

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

Sylvia C. Eisele¹, Corey M. Gill¹, Ganesh M. Shankar², and Priscilla K. Brastianos^{1,3}

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 inves-

tigation is warranted to explore the use of PLEKHA5 as a potential therapeutic target. *Clin Cancer Res*; 21(9); 1978–80. ©2015 AACR.

See related article by Jilaveanu et al., p. 2138

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 develop central nervous system (CNS) metastases during the course of their disease. Historically, overall survival after diagnosis of brain metastases ranges between 4 and 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 (1) 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 found differential expression of *PLEKHA5*. Based on an impressive cohort of patients with a variable length of time between diagnosis of melanoma and development of brain metastasis, the authors also demonstrate that *PLEKHA5* protein expression correlates with brain metastasis-free survival. Silencing of *PLEKHA5* expression by siRNA resulted in decreased cell viability and also decreased *in vitro* potential for crossing the blood-brain barrier.

Although the mechanism by which *PLEKHA5* mediates this clinical phenotype has yet to be elucidated, Jilaveanu and colleagues (1) postulate that *PLEKHA5* may interact with the PI3K-AKT pathway (Fig. 1). A preferential upregulation of the PI3K-AKT

pathway was recently recognized in cerebral compared with extracerebral metastases (2), and loss of *PTEN* was correlated with earlier development of brain metastases (3), perhaps as a result of an intrinsic activation of tropism for the cerebral microenvironment. The PI3K-AKT pathway in melanoma is commonly activated via 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 and colleagues (6) observed that although patients treated with vemurafenib had an extracranial response to treatment, they also showed concomitant development of brain metastases. In an analysis of matched brain and systemic metastases in 9 patients, these authors 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 leads to growth inhibition of brain metastasis-derived melanoma cells *in vitro*. Upregulation of the PI3K-AKT pathway was also reported in a recent study of matched cerebral and extracerebral metastasis samples using analysis of hotspot mutations, copy-number variations, mRNA expression patterns, quantitative analysis of protein expression, and activation by reverse-phase protein array analysis (2).

The PLEKHA family consists of seven 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 and colleagues (1) therefore propose that *PLEKHA5* may intersect with the PI3K-AKT pathway via the PH domain, hence guiding the cerebrotropic phenotype. In the earlier literature, Dowler and colleagues (9) described ubiquitous expression of *PLEKHA5* (*PEPP-2*) in several human tissue and cancer cell lines. Another member of the PLEKHA family, *PLEKHA4*, was expressed in a human melanoma cell line (9). Later, Yamada and colleagues (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 and colleagues (11) also demonstrated expression of *PLEKHA5* in cell membranes and microtubules, implicating its role in cell migration and cell-cell interaction. Given these previously described properties,

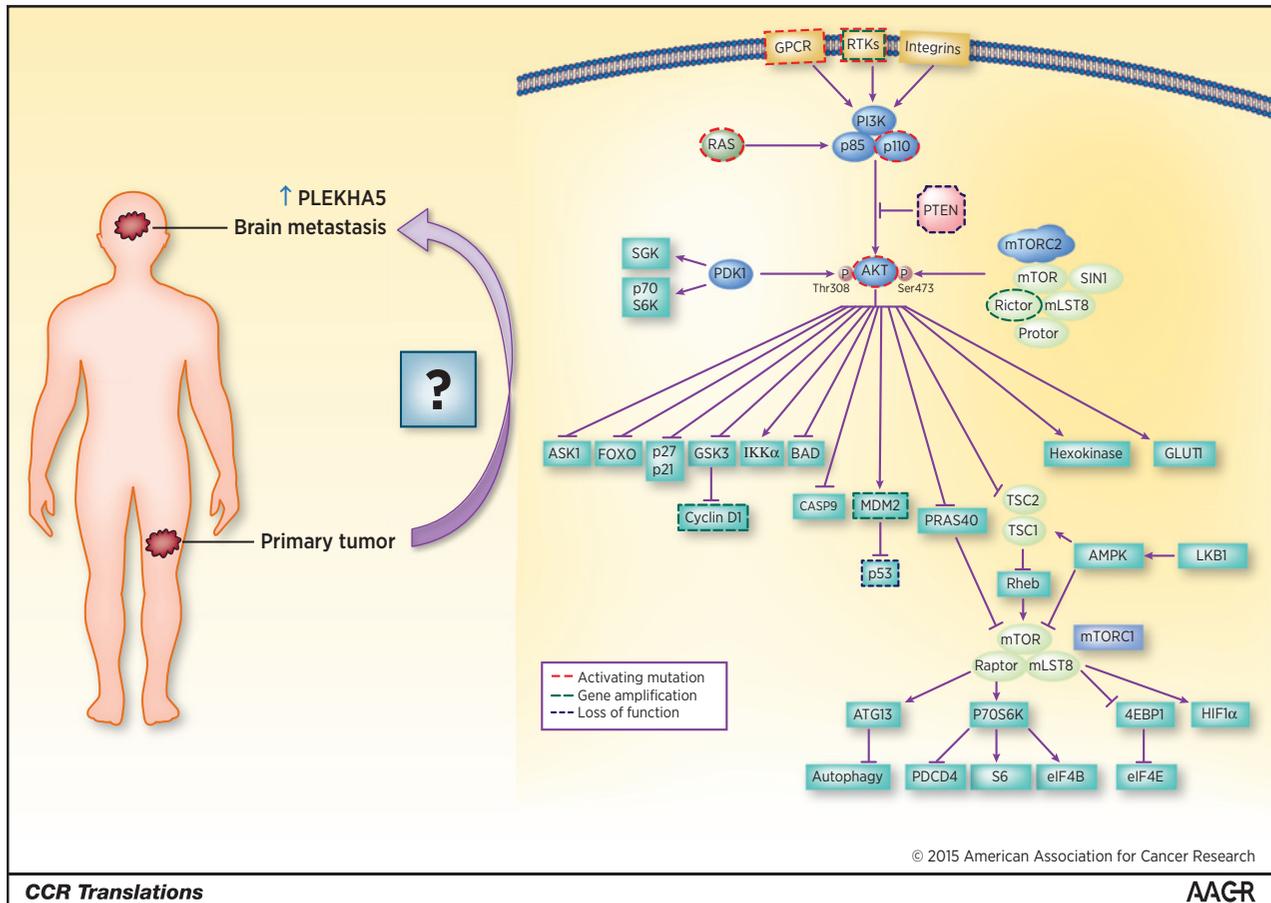
¹Division of Neuro-Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. ²Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. ³Division of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Note: S.C. Eisele, C.M. Gill, and G.M. Shankar contributed equally to this article.

Corresponding Author: Priscilla K. Brastianos, Central Nervous System Metastasis Program, Division of Neuro-Oncology, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9E, Boston, MA 02115. Phone: 617-643-1938; Fax: 617-643-2591; E-mail: pbrastianos@mgh.harvard.edu

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**Figure 1.**

Schematic of the alterations of the PI3K-AKT pathway in metastatic melanoma. The interaction of PLEKHA5 with the PI3K-AKT pathway is an area of active investigation. Adapted from Kwong and Davies (4).

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 report on their investigation of the cross-talk between PLEKHA5 and the PI3K pathway in the present article.

Future studies should examine the change of *PLEKHA5* expression over time. Furthermore, given the trend correlating *PLEKHA5* expression with early development of brain metastases, future work will be needed to correlate *PLEKHA5* expression with brain metastasis in a larger cohort of patients with melanoma. As the authors suggest, although *PLEKHA5* does not represent a therapeutic target at the moment, the expression level of this gene may be worth exploring as a biomarker to guide clinical decisions regarding CNS surveillance for patients with melanoma. In addition, mechanistic studies in animal models to enhance our understanding of the role of PLEKHA5 in cerebrotropism are warranted. Systematic characterization of the promoter region of *PLEKHA5* to determine the cancer-specific genomic and epigenomic alterations that drive increased expression may also be of interest. This type of analysis could provide a mechanistic insight analogous to the identification of noncoding mutations in the promoter of the overexpressed *TERT* gene identified in a wide range of cancers, including melanoma (12). The work of Jilaveanu and colleagues (1) adds significantly to our current understanding of melanoma metastasis to the brain, an area of great clinical need.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.K. Brastianos

Development of methodology: P.K. Brastianos

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.K. Brastianos

Writing, review, and/or revision of the manuscript: S.C. Eisele, C.M. Gill, G.M. Shankar, P.K. Brastianos

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.K. Brastianos

Study supervision: P.K. Brastianos

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