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ALLERGY

Pollutants drive atopic dermatitis

> AhR activation drives epidermal hyper-innervation by upregulating the axon-guidance molecule artemin

Studies have correlated the increased incidence of atopic dermatitis with rising levels of air pollution, but the mechanisms involved are not clear. Hidaka *et al.* now report that air pollutants can activate the aryl hydrocarbon receptor (AhR) in keratinocytes to induce the expression of type 2 cytokines and the neurotrophic factor artemin; these factors subsequently promote the disease symptoms characteristic of atopic dermatitis.

Initial experiments showed that AhR-CA mice (which express a constitutively active form of AhR in keratinocytes) develop an inflammatory skin disease resembling atopic dermatitis and characterized by infiltration of allergic-type immune cells, pruritus (itching) and barrier dysfunction in the skin. Pro-inflammatory and type 2 cytokines, including thymic stromal lymphopoietin (TSLP), interleukin-18 (IL-18), IL-33, IL-4 and IL-13, were also upregulated in the skin of AhR-CA mice, with ChIP-seq analyses in primary keratinocytes showing that the AhR-CA construct binds to the promoter and intronic regions of *Tslp* and *Il33*, respectively. Both TSLP and IL-33 have been shown to induce dermatitis when overexpressed in mice. Therefore, these findings support the idea that AhR-mediated changes in gene expression induce the development of dermatitis in AhR-CA mice.

In a similar manner to patients with atopic dermatitis, AhR-CA mice also showed enhanced allergic-type sensitization against cutaneously applied antigens. Compared with wild-type mice, AhR-CA mice developed increased T helper 2 (T_H2) cell responses in draining lymph nodes following cutaneous application of ovalbumin (OVA) and showed an asthma-like response to subsequent intranasal challenge with OVA. The authors found that scratching behaviours contributed to antigen penetration and percutaneous sensitization; AhR-CA mice that had their nails clipped showed improved barrier function, had lower numbers of OVA-bearing cells in draining lymph nodes and fewer $CD4^+$ T cells in the skin.

In general, AhR-CA mice showed increased scratching behaviour compared with wild-type mice and signs of alloknesis, a sensory abnormality in which weak stimulation induces pruritus. Epidermal hyper-innervation has been linked to pruritus in patients with atopic dermatitis, and the authors found that epidermal hyper-innervation also occurred in AhR-CA mice and preceded their increase in scratching behaviour. Further analyses suggested that AhR activation drives epidermal hyper-innervation by upregulating the axon-guidance molecule artemin (encoded by *Artn*); indeed, administration of artemin-neutralizing antibodies blocked epidermal hyper-innervation in AhR-CA mice and attenuated alloknesis.

The authors next assessed whether air pollutants induce *Artn* expression and atopic dermatitis via AhR activation. They generated $Ahr^{fl/fl}$*Krt5*-Cre mice (in which AhR is specifically deleted in the epidermis) and found that epicutaneous application of diesel exhaust particles (DEPs) or DMBA, which is a DEP constituent, led to upregulation of *Artn* in the skin of control $Ahr^{fl/fl}$ mice but not in $Ahr^{fl/fl}$Krt5-Cre mice. Furthermore, exposure of primary keratinocytes from wild-type mice to benzo[*a*]pyrene (another constituent of DEPs) led to the induction of *Tslp* and *Il33*, and this was prevented by knockdown of *Ahr*. Of note, chronic exposure of $Ahr^{fl/fl}$ mice to DMBA (but not to the endogenous AhR ligand FICZ) led to the development of a skin disease similar to that seen in AhR-CA mice, but $Ahr^{fl/fl}$Krt5-Cre mice chronically exposed to DMBA showed greatly reduced disease.

These findings show that air pollutants can induce the development of atopic dermatitis in mice via AhR-mediated upregulation of type 2 cytokines and a neurotrophic factor, artemin. Importantly, the authors also found that ARTN expression was upregulated in the epidermis of patients with atopic dermatitis, but not in healthy controls, and that the upregulation of ARTN positively correlated with the expression of CYP1A1, an indicator of AhR activation. They caution that further studies are needed to establish whether the AhR–artemin pathway is a major driver of atopic dermatitis in humans but suggest that targeting this axis could be helpful in treating pruritus.

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