PLEKHA5: A Key to Unlock the Blood–Brain Barrier?

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Running Title: Role of PLEKHA5 in CNS Homing

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Summary

Brain metastases represent a devastating complication of melanoma. Our understanding of the mechanisms driving metastasis to the brain is limited. PLEKHA5 functions as a regulator of brain metastasis in melanoma and further investigation is warranted to explore this as a potential therapeutic target.
In this issue of *Clinical Cancer Research*, Jilaveanu and colleagues (1) nominate PLEKHA5 as a candidate regulator of brain metastasis in melanoma.

Up to 75% of patients with stage IV melanoma will develop central nervous system (CNS) metastasis during the course of their disease. Historically, overall survival after diagnosis of brain metastases ranges between 4-5 months. Recently, remarkable progress has been made in the development of effective therapies in advanced melanoma, specifically with immunotherapy and targeting of the RAS-RAF-MAPK pathway. Although these treatments have demonstrated success in systemic disease, patients often develop brain metastases while on these treatments. Unfortunately, little is known about the mechanisms implicated in CNS evasion of these therapies and cerebrotropism.

Jilaveanu and colleagues identify PLEKHA5 as a gene involved in the mechanism of CNS homing of metastatic disease. Through gene expression profiling of a parental melanoma cell line (A375P) and a cerebrotropic derivative (A375Br), the investigators find differential expression of PLEKHA5. Using an impressive cohort of metastatic melanoma cases of variable time to brain metastasis development, the authors also demonstrate that PLEKHA5 protein expression correlates with brain metastasis free survival. Silencing of PLEKHA5 expression by siRNA results in decreased cell viability and also decreased *in vitro* potential for crossing the blood-brain barrier.

While the mechanism by which PLEKHA5 mediates this clinical phenotype has yet to be elucidated, Jilaveanu and colleagues postulate that PLEKHA5 may interact with the PI3K/AKT pathway (Fig. 1). It has recently been recognized that there is preferential up-regulation of the PI3K-AKT pathway in cerebral compared to extracerebral metastases (2), and that loss of PTEN correlates with earlier development of brain metastases (3), perhaps as a result of an intrinsic
The PI3K-AKT pathway in melanoma is commonly activated via activating mutations in NRAS or loss of PTEN (4). Loss of PTEN not only appears to lead to higher activation of the PI3K-AKT pathway, but also increases invasiveness and metastatic potential in melanoma (5). Moreover, there appears to be a strong correlation between PTEN loss and BRAF activation (4). Consistent with other reports, Niessner et al. (2013) observed that while patients treated with vemurafenib for metastatic melanoma demonstrate treatment response extracranially, they can concomitantly develop brain metastases (6). In an analysis of matched brain and systemic metastases of nine patients, they found activation of the PI3K-AKT pathway in the brain, but not in other metastatic lesions. Of note, inhibition of the PI3K-AKT pathway with the PI3K-inhibitor GDC-0941 lead to growth inhibition of brain metastasis derived melanoma cells \textit{in vitro}. Upregulation of the PI3K-AKT pathway was also reported in a recent study of matched cerebral and extracerebral metastases samples using analysis of hotspot mutations, copy-number variations, mRNA expression patterns and quantitative analysis of protein expression and activation by reverse-phase protein array analysis (2).

The PLEKHA family consists of 7 proteins (PLEKHA1-7) characterized by the pleckstrin homology (PH) and Trp-Trp WW domains. The PH domain is thought to mediate phosphoinositide binding properties and therefore has been associated with various intracellular functions, including phosphoinositide (PI3) metabolism, protein phosphorylation, and cytoskeletal organization (7,8). Jilaveanu et al. therefore propose that PLEKHA5 may intersect with the PI3K-AKT pathway via the PH domain, hence guiding the cerebrotropic phenotype. Dowler et al. described ubiquitous expression of PLEKHA5 (PEPP-2) in several human tissue and cancer cell lines (9). Another member of the PLEKHA family, PLEKHA4 was expressed in
a human melanoma cell line (9). The work of Yamada et al. (10) identified several splicing variants of the PLEKHA5 transcript in various human tissues, confirming binding specificity of PLEKHA5 to PI(3,5)P2. In the developing mouse brain, PLEKHA5 is localized to the cytosol of neurons (10). Zou et al. also demonstrated expression of PLEKHA5 in cell membranes and microtubules, implicating roles in cell migration and cell-cell interaction (11). Given these previously described properties, PLEKHA5 may indeed play an important role at the blood brain barrier, facilitating transmigration and homing for cerebrotropic melanoma cells via activation of the PI3K pathway. Jilaveanu and colleagues are now studying the crosstalk between PLEKHA5 and the PI3K pathway.

Future studies should investigate the change of PLEKHA5 expression over time. Furthermore, given the trend correlating PLEKHA5 expression with developing earlier brain metastases, future work will be needed to correlate PLEKHA5 expression in a larger cohort. As the authors suggest, while PLEKHA5 does not represent a therapeutic target at the moment, expression level of this gene may be explored as a biomarker to guide clinical decisions regarding CNS surveillance for patients with melanoma. In addition, mechanistic studies in animal models to understand the role of PLEKHA5 in cerebrotropism are warranted. It may be of interest to also systematically characterize the promoter region of PLEKHA5 to determine the cancer-specific genomic and epigenomic alterations that drive increased expression. This type of analysis could provide a mechanistic insight analogous to the identification of non-coding mutations in the promoter of the overexpressed TERT gene, which have been identified in a wide range of cancers including melanoma (12). The research by Jilaveanu and colleagues adds significantly to our current understanding of metastatic melanoma to the brain, an area of great clinical need.
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Figure 1. Schematic of the alterations of the PI3K/AKT pathway in metastatic melanoma. Activation of the PI3K/AKT pathway has been reported in brain metastases from melanoma. PLEKHA5 functions as a regulator of brain metastasis in melanoma. It is postulated that PLEKHA5 may interact with the PI3K/AKT pathway, which is an area of active investigation. Illustration of the PI3K/AKT pathway adapted from Kwong and Davies (13).
Figure 1:
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