Conditional knockout of aryl hydrocarbon receptor in langerin-expressing cells diminishes epidermal Langerhans cells while polarizes a Th2 response in epicutaneous protein sensitization

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Abstract

Aryl hydrocarbon receptor (AhR) is an environmental sensor for immune responses. In skin, AhR is expressed in several cells, including keratinocytes and Langerhans cells (LC). The current evidence of how AhR would activate or inhibit skin immune responses is controversial, likely due to the differential role of AhR in different cells and different haptens or peptides used. We then crossbred Langerin-Cre or CD11c-Cre with AhR-loxP (AhRFL/FL) to generate Langerin-AhR+/- or -/- (LC) and CD11c-AhR-/- (dendritic cells) to address the role of AhR in langerin- or CD11c-expressing cells using epicutaneous ovalbumin sensitization. The result showed that Langerin-AhR-/- mice but not CD11c-AhR-/- mice showed decreased numbers of epidermal LC in epicutaneous ova sensitization. Langerin-AhR-/- mice also showed an enhancement of Th2 (increased IL-4 and IL-5) and Treg (increased IL-10) responses in vitro when their lymph node cells were challenged with Ova, although the numbers of Treg in lymph nodes remained similar. Ova-specific IgE blood level was increased in Langerin-AhR-/- mice. The indicated that AhR knockout in langerin-expressing cells diminishes epidermal LC while enhances Th2 response in epicutaneous protein sensitization. This study indicated AhR in LC helps dampen Th2 response and supported that natural AhR agonist may resolve atopic dermatitis.

Introduction

LC are involved in tolerance induction by hapten DNTB. However, epicutaneous protein (ovalbumin, Ova) sensitization on the conditional knockout mice with EpCAM-deficient LC induced type 2 Ova-specific antibodies and enhanced proliferation of Ova-reactive T cells, along with increased numbers of LCs in lymph nodes (Ouchi et al., J Invest Dermatol 2016).

We have demonstrated that arsenic, an environmental carcinogen, mobilizes LC migration and induces Th1 response in epicutaneous protein sensitization via CCL21 (Clausen et al., Front Immunol 2015; Lee et al., Biochemical Pharmarcol 2012)

Our groups also showed the cigarette smoking is associated with the development of adult-onset atopic dermatitis (Lee et al., Br J Dermatol 2011)

We subsequently demonstrated that benzopyrene (BP), a major polyaromatic hydrocarbon (PAH) present in the smoking fume, mobilized LC migration and induced Th2 and Th17 responses through aryl hydrocarbon receptor (AhR) activation and E-cadherin downregulation in keratinocytes using AhR depleted mice (Hong et al., Int Immunopharmacol 2016)

Immunoregulation of AhR in skin

In skin, AhR is expressed by keratinocytes and by Langerhans cells (Lee et al., Int Immunopharmacol 2016; Koch et al., Allergy 2017)

Activation of AhR by these xenobiotics and cognate ligands regulates the development of allergies and autoimmunity. Activation of AhR induces activation of ARNT (aryl hydrocarbon receptor nuclear translocator), which regulates CYP1A1, leading to DNA responsive element activation and subsequent immune responses (Esser et al., Trends Immunol 2009)

The up or downregulation of immune responses by AhR in LC remains unknown

In skin, AhR is expressed by keratinocytes and by Langerhans cells (Lee et al., Int Immunopharmacol 2016; Koch et al., Allergy 2017)

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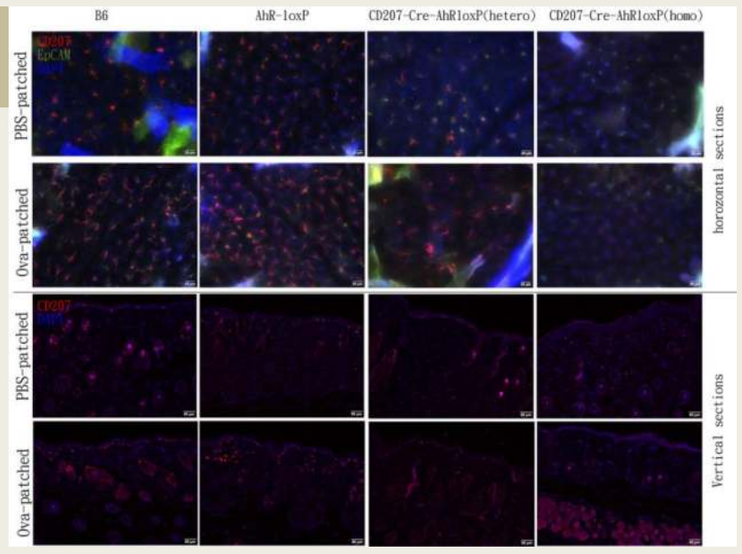
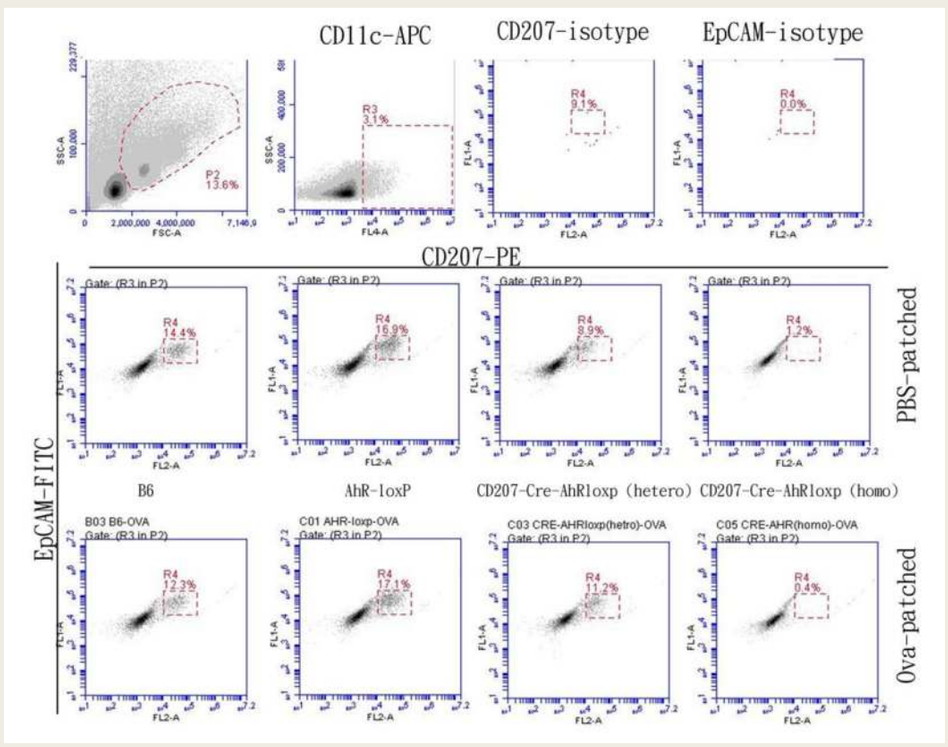
Results

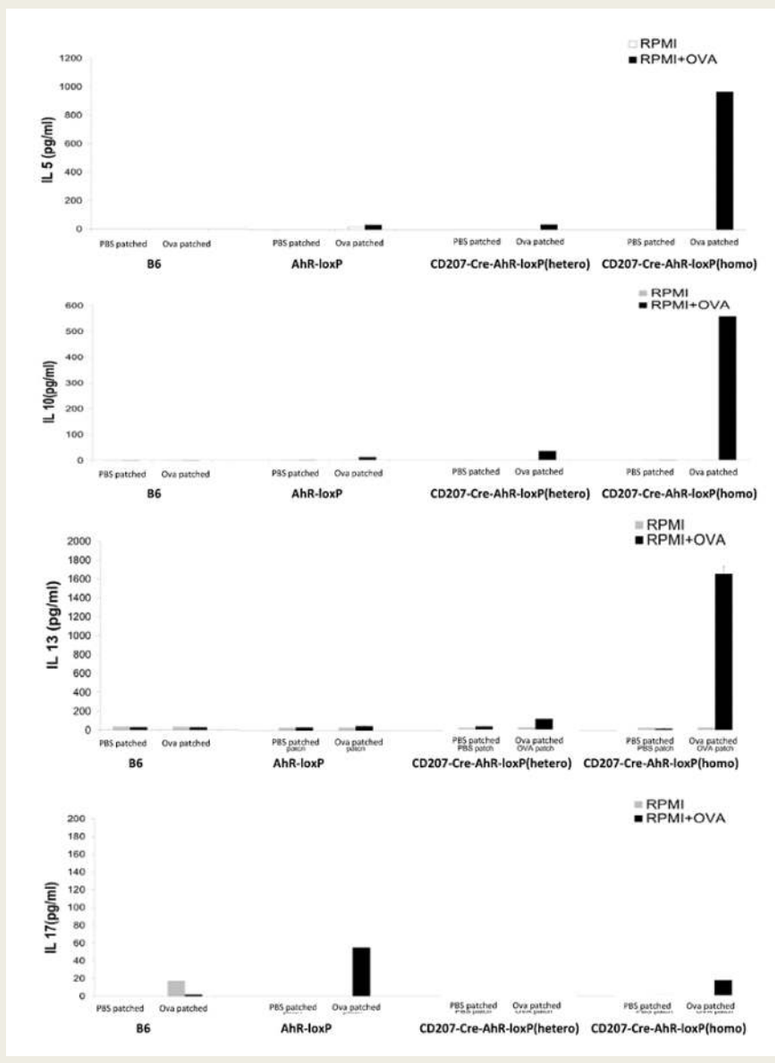
Depletion of AhR in langerin-expressing cells diminishes the numbers of epidermal Langerhans cells



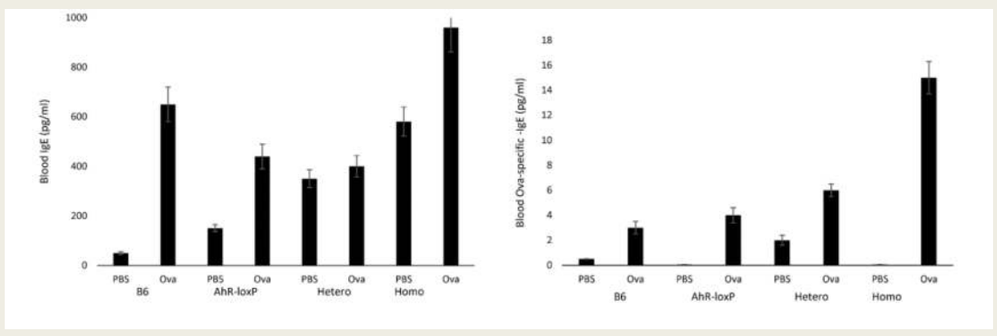
The numbers of Langerhans cells in skin draining lymph nodes were diminished in Langerin-AhR-/-



Challenge of the lymph node cells with Ova revealed a polarized Th2 response in Langerin-AhR-/- mice



Blood levels of Ova-specific IgE were increased in Langerin-AhR-/- mice



Conclusions

1. The conditional knock out of AhR in langerin-expressing cell (but not CD11c-expressing cells) decreased numbers of epidermal LC and polarized a Th2 response in ova epicutaneous sensitization with increased blood level of ova-specific IgE.
2. This study indicated AhR in LC helps dampen Th2 response and supported that natural AhR agonist may resolve atopic dermatitis.