The Skinny of the Immune System

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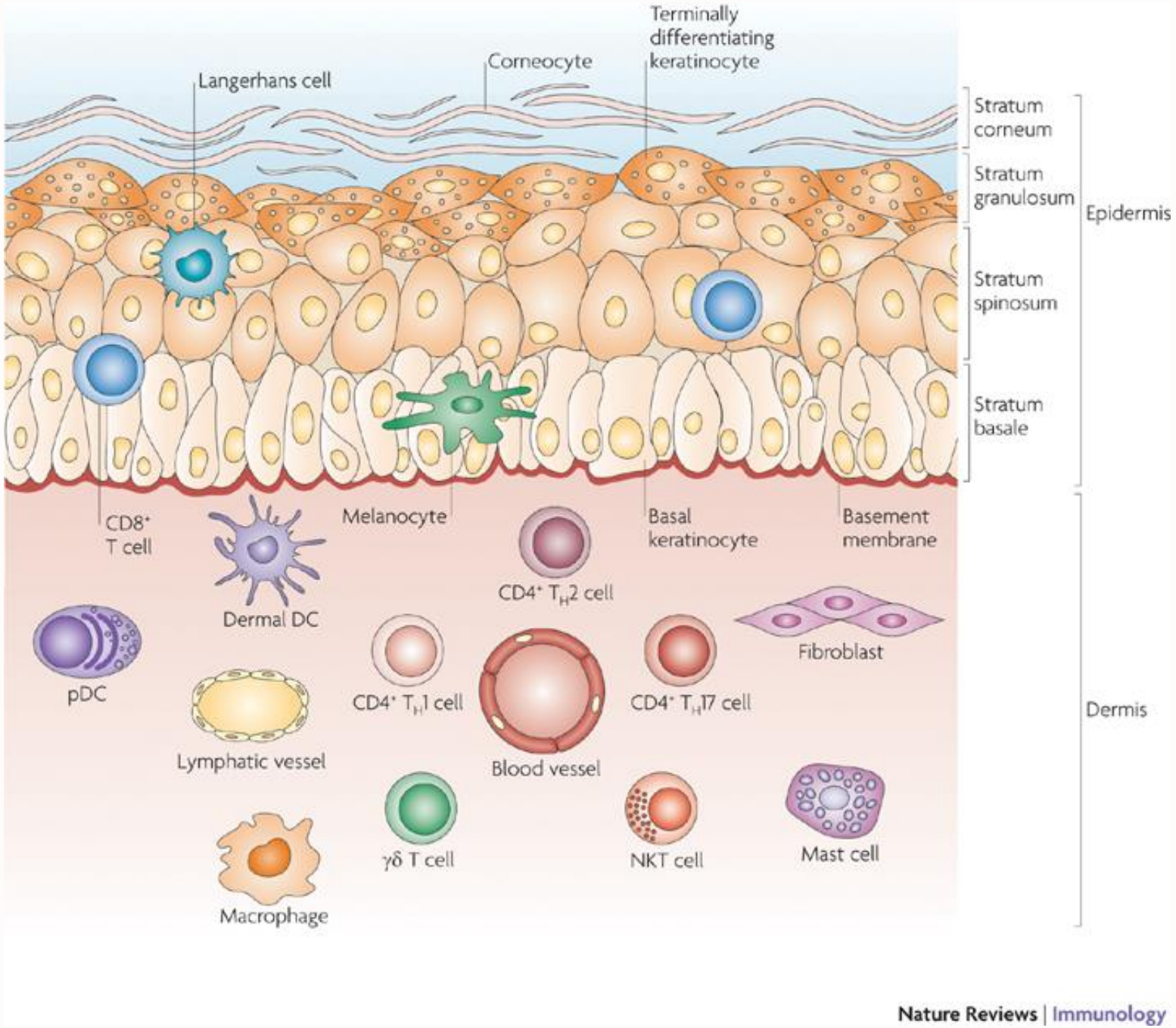
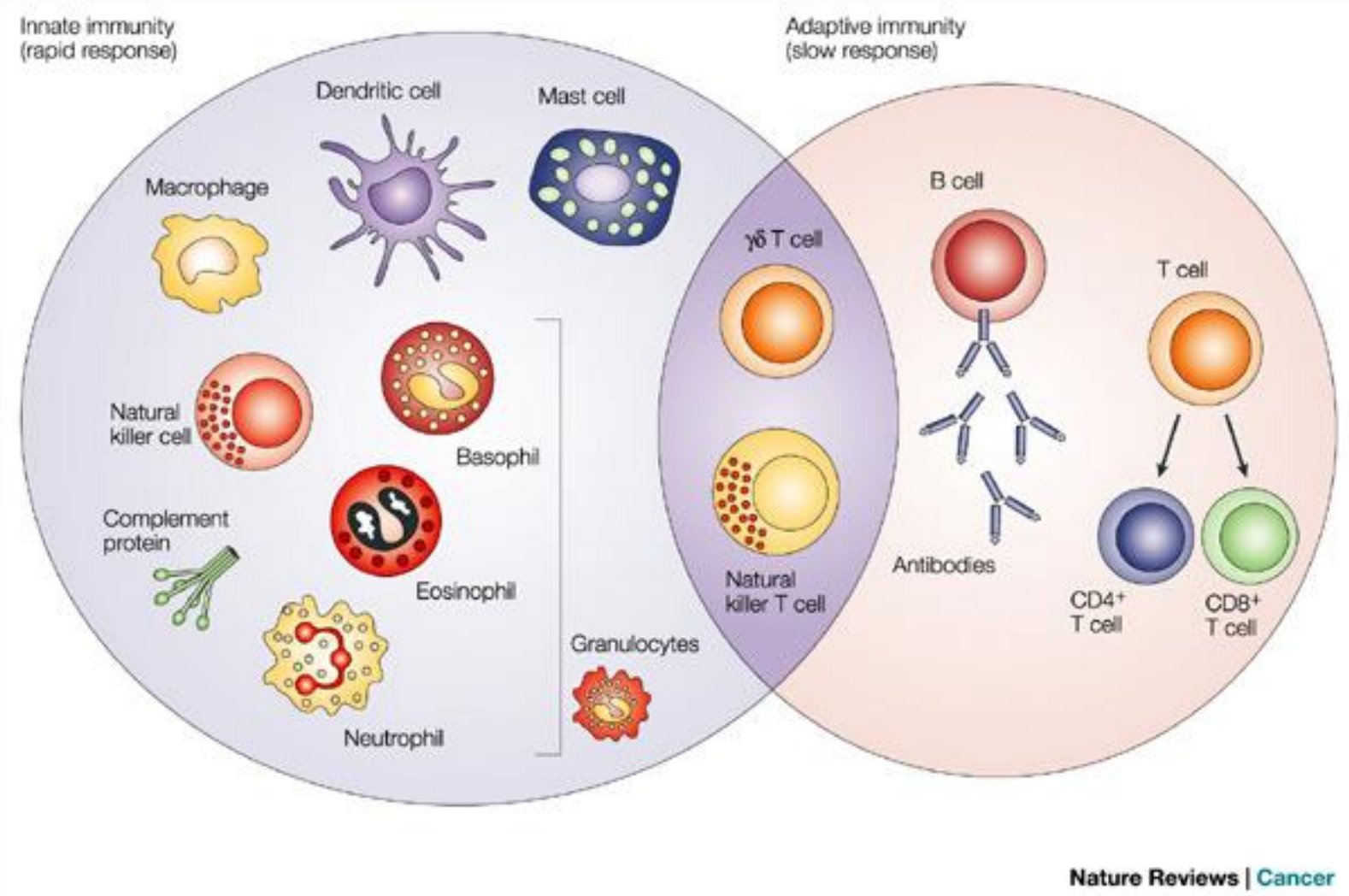
Overview

- 1. Immune system of the skin
- 2. Immune Players of the skin
- 3. Biologicals for the skin
- 4. Conclusion


Terminally differentiating keratinocyte
Corneocyte
Langerhans cell
Stratum corneum
Stratum granulosum
Stratum spinosum
Stratum basale
Epidermis
CD8+ T cell
Melanocyte
Basal keratinocyte
Basement membrane
CD4+ TH2 cell
Dermal DC
Fibroblast
pDC
CD4+ TH1 cell
CD4+ TH17 cell
Lymphatic vessel
Blood vessel
Dermis
γδ T cell
NKT cell
Mast cell
Macrophage
Nature Reviews | Immunology


Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
γδ T cell
B cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil
Nature Reviews | Cancer

Innate Immune System

- Hand grenade
- Rapid response

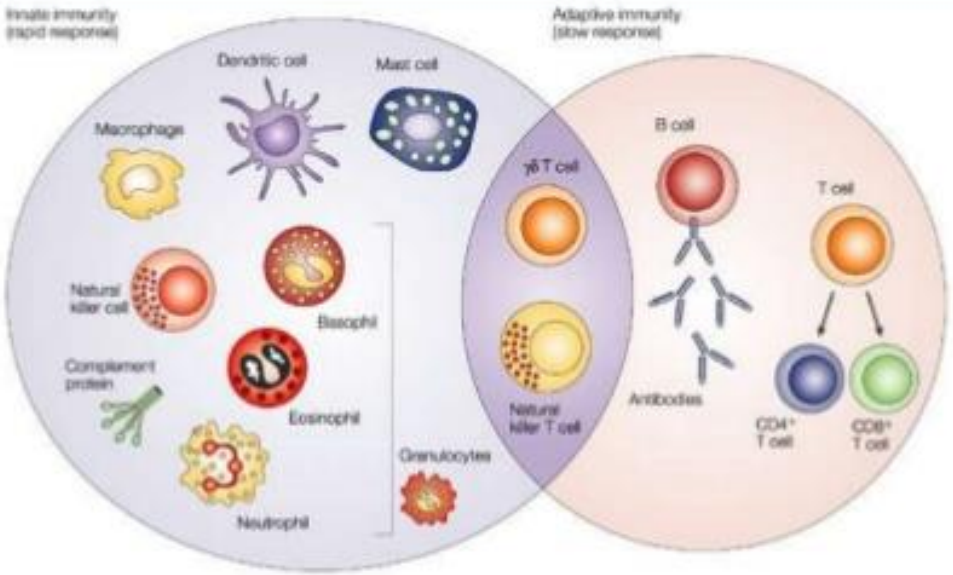
Adaptive Immune System

- Smart Bomb

Immune System – Innate vs Adaptive

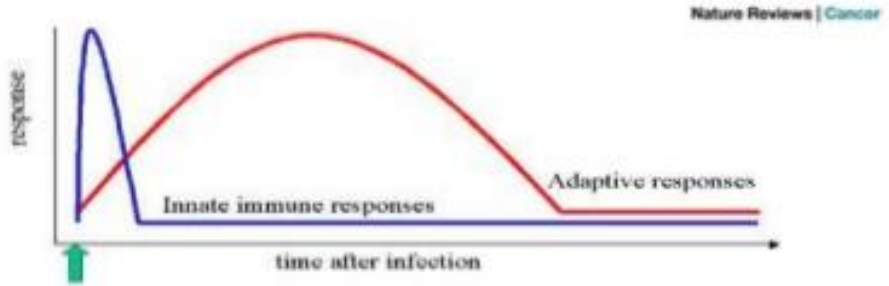
Innate:

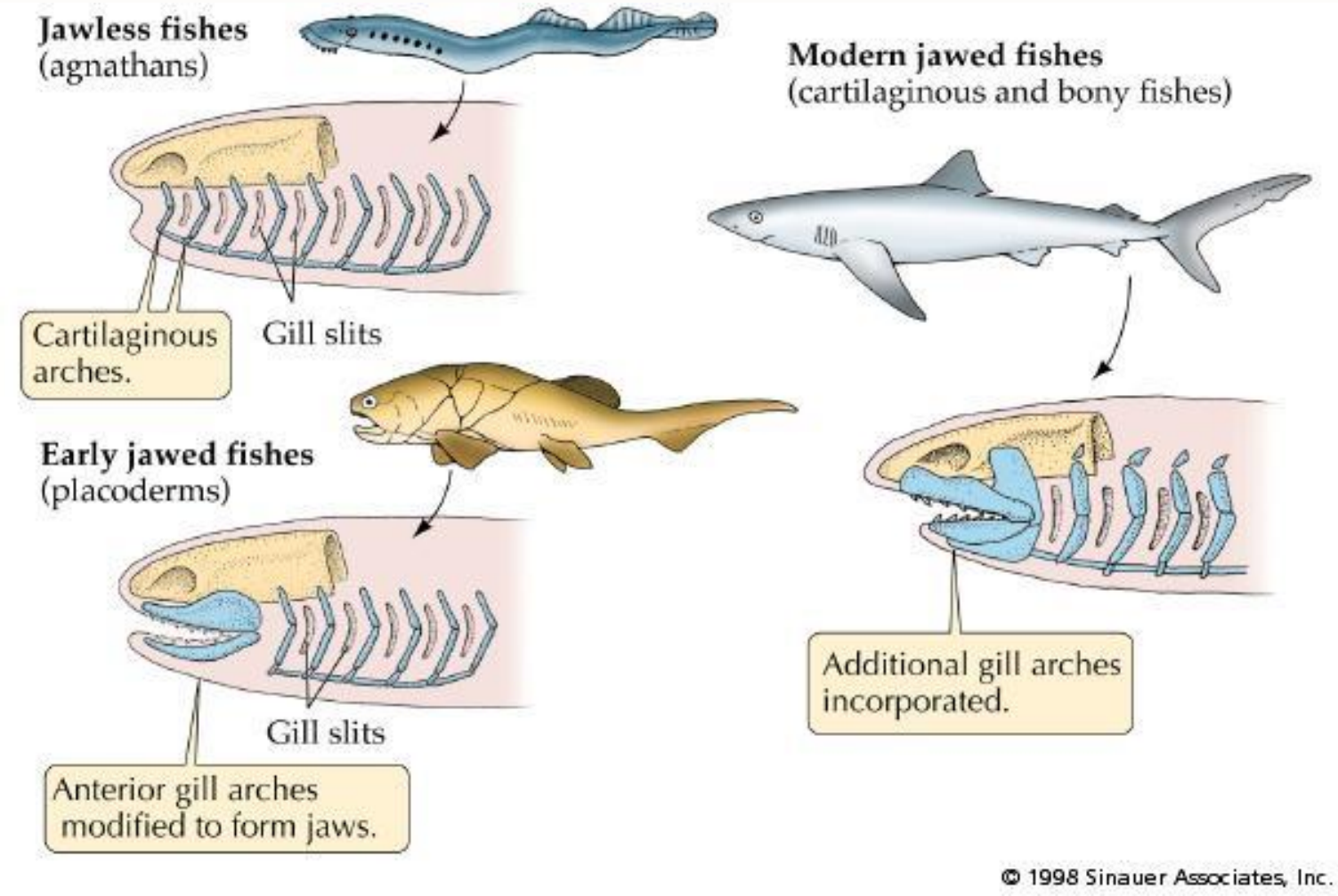
- Nonspecific
- Responds quickly



Adaptive:

- Specific
- Responds Slowly the 1st time




Jawless fishes
(agnathans)
Cartilaginous arches.
Gill slits
Modern jawed fishes
(cartilaginous and bony fishes)
Early jawed fishes
(placoderms)
Gill slits
Anterior gill arches modified to form jaws.
Additional gill arches incorporated.
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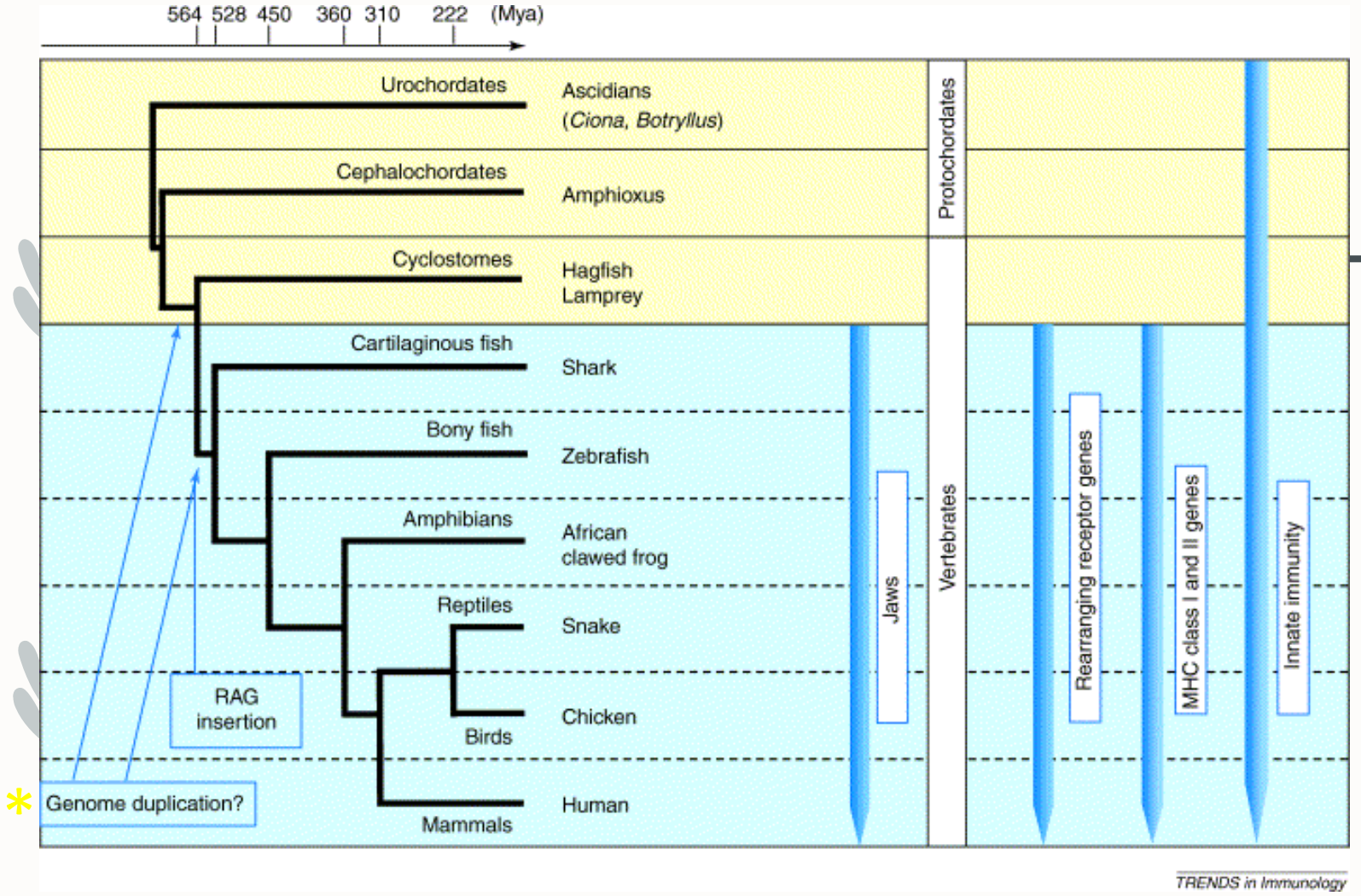
Phylogeny of Chordates and the Major Events in the Evolution of Adaptive Immunity



Genome Duplication : Large-scale gene duplication and subsequent reshuffling of exons lead the emergence of new genes

Skin Residents of the Innate Immune System

- Macrophages
- Dendritic cells
- Langerhans Cells

Tay et al. The skin-Resident Immune Network. (2014) Curr Derm Rep 3:12-22.

Macrophages

- Most abundant haematopoietic population in the skin
- Important in wound healing
- Express PAMP receptors
- Secrete pro-inflammatory cytokines/chemokines
- Growth promoting/phagocytose apoptotic cells
- Thought to be derived from monocytes but may have been established prenatally from yolk-sac.
- Heterogeneous population in skin

Population

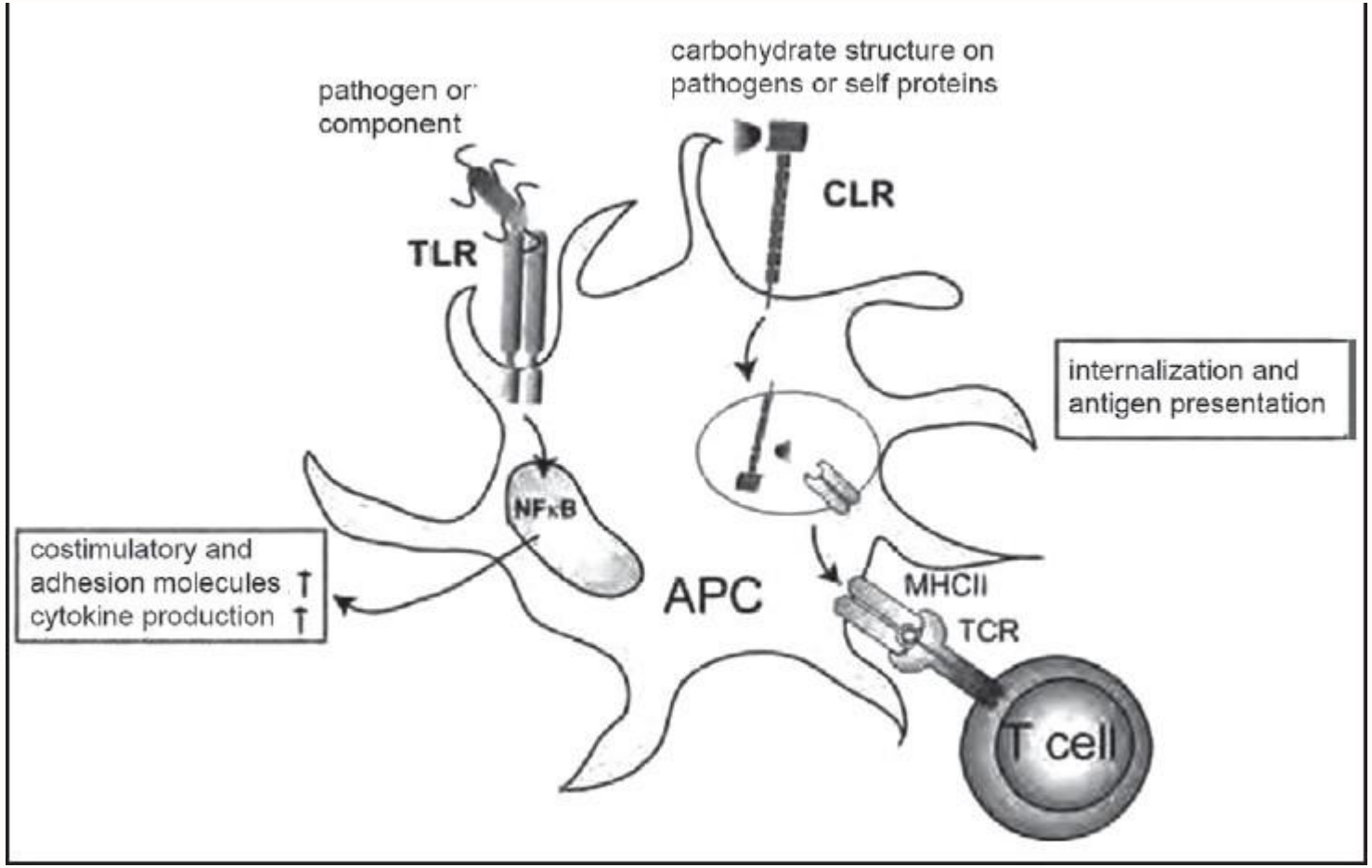
- Perivascular macrophages: regulating leukocyte extravasation, regulating iron homeostasis
- Associated with lymphatic vessels: important during lymphangiogenesis

Dendritic cells

- Antigen presenting cells to naïve T cells
  - Immune response against invasion
  - Tolerance to commensal bacteria
- Capacity to migrate via the lymphatics to skin-draining lymph nodes
- They initiate the downstream adaptive response
- Two populations:
  - Langerhans cells
  - Dermal dendritic cells

Langerhan Cells

- Basal and supra-basal epidermis
- Capture and present antigen: +/- presentation to T cells
- Develop from primitive macrophage
- Self-renewal
- Maybe replenished by BM monocytes
- Initiating tolerance of T cells


pathogen or
component
carbohydrate structure on
pathogens or self proteins
TLR
CLR
internalization and
antigen presentation
NFκB
costimulatory and
adhesion molecules ↑
cytokine production ↑
APC
MHCII
TCR
T cell

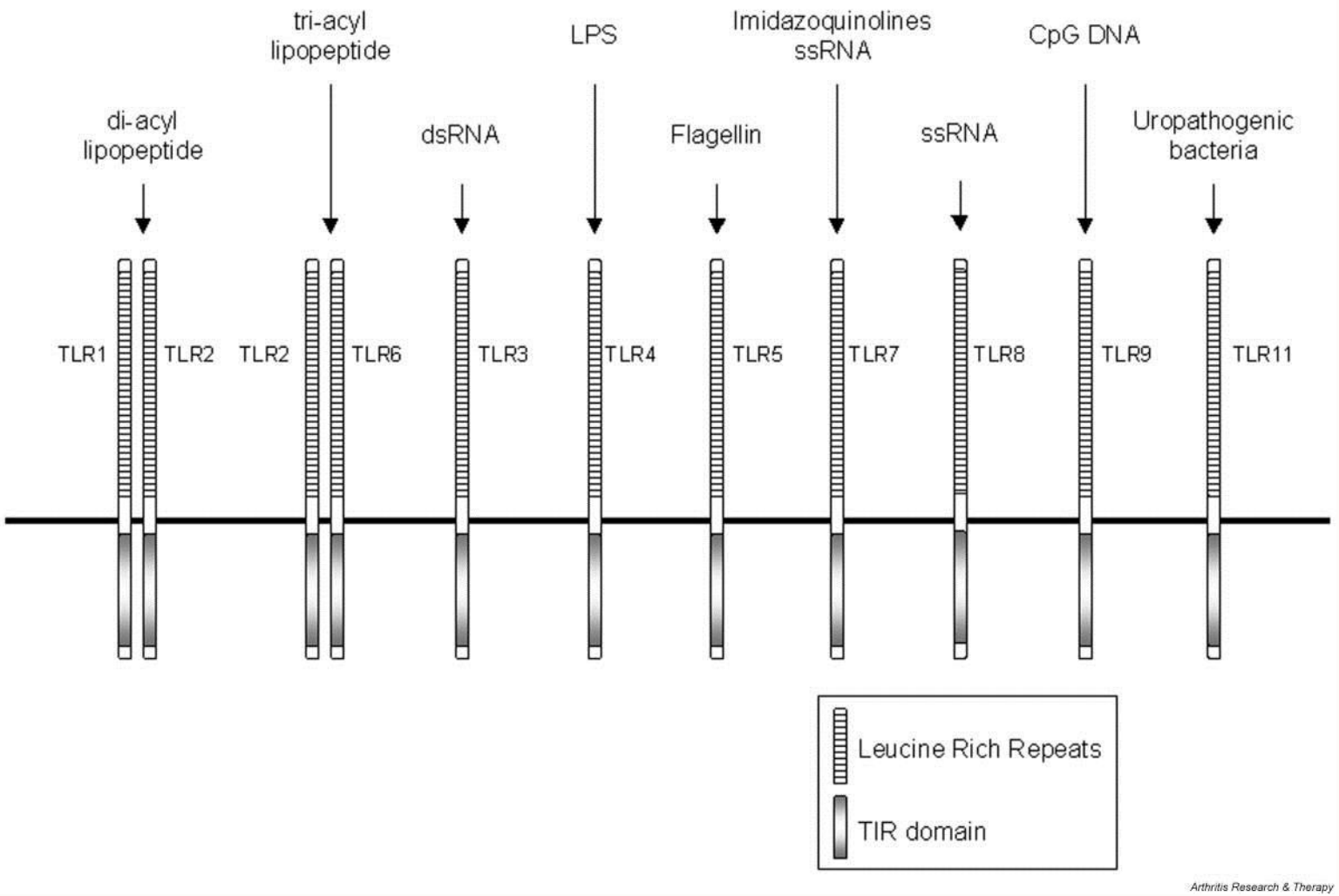
Toll receptors

- One of a family of receptors that provide a critical link between immune stimulants produced by microorganisms and the initiation of the host defense. Activation of the toll receptors causes the release of antimicrobial peptides, inflammatory cytokines, and molecules that initiate adaptive immunity.
- German for: mad, bedlum, madcap
- Genetic studies initially performed in the fruitfly *Drosophila* and later in mice have revealed the importance of proteins of the Toll family in the innate immune response.
- Ancient receptor

Toll-like receptors

- There are eleven protein receptors, TLR1-TLR11
- TLR12 and TLR13 have been found in murine models

Toll-like receptors and their ligand



Dermal Dendritic Cells

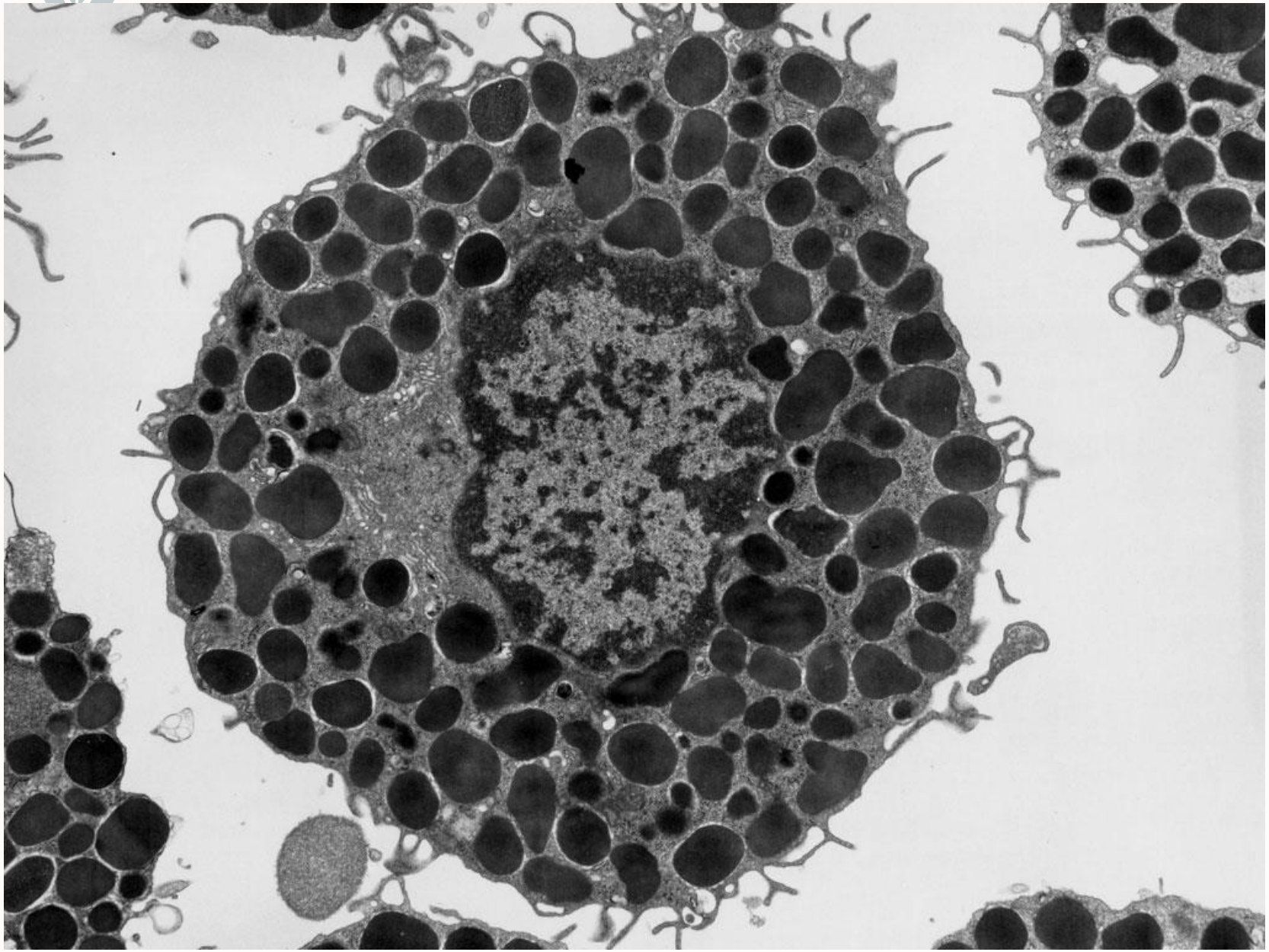
- Depends on constant resupply from BM
- Multiple dermal subsets
- Immune-surveillance role
- During inflammation they run to lymph node within 48 hours preceding LC
- Shapes the initial T cell response
- Found in lymph nodes at steady-state= tolerance

Adaptive Immune System

- Mast cells
- Gamma/Delta T cells
- Dermal Gamma/Delta T cells

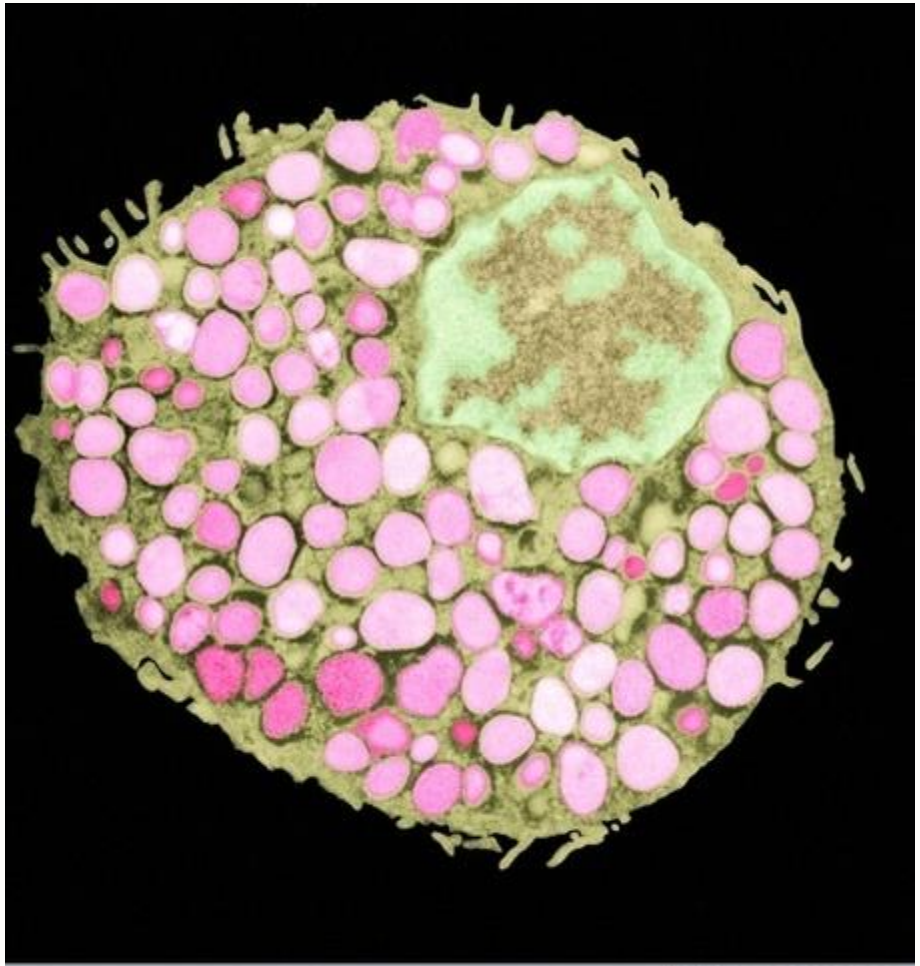
Mast Cells

- Mast cells were first described by Paul Ehrlich in his 1878 doctoral thesis on the basis of their unique staining characteristics and large granules.
- These granules also led him to the mistaken belief that they existed to nourish the surrounding tissue, and he named them "*Mastzellen*" (from the German: *Mast*, "fattening" as of animals).[



preformed mediators (from the granules):

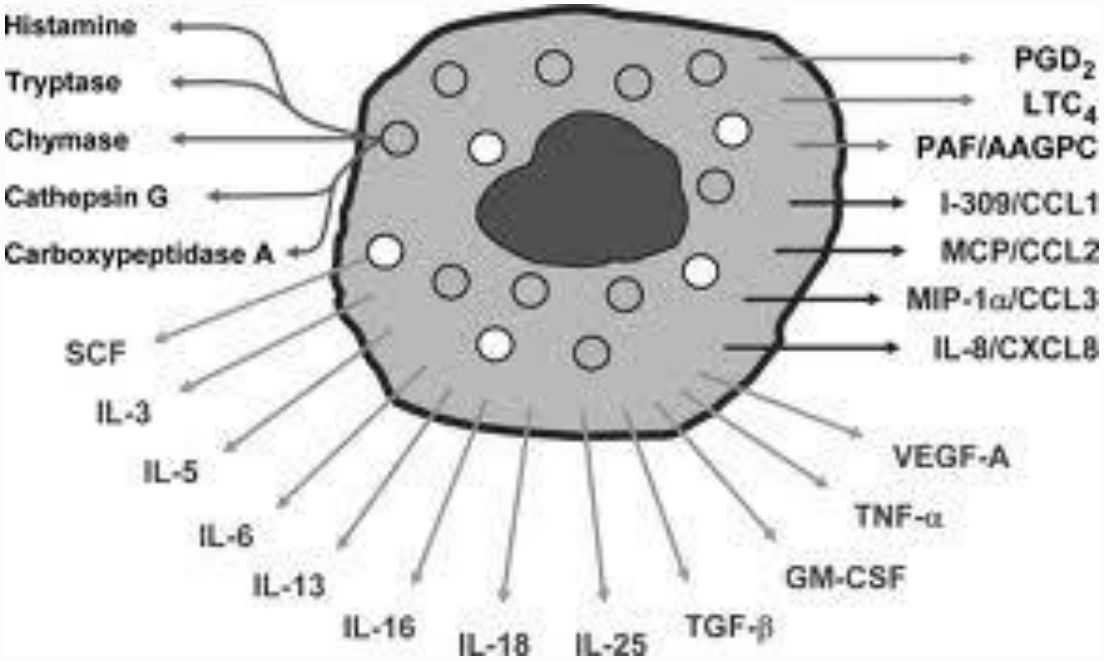
- serine proteases, such as tryptase
- histamine (2-5 pg/cell)
- serotonin
- proteoglycans, mainly heparin (active as anticoagulant)

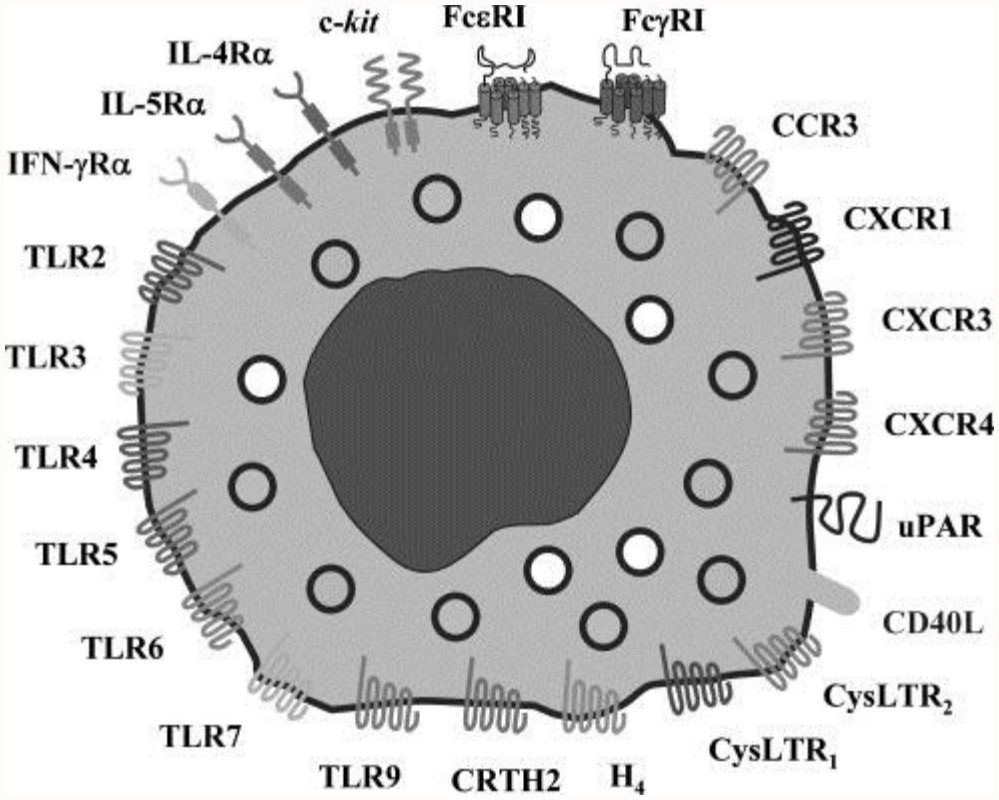


Wellcome Images

newly formed lipid mediators (eicosanoids):

- thromboxane
- prostaglandin D2
- leukotriene C4
- platelet-activating factor

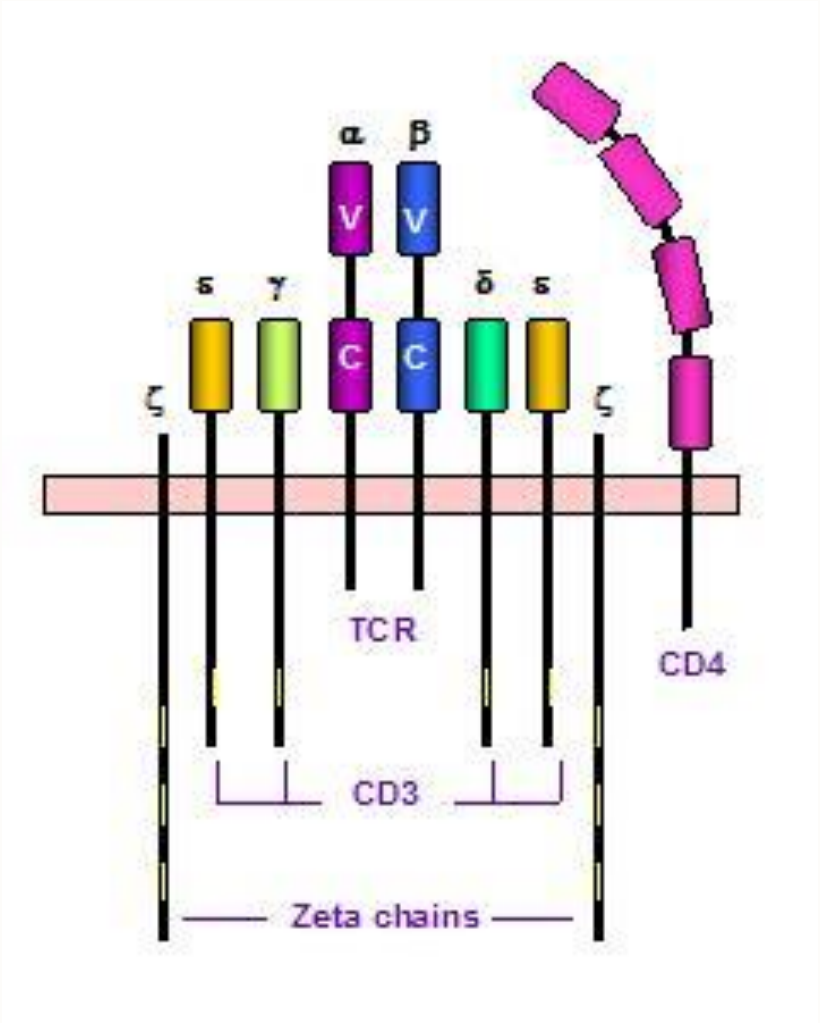

Histamine
Tryptase
Chymase
Cathepsin G
Carboxypeptidase A
SCF
IL-3
IL-5
IL-6
IL-13
IL-16
IL-18
IL-25
TGF-β
GM-CSF
TNF-α
VEGF-A
PGD2
LTC4
PAF/AAGPC
I-309/CCL1
MCP/CCL2
MIP-1α/CCL3
IL-8/CXCL8


c-kit
FcεRI
FcγRI
IL-4Rα
IL-5Rα
IFN-γRα
CCR3
CXCR1
TLR2
CXCR3
TLR3
CXCR4
TLR4
uPAR
TLR5
CD40L
TLR6
CysLTR2
TLR7
CysLTR1
TLR9
CRTH2
H4

Dermal Gamma/Delta T Cells

- 50% of all dermal T cells
- Require IL-7 not IL15 for development
- Self-renewal
- TH17-like
- Augment neutrophil recruitment
- ? Involved in human psoriasis

Structure



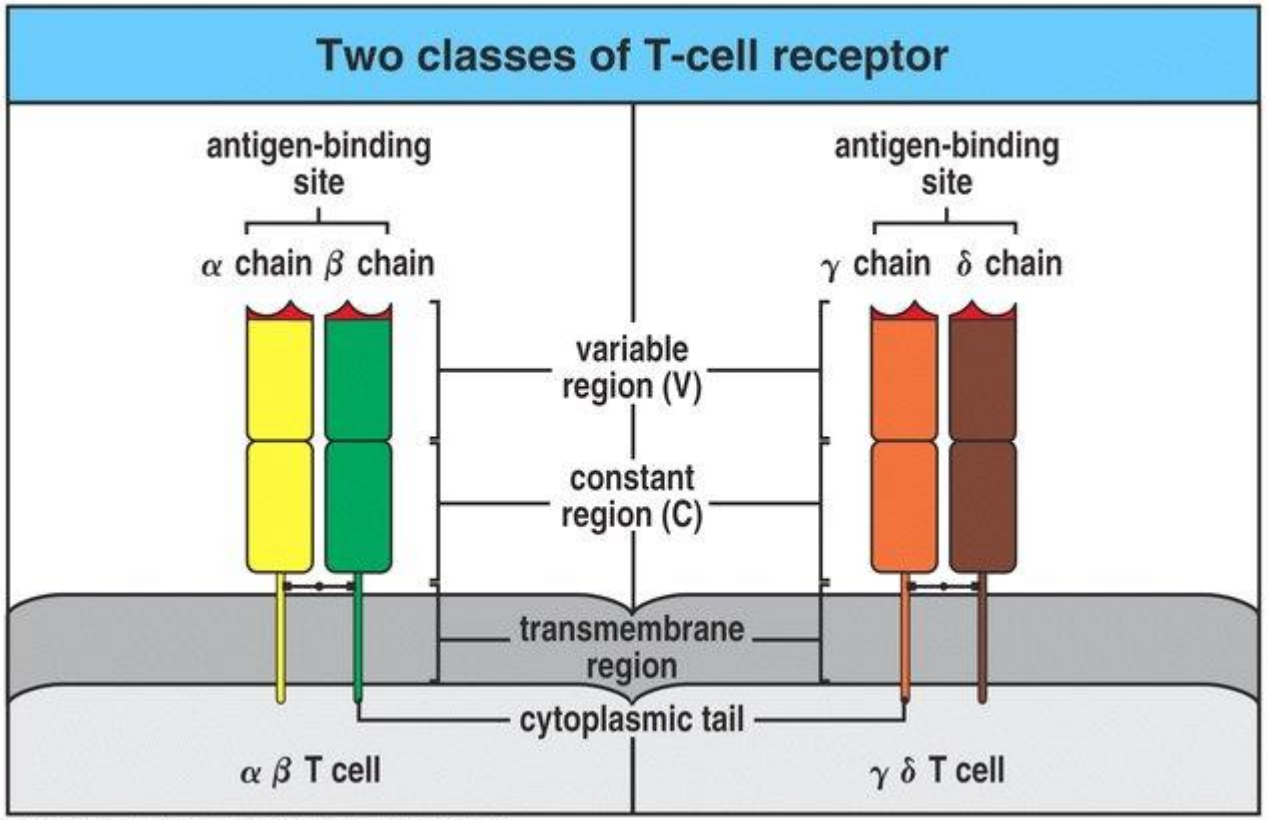


Figure 3-7 The Immune System, 2/e (© Garland Science 2005)

Innate Lymphoid Cells (ILC)

- Look lymphoid but no markers for T or B cells
- Subpopulations: grouped by what they produce
  - ILC1 produces IFN gamma
  - ILC2 produces IL5 and IL13 (enriched in atopic derm)
  - ILC3 produces IL17, IL22 (?psoriasis)

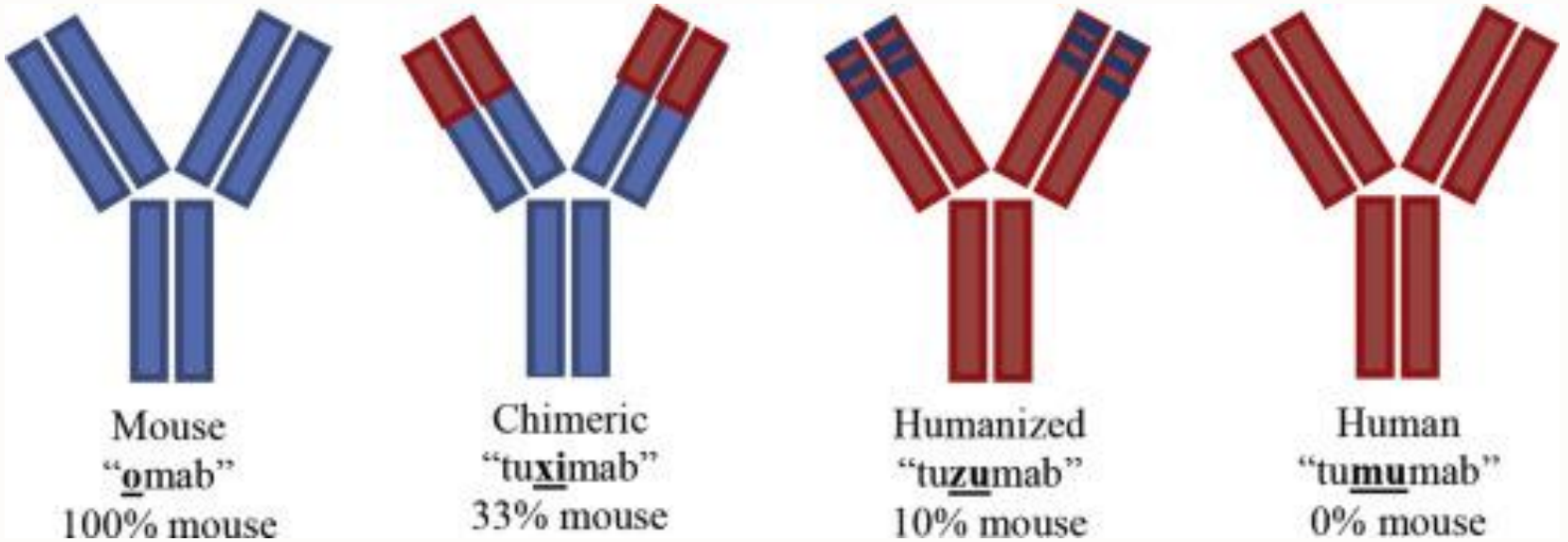
Biologics for Atopic Dermatitis

- Anti- CD 20
- Anti-IgE
- Anti-IL4R
- Anti-TNF
- Anti-IL5
- Anti-IL6
- Anti-31
- Anti-TSLP

Hyun Le,J, (2016).A Comprehensive Review of the Treatment of Atopic Eczema. Allergy Asthma Immunol Res. 2016 May;8(3):181-190. http://dx.doi.org/10.4168/aair.2016.8.3.181.

Medscape® www.medscape.com

Prefix	Original application		Species source		Suffix
Individual	-vi(r)-	viral	-o-	mouse	-mab
	-ba(c)-	bacterial	-a-	rat	
	-fun(g)-	fungal	-u-	human	
	-li(m)-	immune	-i-	primate	
	-neu(r)-	neural	-xi-	chimeric	
	-mu(l)-	musculoskeletal	-zu-	humanized	
	-tu(m)-	tumor			
	-ci(r)-	circulatory			
Nata-	-li-		-zu-		-mab
Alem-	-tu-		-zu-		-mab
Dac-	-li-		-zu-		-mab
Ri-	-tu-		-xi-		-mab


Mouse
“omab”
100% mouse
Chimeric
“tuximab”
33% mouse
Humanized
“tuzumab”
10% mouse
Human
“tumumab”
0% mouse

Abciximab			Trastuzumab			Catumaxomab			Otelixizumab		
Ab-	=	Non-specific prefix	Tras-	=	Non-specific prefix	Ca-	=	Non-specific prefix	Ote-	=	Non-specific prefix
-ci-	=	circulatory target	-tu-	=	tumour target	-tum-	=	tumour target	-li-	=	immune system target
-xi-	=	chimeric structure	-zu-	=	humanized structure	-axo-	=	rat-mouse hybrid structure	-xizu-	=	chimeric/ humanized hybrid structure
-mab	=	monoclonal antibody	-mab	=	monoclonal antibody	-mab	=	monoclonal antibody	-mab	=	monoclonal antibody

Anti-CD20

- Rituximab is an antibody against CD20 which depletes B cells.
- Treatment with Rituximab improved skin symptoms in patients with severe AE, suggesting its potential role for B-cells in the pathogenesis of AE

Anti-IgE

Anti-IgE Omalizumab is a monoclonal antibody which binds and neutralizes IgE. Some AE patients have shown clinical improvement with anti-IgE therapy, but others have experienced no response or even aggravation of their symptoms. Further studies are needed to determine whether omalizumab deserves a place in routine AE therapy, or whether its costs or side effects outweigh possible benefits.

Anti-IL4R

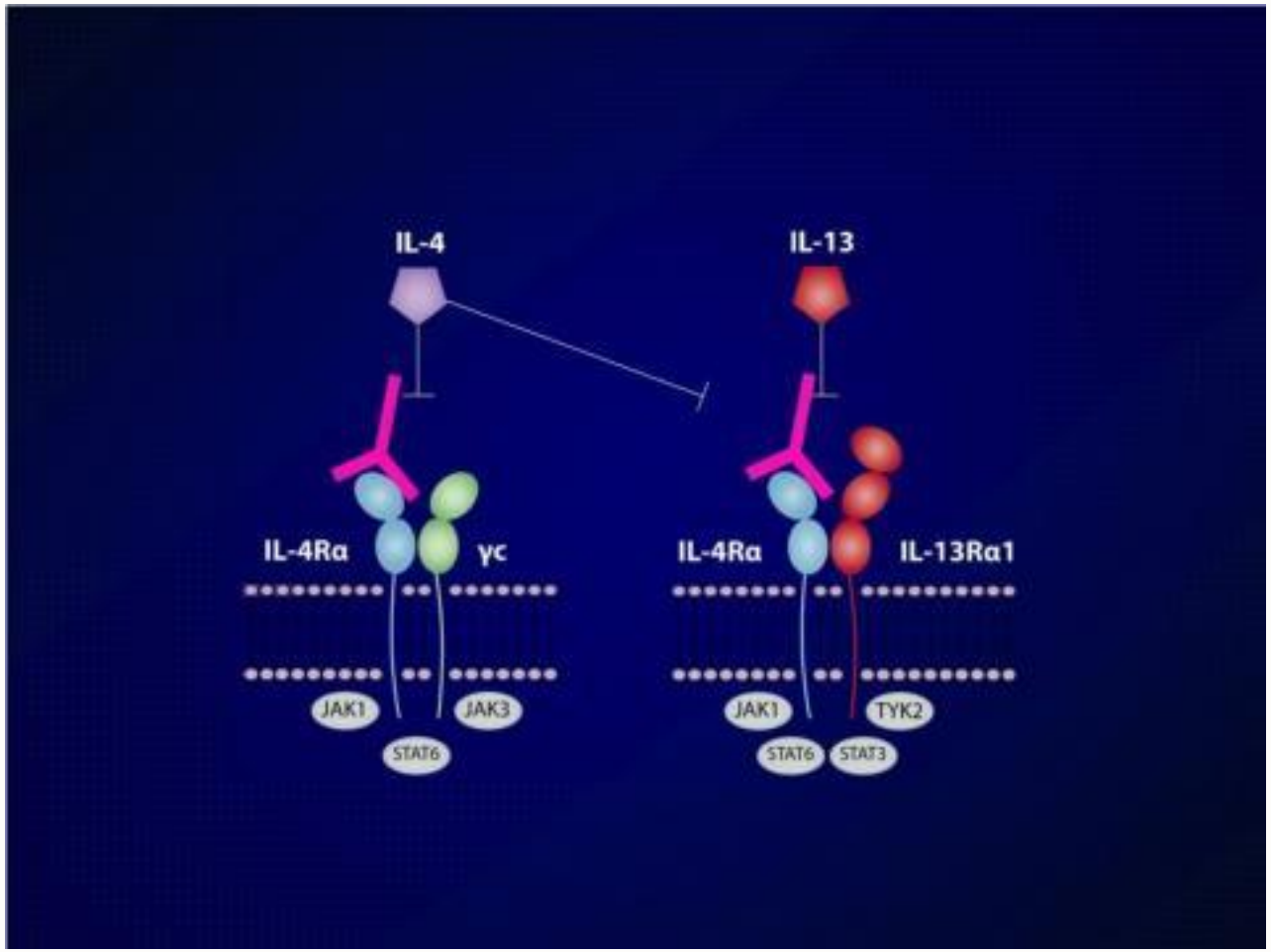
Anti-IL-4 receptor therapy It is well known that Th 2 cytokine plays an important role in atopy.

Dupilumab

- A IL4R alpha antagonist
- Adults; 18 and above
- moderate to severe AD
- Not controlled by topicals
- Or when those therapies are not advisable

Dosage

- Two 300mg initially subcutaneous different sites
- Then 300mg every other week
- Avoid live viral vaccines during use


IL-4
IL-13
IL-4Rα
γc
IL-4Rα
IL-13Rα1
JAK1
JAK3
STAT6
JAK1
TYK2
STAT6
STAT3

Anti-TNF

Anti-TNFα therapy

A pilot study with a TNF antagonist, infliximab, was conducted in 9 patients with moderate or severe AE.

Treatment with infliximab improved clinical symptoms, but the effect was not continued through the maintenance therapy.

Anti-IL-5

Anti-IL-5 therapy

IL-5 is also another important cytokine produced by Th2 cells.

Treatment with mepolizumab, a humanized monoclonal antibody, which binds to IL-5, did not induce clinical improvement in patients with AE, despite a significant decrease in peripheral blood eosinophils.

However, a recent double-blind study showed that mepolizumab had a significant glucocorticoid-sparing effect in patients with severe eosinophilic asthma.

Further studies are required to determine whether anti-IL5 therapy may be used to treat AE.

Anti-IL6

Anti-IL-6 receptor therapy
Tocilizumab or atlizumab is a humanized monoclonal antibody against the IL-6 receptor which is used mainly for the treatment of rheumatoid arthritis.
A recent study showed the potential effectiveness of interrupting IL-6-receptor signaling in patients with AE.
However, bacterial superinfections were also reported to be associated with the therapy.
Further studies are needed to investigate the efficacy and safety of IL-6 receptor antagonists.

Anti-IL31

- Anti-IL-31 therapy
- IL-31 is primarily produced by type 2 helper T cells (Th2).
- The structure of IL-31 places it in the IL-6 family of cytokines. IL-31 serum levels correlate with disease activity and Th2 cytokine levels in children with AE.
- Anti-IL 31 monoclonal antibody is under investigation in a phase I clinical trial (clinicaltrials.gov)

Anti-TSLP

- Anti-TSLP therapy
- TSLP is an epithelial-cell-derived cytokine, which plays a key role in the maturation of T cell populations through activation of antigen presenting cells. TSLP production may initiate allergic inflammation.
- AMG 157 is a human anti-TSLP monoclonal immunoglobulin G2λ that binds human TSLP and prevents receptor interaction.
- Treatment with anti-TSLP antibody decreased allergen-induced early and late asthmatic responses in patients with mild allergic asthma.

Conclusions

- The skin is a communicating organ
- The skin contains multiple immune components that interact in health and disease
- Regulation of these components may influence disease outcomes.