To the Editor-in-Chief:
We read with great interest the article by Dadras et al 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, 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 al state in their abstract that “PEDF expression and/or regulation during melanoma development have not been investigated previously.” This statement is inaccurate, as our group and another 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. 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. 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). The mention of a subsequent study identifying the mechanisms by which PEDF exerts its antimetastatic actions is also missing from the article by Dadras et al. Importantly, this study showed that PEDF is able to efficiently block two modes of melanoma invasion by suppressing ameboid morphology and mesenchymal proteolysis. Second, Dadras et al 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. 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 article and confirmed by Dadras et al. Furthermore, we identified three MITF regulatory sites in the first intron of SERPINF1 based on published ChIP-seq data that were further validated by an independent ChIP-seq experiment 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. 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, 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 al 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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