CORRESPONDENCE

Microphthalmia-Associated Transcription Factor

A Central Regulator of Pigment Epithelium-Derived Factor Controlling Human Melanoma Progression

To the Editor-in-Chief:

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We read with great interest the article by Dadras et al¹ in *The American Journal of Pathology* describing microphthalmia-associated transcription factor (MITF) as a regulator of pigment epithelium-derived factor (PEDF) in human melanoma. Although we are pleased to see that the authors have confirmed our recent results,² we feel that the authors overlooked a careful review of the concurrent literature on the biological role of PEDF during melanoma progression and the identification of MITF as a transcriptional regulator of PEDF.

First, Dadras et al¹ state in their abstract that “PEDF expression and/or regulation during melanoma development have not been investigated previously.”^{p.252} This statement is inaccurate, as our group³ and another⁴ have previously addressed this point. Specifically, by performing a high-throughput analysis of the data from molecular profiling studies of human melanoma cell lines, we demonstrated that PEDF is highly expressed in melanocytes and low aggressive melanoma cells but is lost in highly aggressive melanomas.³ Furthermore, we studied paired cell lines isolated from human metastatic lesions displaying extreme phenotypes and demonstrated that PEDF expression is restricted to the less aggressive counterparts.³ In mouse models of human melanoma metastases, we established that PEDF levels critically impact melanoma progression by gain and loss of function experiments (PEDF overexpression or silencing, respectively).³ The mention of a subsequent study

identifying the mechanisms by which PEDF exerts its anti-metastatic actions⁴ is also missing from the article by Dadras et al.¹ Importantly, this study showed that PEDF is able to efficiently block two modes of melanoma invasion by suppressing amoeboid morphology and mesenchymal proteolysis.⁴

Second, Dadras et al¹ show that PEDF is a direct transcriptional target of MITF in human melanocytes and melanoma cells but overstate the novelty of their discoveries. We have recently demonstrated that PEDF expression positively correlates with MITF during human melanoma progression.² Of note, we showed that oncogene-induced senescence promotes down-regulation of PEDF and MITF in primary melanocytes, providing a likely explanation to the lack of PEDF and MITF expression in nevi described in our article² and confirmed by Dadras et al.¹ Furthermore, we identified three MITF regulatory sites in the first intron of *SERPINF1* based on published ChIP-seq data⁵ that were further validated by an independent ChIP-seq experiment² and reporter assays that revealed that at least two of the identified MITF-binding sites have functional activity. Importantly, our study also provided a functional connection between MITF and PEDF, which is critical for melanoma dissemination.² Using an established zebrafish model of metastasis, we demonstrated that *in vivo* dissemination of human melanoma cells induced by *MITF* silencing is halted by PEDF sustained expression,² providing solid evidence for the role of the MITF–PEDF axis in the control of melanoma biology.

In summary, we believe that the article published by Dadras et al¹ lacks a complete description of the previous findings describing the biological role of PEDF and its regulation by MITF during human melanoma progression. We consider it important to highlight these references to the readers of the *Journal*.

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Authors' Reply

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We thank Dr. Benilde Jiménez Cuenca and colleagues for bringing to our attention the research by Fernandez-Barral et al¹ reporting the regulatory and functional relationship imposed by microphthalmia-associated transcription factor (MITF) on pigment epithelium-derived factor (PEDF) in melanoma. We assure the authors that we were completely unaware of their publication, presumably because both

manuscripts were likely under review at the same time. By the time our manuscript² was accepted for publication (September 5, 2014), their article had only recently been published (June 2014).

Nevertheless, we are pleased that our *in vitro* findings were independently confirmed by another group of investigators. The two papers have indeed taken similar approaches in demonstrating the transcriptional control of PEDF by MITF *in vitro* and decreased PEDF expression during melanoma progression. In addition, our focus was more clinical by taking a cohort of 102 patients with well-defined and characterized melanocytic tumors to be investigated for PEDF expression by immunohistochemistry. We also correlated the expression of PEDF to the extent of measured angiogenesis in the melanoma biopsies, American Joint Committee on Cancer melanoma staging, and patient clinical outcome. Our finding of inverse correlation between PEDF expression and Breslow's depth of tumor invasion is a critical clinical parameter related to tumor progression. Depth of tumor invasion, along with ulceration and mitotic index, are currently the most important criteria to predict prognosis for melanoma patients. Thus we enthusiastically agree that Fernandez-Barral et al¹ have made significant contributions to the field. We also wish to highlight the value of extending the field by addition of the clinical correlations that our study provides.

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