Atopic Dermatitis

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- **the most common chronic inflammatory skin Disease.**

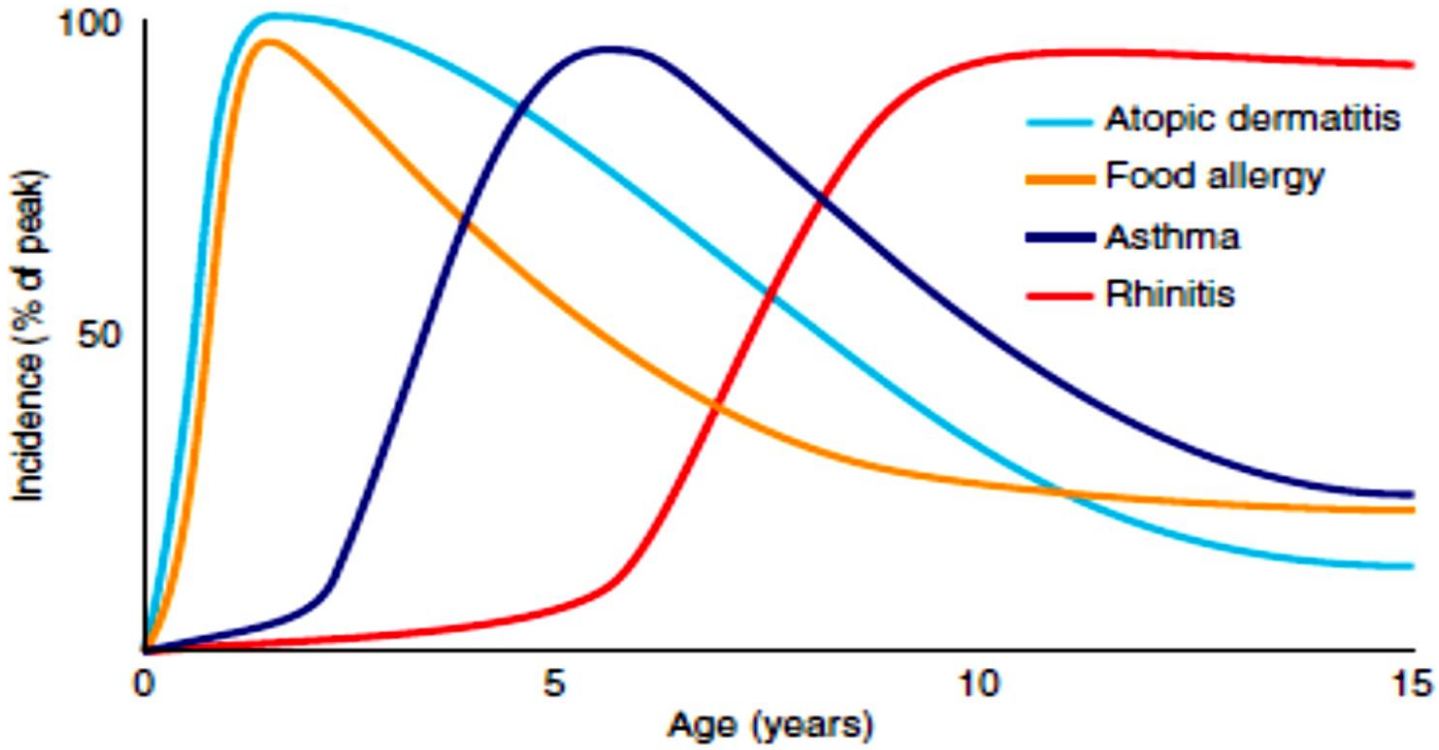
- pruritus and a chronic or chronically relapsing course, usually beginning during infancy (early onset) but occasionally first developing in adulthood (late onset).

- a complex genetic disease and is often accompanied by other atopic disorders such as ***allergic rhinoconjunctivitis*** , ***asthma***, ***food allergies***, and less often ***eosinophilic esophagitis***. These conditions may appear simultaneously or develop in succession.

- **AD and food allergy** have a predilection for **infants** and **young children**, while **asthma** favors **older children** and **rhinoconjunctivitis** predominates in **adolescents**.

- This characteristic age-dependent sequence is referred to as the **“atopic march”** .

- Given that atopic disease progression starts with AD, management should not be concentrated solely on **the treatment of acute flares**, but also be directed towards **ameliorating the underlying genetically determined epidermal barrier dysfunction and preventing active dermatitis via maintenance therapy**. Such an approach could potentially block the sensitizations and ongoing inflammation that drive the atopic march!!


100
50
Incidence (% of peak)
0
5
10
15
Age (years)
Atopic dermatitis
Food allergy
Asthma
Rhinitis

- The term “atopy” originates from the Greek word atopos meaning **strange** or **unusual**.

- The association of **AD** with **allergic rhinitis** and **asthma** was recognized by Besnier in ***1892***.

- ATOPY was first applied to this triad in the **1920s**.

PATHOGENESIS

The pathogenesis of AD can be divided into three major categories:

(1) epidermal barrier dysfunction

(2) *immune dysregulation*

(3) alteration of the microbiome

Each of these can be modulated by **genetic** and **environmental** factors.

Genetic Factors

- Genetic factors account for **~90%** of susceptibility to **early-onset AD**, with a significantly higher concordance rate in monozygotic twins **(77%)** compared to dizygotic twins **(15%).**

- Although the entities in the atopic triad cluster together in families, a **parental history of AD** is a stronger risk factor for the development of AD than either asthma or allergic rhinitis, supporting the existence of genes specific to AD susceptibility.

- AD is a complex genetic disease, and both **gene – gene** and **gene–environment** interactions have important roles.

Candidate gene(s)	Defective protein(s)
Genes encoding epidermal proteins	
FLG	Filaggrin (loss-of-function variants; see text)
FLG2	Filaggrin family member 2
SPINK5	Serine protease inhibitor LETKI
KLK5/SCTE, KLK7/SCCE	Kallikrein-related peptidases 5 & 7/stratum corneum tryptic & chymotryptic enzymes
CLDN1	Claudin-1
SPRR3	Small proline-rich protein 3
TMEM79	Transmembrane protein 79 (mattrin)

Genes encoding immunologic proteins	
FCER1A	Fc fragment of high-affinity IgE receptor I, α chain
TLR2, 4, 6, 9	Toll-like receptor-2, -4, -6, and -9
IRF2	Interferon regulatory factor 2
IL4, 5, 12B, 13, 18, 31	Interleukin-4, -5, -12B, -13, -18, and -31
IL4RA, IL5RA, IL13RA	Interleukin-4, -5, and -13 receptors, α subunits
GM-CSF	Granulocyte–macrophage colony-stimulating factor
CD14	Monocyte differentiation antigen CD14
DEFB1	β-defensin 1
GSTP1	Glutathione S-transferase P1
CMA1	Mast cell chymase
CCL5/RANTES	Chemokine (C-C motif) ligand 5/RANTES
TSLP	Thymic stromal lymphopoietin
MIF	Macrophage migration inhibitory factor
VDR	Vitamin D receptor
CYP27A1, CYP2R1	Cytochrome p450 family members 27A1 and 2R1

Epidermal Barrier Dysfunction

- A defective epidermal permeability barrier represents **a consistent feature** of AD and is evident in the **nonlesional** as well as **lesional** skin of affected individuals.
- A higher level of TEWL, **an indicator of barrier dysfunction**, on day 2 of life predicts an increased risk of AD at 1 year of age.
- the level of TEWL in the **nonlesional skin of children with AD** correlates with **disease severity**.
- Epidermal barrier dysfunction permits an easier entry for irritants, allergens and microbes, which trigger immune responses that include the release of proinflammatory cytokines.
- In infants, **greater TEWL** is associated with an increased likelihood of **epicutaneous sensitization to aeroallergens**, which could potentially play a role in the development of **asthma** and **allergic rhinoconjunctivitis**.

Factors that contribute to the impaired cutaneous barrier in AD

Filaggrin and other structural proteins

Filaggrin is a keratin filament-aggregating protein that serves as a major structural component of the stratum corneum. Loss-of-function FLG mutation represent **the strongest known genetic risk factor** for AD an are also responsible for ichthyosis vulgaris.

Approximately **20–50%** of European and Asian children with **moderate-to-severe** AD have at least one FLG mutation.

the penetrance of AD is **~40%** for one and **~90%** for two mutant alleles.

This implicates epidermal barrier dysfunction in the initiation of AD with subsequent development of Th2-biased immune responses.

Of note, filaggrin expression is also affected by **intragenic copy number variation** and reduced by **increased local pH**, **protease activity**, and **Th2 cytokine levels**.

- FLG mutations are associated with **early-onset AD**, **greater disease severity**, and **persistence into adulthood** as well as **enhanced epicutaneous sensitization** and an increased risk of **irritant contact dermatitis**, **hand eczema**, **herpes simplex virus (HSV) infections**, and **food allergy**.

- FLG mutations have also been linked to an increased risk for the development of **asthma** and **greater asthma severity**; however, these effects are only seen in patients with **pre-existing AD**.

- Since filaggrin is not found in the gastrointestinal or bronchial mucosa, the association of FLG mutations with food allergy and asthma strongly suggests that **epicutaneous sensitization and/or cutaneous inflammation** can contribute to the development of systemic atopic disease.

- Filaggrin breakdown products such as **histidine** contribute to **epidermal hydration**, **acid mantle formation**, **lipid processing**, and **barrier function**.

- Gene expression profiling and immunohistochemical analysis of lesional and nonlesional skin from AD patients have shown broad defects in terminal differentiation, with down-regulation of other epidermal barrier proteins such as **loricrin**, **corneodesmosin**, **involucrin**, **small proline rich proteins 3/4** ,**claudin-1**, and **late cornified envelope protein 2B**.

Stratum corneum lipids

- The **composition**, **organization**, and **biochemical processing** of stratum corneum lipids are critical determinants of epidermal permeability barrier function .

- In AD, a filaggrin-deficient cytoskeletal scaffold contributes to **abnormal loading** and **secretion of lamellar bodies**, with subsequent defects in **post-secretory lipid organization** and **processing**.

- Disruption of the **skin's acidic mantle** leads to reduced activity of lipid-processing enzymes such as **β-glucoscerebrosidase** and **acid sphingomyelinase**.

- Th2 cytokines also **negatively** affect generation of stratum corneum lipid components.

Proteases and protease inhibitors

- Lesional AD skin demonstrates **elevated levels** of **endogenous serine proteases**, e.g. kallikrein 5 and 7 (KLK5/7), due to an imbalance in the activities of these proteolytic enzymes and protease inhibitors such as the lymphoepithelial Kazal-type trypsin inhibitor (LEKTI) encoded by SPINK5.

- **Biallelic loss-of-function SPINK5** mutations underlies **Netherton syndrome**, which features **profoundly compromised barrier function** and **atopy** .

- Other factors that enhance proteolysis include **increased skin surface pH** and **exogenous proteases from allergens** (e.g. house dust mites, pollens), **Staphylococcus aureus**, and **Malassezia**.

- The **LEKTI deficiency** results in excessive degradation of the **corneodesmosomal component desmoglein-1 (Dsg1)**, causing abnormal stratum corneum detachment and thereby disrupting the epidermal barrier.

- The **S. aureus extracellular V8 protease**, which has a sequence similar to those of **S. aureus exfoliative toxins**, is also thought to degrade **Dsg1**.

- In addition, unrestrained protease activity leads to **degradation of lipid-processing enzymes** and **antimicrobial peptides** as well as **activation of proinflammatory cytokines**.

Immune Dysregulation

- The **innate** and **adaptive** immune systems play dynamic interrelated roles in the pathogenesis of AD.
- Acute AD lesions have a predominance of **Th2 cytokines**, but there is subsequent evolution to a chronic phase characterized by **Th1** and **Th22 cytokine profiles**, as well as **variable levels of Th17 cytokines in both acute** and **chronic AD**.
- The **acute phase** features **IL-4**, **IL-5**, and **IL-13**; **activation of eosinophils** and **mast cells**; and **production of allergen-specific IgE**.
- Keratinocyte-derive cytokines including **IL-1**, **thymic stromal lymphopoietin (TSLP)**, **IL-25(IL-17E)**, and **IL-33** promote a Th2 immune response.
- Th2 cytokines inhibit expression of major terminal differentiation proteins such as **loricrin**, **filaggrin**, and **involucrin** as well as **β-defensin-2/3 antimicrobial peptides.**

Thymic stromal lymphopoietin (TSLP)

- TSLP is an **IL-7-like cytokine** that is known as the **“master-switch of allergic inflammation”** due to its central role in evoking a Th2 response via dendritic cell activation.

- Exposure to **allergens**, **viral infections**, **trauma**, and **other cytokines (e.g. IL-1β, TNF)** can trigger TSLP production by **keratinocytes**, **fibroblasts**, and **mast cells**.

- TSLP is highly expressed in **acute** and **chronic** lesions of AD, but not in the **nonlesional** skin of patients with AD or in **unaffected individuals**.

IL-4 and IL-13

- IL-4 has a key role in driving **Th2 cell differentiation**, **IgE production**, and **eosinophil recruitment**.

- Transgenic mice overexpressing IL-4 in their epidermis develop **atopic dermatitis-like lesions**, **pruritus**, **an altered microbiome**, and **elevated IgE levels**.

- The heterodimeric receptors for IL-4 and IL-13 both contain the IL-4 receptor α subunit and activate signal transducer and activator of transcription 6 (STAT6), which promotes the differentiation of **naive T cells** into **Th2 effector cells**. Although IL-4 and IL-13 share 25% sequence homology and effector functions, studies in human subjects and human keratinocyte cell lines support an independent role for IL-13 in AD pathogenesis.

- **Anti-IL-4/13 therapy with dupilumab , a monoclonal antibody that targets the IL-4Rα, is FDA-approved for the treatment of AD.**

Other cytokines

- Th17 cells are important in the regulation of **innate immunity**, in particular **neutrophil recruitment**, and have also been implicated in **allergic disorders**.
- Th17 cells are found in **acute** as well as **chronic** AD lesions, and production of **IL-17** and **IL-19** is especially characteristic of **new-onset pediatric AD**.
- IL-31 is a **Th2 cytokine** that is highly expressed in lesions of **AD** and other pruritic skin disorders such as **prurigo nodularis**.
- Cutaneous exposure to staphylococcal super antigen rapidly induces IL-31 expression in atopic individuals, establishing a link between staphylococcal colonization of the skin and pruritus. The heterodimeric receptor for IL-31 is expressed by **keratinocytes**, **eosinophils**, **activated macrophages**, **cutaneous C nerve fibers**, and **dorsal root ganglia**.
- A randomized, placebo-controlled study showed that **nemolizumab**, a humanized monoclonal antibody against the IL-31 receptor A subunit, can significantly reduce pruritus in patients with moderate to severe AD.
- IL-33, **a member of the IL-1 cytokine family**, protects against helminth infection by promoting a Th2-type immune response. IL-33 expression is increased in **AD lesions** compared to **the skin of unaffected individuals**.

Innate lymphoid cells

- The innate lymphoid cell **(ILC)** family includes **natural killer cells** and three groups of **non-cytotoxic ILCs** that orchestrate **immunity**, **inflammation**, and **homeostasis** in multiple tissues.

- The group 2 ILC (ILC2) population is expanded in AD lesions and stimulated by **TSLP**, **IL-25 (IL-17E)**, and **IL-33**.

- ILC2s interact with other immune cells (e.g. **mast cells**, **eosinophils**) in the skin to promote **Th2-type inflammation** in a **T-cell independent manner**.

The Cutaneous Microbiome

- More than **90% of patients with AD** have skin colonized with S. aureus, compared to about **5% of unaffected individuals**, presumably reflecting the **disrupted acid mantle**, **decreased antimicrobial peptides** (e.g. cathelicidins, defensins), and **altered cytokine milieu** of AD skin.

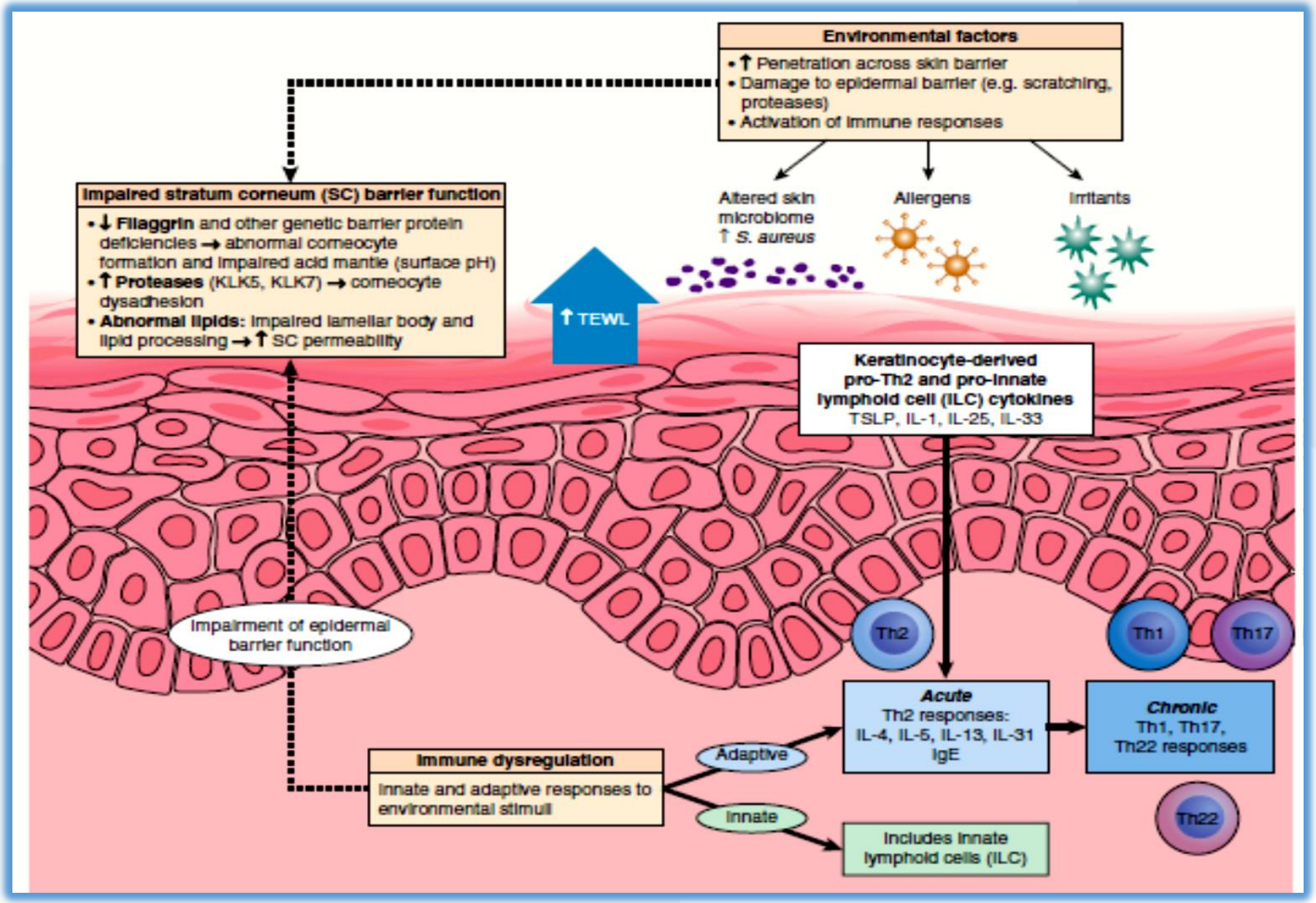
- During AD flares, bacterial diversity **decreases** and the proportion of the microbiome accounted for by Staphylococcus spp. **increases** from ~35% to ~90%. Superantigens can promote the development of a Th2 immune response, and **exotoxins** with **superantigenic properties** are produced by up to 65% of the S. aureus strains that colonize AD patients.

- In addition, the **S. aureus δ-toxin** stimulates **mast cell degranulation** and **Th2 inflammation**.

- Filaggrin deficiency also increases the susceptibility of keratinocytes to S. aureus **α-toxin-induced cytotoxicity**.

- Alterations in the skin microbiome of AD patients related to the use of **cleansers** and topical **immunomodulatory** or **antimicrobial** agents may have potential effects on cutaneous inflammation and barrier function.

- In addition, topical administration of coagulase negative Staphylococcus strains with antimicrobial activity has been shown to markedly reduce S. aureus colonization in AD patients, providing the basis for **bacteriotherapy** as a potential AD treatment.


Environmental factors
• ↑ Penetration across skin barrier
• Damage to epidermal barrier (e.g. scratching, proteases)
• Activation of immune responses
Altered skin microbiome ↑ S. aureus
Allergens
Irritants
Impaired stratum corneum (SC) barrier function
• ↓ Filaggrin and other genetic barrier protein deficiencies → abnormal corneocyte formation and impaired acid mantle (surface pH)
• ↑ Proteases (KLK5, KLK7) → corneocyte dysadhesion
• Abnormal lipids: impaired lamellar body and lipid processing → ↑ SC permeability
↑ TEWL
Keratinocyte-derived pro-Th2 and pro-innate lymphoid cell (ILC) cytokines
TSLP, IL-1, IL-25, IL-33
Impairment of epidermal barrier function
Th2
Th1
Th17
Acute
Th2 responses:
IL-4, IL-5, IL-13, IL-31
IgE
Chronic
Th1, Th17, Th22 responses
Th22
Immune dysregulation
Innate and adaptive responses to environmental stimuli
Adaptive
Innate
Includes innate lymphoid cells (ILC)

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