CORRESPONDENCE

Does a Microphthalmia-Associated Transcription Factor—Pigment Epithelium—Derived Factor Axis Exist in All Types of Pigment Cells?

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To the Editor-in-Chief:

In a recent article¹ published and highlighted² in the correspondence section in *The American Journal of Pathology*, Dadras et al¹ found that, in primary melanocytes and melanoma cells, the microphthalmia-associated transcription factor (MITF) regulates the expression of the gene-encoding pigment epithelium—derived factor (PEDF). In addition, the authors suggested that PEDF plays critical roles in melanoma progression. Consistent with these results, Fernández-Barral et al³ earlier reported that MITF regulates the expression of PEDF in melanoma cells and inhibits melanoma metastasis. On the basis of the similar results published by two independent research groups, there seems to be little doubt that the MITF-PEDF axis regulates melanoma metastasis.

PEDF was originally discovered not in melanoma cells but in a different melanin-bearing, non-transformed cell type, human retinal pigment epithelial cells.⁴ We have previously shown that MITF regulates PEDF in retinal pigment epithelial cells to inhibit their migration.⁵ Because retinal pigment epithelial cells are embryologically derived from the optic neuroepithelium, and melanoma cells, ultimately from the neural crest, it follows that pigment cells of distinct embryological origin and functions are apparently both under the control of the same transcription factor or target gene. Nevertheless, several important questions still need to be addressed.

First, are PEDF functions limited to migration of melanoma cells or can they be extended to melanoblasts and melanocytes during development or in wound healing and vitiligo repigmentation? It is well known that *MITF* mutations in humans are associated with Waardenburg syndrome type 2, a syndrome characterized by skin hypopigmentation and ocular

pigmentation defects.⁶ Indeed, MITF plays important roles in melanoblast migration, and we recently found that it regulates melanoblast migration by repressing the melanoma cell adhesion molecule.⁷ Involvement of PEDF in this pathway, however, has not yet been demonstrated.

Second, how does PEDF inhibit melanoma metastasis? Both Dadras et al¹ and Fernández-Barral et al³ clearly show a role for MITF to regulate PEDF, but how PEDF inhibits migration remains open. Because our earlier work⁵ identified impairment of microtubule dynamics as at least one of the mechanisms underlying migration inhibition, it is tempting to speculate that a similar mechanism might be operating in melanoma.

In summary, we do believe that the MITF-PEDF axis plays important roles in pigment cell migration. The above considerations make it important now to identify the underlying mechanisms by which PEDF controls melanoma metastasis.

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