

insight that is essential to improving the efficacy of KIT inhibition. Additional studies on tumor biopsies to further define the complex interplay between different *KIT* mutations and downstream signaling pathways, as well as evaluation of novel targeted therapy and immunotherapy combinations with KIT inhibitors, are needed. Effective collaboration between investigators and research consortia, the creation of international registries and tumor banks to facilitate larger biological studies, and the use of novel clinical trial designs for rare tumors will be critical to the advancement of care for *KIT*-altered melanoma moving forward.

CONFLICT OF INTEREST

RDC is a consultant for AstraZeneca, BMS, Iconic Therapeutics, Janssen, Merck, Novartis, Roche/Genentech, and Thomas Reuters; and is in clinical/advisory board of Aura Biosciences, Chimeron, and RGenix. The rest of the authors state no conflict of interest.

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See related article on pg 109

PXR: A New Player in Atopic Dermatitis



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Epidemiological evidence suggests that environmental pollutants contribute to atopic dermatitis, but mechanistic details are currently lacking. Elentner et al. show that PXR, a key transcription factor involved in pollutant metabolism, drives features of subclinical atopic dermatitis. These observations provide new insight into how environmental insults may predispose individuals to atopic dermatitis.

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Atopic dermatitis (AD) is a chronic, relapsing skin disease that places a substantial social and economic burden on both patients and their caretakers. Although AD currently affects up to 10–20% of the population, its prevalence is on the rise, particularly in developing, urban areas (Kantor and Silverberg, 2017; Weidinger and Novak, 2016). Although genetic factors are known to contribute to disease susceptibility, this increase in prevalence suggests that the environment plays a prominent role in the

development of AD. A growing body of evidence points to the surge in exposure to chemical contaminants common in urban environments as a driving factor of disease (Hidaka et al., 2017; Kim, 2015). These contaminants, known broadly as xenobiotics, encompass a wide range of compounds encountered in daily life, from cosmetics to air pollutants, and many have been shown to penetrate the skin and accumulate over time (Chu et al., 1996; Hidaka et al., 2017; Kantor and Silverberg, 2017). Although numerous

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Compromised barrier function as observed in AD might lead to increased penetration by lipophilic pollutants, thereby triggering PXR in keratinocytes and sustaining a vicious circle of immune hyperresponsiveness and impaired barrier function.

epidemiological studies have found that xenobiotic exposure increases the risk of AD development, the mechanistic evidence detailing the role of xenobiotics in AD has remained elusive.

Central to the body's defense against the continuous barrage of xenobiotics is

the transcription factor PXR, a member of the nuclear hormone receptor family. Activated by many different compounds, PXR regulates the expression of enzymes involved in all stages of xenobiotic metabolism and elimination (Kliewer et al., 2002). Although past research has focused on the role of PXR in the digestive tract and lung (Kliewer et al., 2002), previous work by Elentner et al. (2015) has helped expand our understanding of PXR in the skin by showing that this factor responds to cutaneous pollutant exposure. However, the role of PXR signaling in AD pathogenesis, particularly when driven by the myriad of xenobiotics that patients encounter throughout their lifetimes, is unknown.

Elentner et al. (2017) tackled this problem by generating a novel transgenic mouse that overexpresses humanized PXR specifically in the epidermis under the keratin-14 promoter (K14-VPPXR mice). This model system aimed to mimic what may occur in vivo after repeated exposure to xenobiotics.

Surprisingly, the skin of K14-VPPXR mice appeared grossly normal and lacked other clinical features of skin barrier dysfunction such as chronic itch (Elentner et al., 2017). However, upon closer examination, constitutive activation of PXR triggered changes in the skin microenvironment that recapitulated several key histopathologic and physiologic features of AD such as epidermal hyperplasia, enhanced transepithelial water loss, and elevated skin pH. Additionally, the skin of K14-VPPXR mice had elevated expression of chemokines and cytokines associated with global T helper type 2 and T helper type 17 cell responses (CCL27, TSLP, IL-13, IL-6, and IL-17A) (Figure 1). Thus, this article shows that dysregulation of a single xenobiotic metabolic pathway in the skin is sufficient to drive epithelial dysfunction and inflammation.

Strikingly, the changes found in K14-VPPXR mice resemble what has been previously observed in nonlesional skin of AD patients. Similar to K14-VPPXR mice, nonlesional AD skin is characterized by barrier dysfunction, subclinical signs of inflammation, and a distinct transcriptional signature despite a normal clinical appearance (Suárez-Fariñas et al., 2011). To more thoroughly characterize the connection between the overactivation of PXR and the pathologic changes found in nonlesional AD skin, Elentner et al. (2017) sought to examine PXR signaling levels in patient biopsy samples. Using this approach, an elevation of the downstream PXR targets CYP3A4 and UGT1A1 was found in nonlesional AD skin, although the expression of PXR itself was not changed. Thus, this work suggests that PXR overactivation by xenobiotics may help propagate the abnormalities observed in nonlesional AD skin. However, whether these subclinical changes due to aberrant PXR signaling sets the stage for future disease exacerbations, such as active lesion and itch development, remains to be determined.

This current work complements a recent study showing that keratinocyte-specific expression of a constitutively active form of another key mediator of xenobiotic metabolism, aryl hydrocarbon receptor (AhR), leads to an AD-like phenotype (Hidaka et al., 2017). Like PXR, AhR can be activated by multiple environmental compounds and promote expression of genes important in

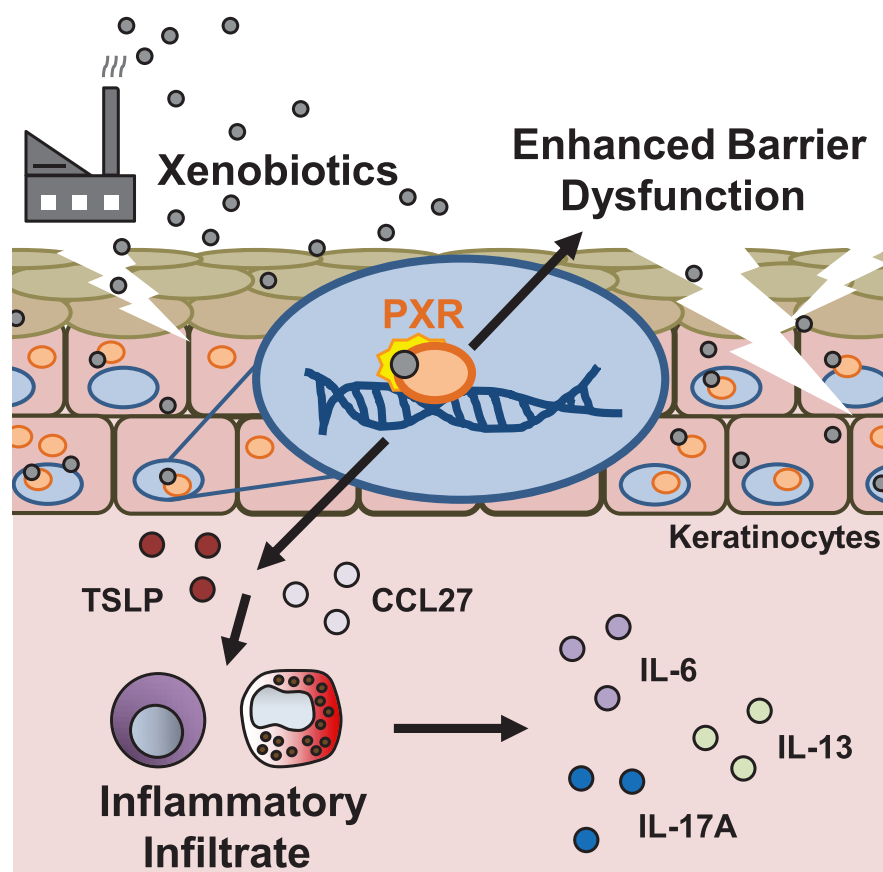


Figure 1. A role of PXR in atopic dermatitis. Xenobiotics, or foreign compounds and contaminants, are able to penetrate the skin and activate PXR. Elentner et al. (2017) show that PXR overexpression in keratinocytes drives features of atopic dermatitis, including epidermal barrier dysfunction and an immune response that includes increased levels of chemokines and cytokines (CCL27, TSLP, IL-13, IL-6, and IL-17A).

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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See related article on pg 141

Get with the Program! Stemness and Reprogramming in Melanoma Metastasis



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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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