerization necessary for oriented cell migration. Whether the mechanistic basis

of epidermal wound-healing defects caused by loss of the core PCP genes relates to altered *RhoGEF19* expression remains to be determined.

PCP in Epidermal Cancer

In Drosophila, several components that interact with the PCP pathway in determining both planar and apico-basal polarity, including *disc large* (*dlg*),[84] *lethal giant larvae* (*lgl*) [85,86] and *scribble* (*scrib*),[87,88] function as tumor suppressor genes.[89] Loss of these genes causes overgrowth of imaginal disc epithelia, a hyperproliferation accompanied by loss of apical-basal polarity and abnormal cell shapes.[90] In mammals, several studies suggest a link between PCP genes and cancer,[91,92] potentially via involvement of the ERK/MAPK[93] or Rac1-JNK[30] pathways. These studies show that the PCP pathway can interfere with other signaling pathways to influence proliferation and, as such, represent suitable targets for cancer prevention and therapy. The PCP activator Wnt is implicated in vertebrate tumor progression via non-canonical (including PCP) signaling,[30,94,95] and loss of the core PCP-component *Vangl2* promotes cellular migration and ECM invasion of fibrosarcoma tumor cells.[96] Aberrant distribution of core PCP proteins could lead to subsequent localized deregulation of PCP signaling and would represent a critical step in tumorigenesis by deregulating control of not only proliferation, but also metastasis, angiogenesis and tumor invasion.[30]

The concept of cancer as an aberrant developmental process is not new, and putative links between the core PCP genes and tumor suppressor function are emerging. While less is known about PCP and skin cancer, two interesting yet contradictory theories exist, namely, that of skin cancer arising from a wound that doesn't heal, vs. cancer arising from an "overhealing" wound.[97] However, it remains crucial to uncover the molecular determinants that affect PCP signaling in cancer under variable transforming conditions, including exposure to UV irradiation, carcinogens, mechanical or oxidative stress and inflammation as well as wound healing.

Consistent with a role for the PCP pathway in suppression of proliferation and armed with the knowledge that wounding, and by extension aberrant wound healing, can promote both tumor initiation[98] and metastasis,[99] we show that *Grhl3* is implicated in the prevention of skin cancer (Darido, Cancer Cell 2011, In press). Additionally, we and others have shown that loss of *Grhl3* in embryonic epidermis results in both impaired epidermal terminal differentiation[100] and increased cellular proliferation.[78,100] Given the suggested antiproliferative role of this gene, further investigations into the PCP-mediated functions of *Grhl3* and GRHL3 target genes in maintaining the balance between proliferation and differentiation are warranted and could provide further insights into the link between PCP signaling and regulation of skin homeostasis.

Conclusion

Although many aspects of the PCP signaling pathway are well-characterized, continuing studies in the field reveal new roles attributable to increasing numbers of PCP regulators, effectors and partner proteins. The epidermis provides a unique system to study the roles of the PCP pathway in both Drosophila and vertebrates through its myriad of developmental, homeostatic, protective and pathological states. Future directions will ultimately bring regulators of PCP signaling into the clinic, whereby treatment of skin-related disorders will greatly benefit.

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