Keratinocytic TSLP: a key player in the progression from atopic dermatitis to asthma

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Cellular and molecular pathophysiological mechanisms involved in the generation of atopic dermatitis and asthma. Mouse models of atopic diseases

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Contexte

Atopic dermatitis (AD), asthma and allergic rhinitis are collectively called "atopic diseases". The expanding population of affected patients adds a huge burden to health care costs. A phenomenon known as the "atopic march" has been long observed, namely that the development of asthma and allergic rhinitis is often preceded by clinical signs of AD. However, what could be the mechanisms linking AD and asthma, remained still unclear. Moreover, long-term effective treatments and prevention of atopic diseases are still missing.

Our previous studies have contributed to the understanding of patho-genesis of AD by using mouse models. We have shown that selective ablation of nuclear receptors RXRα and RXRβ in adult mouse epidermal keratinocytes (RXRαβ$^{ep-/-}$) generates an AD-like syndrome, and have revealed the crucial role of the cytokine TSLP (Thymic Stromal LymphoPoietin) in AD pathogenesis (*Li M. et. al. 2005. Proc Natl Acad Sci U S A. 102, 14795-14800)*. Furthermore, in an effort to investigate how TSLP expression could be induced in RXRαβ$^{ep-/-}$ mice, we discovered that topical treatment of mouse skin with active vitamin D3 1α,25-$(OH)_2D_3$ or its low-calcemic analog MC903 (calcipotriol, currently used for human psoriasis treatment) induces TSLP expression in skin keratinocytes, and triggers an AD (*Li M. et. al. 2006. Proc Natl Acad Sci U S A. 103, 11736-41*). This study not only suggested that vitamin D (and vitamin A) signaling could be involved in the pathogenesis of AD, but also established a highly convenient AD preclinical model (by topical MC903 treatment on mouse skin), to study various aspects of pathogenesis of atopic diseases and to explore novel therapeutic avenues.

Objectifs

Our objective was to elucidate the molecular mechanisms underlying the pathogenesis of AD and the progression of the AD to asthma. We intended to answer:

1) Is the expression of TSLP in keratinocytes not only sufficient, but also necessary to generate an AD?

2) Does TSLP produced in AD skin keratinocytes play a role in the atopic march, the progression from AD to asthma?

Principaux résultats

Part I

We generated loxP-flanked ("floxed") TSLP mouse line, which permits us to develop mice in which TSLP gene is knocked out either in the germ line (TSLP$^{-/-}$) or selectively in keratinocytes (TSLP$^{ep-/-}$) by crossing TSLP floxed mice with K14-CreER^{T2} or K14-Cre transgenic lines. We showed that when topically treated with MC903, TSLP$^{-/-}$ and TSLP$^{ep-/-}$ mice failed to develop AD-like skin lesions. Moreover, by generating compound mutant RXRαβ $^{ep-/-}$/ TSLP$^{ep-/-}$ mice in which both RXRαβ and TSLP are ablated in keratinocytes, we showed that the AD phenotype observed in RXRαβ$^{ep-/-}$mice is mediated through keratinocytic TSLP.

These studies demonstrate unequivocally that the **induction of TSLP expression in keratinocytes was not only sufficient, but also necessary for generating an AD.**

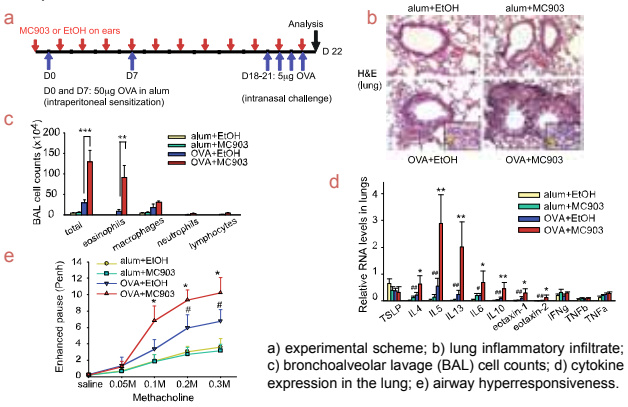
Part II

To examine our hypothesis that TSLP produced in AD skin keratinocytes may represent a molecular link from AD to asthma in the "atopic march", we made use of our AD mouse models, and subjected these mice to a well established experimental asthma protocol that includes a systemic ovalbumin (OVA) sensitization and an OVA intranasal challenge, which results in characteristic features of allergic asthma.

❖ In a first study, RXRαβ$^{ep-/-}$ mutant mice, which exhibited a spontaneous AD with TSLP expression in epidermal keratinocytes, developed an aggravated airway inflammation upon OVA sensitization and challenge.

❖ In a second study, wildtype mice topically treated with MC903 on the ears, to induce TSLP expression in keratinocytes and to generate an AD, were concomitantly subjected to the OVA experimental asthma protocol.

- Mice bearing MC903-triggered AD develop an aggravated OVA-induced experimental asthma.



a) experimental scheme; b) lung inflammatory infiltrate; c) bronchoalveolar lavage (BAL) cell counts; d) cytokine expression in the lung; e) airway hyperresponsiveness.

- In TSLP$^{ep-/-}$ mice, MC903 failed to aggravate OVA-induced asthma, demonstrating MC903-induced aggravation of OVA asthma is mediated by TSLP produced in epidermal keratinocytes.
- Increased production of epidermal TSLP during the OVA sensitization phase was sufficient to trigger the aggravation of OVA-induced asthma.

In conclusion, these results indicate that epidermal keratinocyte-produced TSLP may represent a key factor in the "atopic march", by linking AD to asthma.

Our study not only provides a mouse model for studying possible mechanisms involved in the "atopic march", but also suggests that overproduction of TSLP in the skin of patients with AD could be a risk factor for the development of allergic airway inflammation.

Publications

Li, M. et. al. 2009. ***J Invest Dermatol*** *129, 498-502.*
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Surjit, M et. al. 2011. ***Cell*** *145: 224-41.*

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