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Is there a pathogenic role for IgE in psoriasis?

DOI: 10.1111/bjd.14607

Linked Article: Yan et al. *Br J Dermatol* 2016; **175**:122–133.

Psoriasis is generally thought to be an auto-inflammatory disease of the skin, mediated by T-helper (Th)1 and Th17 cells. DNA-LL37 complexes stimulate dendritic cells (DC),¹ which induce Th1 and Th17 cell differentiation through production of interleukin (IL)-12 and IL-23. IL-17A produced by Th17 cells is an important mediator in keratinocyte activation and proliferation.² The efficacy of biologicals targeting IL-12/23 (ustekinumab) and IL-17A highlights the importance of the Th17 axis in psoriasis.³

Unexpectedly, increased levels of serum immunoglobulin (Ig)E have been reported in subsets of patients with psoriasis since the early 1980s.^{4–6} IgE is a typical mediator of allergies, such as asthma and atopic dermatitis, and increased serum IgE levels are the result of exaggerated Th2 cell responses. IgE binds the high-affinity receptor FcεRI on mast cells and basophils, and binding to allergen induces receptor cross-linking and cellular

degranulation, resulting in allergic complaints (Fig. 1a). It has remained unclear whether the IgE in psoriasis induces similar responses and thereby contributes to the pathogenesis.

In this issue of the *BJD*, Yan et al. show that on top of increased serum IgE, lesional skin of patients with psoriasis contains more IgE- and FcεRI-bearing cells than nonlesional skin.⁷ These concerned especially mast cells, dermal Langerhans cells, epidermal DCs and macrophages. Ustekinumab therapy lowered the numbers of IgE- and FcεRI-bearing cells. Based on these findings and recent observations in the literature, we here propose a model for a Th2-independent pathway driving IgE responses (Fig. 1b).

Indeed, alternative to IL-4 and IL-13, IgE production by B cells can also be promoted by IL-17A.⁸ Furthermore, in patients with systemic lupus erythematosus (SLE), autoreactive IgE has been identified that can activate plasmacytoid (p)DCs to secrete interferon-α.⁹ These observations would suggest a role for an IL-17–IgE–pDC axis that contributes to self-destructive autoimmune responses (Fig. 1b). Most likely, the IgE response is not the primary mediator of pathogenesis, but is produced after the initial autoreactive IgG. Chronic stimulation of autoreactive IgG memory B cells could lead to secondary Ig class switching to IgE.¹⁰ The resulting soluble IgE will then be included in immune complexes and augment pDC responses by involving FcεRI.⁹

The study by Yan et al. extends this mechanism to psoriasis.⁷ However, more functional studies would be needed to substantiate this. In contrast to atopic dermatitis, patients with psoriasis do not have increased numbers of IgE-expressing B cells,^{10,11} potentially because the IgE in psoriasis is derived from sequential Ig class switching of IgG memory B cells. This could be addressed by *in vitro* stimulation of IgG memory B cells with Th17 cytokines. Furthermore, it would be important to detect the presence of autoreactive IgE in those patients with antinuclear antibodies.¹² Upon detection of autoreactive IgE, this can be used in functional assays to identify the effector cells in the skin. Are these the mast cells and basophils that mediate allergies, or the pDCs that are thought to be the main effector cells in SLE? Such detailed studies could help to unravel pathogenic processes in patients with psoriasis, to identify similarities and differences with other (auto-)inflammatory diseases, and provide new targets for therapeutics.

Acknowledgments

We thank Drs E. Hajdarbegovic and M.B. Thio for advice and for critical reading of the manuscript.

Funding sources

Grant S698 from the Sophia Children's Hospital Fund (SKF).

Conflicts of interest

None declared.

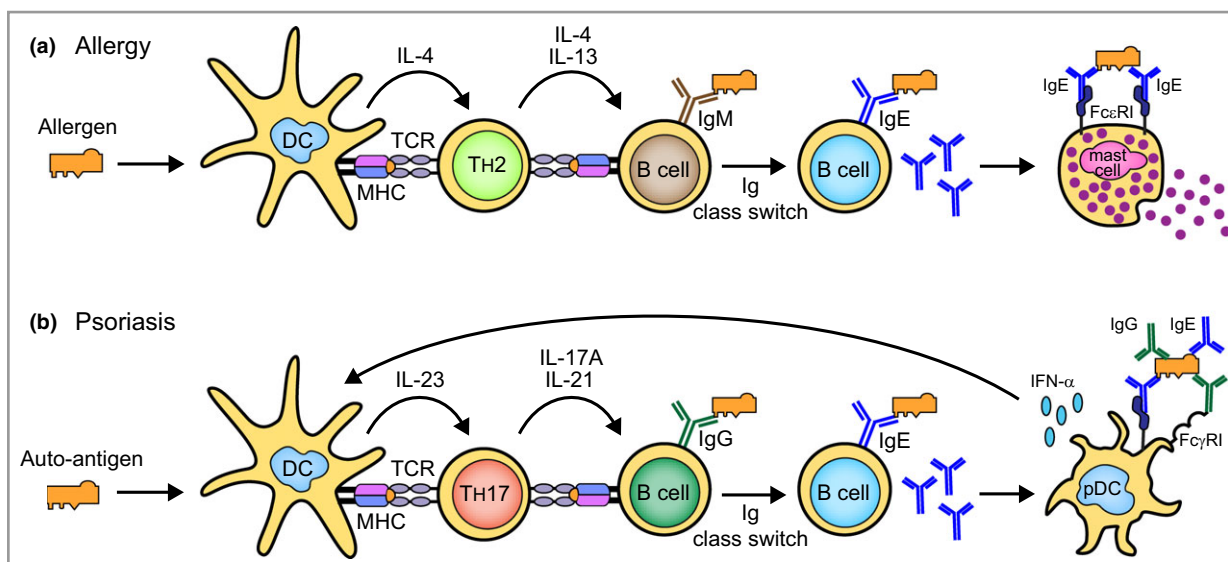


Fig 1. Models for immunoglobulin (Ig) E responses in allergy and the nonclassical IgE response in psoriasis. (a) Allergen is taken up by dendritic cells (DC) and presented to naive T-cells, which differentiate into T-helper 2 (TH2) cells. Interleukin (IL)-4 and IL-13 induce class switching in naive B cells to IgE. Allergen-specific soluble IgE produced by plasma cells binds to FcεRI on mast cells and basophils. Subsequent allergen exposure leads to cross-linking of cell-bound IgE, resulting in allergic complaints. (b) Self-antigen is taken up by DC and presented to naive T-cells, which differentiate into TH17 cells. IL-17A induces class switching to IgE. Antigen–IgG–IgE complexes can bind to plasmacytoid DC (pDC) and recognition of self-antigen leads to the production of interferon-α, augmenting the psoriatic immune reaction.

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CARD14 mutations may predict response to antitumour necrosis factor-α therapy in psoriasis: a potential further step towards personalized medicine

DOI: 10.1111/bjd.14795

Linked Article: Coto-Segura et al. *Br J Dermatol* 2016; **175**:134–141.

There has been considerable interest in the concept of personalized or stratified medicine, in which a patient's individual characteristics, such as demographics, genotype and clinical phenotype, are used to select particular interventions or to predict response to therapy or its side-effects.¹ In some cases personalized medicine is already a reality and used in everyday