xenobiotic metabolism. Similar to K14-VPPXR mice, mice that expressed constitutively active AhR in the skin (AhR-CA mice) developed AD-like inflammation, including barrier disruption and increased expression of cytokines associated with type 2 inflammation. However, AhR-CA mice developed more apparent skin lesions and itch symptoms compared with K14-VPPXR mice. AhR was suggested to directly bind the promoters for the proinflammatory factors TSLP and IL-33 in keratinocytes to drive expression of these cytokines and downstream inflammation (Hidaka et al., 2017). The observation that K14-VPPXR mice do not have increased IL-33 expression in the skin shows divergence in the functions of PXR and AhR in keratinocytes. Further investigation on the relative roles of PXR and AhR signaling in AD, including how these transcription factors may regulate each other in response to cutaneous xenobiotic exposure, is warranted.

Although emerging evidence indicates that increased activity of factors related to xenobiotic metabolism leads to skin barrier disruption, previous studies have shown that these pathways are critical for maintaining normal skin development and function. For instance, mice globally deficient in AhR, as well as mice that lack AhR ligands in their diet, develop epidermal dysfunction, although the factors responsible for these changes have not been completely characterized (Haas et al., 2016). These findings suggest that a balance of xenobiotic ligand-receptor interactions is needed for optimal barrier homeostasis and results in disease when dysregulated. Thus, a better understanding of these metabolic pathways may pave the way for novel therapeutic interventions in AD.

Although the causes of AD remain mysterious, Elentner et al. (2017) shed light on a mechanism linking xenobiotic metabolism to AD pathogenesis. As more of the world's population begins to encounter increasing levels of xenobiotics through urbanization, a better understanding of how these factors influence the skin becomes paramount. Beyond the skin, this work has implications across multiple barrier surfaces as AD is often the first step in a disease progression, called the atopic march, that includes food allergy and asthma. Based on this work, an examination of whether modulation of cutaneous xenobiotic metabolism can influence other organ systems such as the gut and lung remains a provocative question that could have broad implications for multiple allergic disorders.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Get with the Program! Stemness and Reprogramming in Melanoma Metastasis

Fernanda Faião-Flores[1] and Keiran S.M. Smalley[1,2]

Cancer cells are highly plastic and adopt multiple phenotypic states that contribute to tumor progression. Heppt et al. demonstrate that the homeodomain transcription factor Msh homeobox 1 reprograms melanoma cells to a precursor state associated with melanoma progression and increased liver metastasis. Identification of this new role for Msh homeobox 1 may facilitate the development of new therapies that limit melanoma dissemination.

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Heppt et al. (2017) report new data that identify the homeodomain transcription factor Msh homeobox 1 (MSX1) as a master regulator that reprograms melanocytes to a de-differentiated, stem-like state (Figure 1). The authors further demonstrate that MSX1 plays an important role in melanoma progression, potentially through the regulation of liver metastasis development (Heppt et al., 2017). To date, MSX1 has been most widely studied in embryonic development, where it has been implicated in neural crest specification and primordial germ cell migration through the induction of

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> The likelihood that these primitive cells are those that metastasize and maybe even resist therapies makes them attractive future targets for drug discovery.

multiple transcription factors including SNAIL, SLUG, and FOXD3 (Tribulo et al., 2003).

Melanocyte Development and Tissue Homeostasis

Under normal homeostasis, the behavior of nontransformed cells is subject to tight regulation by local host microenvironments. These interactions, which can be mediated through cell-cell adhesion, cell-matrix adhesion, gap junctions, and growth factors, give rise to critical signals that dictate whether cells grow, divide, or move (Smalley et al., 2005). Much of the control, and the tissue architecture of epithelial cell layers, is dependent on homotypic E-cadherin/E-cadherin-based adhesions between neighboring cells. This strong E-cadherin-mediated adhesion, along with that involving tight junction proteins, physically locks cells together ensuring tissue stability and optimal organ function. In early embryonic development, some epithelial cells downregulate their E-cadherin expression, acquire the phenotypic and motile characteristics of mesenchymal cells, and migrate to other anatomical sites. This process, called the epithelial-to-mesenchymal transition (EMT), is a key developmental program that permits cells to move over long distances before redifferentiating, restoring their epithelial characteristics, and re-establishing contact with their neighbors (a process called the mesenchymal-to-epithelial transition, or MET). In addition to being critical for normal organismal development, reactivation of the EMT transcriptional program can also occur in cancer, where it is frequently associated with metastasis (Smalley et al., 2005).

Melanocytes, the pigment-producing cells of the skin, develop from neural crest progenitor cells that have migrated to the skin and differentiated following the expression of the lineage-specific microphthalmia-associated transcription factor (MITF). Once located at the dermal-epidermal junction, differentiated melanocytes interact closely with the surrounding skin keratinocytes, in part through though E-cadherin-based cell-cell adhesion (Smalley et al., 2005). Keratinocytes regulate melanocytes, controlling everything from their growth to the synthesis and transport of melanin following ultraviolet light exposure (through the release of paracrine α-melanocyte stimulating hormone from the keratinocytes) (Kawakami and Fisher, 2017; Smalley et al., 2005). Escape of melanocytes from keratinocyte control is a key step in melanoma development, and it is absolutely required for nascent melanoma cells to both grow in an uncontrolled manner and migrate out of skin. This process is still incompletely understood, but it is frequently accompanied by an EMT-like switch associated with the loss of E-cadherin expression and acquisition of mesenchymal markers such as SNAIL, SLUG, TWIST, and ZEB1 (Caramel et al., 2013; Smalley et al., 2005) (Figure 1).

The Link between Melanocyte Reprogramming and Melanoma Metastasis

The goal of the study by Heppt et al. (2017) was to identify novel factors involved in melanocyte reprogramming and de-differentiation. This work is a continuation of a prior study in which the same authors identified the developmental regulator Notch-1 as a factor that reprogrammed fully-differentiated melanocytes into multipotent neural crest stem cells (Heppt et al., 2017). MSX1 was chosen based on its significantly increased expression in the Notch-1 reprogrammed cells. For this reason, and also because of its known role in neural crest differentiation, the authors hypothesized that MSX1 might drive melanocyte reprogramming and stemness.

The authors began by demonstrating that multiple, normal, nontransformed human melanocytes expressed very low levels of MSX1. Re-expression of MSX1 in the melanocytes led to

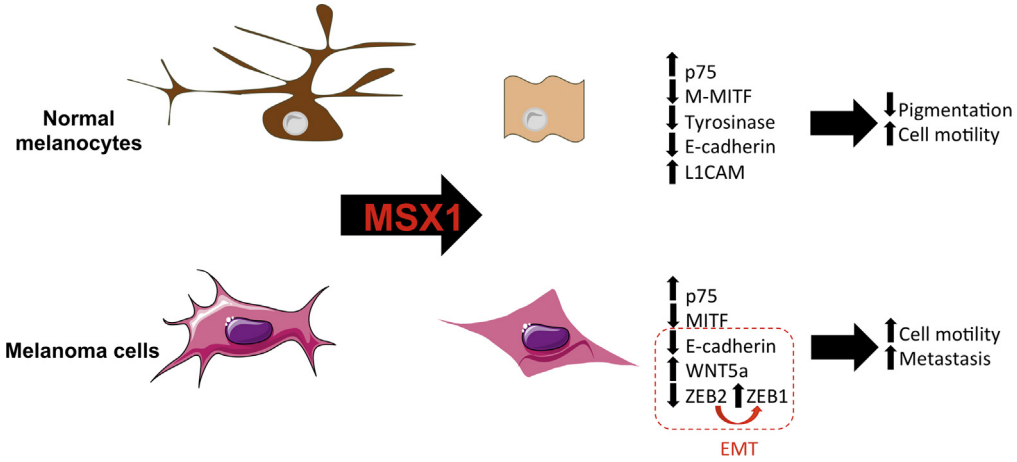

Figure 1. MSX1 provides the link between melanocyte reprogramming and melanoma metastasis. Induction of MSX1 expression leads to decreased expression of melanocyte lineage factors and drives a switch to a neural crest-like phenotype. Increased expression of MSX1 in melanoma cells is associated with suppression of MITF expression and increased metastasis associated with increased p75 nerve growth factor receptor, Wnt5a, and ZEB1 expression. EMT, epithelial-to-mesenchymal transition; MITF, microphthalmia-associated transcription factor; MSX1, Msh homeobox 1.