

Hypersensibilités et allergies cutanées



Gell & Coombs revisited

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Hypersensitivity reactions

1. Immunology definition – Gell & Coombs

Hypersensitivity reactions = inappropriate and damaging immune response to an antigen caused by adaptive immunity (Igs and/or T cells)

- Allergic diseases
- Autoimmune diseases

2. Allergy définition

Hypersensitivity reactions = inappropriate and damaging immune response to a molecule caused by both innate and/or adaptive immunity

- Allergic HS
- Non allergic HS

Hypersensibilité (HS)

```
graph TD; HS[Hypersensibilité (HS)] --> HS_A[HS adaptative Allergique]; HS --> HS_I[HS innée Non Allergique];
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HS adaptative
Allergique

HS innée
Non Allergique

Hypersensibilité (HS)

Eczéma



HS Allergique

Eczéma allergique de contact
Eczéma atopique extrinsèque



HS Non Allergique

Eczéma irritatif de contact
Eczéma atopique intrinsèque

Hypersensibilité (HS) aux médicaments

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graph TD; A[Hypersensibilité (HS) aux médicaments] --> B[HS Allergique  
Rare (5%)]; A --> C[HS Non Allergique  
Fréquente (95%)]; B --- D[sévère]; C --- E[bénigne];
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HS Allergique
Rare (5%)

HS Non Allergique
Fréquente (95%)

sévère

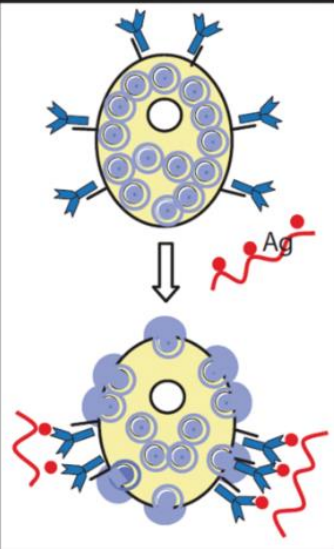
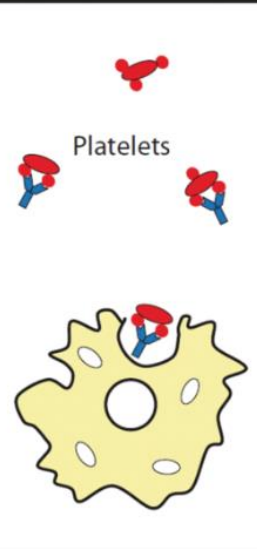
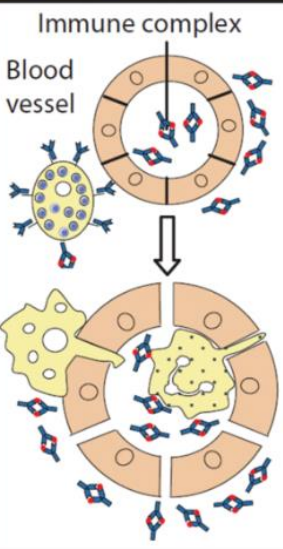
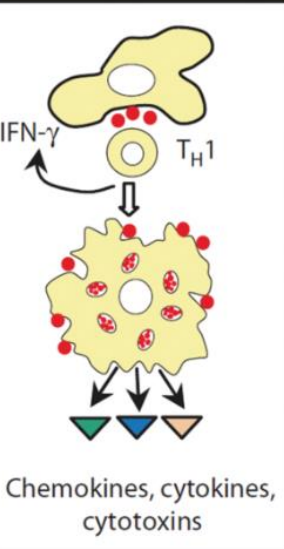
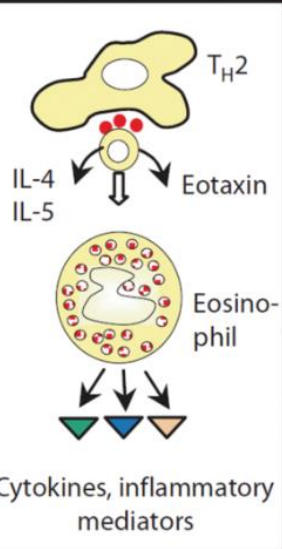
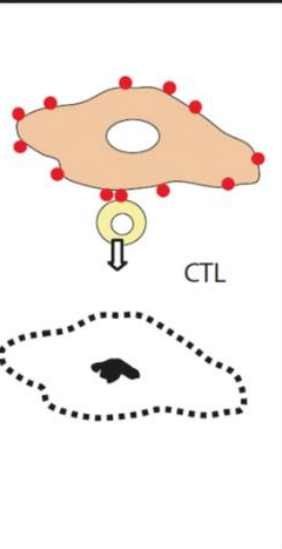
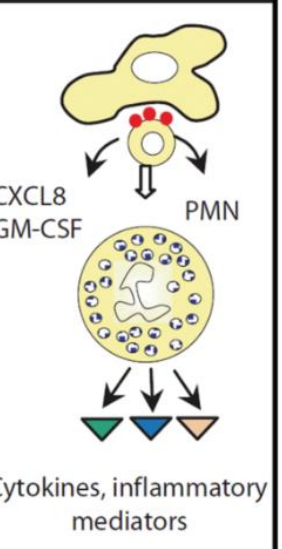
bénigne

Hypersensibilités

Classification de Gell & Coombs

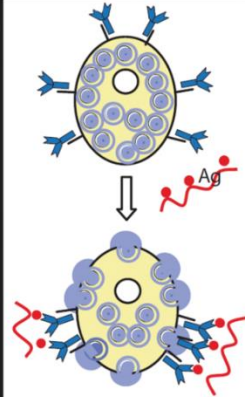
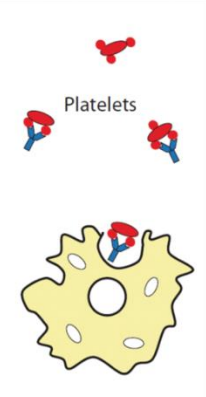
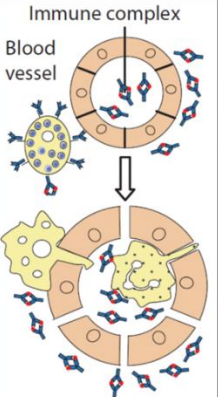
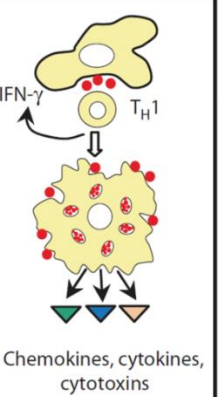
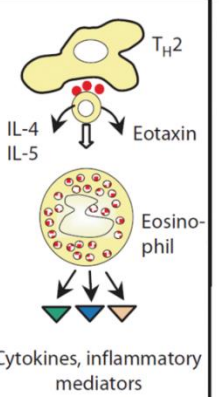
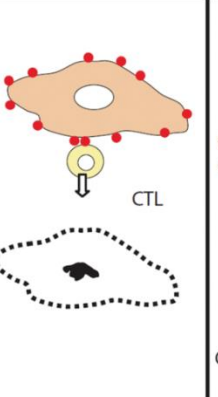
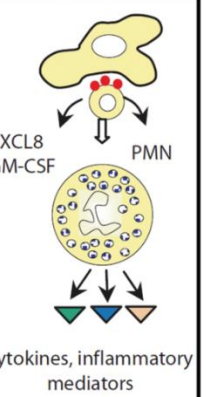
Antibody

T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN- γ , TNF- α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							

Hypersensibilités

Classification de Gell & Coombs

	Antibody			T cells			
	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN- γ , TNF- α Type 1	IL-5, IL-4/IL-13 Type 2	Perforin/ granzyme B Cytotoxic	IL-17, IL-22 Type 17/3
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
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Maladies autoimmunes et allergiques	Anaphylaxie Rhinite allergique Asthme (crise)	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme chron. Rhinite chron.	Rejet de greffe Diabète SEP	Polyarthrite Sclérose en plaque Mal. de Crohn
Dermatoses autoimmunes et allergiques	Urticaire contact	Pemphigus Pemphigoïde Urticaire chroni.	Vascularites	Psoriasis	Dermatite atopique	Vitiligo Pelade Eczéma contact	Psoriasis
Allergies médicaments	Choc anaphylactique	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème médic.	DRESS	Lyell Stevens-Johnson	Pustulose exanthématique aiguë généralisée

Hypersensibilités

Classification de Gell & Coombs

Antibody

T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN- γ , TNF- α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/ granzyme B (CTL)	IL-17, IL-22 (Th17)
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	<div style="border: 1px solid red; padding: 2px;"> <p>HSI non allergique</p> </div> <hr style="border: 2px solid red;"/> <div style="border: 1px solid red; padding: 2px;"> <p>HSI allergique</p> </div>			Chemokines, cytokines, cytotoxins	Cytokines, inflammatory mediators		Cytokines, inflammatory mediators

Hypersensibilités

Classification de Gell & Coombs

Antibody

Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	Th1/Tc1/ILC1 Type 1 inflammation	Th2/Tc2/ILC2 Type 2 inflammation	Perforin/ granzyme B (CTL)	Th17/Tc17/ILC3 Type 3 (17) inflammation
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
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	<div data-bbox="76 1063 318 1199" data-label="Text"> <p>HSI non allergique</p> </div> <hr/> <div data-bbox="76 1206 318 1342" data-label="Text"> <p>HSI allergique</p> </div>			Chemokines, cytokines, cytotoxins	Cytokines, inflammatory mediators		Cytokines, inflammatory mediators

Hypersensibilités

Classification de Gell & Coombs

Antibody

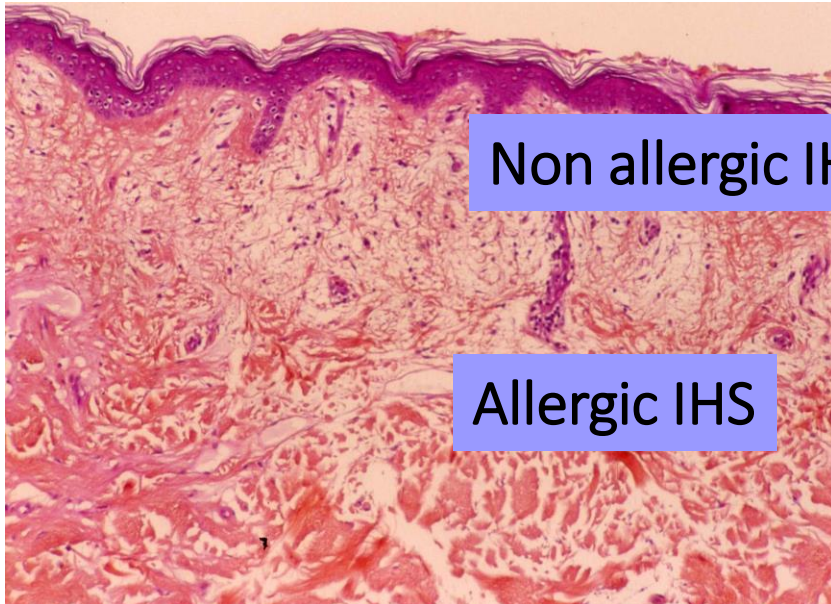
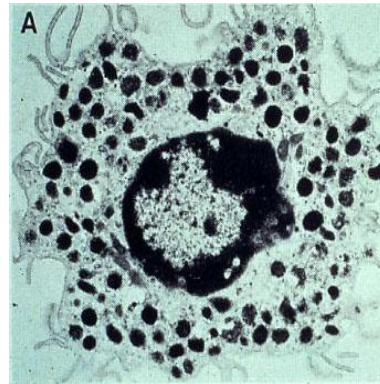
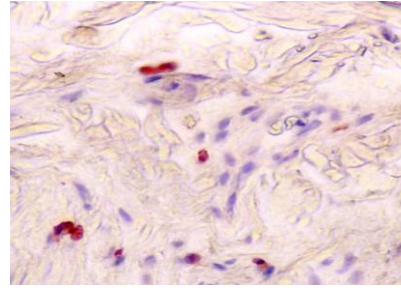
Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	Th1/Tc1/ILC1 Type 1 inflammation	Th2/Tc2/ILC2 Type 2 inflammation	Perforin/ granzyme B (CTL)	Th17/Tc17/ILC3 Type 3 (17) inflammation
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Maladies autoimmunes, allergiques et HS	Anaphylaxie Rhinite Asthme	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.		Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.
Dermatoses autoimmunes, allergiques et HS	Urticaire SAMA	Pemphigus Pemphigoïde Urticaire chroni.	Vascularites	Vitiligo Pelade Eczéma contact	Dermatite atopique Prurigo nodulaire Urticaire chronique		Psoriasis
Allergie et HS médicaments	Choc anaphylactique Urticaire aux médicaments	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème Lyell Stevens-Johnson	DRESS		Pustulose exanthématique aiguë généralisée

TYPE I HYPERSENSITIVITY

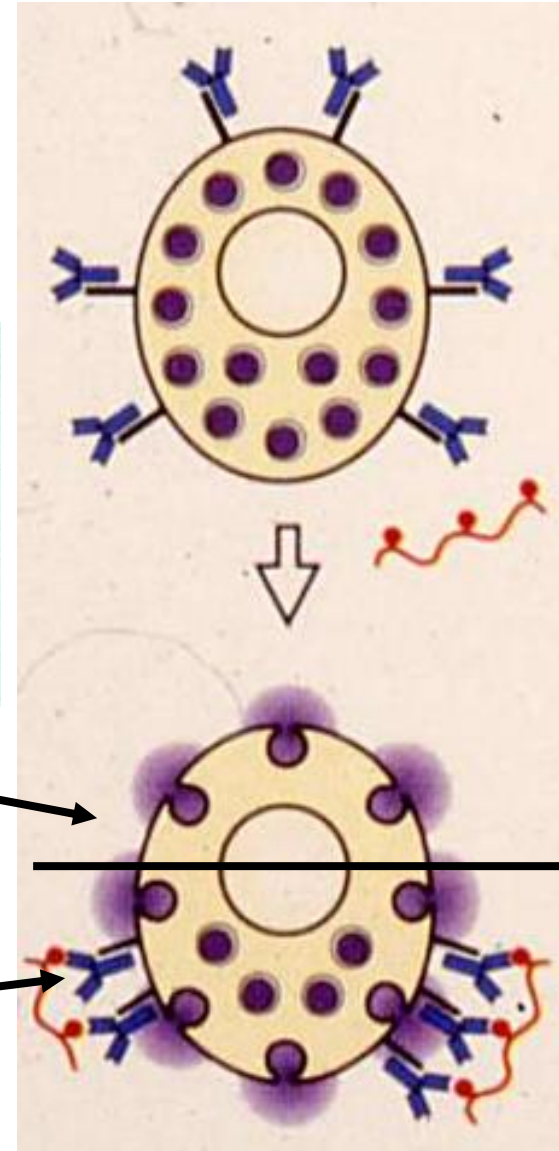


Œdème du derme / Vaisseaux



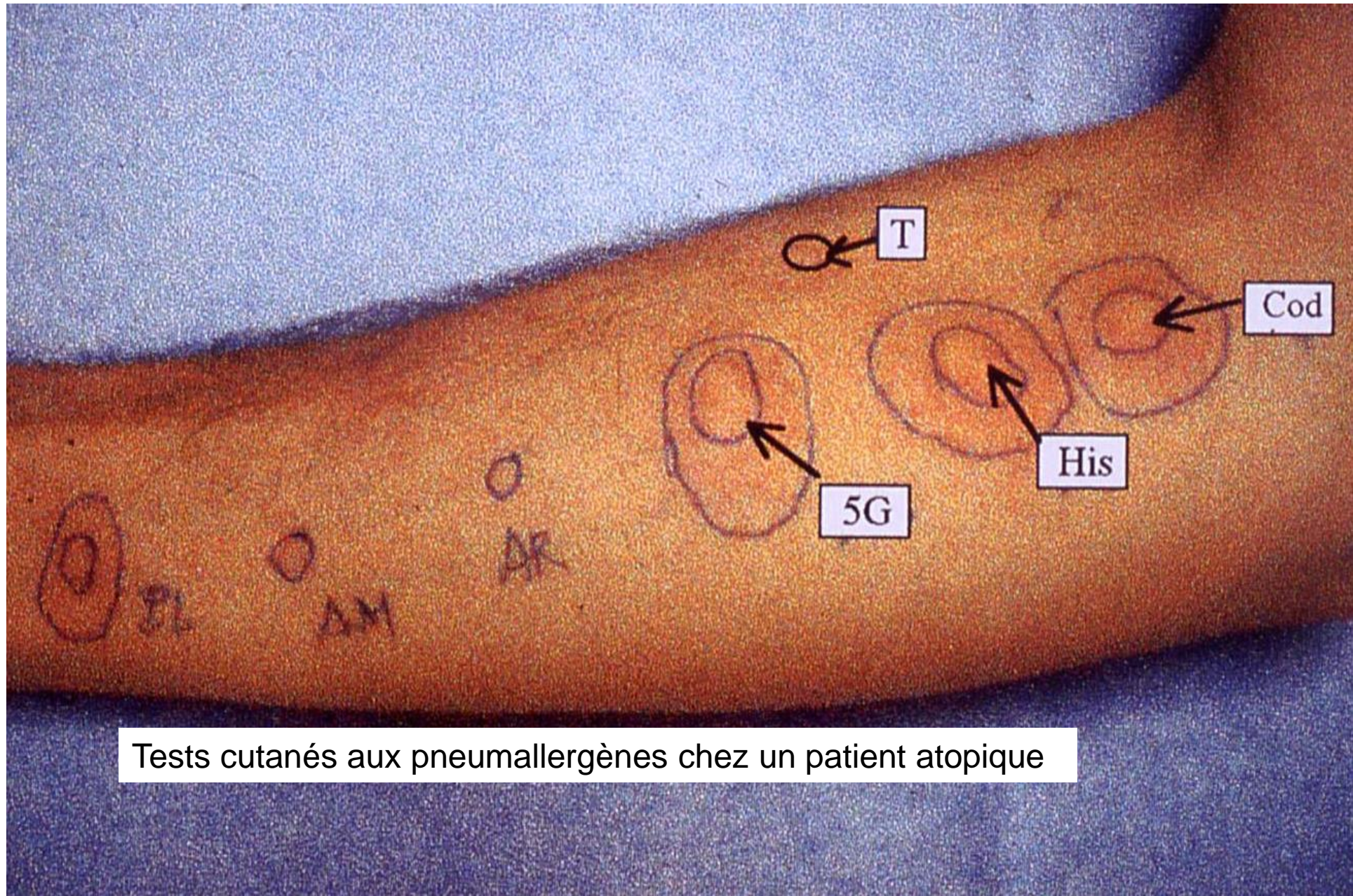
Non allergic IHS

Allergic IHS



Mastocytes / Histamine

HSI allergique et non allergique



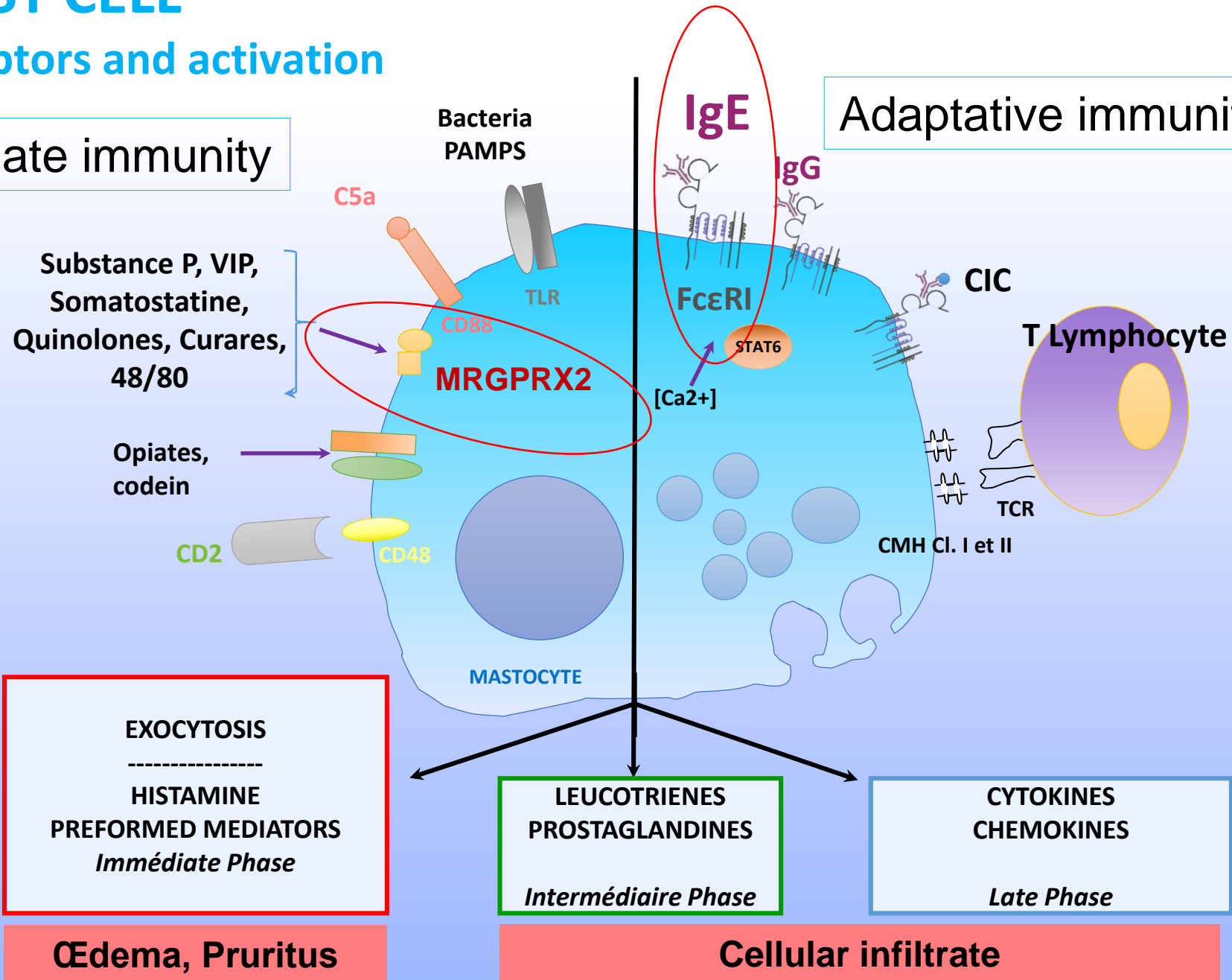
Tests cutanés aux pneumallergènes chez un patient atopique

MAST CELL

Receptors and activation

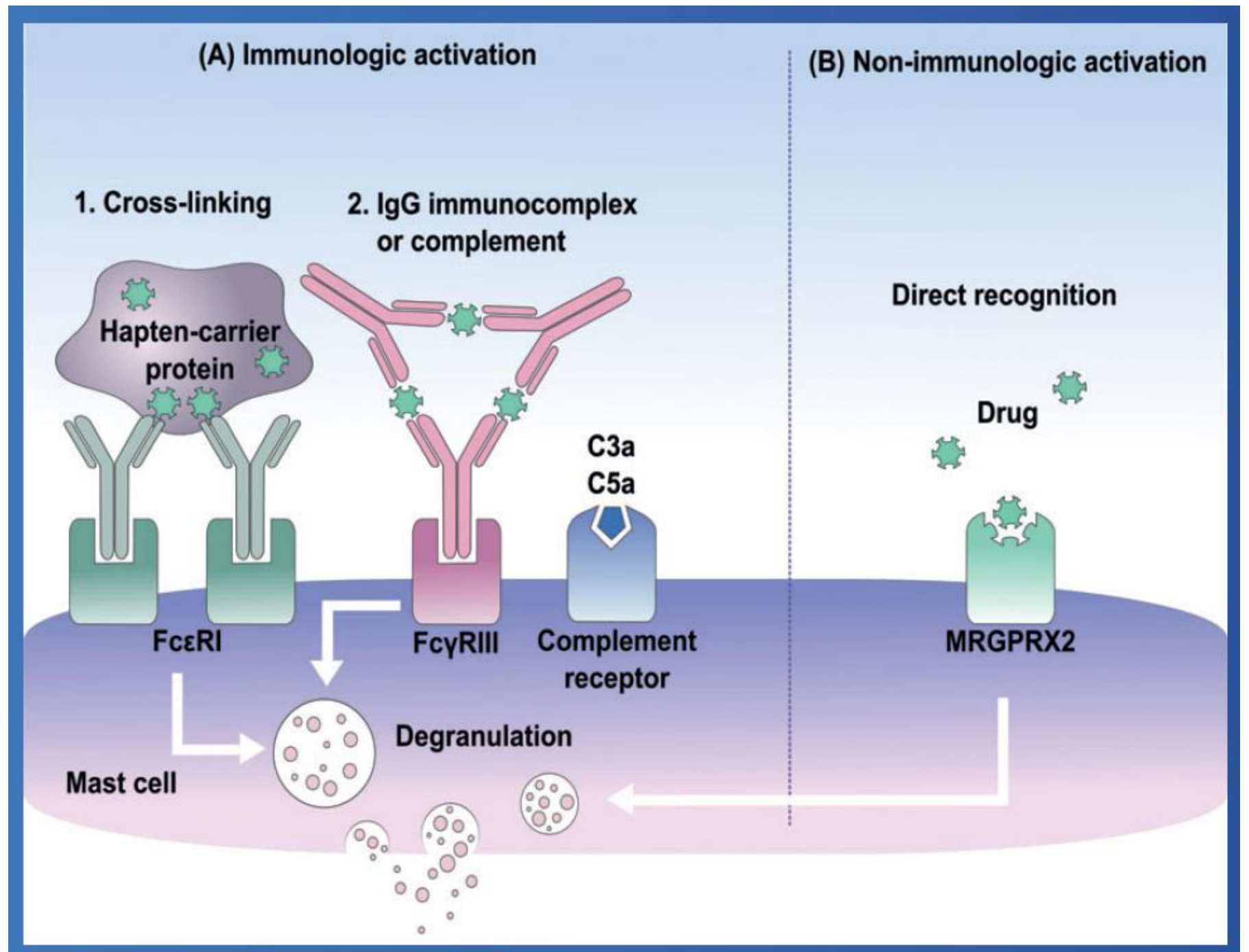
Innate immunity

Adaptative immunity

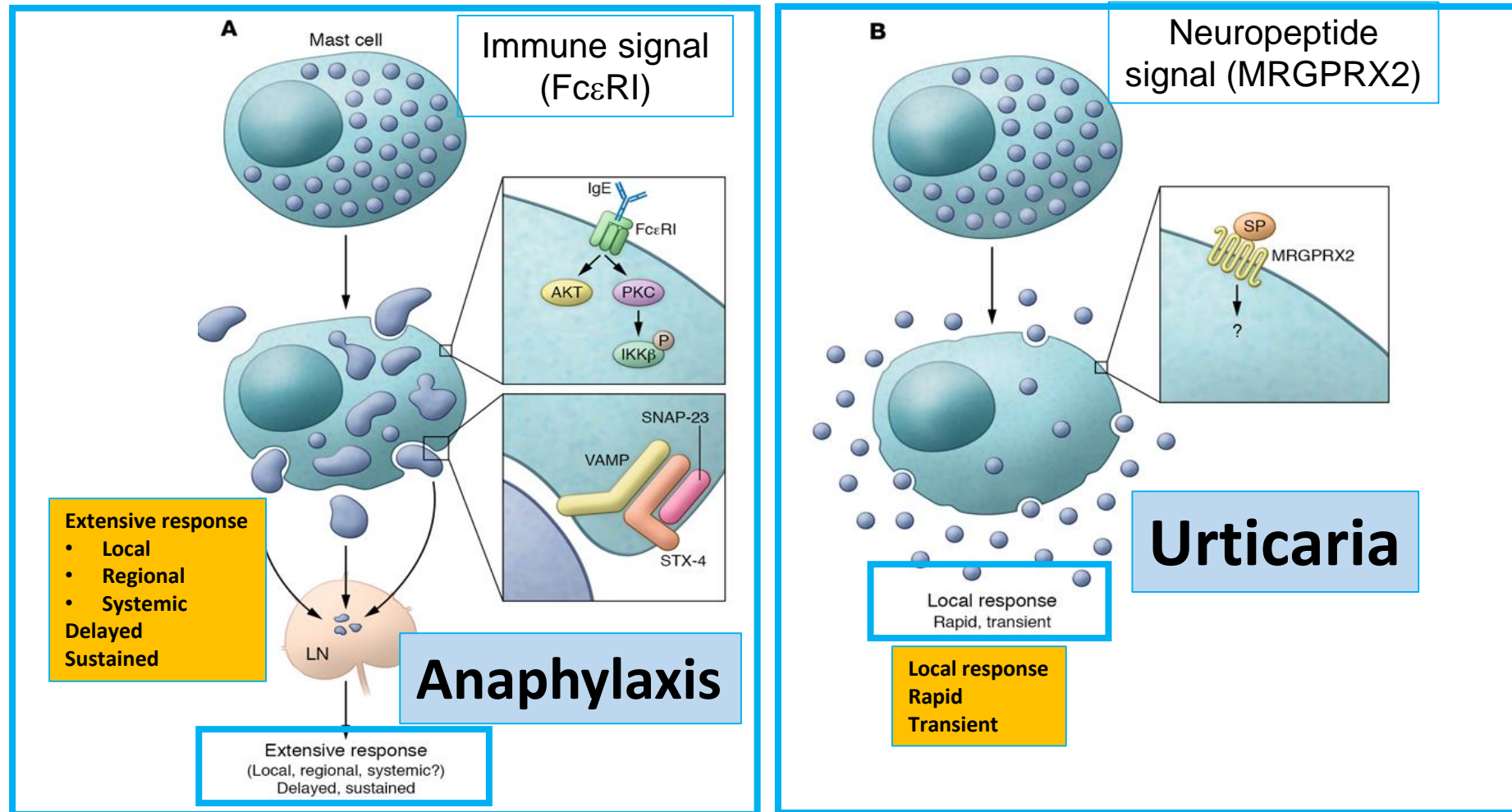


MASTOCYTES

Récepteurs et activation



Two fundamental degranulation pathways in **IgE/FcεRI** mast cells **Other receptor**



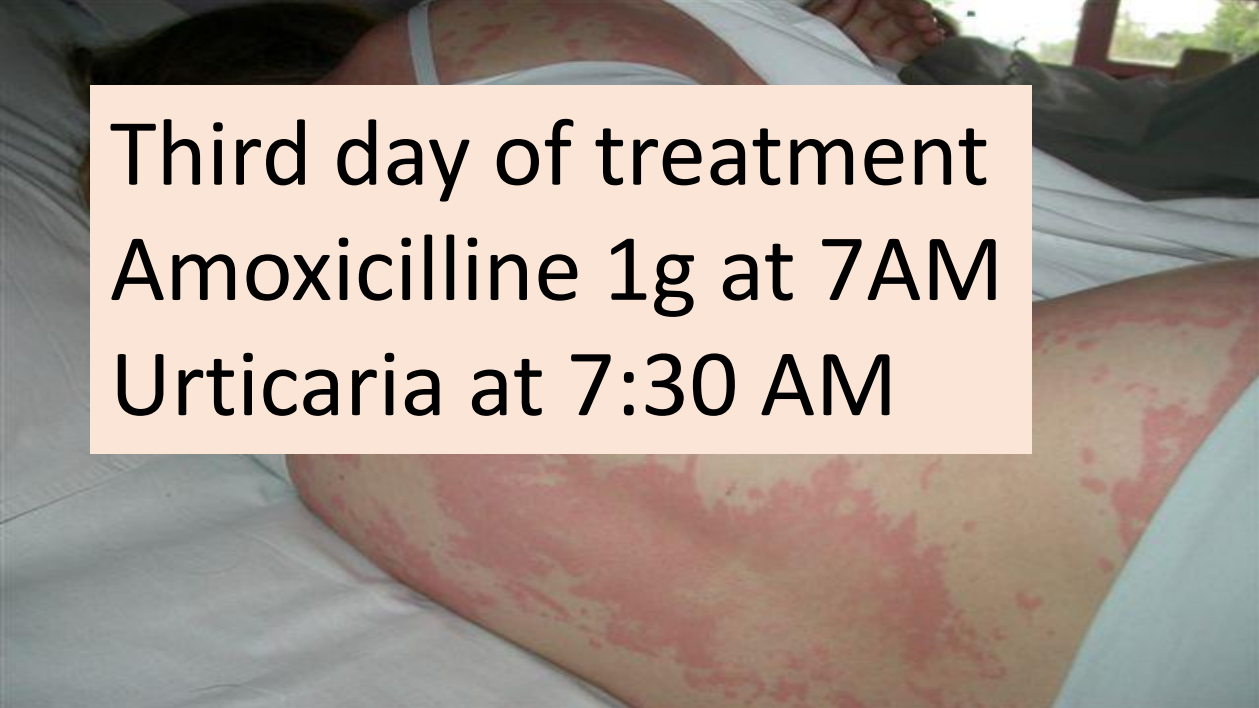
Drug-induced urticaria and angioedema

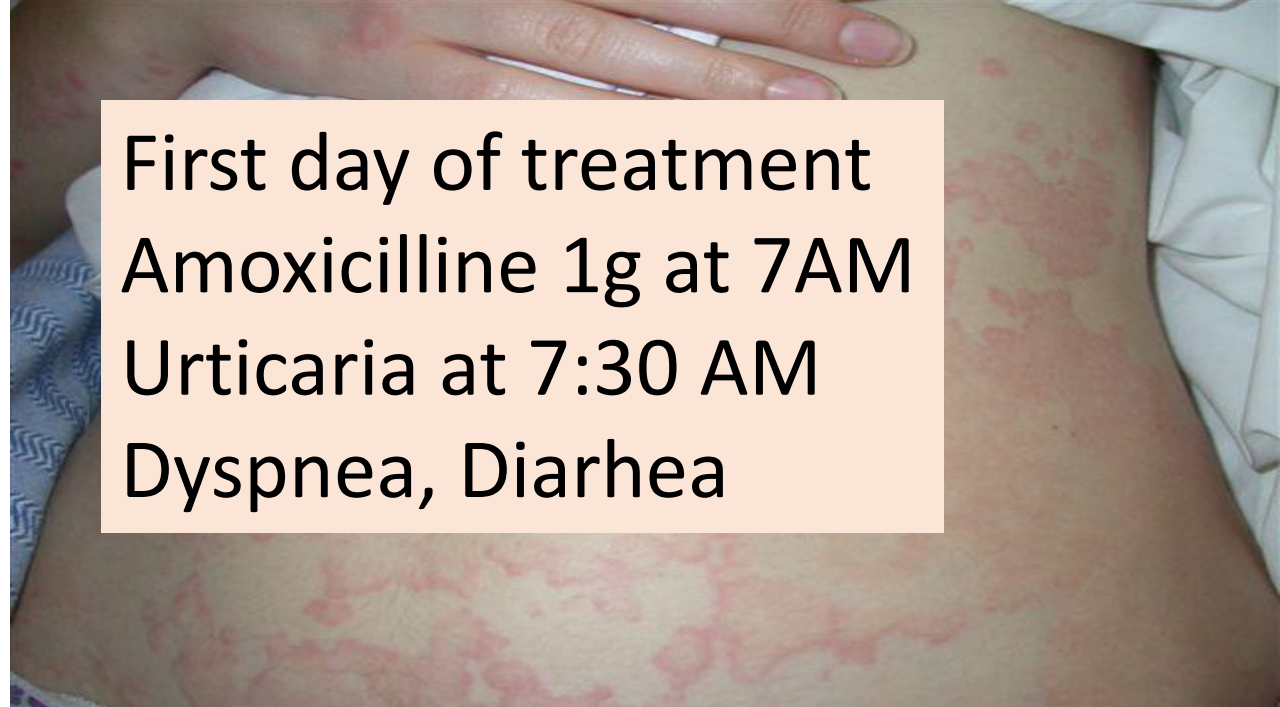
- **Allergic (IgE):** rares (5%) and exceptionally isolated
- **Non allergic:** frequent (95%) and almost always benign

First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM



Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM





First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea





**More a drug-induced reaction is severe,
more it has a chance to be allergic**



Hypersensibilités

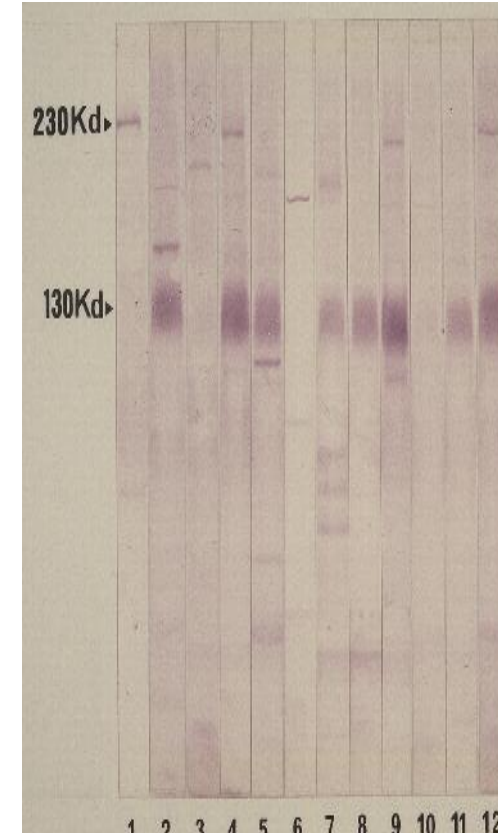
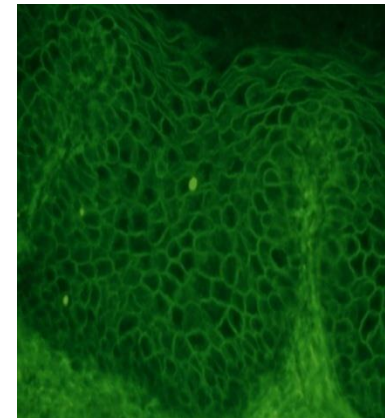
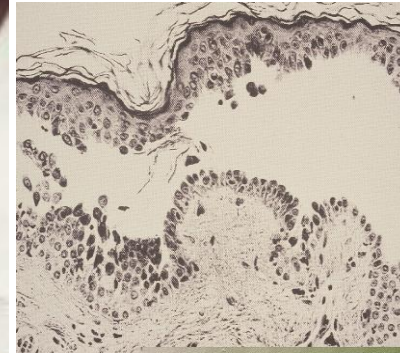
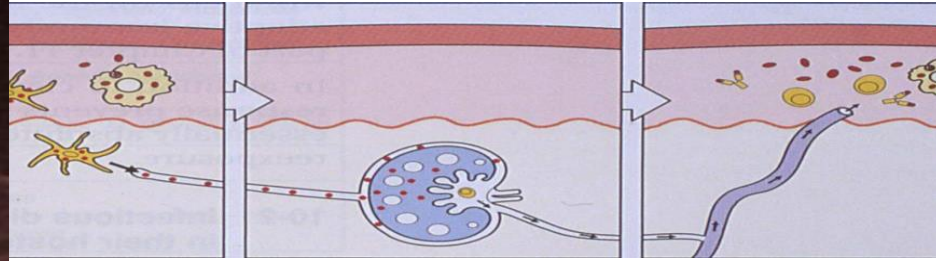
Classification de Gell & Coombs

Antibody

Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	Th1/Tc1/ILC1 Type 1 inflammation	Th2/Tc2/ILC2 Type 2 inflammation	Perforin/ granzyme B (CTL)	Th17/Tc17/ILC3 Type 3 (17) inflammation
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector	Mast cell activation	FcR+ cells (phagocytes, NK cells)	FcR+ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
Maladies autoimmunes, allergiques et HS	Anaphylaxie Rhinite Asthme	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme T2 Rhinite, Conjonctivite Œsophagite eosin.		Polyarthrite Sclérose en plaque Mal. de Crohn Asthme neutro.
Dermatoses autoimmunes, allergiques et HS	Urticaire SAMA	Pemphigus Pemphigoïde Urticaire chroni.	Vascularites	Vitiligo Pelade Eczéma contact	Dermatite atopique Prurigo nodulaire Urticaire chronique		Psoriasis
Allergie et HS médicaments	Choc anaphylactique Urticaire aux médicaments	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème Lyell Stevens-Johnson	DRESS		Pustulose exanthématique aiguë généralisée

Hypersensibilité de type II due à des IgG spécifiques PEMPHIGUS



Hypersensibilités

Classification de Gell & Coombs

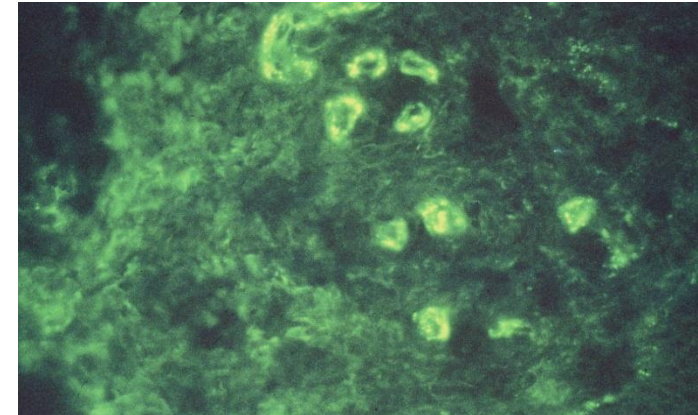
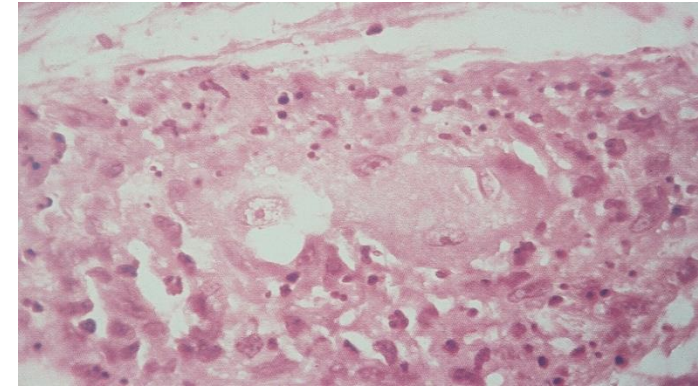
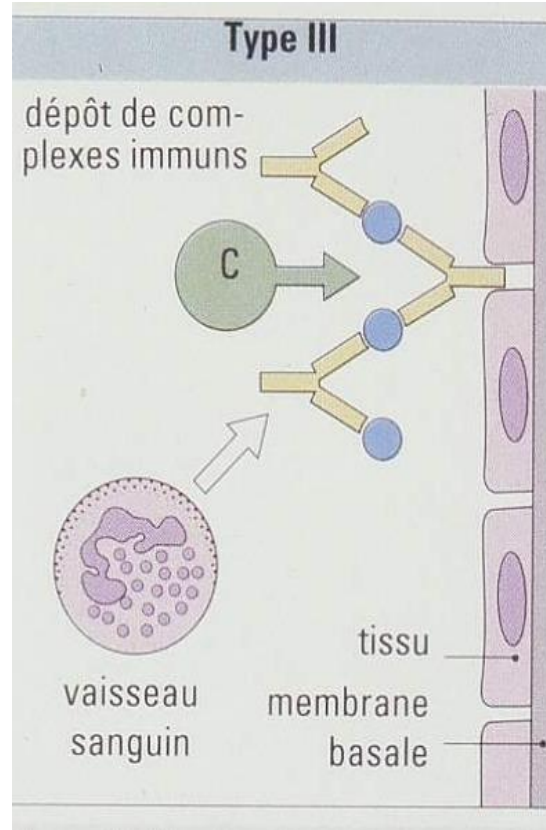
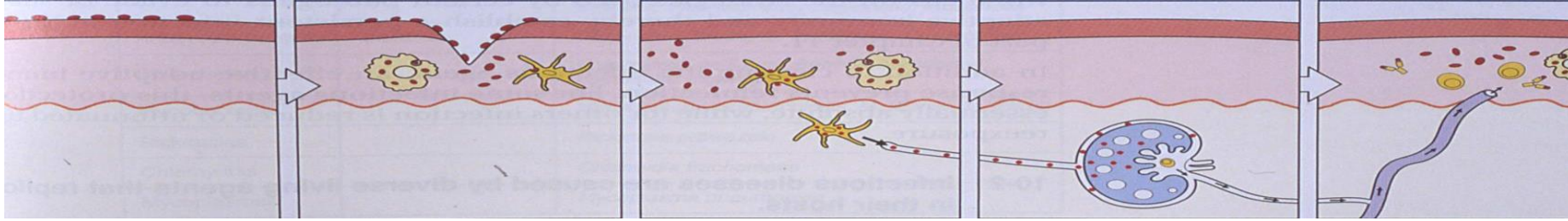
Antibody

Lymphocytes

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	Th1/Tc1/ILC1 Type 1 inflammation	Th2/Tc2/ILC2 Type 2 inflammation	Perforin/ granzyme B (CTL)	Th17/Tc17/ILC3 Type 3 (17) inflammation
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
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Allergie et HS médicaments	Choc anaphylactique Urticaire aux médicaments	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème Lyell Stevens-Johnson	DRESS		Pustulose exanthématique aiguë généralisée

Hypersensibilité de type III due à des complexes immuns

VASCULARITES – PURPURA RHUMATOÏDE



Hypersensibilités

Classification de Gell & Coombs

Antibody

Lymphocytes

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Allergie et HS médicaments	Choc anaphylactique Urticaire aux médicaments	Cytopénies medic.	Vascularites immuno-allerg.	Exanthème Lyell Stevens-Johnson	DRESS		Pustulose exanthématique aiguë généralisée

The 3 major types of innate and adaptive cell-mediated effector immunity

Francesco Annunziato, PhD,^a Chiara Romagnani, MD, PhD,^b and Sergio Romagnani, MD^a *Florence, Italy, and Berlin, Germany*

The immune system has tailored its effector functions to optimally respond to distinct species of microbes. Based on emerging knowledge on the different effector T-cell and innate lymphoid cell (ILC) lineages, it is clear that the innate and adaptive immune systems converge into 3 major kinds of cell-mediated effector immunity, which we propose to categorize as type 1, type 2, and type 3. Type 1 immunity consists of T-bet⁺ IFN- γ -producing group 1 ILCs (ILC1 and natural killer cells), CD8⁺ cytotoxic T cells (T_C1), and CD4⁺ T_H1 cells, which protect against intracellular microbes through activation of mononuclear phagocytes. Type 2 immunity consists of GATA-3⁺ ILC2s, T_C2 cells, and T_H2 cells producing IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation, as well as IgE antibody production, thus protecting against helminthes and venoms. Type 3 immunity is mediated by retinoic acid-related orphan receptor γ t⁺ ILC3s, T_C17 cells, and T_H17 cells producing IL-17, IL-22, or both, which activate mononuclear phagocytes but also recruit neutrophils and induce epithelial antimicrobial responses, thus protecting against extracellular bacteria and fungi. On the other hand, type 1 and 3 immunity mediate autoimmune diseases, whereas type 2 responses can cause allergic diseases. (*J Allergy Clin Immunol* 2015;135:626-35.)

Key words: Type 1 immunity, type 2 immunity, type 3 immunity, innate lymphoid cells, T_H1, T_C1, T_H2, T_C2, T_H17/T_H22, T_C17/T_C22

Abbreviations used

APC: Antigen-presenting cell
CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 cells
DC: Dendritic cell
Eomes: Eomesodermin
IBD: Inflammatory bowel disease
IL-7R: IL-7 receptor
ILC: Innate lymphoid cell
LT: Lymphotoxin
MP: Mononuclear phagocyte
MS: Multiple sclerosis
NK: Natural killer
NKp: Natural killer progenitor
PB: Peripheral blood
RA: Rheumatoid arthritis
ROR: Retinoic acid-related orphan receptor
STAT: Signal transducer and activator of transcription
T_C: Cytotoxic T
TSLP: Thymic stromal lymphopoietin

whereas T_H2 cells produce IL-4, IL-5, and IL-13.³ Subsequently, a similar dichotomy within the CD8⁺ cytotoxic T (T_C) cell population was discovered in both mice and human subjects, and the 2 subsets were named T_C1 and T_C2,

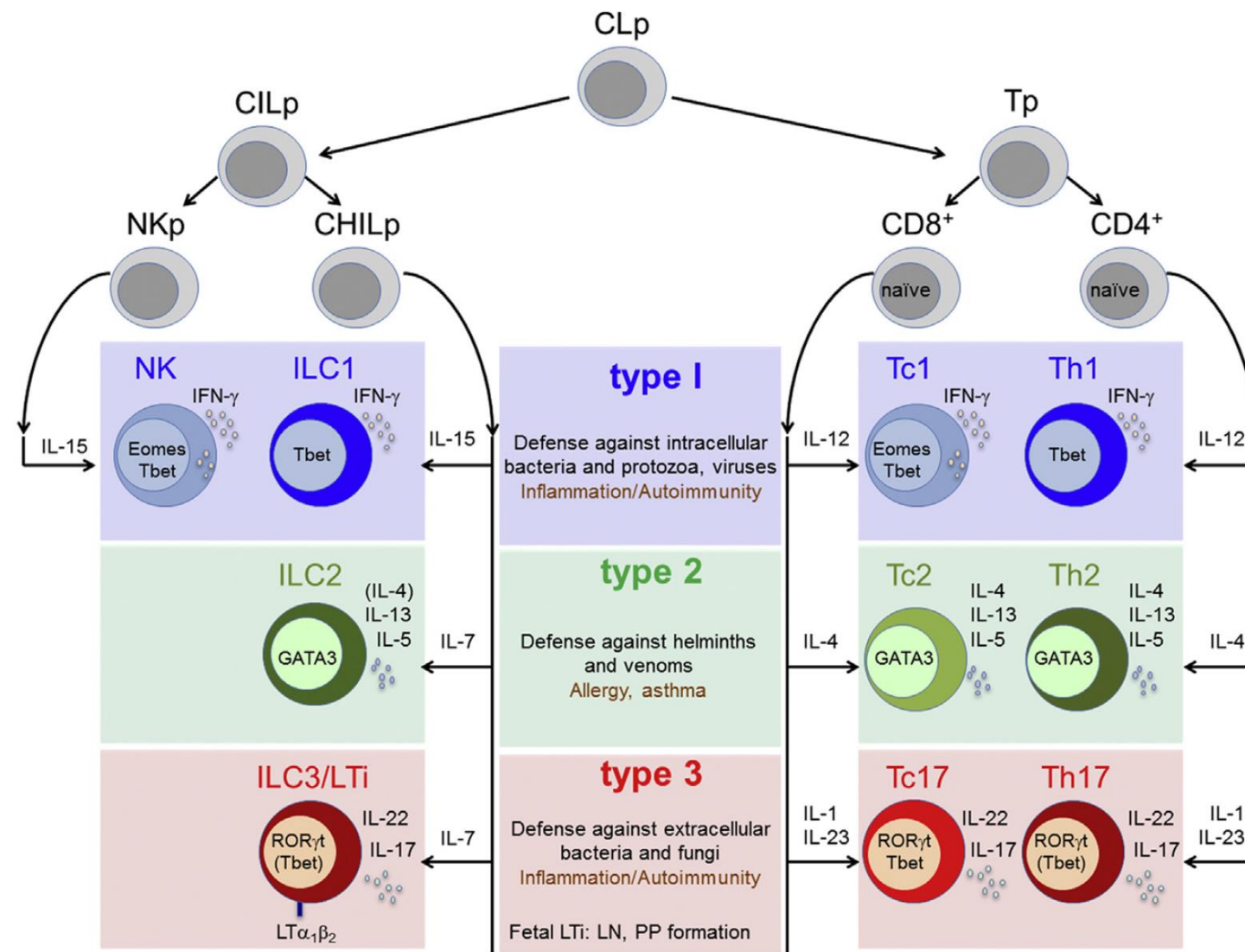
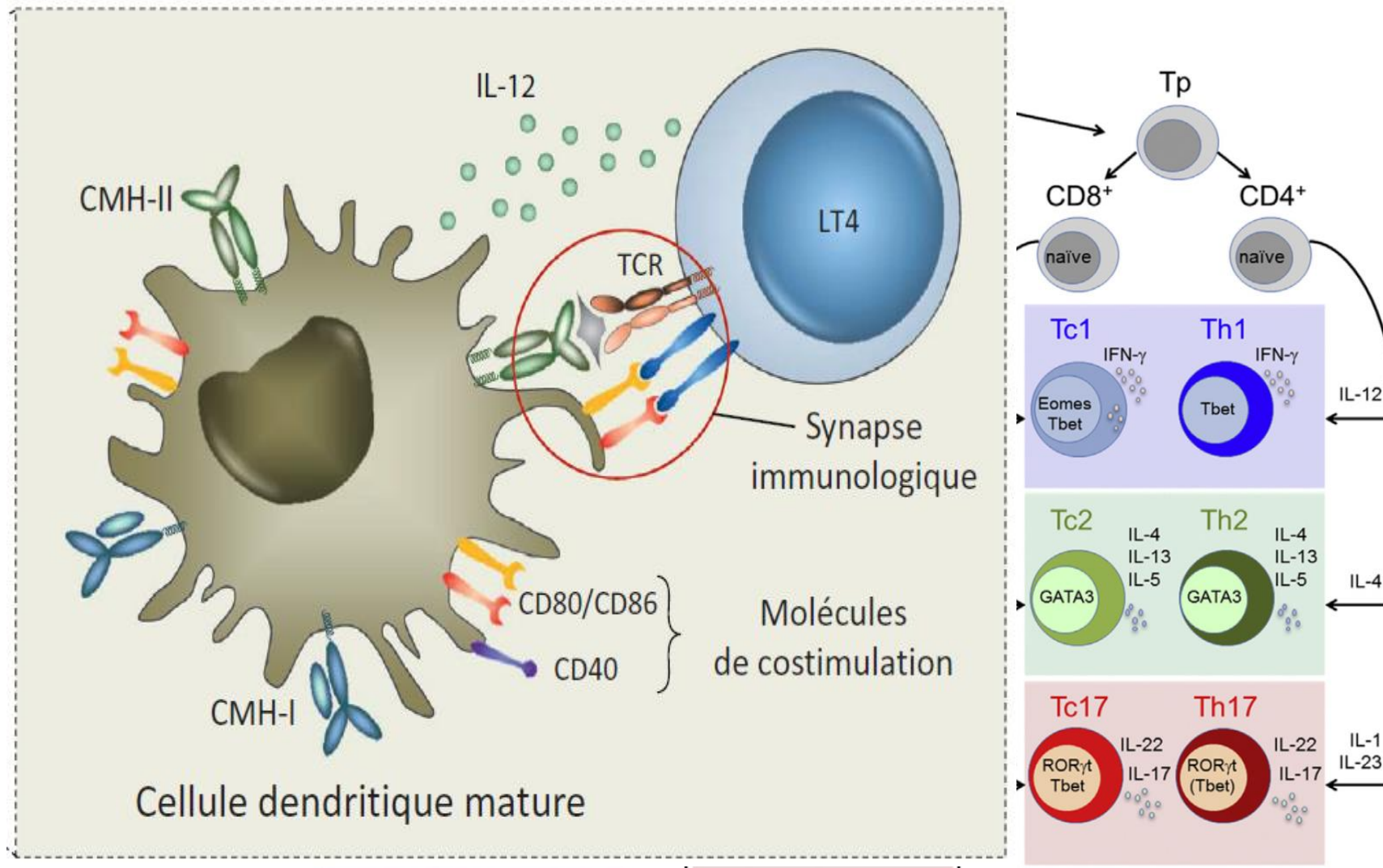


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet⁺ IFN- γ -producing CD4⁺ T_H1 cells and ILC1s and T-bet⁺Eomes⁺CD8⁺ T_C1 and NK cells. Type 2 immunity is composed of GATA-3⁺CD4⁺ T_H2 cells, CD8⁺ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of ROR γ t (RORC)⁺CD4⁺T_H17 cells, CD8⁺ T_C17 cells, and ILC3s, producing IL-17, IL-22, or both. *CILp*, Common innate lymphoid precursor; *CLp*, common lymphoid precursor; *LN*, lymph node; *LTi*, lymphoid tissue inducer; *PP*, Peyer patch; *Tp*, T-cell progenitor.

The 3 major types of innate and adaptive cell-mediated immunity



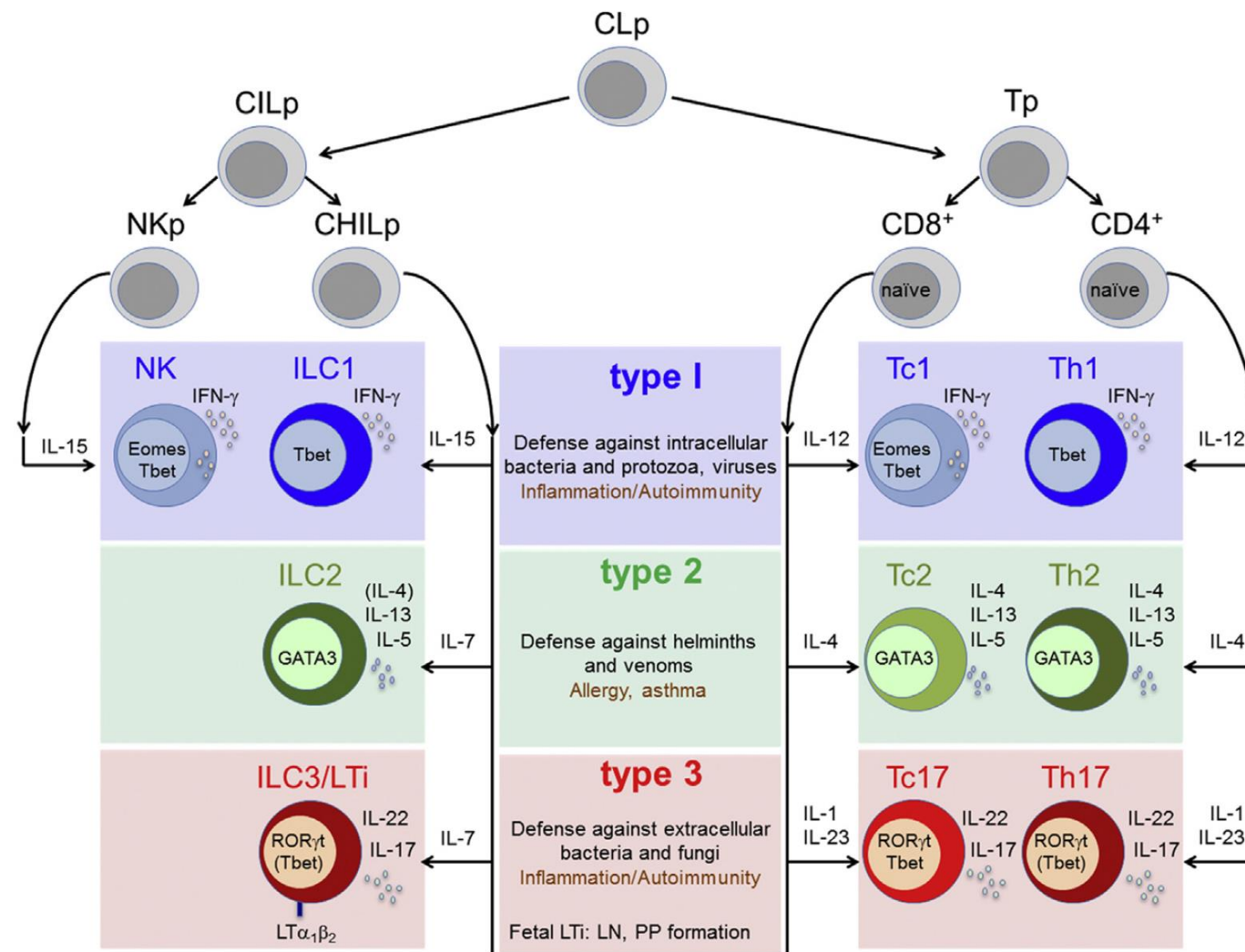
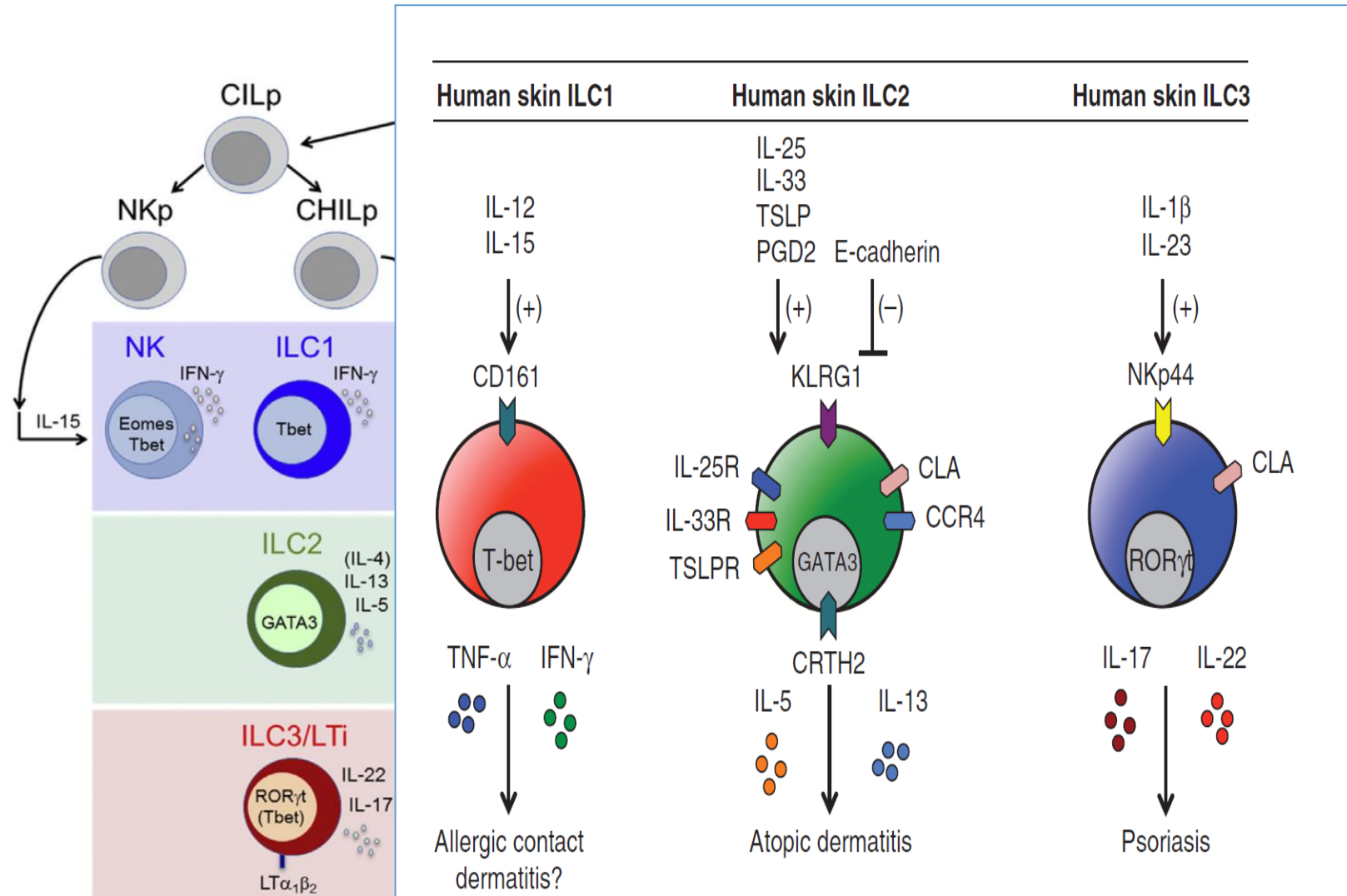


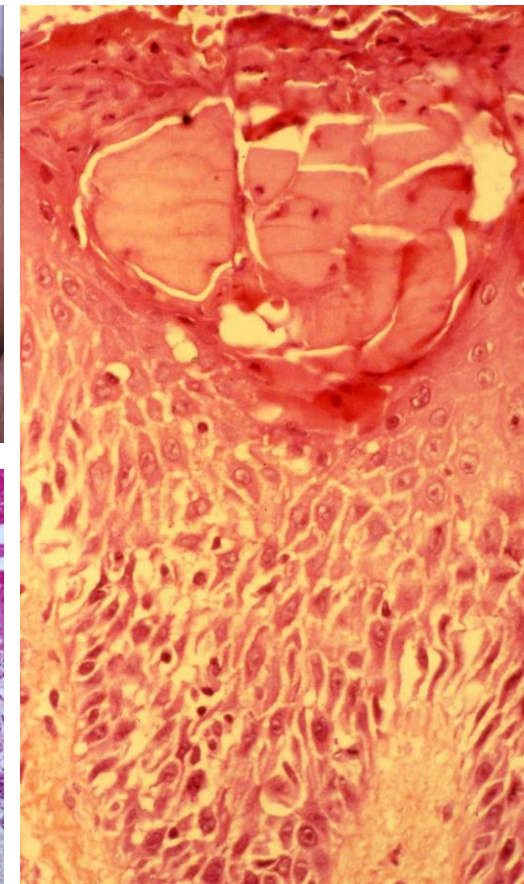
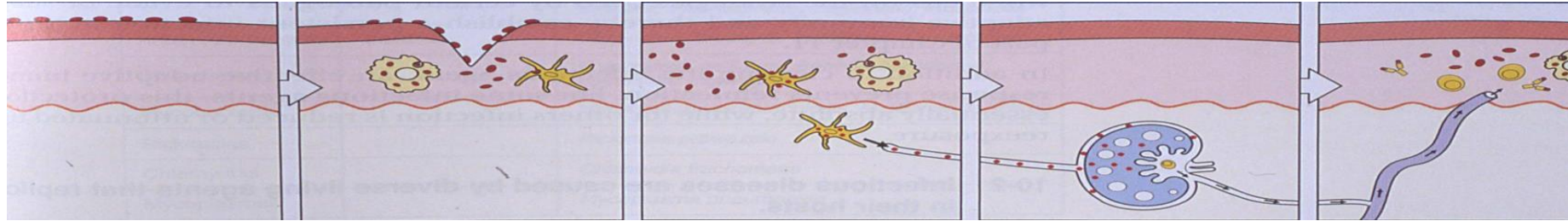
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The 3 major types of innate and adaptive cell-mediated immunity

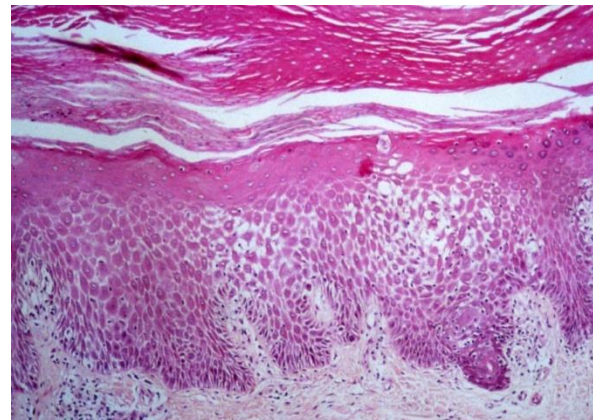


Hypersensibilité de type IV (HS retardée) due à des LT1 ECZEMA DE CONTACT

Type 1



Skin tests represent experimental models of allergic type IV DTH reactions



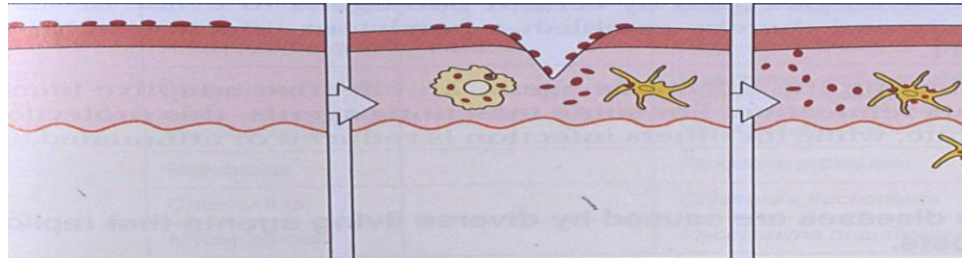
Hypersensibilité de type IV (HS retardée) due à des LT1 EXANTHEMES MEDICAMENTEUX

Type 1

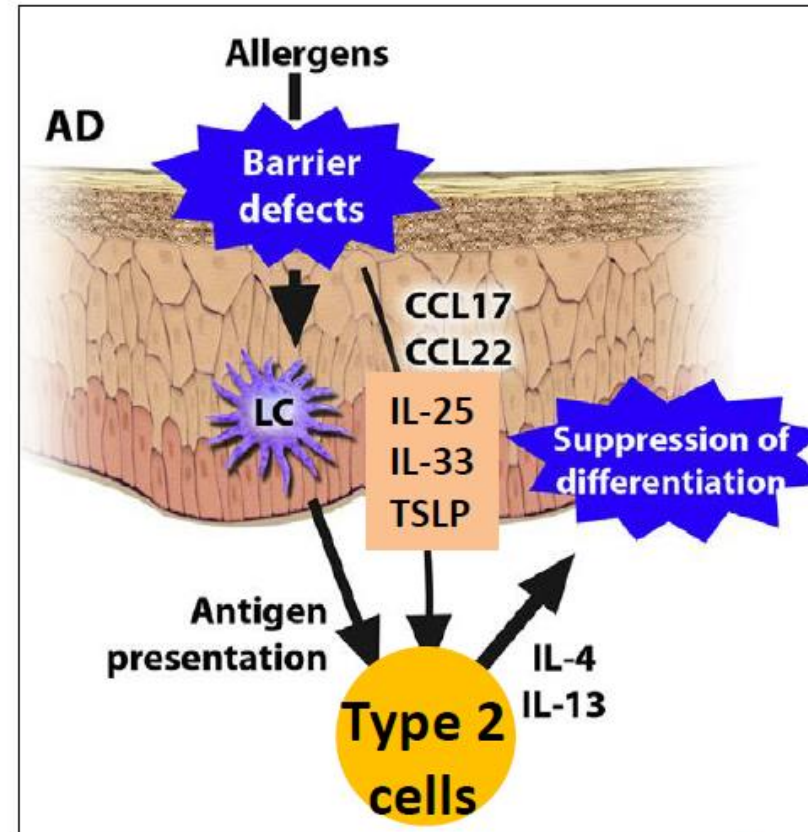


Hypersensibilité de type IV (HS retardée) due à des LT2 DERMATITE ATOPIQUE

Type 2



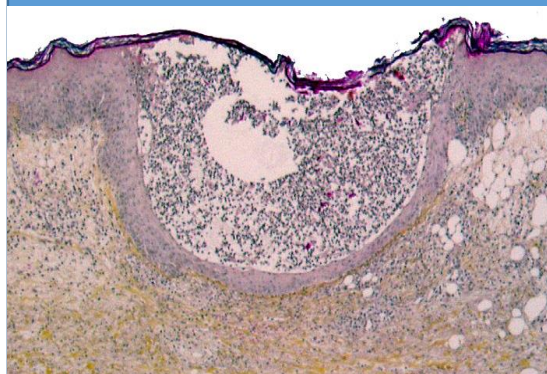
Type 2 phenotype



Type 2 inflammation
Type 2 immunity

Hypersensibilité de type IV (HS retardée) due à des LT 17 PEAG pustulose exanthématique aiguë généralisée

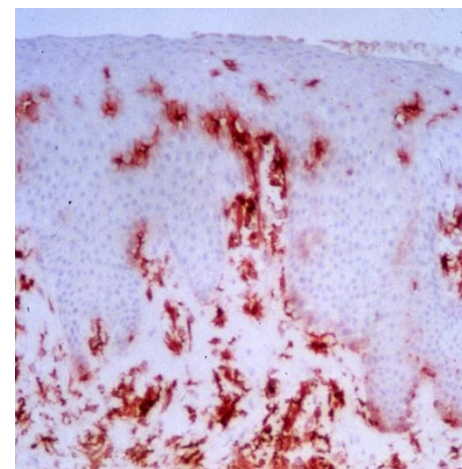
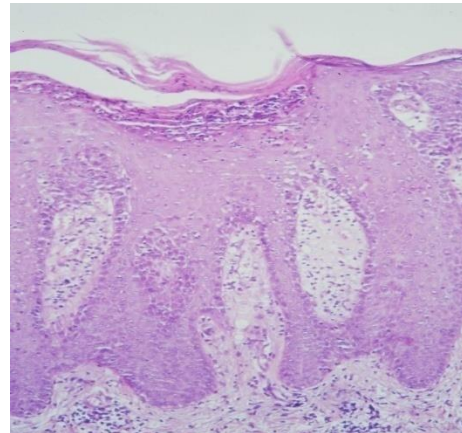
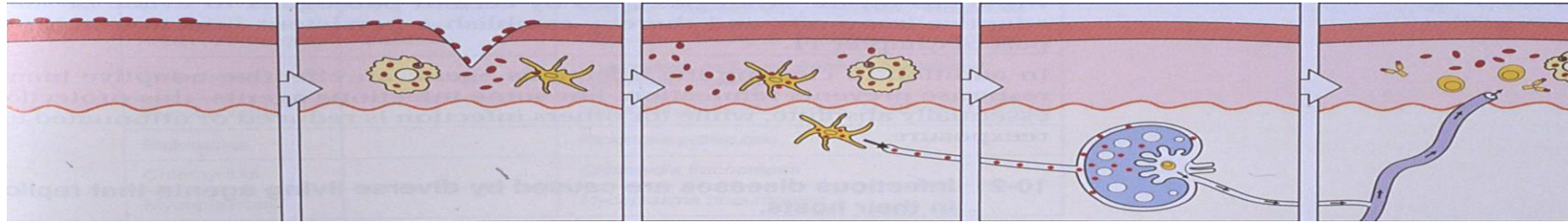
Type 3 /
17



- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
 - Altération de l'état général, fièvre,
 - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
 - Hyperleucocytose à PNN ou PNE,
 - Hypocalcémie
- **Atteinte viscérale:** foie, rein
- **Histologie:** pustules intraépidermiques ou sous cornées
- **Médicaments :** pénicillines, macrolides, carbamazépine, inhibiteurs calciques, terbinafine
- **Guérison** rapide (7 jours)
- **Mortalité:** 5%

Hypersensibilité de type IV (HS retardée) due à des LT 17 PSORIASIS

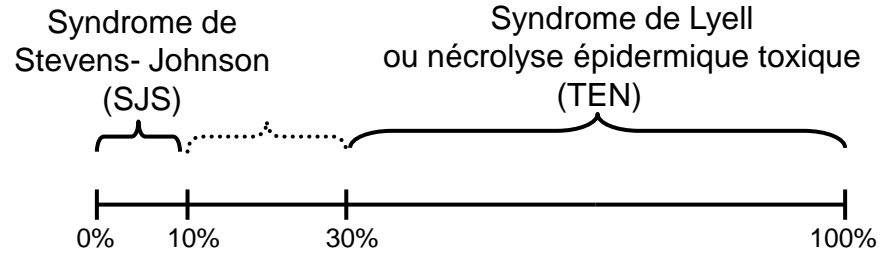
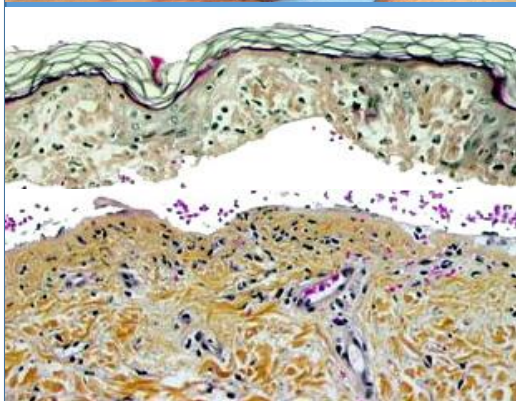
Type 3 /
17



Hypersensibilité de type IV (HS retardée) due à des LT cytotoxiques

Nécrolyse épidermique toxique – Sd de Stevens-Johnson – Sd de Lyell

Type 1
Tc1



- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai :** 1 à 21 jours
- **Clinique:**
 - Altération de l'état général, fièvre
 - Erosions muqueuses (>2 sites)
 - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie fréquente
- **Atteinte viscérale:** rénale, pulmonaire, digestive, foie
- **Histologie:** nécrolyse épidermique totale
- **Médicaments:** allopurinol+++, lamotrigine, carbamazépine, sulfaméthoxazole, AINS (oxicams), nevirapine,...
- **Mortalité:** 30-35% (estimée par le SCORTEN)



Département Allergologie et Immunologie Clinique



Clinical Research Unit



INSERM translational research team



Allergy & Clinical Immunology Department

