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PHIPing Out: A Genetic Basis for Tumor Ulceration

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Abstract

Ulceration is a common negative prognostic marker of solid tumors including melanoma. The signaling basis of ulceration is being elucidated. PHIP has been found to be amplified in wild-type melanomas, resulting in Akt activation and aerobic glycolysis (Warburg effect), associated with ulceration. The ulceration phenotype likely represents the genotype of the reactive oxygen driven tumor, in which reactive oxygen drives angiopoietin-2 production, tumor growth, and invasion. This phenotype is amenable to pharmacologic intervention.

Ulceration is a common phenomenon in dermatology and an adverse prognostic factor in melanoma. For many years, ulceration has been described as “a tumor outgrowing its blood supply”. However, if blood supply is insufficient, why is ulceration an adverse prognostic factor? We have shown that the majority of cutaneous ulcers are not due to insufficient vascularity, but due to excess vascularity (Arbiser *et al.*, 2003). High levels of matrix metalloproteinases and unstable vasculature result in a “hostile” environment for epithelialization, leading to ulceration (Munavalli *et al.*, 2003). Ultimately, the factors that promote ulceration are not well understood.

Kashani-Sabet *et al.* have now identified pleckstrin homology domain–interacting protein (PHIP) copy number, initially as the top-rated gene differentially expressed between metastatic melanoma and primary melanoma (Bezrookove *et al.* 2014). 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 counter-intuitive 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- κ B activation and the ability to survive under extreme hypoxia (Govindarajan *et al.*, 2007). The authors demonstrated the downregulation of biomarkers of the Warburg phenomenon, including LDH5, HIF1a, and VEGF.

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CONFLICT OF INTEREST

The author states no conflict of interest.

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 in melanoma with the reactive oxygen–driven phenotype, in which reactive oxygen drives NF- κ B 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 in sepsis (Tanaka *et al.*, 1999; Helfrich *et al.*, 2009; Kranidioti *et al.*, 2009). If this is the case, PHIP-overexpressing melanomas might be susceptible to reactive oxygen inhibition. Finally, could PHIP overexpression be a mechanism of resistance to Braf inhibition, especially as PHIP has been associated with insulin growth factor receptor 1 (IGFR1) signaling (Reuveni *et al.*, 2013)?

So-called targeted therapies have focused on either Braf inhibition alone or combination treatment with MEK inhibitors. Predictably, resistance has arisen owing to failure to affect the phosphoinositol-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 phosphoinositol-3 kinase/Akt/reactive oxygen pathway inhibitors could well result in improved long-term survival and even the possibility of cure.

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References

- Arbiser JL, Bips M, Seidler A, et al. Combination therapy of imiquimod and gentian violet for cutaneous melanoma metastases. *J Am Acad Dermatol.* 2012; 67:e81–3. [PubMed: 22794825]
- Arbiser JL, Johnson D, Cohen C, et al. High-level expression of vascular endothelial growth factor and its receptors in an aphthous ulcer. *J Cutan Med Surg.* 2003; 7:225–8. [PubMed: 12574903]
- Bezrookove V, De Semir D, Nosrati M, et al. Prognostic Impact of PHIP copy number in melanoma: linkage to ulceration. *J Invest Dermatol.* 2014; 134:783–90. [PubMed: 24005052]
- Fried L, Arbiser JL. The reactive oxygen-driven tumor: relevance to melanoma. *Pigment Cell Melanoma Res.* 2008; 21:117–22. [PubMed: 18384505]
- Govindarajan B, Sligh JE, Vincent BJ, et al. Overexpression of Akt converts radial growth melanoma to vertical growth melanoma. *J Clin Invest.* 2007; 117:719–29. [PubMed: 17318262]
- Helfrich I, Edler L, Sucker A, et al. Angiopoietin-2 levels are associated with disease progression in metastatic malignant melanoma. *Clin Cancer Res.* 2009; 15:1384–92. [PubMed: 19228739]
- Kranidioti H, Orfanos SE, Vaki I, et al. Angiopoietin-2 is increased in septic shock: evidence for the existence of a circulating factor stimulating its release from human monocytes. *Immunol Lett.* 2009; 125:65–71. [PubMed: 19539650]

- Lapidoth M, Ben-Amitai D, Bhandarkar S, et al. Efficacy of topical application of eosin for ulcerated hemangiomas. *J Am Acad Dermatol.* 2009; 60:350–1. [PubMed: 19150285]
- Munavalli G, Reisenauer A, Moses M, et al. Weight loss-induced calciphylaxis: potential role of matrix metalloproteinases. *J Dermatol.* 2003; 30:915–9. [PubMed: 14739520]
- Munson JM, Fried L, Rowson SA, et al. Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma. *Sci Transl Med.* 2012; 4:127ra36.
- Reuveni H, Flashner-Abramson E, Steiner L, et al. Therapeutic destruction of insulin receptor substrates for cancer treatment. *Cancer Res.* 2013; 73:4383–94. [PubMed: 23651636]
- Tanaka S, Mori M, Sakamoto Y, et al. Biologic significance of angiotensin-2 expression in human hepatocellular carcinoma. *J Clin Invest.* 1999; 103:341–5. [PubMed: 9927494]

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).

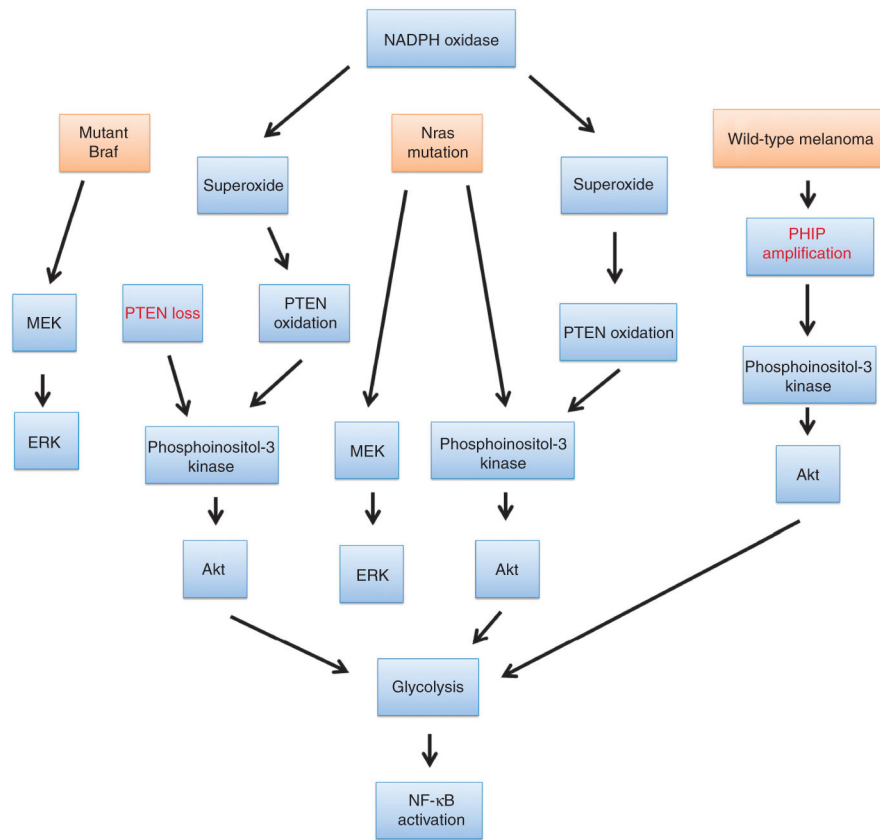


Figure 1. Convergence of pathways in melanoma leads to NF-κB activation and glycolysis
 The major pathways in melanoma, Braf mutation, Nras mutation, and PIP3 mutation all potentially involve a superoxide/Akt/NF-κB pathway (reactive oxygen-driven pathway) to result in glycolysis, NF-κB activation, and ulceration through angiopoietin-2 expression.