Ulceration is a common negative prognostic marker of solid tumors including melanoma. The signaling basis of ulceration is being elucidated. PHIP has been shown to be amplified in wild-type melanomas, resulting in Akt activation and ulceration. The signaling basis of ulceration is being elucidated. PHIP has been characterized as being expressed between metastatic melanoma and primary melanoma. In this study, they characterized PHIP as being expressed at high levels in ulcerated melanomas. Not only was it present, the investigators also demonstrated functional consequences of PHIP overexpression. Inhibition of PHIP led to a decrease in aerobic glycolysis (Warburg effect). The Warburg effect is commonly associated with defective glucose metabolism, with glucose being metabolized to lactate instead of full metabolism through to respiration. Although the ineffective metabolism of glucose is initially counterintuitive in terms of tumor growth, more recent studies have established that tumor cells gain certain survival advantages in exchange for switching to aerobic glycolysis, namely NF-κB activation and the ability to survive under extreme hypoxia (Govindarajan et al., 2007). The authors demonstrated the downregulation of biomarkers of the Warburg phenotype, including LDH5, HIF1α, and VEGF.

Although this study demonstrates PHIP elegantly as a potential therapeutic target, several questions can be asked that might provide elaboration and answers about the role of PHIP in melanoma. First, is amplification the sole mechanism of increased PHIP expression? If this is the case, adjacent genes might provide advantages to melanoma, because coamplification might increase the expression of PHIP and an additional gene in a single step. Second, what are the signaling pathways downstream of PHIP amplification? Glycolysis is associated with melanoma with the reactive oxygen–driven phenotype, in which reactive oxygen drives angiopoietin-2 production, tumor growth, and invasion. This phenotype is amenable to pharmacologic intervention.

Clinical Implications

- Ulceration is a known poor prognostic factor for melanoma.
- We now are beginning to understand that ulceration is a phenotype of a specific type of signal transduction abnormality, likely that of the reactive oxygen–induced phenotype.
- This phenotype can be targeted with inhibitors of superoxide production (Munson et al., 2012), and in fact has already been used in patients with melanoma (Arbiser et al., 2012).

which reactive oxygen drives NF-κB and angiopoietin-2 (Fried and Arbiser, 2008). Angiopoietin-2 is highly associated with ulceration, and it would be of interest to determine whether PHIP overexpression causes increased reactive oxygen generation and angiopoietin-2 expression (Lapidoth et al., 2009). Notably, as with ulceration, angiopoietin-2 is associated with poor prognosis in solid tumors, including melanoma, lymphoid malignancies, and

Ulceration is a known poor prognostic factor for melanoma. We now are beginning to understand that ulceration is a phenotype of a specific type of signal transduction abnormality, likely that of the reactive oxygen–induced phenotype. This phenotype can be targeted with inhibitors of superoxide production (Munson et al., 2012), and in fact has already been used in patients with melanoma (Arbiser et al., 2012).

The major pathways in melanoma, Braf mutation, Nras mutation, and PHIP mutation all potentially involve a superoxide/Akt/NF-κB pathway (reactive oxygen–driven pathway) to result in glycolysis, NF-κB activation, and ulceration through angiopoietin-2 expression.

or combination treatment with MEK inhibitors. Predictably, resistance has arisen owing to failure to affect the phosphoinositols-3 kinase/Akt/reactive oxygen pathway. The findings of PHIP amplification in ulcerative primary melanoma should provide an impetus for targeting non-MEK/Braf pathways in melanoma, as this has been a relatively overlooked signaling pathway and one that is readily targeted (Figure 1). Combination or sequential targeting of MEK/Braf inhibitors plus phosphoinositols-3 kinase/Akt/reactive oxygen pathway inhibitors could well result in improved long-term survival and even the possibility of cure.

CONFLICT OF INTEREST
The author states no conflict of interest.

ACKNOWLEDGMENTS
ILA was supported by the grant RO1 AR47901 and P30 AR42687, Emory Skin Disease Research Core Center Grant from the National Institutes of Health, a Veterans Administration Hospital Merit Award, as well as funds from the Margolis Foundation, Rabinowitch-Davis Foundation for Melanoma Research, and the Betty Minsk Foundation for Melanoma Research.

REFERENCES

**Figure 1. Convergence of pathways in melanoma leads to NF-κB activation and glycolysis.** The major pathways in melanoma, Braf mutation, Nras mutation, and PHIP mutation all potentially involve a superoxide/Akt/NF-κB pathway (reactive oxygen–driven pathway) to result in glycolysis, NF-κB activation, and ulceration through angiopoietin-2 expression.
COMMENTARY


See related article on pg 845

Secrets of the Cutaneous Basement Membrane

Sarolta Karpati

The paper in this issue by Has and co-workers reports 15 non-Herlitz epidermolysis bullosa patients with the same single amino-acid substitution in collagen XVII, all of whom presented with clinical and pathological features resembling Kindler syndrome. Here we consider why and how a hemidesmosomal pathology can mimic a focal adhesion bond disease, both clinically and ultrastructurally.


In this issue of JID, Cristina Has and an international group of specialists on epidermolysis bullosa (EB) report on a substitution mutation of collagen XVII that is associated with several unexpected skin and mucosal features that are ordinarily not observed in patients with junctional EB other (non-Herlitz-type junctional) EB disease. The authors also find a clinical overlap with another inherited EB, the Kindler syndrome. Furthermore, the clinical features developed rather late, years and even decades after birth in most of the patients, indicating a long-lasting mechanism of functional compensation and slow progression of the inherited basement membrane (BM) damage.

Structural stability and dynamics of collagen XVII within the hemidesmosomal anchoring complex

The collagen XVII (180 kDa) was identified within the cutaneous basement membrane zone (BMZ) chronologically as the second, and functionally as the major, autoantigen of bullous pemphigoid (BP), and therefore it has also been called BPAG2 (BP antigen 2) or BP180. The final product is a trimer of three 180 kDa α1 XVII chains [α1(XVII)3], and it anchors basal keratinocytes at the hemidesmosomal plaque through the lamina lucida to the lamina densa of the BM. Its intracellular N-terminal domain contributes to hemidesmosomal plaque stability, and it interacts with the plaque proteins plectin and BPAG1 (BP230) and also with the intracellular tail of β4 integrin. The 120 kDa extracellular, flexible, collagenous ectodomain of the molecule is part of the anchoring filament and, while binding to the α6 integrin and laminin 332, crosses the lamina lucida of the BM where it anchors the lamina densa. This ectodomain contains 15 collagenous subdomains separated by 16 non-collagenous (NC) interruptions (Birk and Bruckner, 2011).

The 120 kDa ectodomain is shed from the 180 kDa transmembrane molecule at the external surface of basal keratinocytes within the NC16 domain by metalloproteinases of the ADAM (A Disintegrin And Metalloproteinase) family, predominantly by the tumor necrosis factor-converting enzyme (TACE alias ADAM 17) or by ADAM 9 or ADAM 10. The shed ecto-collagen XVII functions as a “mobile” component of the extracellular matrix (ECM); it is present not only in the lamina lucida but also in the uppermost dermal connective tissue. The ectodomain acquires new epitopes through proteolytic cleavage, which identify and distinguish the cleaved molecules from the uncleaved 180 kDa protein. There are also smaller shed ectodomains (e.g., 95 kDa) with distinct cleavage sites and neoepitopes. Neoepitopes within the NC16A domain are recognized preferentially in autoimmune blistering diseases such as BP, pemphigoid gestationis, and the linear IgA dermatosis (Nishie et al., 2010).

Ectodomain shedding weakens basal keratinocyte binding to the underlying BM when the architectural stability of the molecule is disrupted. Shedding may be of physiological importance during the differentiation of the basal keratinocytes, as well as in their movement during wound healing and tissue regeneration (Hashmi and Marinkovich, 2011).

Cross-talk along the BMZ: the key role of β-integrins in adhesion interactions

The bidirectional interaction between cells and their environment is mediated predominantly via integrins that accumulate in adhesomes. There are collagen-, laminin-, and leukocyte-binding integrins. The ability of integrins to be activated and to initiate signaling pathways depends upon the type of adhesion complexes that are formed between cells and the ECM. Activated integrins become clustered and form dynamic integrin adhesomes, which are “signaling points” (Schiller and Fäßler, 2013). Proteins that bind the intracellular domain of β-integrins are able to activate these β-integrins and to increase their adhesion to the ECM. β1 integrins, the largest integrin subfamily, are usually involved in cell migration, proliferation, and differentiation, and they participate in development, tissue homeostasis, and tumor progression. Integrin-targeted biological therapies can be very effective tools for tumor suppression (Marelli et al., 2013).

Recent studies have demonstrated how in genetically engineered cells diff-