The role of epithelial cytokines in atopic march

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The importance of understanding the role of epithelial cytokines in atopic march

The impaired way the epithelial immune-system reacts when exposed to environmental triggers in atopic individuals seems to represent a common immunological background of different T2-related clinical manifestations. From a clinical perspective, specifically interfering with the atopic march at an early stage could prevent or modify its evolution and significantly reduce the morbidity and disease burden of related conditions. "Atopic march" is an old paradigm, but looking at it in a new way will contribute to substantially increasing the standard of care for our patients.

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The opinions and views shown here are those of the external expert.

Contents

Introduction to the atopic march

Children with early-onset allergen sensitisation are at risk of developing multiple atopic diseases:[1]

- Atopic march describes the potential developmental trajectory of atopic disease that usually begins with **early atopic dermatitis (AD)** and can progress to **food allergy, asthma, allergic rhinitis (AR), and eosinophilic esophagitis (EoE)**[1,2]
- Factors that increase the risk of AD advancing to other atopic diseases include **early onset, persistence and severity of AD, polysensitisation, and parental atopy**[1]
- Targeting the atopic march could potentially **prevent or modify the development of some of the most common childhood diseases**, including AD, asthma and AR, which are associated with **significant morbidity and disease burden**[1–5]

Atopy is characterised by aberrant T2 inflammation:[1]

- In genetically predisposed individuals, loss of epithelial barrier integrity contributes to the release of the epithelial cytokines **TSLP, IL-33 and IL-25**, triggering a **T2 inflammatory response** that leads to **total and allergen-specific IgE production**[1]

AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic oesophagitis; IgE, immunoglobulin E; IL, interleukin; T2, type 2; TSLP, thymic stromal lymphopoietin

1. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594; 2. Han H, et al. Immunol Rev 2017;278:116–130; 3. Bawany F, et al. J Allergy Clin Immunol Pract 2020;8:860–875;
4. HaanPää L, et al. BMJ Open 2018;8:e019281; 5. Dierick BJH, et al. Expert Rev Pharmacoecon Outcomes Res 2020;20:437–453

Atopy can result in allergic disease at multiple anatomical sites

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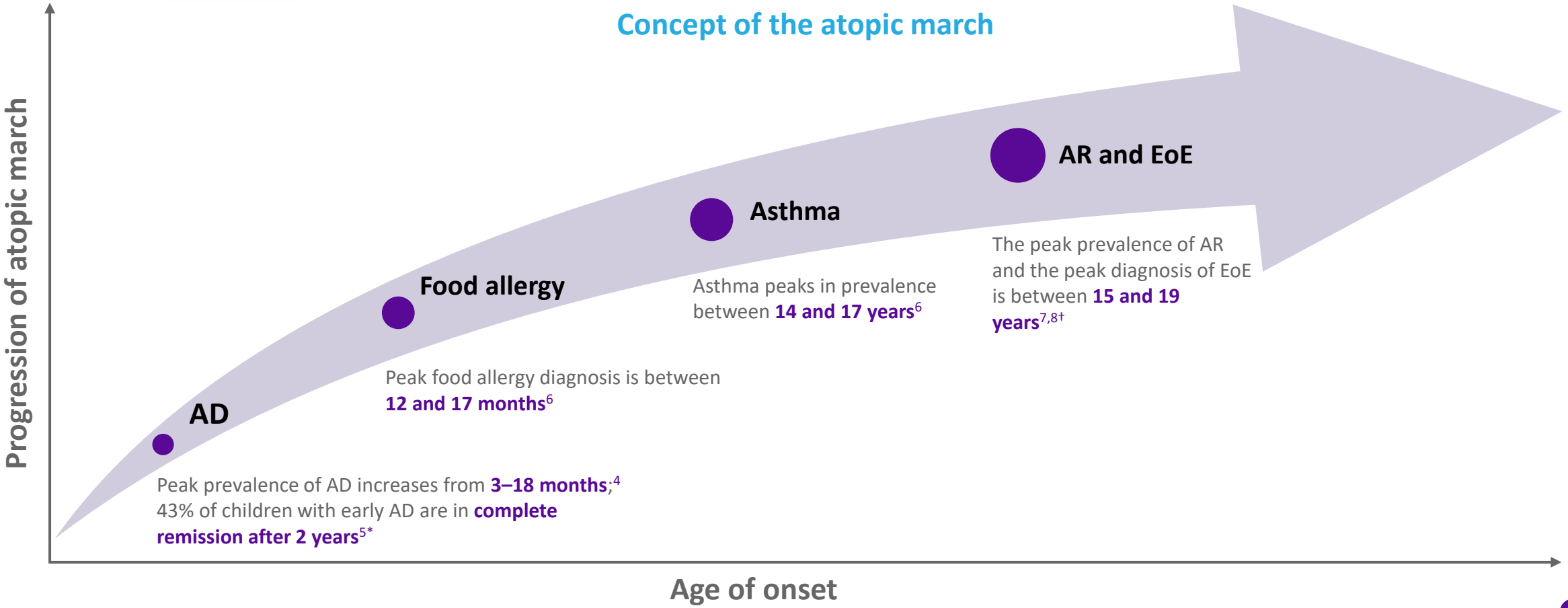
- **Atopic dermatitis is an early manifestation of atopic march, and increases the risk of subsequently developing additional atopic diseases[1,2]**
- **The atopic march can progress non-linearly; children can have AD only, 'skip' one disease, and develop asthma, EoE or AR without having early AD[3]**



*Data are from the German Multicentre Atopy Study (MAS), which recruited German infants born in 1990 from 5 German cities; †Data are from a Swedish cohort recruited between 2004–2015
AD, atopic dermatitis; AR, allergic rhinitis; EoE, eosinophilic oesophagitis

1. Han H, et al. Immunol Rev 2017;278:116–130; 2. Hill DA, et al. J Allergy Clin Immunol Pract 2018;6:1528–1533; 3. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594; 4. Eller E, et al. Pediatr Allergy Immunol 2010;21:307–314; 5. Illi S, et al. J Allergy Clin Immunol 2004;113:925–931; 6. Hill DA, et al. BMC Pediatr 2016;16:133; 7. Ghouri N, et al. J R Soc Med 2008;101:466–472; 8. Garber JJ, et al. Esophagus 2022;19:535–541

Having one or more atopic diseases increases the risk of developing other atopic conditions

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AD is a strong risk factor for the development of food allergy[1]

- 30% (N=50) of children with moderate AD and **50% (N=50) of children with severe AD have a food allergy**[2†]

AD and asthma are significantly associated;[3] however, co-prevalence varies with age and depends on atopy[4]

- Risk of asthma at 6 years old was **increased in young children with AD (OR 2.14)** and was even greater in children with **AD and allergen sensitisation (OR 7.04)**[4]

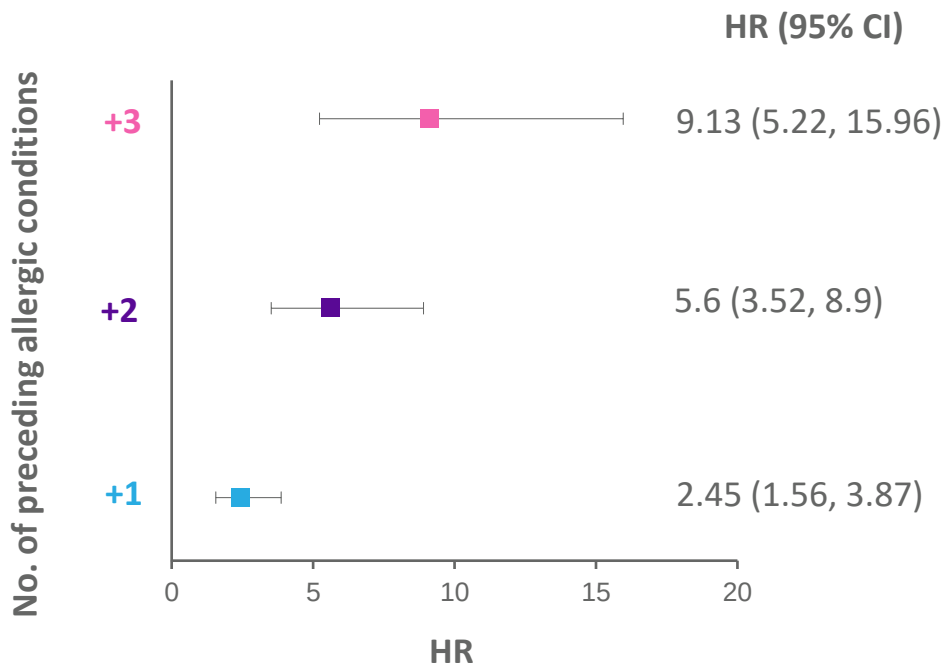
Food sensitisation increases the risk of developing asthma and allergic rhinitis[5]

- Food sensitisation at 6, 12 and 24 months was associated with an **increased risk of asthma and AR at 10–12 years old**[5]

The likelihood of subsequent EoE increases with the presence of preceding atopic conditions[6]

- AR and EoE **are significantly and bi-directionally associated with each other**, suggesting that their peak incidence is **statistically coincident**[6]

There is a cumulative effect of multiple preceding atopic conditions on the rate of subsequent EoE diagnosis (N=130435)*[6]



*Preceding allergic conditions included AD, food allergy, AR and asthma; †Data are from the South African paediatric cohort;
AD, atopic dermatitis; AR, allergic rhinitis; CI, confidence interval; EoE, eosinophilic oesophagitis; HR, hazard ratio; IgE, immunoglobulin E; OR, odds ratio

1. Martin PE, et al. Clin Exp Allergy 2015;45:255–264; 2. Tsakok T, et al. J Allergy Clin Immunol 2016;137:1071–1078; 3. Ravnborg N, et al. J Am Acad Dermatol 2021;84:471–478;
4. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594; 5. Alduraywish SA, et al. Pediatr Allergy Immunol 2016;28:30–37; 6. Hill DA, et al. J Allergy Clin Immunol Pract 2018;6:1528–1533

Environmental and genetic factors are associated with the prevalence of atopic diseases and epithelial dysfunction

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Microbial interactions can influence the development of atopic diseases[1]

- The 'hygiene hypothesis' suggests that **early microbial exposure may 'tolerise' the innate and adaptive immune system**, and protect against atopy[1]
  - Urban living is associated with **higher rates of allergic disease** than farming environments[2,3]
  - Childhood exposure to bacterial products in rural environments may skew immune responses **away from Th2-driven pathways**[4]
- Gut and airway **microbial dysbiosis likely contributes to disease pathogenesis** in children with asthma[3]
- In genetically predisposed children, wheezing rhinovirus illness before 3 years was associated with a **~10-fold increase in asthma risk at 6 years old**[5]

Mutations in proteins of the epithelial barrier appear to be an important factor in the heritability of atopic diseases[1]

- **Atopic diseases are up to 75% heritable**[1] and are associated with mutations that induce epithelial dysfunction[1]
- Mutations in the **filaggrin* gene increase susceptibility to AD, food allergy and asthma, and filaggrin expression is reduced in patients with EoE**[6–9]
- Mutations in the **SPINK5† gene cause an AD-like syndrome and are a risk factor for AD**[1,10–12]
- Mutations in the **corneodesmosin‡ gene** are associated with **skin peeling syndrome type B**, of which **food allergy and asthma are major atopic features**[1,13]

*Filaggrin aggregates keratin filaments and is essential to epidermal structure; †SPINK5 inhibits proteolytic activity in the deeper levels of the skin; ‡corneodesmosin is a secreted glycoprotein which maintains cell-cell adhesion in the outer layer of the skin

AD, atopic dermatitis; EoE, eosinophilic oesophagitis; SPINK5, serine protease inhibitor Kazal type-5; Th2, T helper 2 cell

1. Han H, et al. Immunol Rev 2017;278:116–130; 2. Morgan BW, et al. J Allergy Clin Immunol Pract 2018;6:1580–1587; 3. Hufnagl K, et al. Semin Immunopathol 2020;42:75–93; 4. Gerretsen VI, Schuijs MJ. Allergol Select 2022;6:104–110; 5. Jackson DJ, et al. Am J Respir Crit Care Med 2008;178:667–672; 6. Irvine AD, et al. N Engl J Med 2011;365:1315–1327; 7. Gupta J, Margolis DJ. Curr Treat Options Allergy 2020;7:403–413; 8. Venkataraman D, et al. J Allergy Clin Immunol 2014;134:876–882; 9. Politi E, et al. J Pediatr Gastroenterol Nutr 2017;65:47–52; 10. Kusunoki T, et al. Allergy Clin Immunol 2005;115:636–638; 11. Kato A, et al. Br J Dermatol 2003;148:665–669; 12. Li Y, et al. Medicine (Baltimore) 2020;99:e21256; 13. Oji V, et al. Am J Hum Genet 2010;87:274–281

Epithelial barrier dysfunction plays a key role in atopic disease development

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Epithelial barrier dysfunction is key for skin sensitisation to allergic stimuli and subsequent atopic manifestations[1,2]

- Dysfunctional epithelial barriers are characteristic of **AD, asthma, AR and EoE**[1,2]
- It is unclear what initiates the **cycle of barrier disruption and inflammation** in atopic disease[2]
  - Prolonged allergen exposure at sensitised barrier epithelium can cause **chronic inflammation, damaging the epithelial barrier**[2]
  - However, epithelial damage can be observed in most atopic patients **before atopic diseases manifest**[1] **and prior to specific allergen sensitisation**[1–3]
- Early T2 skin inflammation may set the immune context for T2-driven **respiratory allergy across a distal lung-skin epithelium axis** with a shared genetic basis[4]
  - AD, asthma and AR share **99 potential loci**, and epistatic effects exist between **barrier genes (*FLG*) and immune genes (*IL4R*)**[4]

The skin may be a site of allergen sensitisation for subsequent development of food allergy[5]

- The association of **food allergy and AD** is best understood at a mechanistic level[4]
- Environmental **exposure to peanut allergen in patients with *FLG* mutations** is a risk factor for development of peanut allergy[6]
- In peanut-allergic patients, peanut-specific proliferation is predominated by skin-homing marker CLA+ T cells, suggesting that **allergic sensitisation occurs through the skin**[7]
- Allergen exposure, skin barrier defects/damage and other factors can trigger the release of **TSLP, IL-33 and IL-25 from epithelial cells**, promoting skin sensitisation[5]

AD, atopic dermatitis; AR, allergic rhinitis; CLA, cutaneous lymphocyte-associated antigen; EoE, eosinophilic esophagitis; *FLG*, filaggrin gene; *IL4R*, interleukin 4 receptor gene; IL, interleukin; T2, type 2; TSLP, thymic stromal lymphopoietin

1. Ghezzi M, et al. Children (Basel) 2021;8:1165; 2. Schleimer RP, Berdnikovs S. J Allergy Clin Immunol 2017;139:1752–1761; 3. Horimukai K, et al. Allergol Int 2016;65:103–108; 4. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594; 5. Han H, et al. Immunol Rev 2017;278:116–130; 6. Brough HA, et al. J Allergy Clin Immunol 2014;134:867–875; 7. Chan SM, et al. Allergy 2012;67:336–342

Epithelial cell-derived cytokines are inducers of inflammation at barrier surfaces and contribute to atopic march

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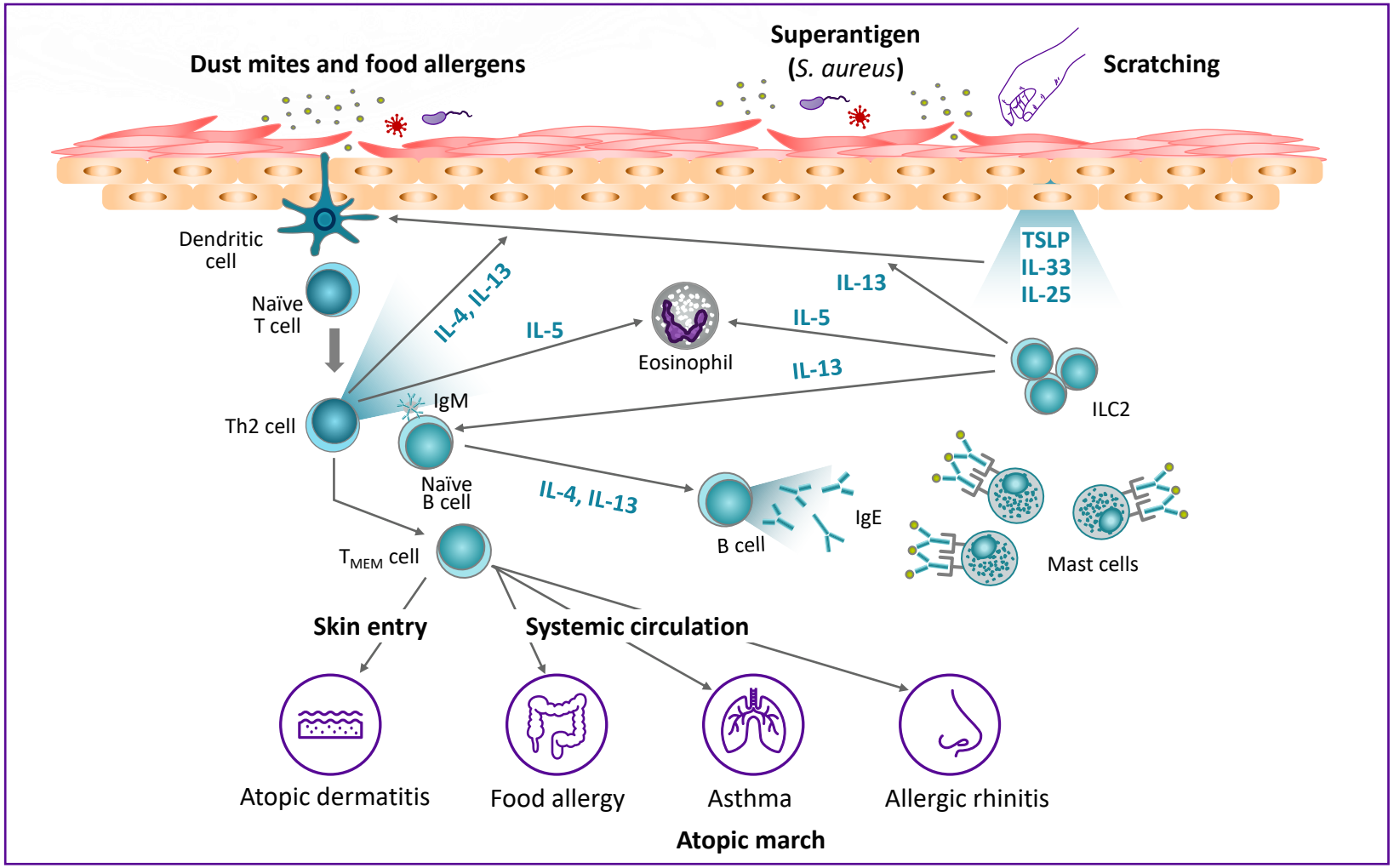


In response to allergens, TSLP, IL-25 and IL-33 are produced by epithelial cells at mucosal surfaces, activating DCs and ILC2s and **promoting a Th2 cascade**[1–3]

Th2 cells produce IL-4 and IL-13, increasing **barrier dysfunction** and causing the production of **specific IgE from B cells**[3]

IgE can bind mast cells and causes **allergic reactions when cross-linked to allergen**[3]

Systemic T-cell migration can result in **atopic manifestations at barrier sites**[3]

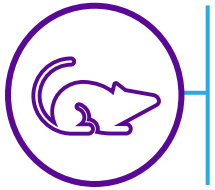
Figure adapted from Tsuge et al[2]
DC, dendritic cell; IgE, immunoglobulin E; IgM, immunoglobulin M; IL, interleukin; ILC2, group 2 innate lymphoid cells; Th2, T helper 2; T_{MEM}, Memory T cell; TSLP, thymic stromal lymphopoietin

1. Han H, et al. Immunol Rev 2017;278:116–130; 2. Tsuge M, et al. Children (Basel) 2021;8:1067; 3. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594

IL-33 is overexpressed in atopic disease and can initiate atopic manifestations in animal models

In response to allergens/stimuli, IL-33 and its receptor, ST2, activate DCs and drive T2 inflammation[1]

- IL-33 expression is increased in the lesional skin of patients with AD and in endobronchial tissue of patients with asthma[2–4]



In mouse models, atopic manifestations were induced in IL-33+OVA sensitised mice[5–8]

- Skin-specific overexpression of IL-33 drove dermatitis and ILC2 infiltration[5]
- In a food allergy model, **IL-33-mast-cell signalling drove food anaphylaxis**[6]
- Intranasal OVA challenge provoked **allergic airway inflammation**[7] **and oral OVA challenge elicited allergic diarrhoea**[8]
- OVA-induced GI allergy progressed **independently of TSLP receptor signalling**[8]

AD, atopic dermatitis; DC, dendritic cell; GI, gastrointestinal; IL, interleukin; ILC2, innate lymphoid cell; OVA, ovalbumin; ST2, Interleukin 1 receptor-like 1; T2, type 2; TSLP, thymic stromal lymphopoietin

1. Drake LY, Kita H. Immunol Rev 2017;278:173–184; 2. Savinko T, et al. J Invest Dermatol 2012;132:1392–1400; 3. Préfontaine D, et al. J Allergy Clin Immunol 2010;125:752–754;
4. Saglani S, et al. J Allergy Clin Immunol 2013;132:676–685; 5. Imai Y, et al. Proc Natl Acad Sci U S A 2013;110:13921–13926; 6. Galand C, et al. J Allergy Clin Immunol 2016;138:1356–1366;
7. Han H, Ziegler SF. Sci Rep 2017;7:1706; 8. Han H, et al. Mucosal Immunol 2018;11:394–403

TSLP is overexpressed in atopic disease and may contribute to initiating atopic march in animal models

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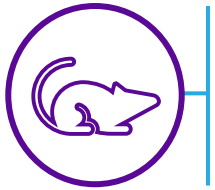
In response to an allergen or non-specific stimuli, TSLP activates DCs, stimulating the differentiation of naïve T cells to Th2 cells and driving T2 inflammation[1–4]

- TSLP is overexpressed in the lesional skin of patients with AD,[5] the airways of patients with asthma[6–8] and the oesophageal tissue of patients with active EoE[9]
- SNPs in TSLP, T2 cytokines and their receptors are associated with **AD, food allergy, asthma, and EoE[10–13]**



In mouse models, TSLP-initiated atopic march requires IL-33 and IL-25 signalling, and may be context dependent[14–19]

- TSLP+OVA intradermal sensitisation caused airway inflammation and food allergy at challenge[14–18]
- In TSLP+OVA sensitised mice, TSLP-driven **GI allergic disease required Il-33 and IL-25 signalling**[17,18]
- In a mouse model of AD, **TSLP was only crucial to epicutaneous skin sensitisation and allergic asthma** at challenge[19]

AD, atopic dermatitis; DC, dendritic cell; EoE, eosinophilic oesophagitis; GI, gastrointestinal; IgE, immunoglobulin E; IL, interleukin; OVA, ovalbumin; SNP, single nucleotide polymorphism; T2, type 2; Th2, T-helper 2 cells; TSLP, thymic stromal lymphopoietin

1. Soumelis V, et al. Nat Immunol 2002;3:673–680; 2. Kitajima M, et al. Eur J Immunol 2011;41:1862–1871; 3. Ziegler SF, et al. Adv Pharmacol 2013;66:129–155; 4. Allakhverdi Z, et al. J Exp Med 2007;204:253–258; 5. Sano Y, et al. Clin Exp Immunol 2013;171:330–337; 6. Ying S, et al. J Immunol 2005;174:8183–8190; 7. Shikotra A, et al. J Allergy Clin Immunol 2012;129:104–111; 8. Cao L, et al. Exp Lung Res 2018;44:288–301; 9. Noti M, et al. Nat Med 2013;19:1005–1013; 10. He JQ, et al. J Allergy Clin Immuno 2009;124:222–229; 11 Han H, et al. Immunol Rev 2017;278:116–130; 12. Rothenberg ME, et al. Nat Genet 2010;42:289–291; 13. Fahey LM, et al. Clin Transl Gastroenterol 2018;9:139; 14. Noti M, et al. J Allergy Clin Immunol 2014;133:1390–1399; 15. Zhang Z, et al. Proc Natl Acad Sci U S A 2009;106:1536–1541; 16. Han H, et al. Mucosal Immunol 2012;5:342–351; 17. Han H, et al. J Clin Invest 2014;124:5442–5452; 18. Han H, et al. Mucosal Immunol 2018;11:394–403; 19. Segaud J, et al. Nat Comms 2022;13:4703

IL-25 is overexpressed in atopic dermatitis and contributes to atopic march in animal models

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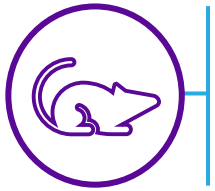
IL-25 is expressed in immune and epithelial cells, and is upregulated at barrier sites in response to allergens or non-specific stimuli[1,2]

- IL-25 is upregulated in the skin of patients with AD and the bronchial epithelium of some patients with asthma[3,4]
- IL-25 contributes to **skin barrier dysfunction by inhibiting filaggrin expression** and promoting T2 responses[3,5,6]



IL-25 is upregulated in response to challenge and is involved in mediating allergic responses, but is not sufficient to initiate atopic march[7–10]

- IL-25 expression levels can influence the susceptibility of OVA/alum sensitised mice to experimental food allergy[7]
- In mouse models, IL-25 enhanced antigen-induced allergic airway inflammation via a Th2 pathway,[8] and **airway hyperresponsiveness was reduced by blocking IL-25**[9]
- Unlike TSLP, **intradermal injection of IL-25/OVA does not promote disease at challenge** in experimental models of asthma[10]

AD, atopic dermatitis; alum, adjuvant aluminium hydroxide; IL, interleukin; OVA, ovalbumin; T2, type 2; Th2, T-helper 2 cells; TSLP, thymic stromal lymphopoietin

1. Han H, et al. Immunol Rev 2017;278:116–130; 2. Duchesne M, et al. Front Immunol 2022;13:975914; 3. Hvid M, et al. J Invest Dermatol 2011;131:150–157; 4. Cheng D, et al. Am J Respir Crit Care Med 2014;190:639–648; 5. Wang YH, et al. J Exp Med 2007;204:1837–1847; 6. Kim BE, et al. J Invest Dermatol 2013;133:2678–2685; 7. Lee JB, et al. J Allergy Clin Immunol 2016;137:1216–1225; 8. Tamachi T, et al. J Allergy Clin Immunol 2006;118:606–614; 9. Ballantyne SJ, et al. J Allergy Clin Immunol 2007;120:1324–1331; 10. Han H, et al. Mucosal Immunol 2012;5:342–351

A complex interplay of epithelial cell-derived cytokines underpins atopic disease

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Cross-regulation at the gene expression level and differing expression kinetics suggest that IL-33, TSLP and IL-25 may be involved in **driving atopic disease at different inflammatory phases**[1–4]

IL-33, TSLP and IL-25 differentially contribute to T2 inflammation in animal models: IL-33 may play a role in amplifying TSLP-initiated T2 responses[5] and is often required to drive inflammation over TSLP or IL-25[4–7]

The relative involvement of IL-33, TSLP, IL-25 in allergic responses is affected by: **type of allergen,[4] allergen dose,[4,8] duration of exposure,[3] and epithelial context[9]**

The epithelial cell-derived cytokines may be signals of local inflammation and tissue damage, serving as checkpoints in the **regulation of T2 inflammation at barrier surfaces[4]**

Further research on the atopic march is required in humans; much of the current information is based on mouse models of atopic disease, and the **clinical relevance of these models is yet to be determined[1–9]**

IL, interleukin; T2, type 2; TSLP, thymic stromal lymphopoietin

1. Angkasekwinai P, et al. J Exp Med 2007;204:1509–1517; 2. Humphreys NE, et al. J Immunol 2008;180:2443–2449; 3. Vannella KM, et al. Sci Transl Med 2016;8:337ra365; 4. Han H, et al. Immunol Rev 2017;278:116–130; 5. Chu DK, et al. J Allergy Clin Immunol 2013;131:187–200; 6. Barlow JL, et al. J Allergy Clin Immunol 2013;132:933–941; 7. Han H, et al. Mucosal Immunol 2018;11:394–403; 8. Sheih A, et al. Mucosal Immunol 2017;10:705–715; 9. Segaud J, et al. Nat Commun 2022;13:4703

Summary

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Atopy often first manifests as AD and food allergy in early childhood, which increase the risk of developing other atopic diseases, such as asthma, in a characteristically sequential manner known as atopic march[1–4]

- Environmental and genetic factors influence the prevalence of atopic disease[1]

The mechanisms underlying atopy are complex and overlapping[1]

- The specific epithelial-cell derived cytokines and effector cells involved in allergic responses may depend on the type of stimulus exposure and the depth of allergen penetration during sensitisation[1,5]

The epithelial cell-derived cytokines IL-33, TSLP and IL-25 are upregulated in atopic diseases and play an important role in animal models of atopic march[1]

- IL-33, TSLP and IL-25 are differentially required for atopic progression in mouse models; IL-33 can initiate atopic march independently, but TSLP requires IL-33 and IL-25 for disease progression[6–8]

The development of treatments that target mechanisms involved in the atopic march could dramatically impact the natural history of some of the most common childhood illnesses such as AD, asthma and AR[4,9,10]

- Further research in humans is required to elucidate the underlying drivers of atopic march and the role that epithelial cytokines play in this process[4,9]

AD, atopic dermatitis; AR, allergic rhinitis; IL, interleukin; TSLP, thymic stromal lymphopoietin

1. Han H, et al. Immunol Rev 2017;278:116–130; 2. Martin PE, et al. Clin Exp Allergy 2015;45:255–264; 3. Illi S, et al. J Allergy Clin Immunol 2004;113:925–931; 4. Spergel JM, et al. J Allergy Clin Immunol 2023;151:590–594; 5. Segaud J, et al. Nat Commun 2022;13:4703; 6. Han H, et al. Mucosal Immunol 2018;11:394–403; 7. Han H, et al. J Clin Invest 2014;124:5442–5452; 8. Han H, et al. Mucosal Immunol 2012;5:342–351; 8.; 9. Bawany F, et al. J Allergy Clin Immunol Pract 2020;8:860–875; 10. Haanpää L, et al. BMJ Open 2018;8:e019281