Pathophysiologie of autoimmune and allergic diseases

Hypersensitivity reactions

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Allergology & Clinical Immunology Department

[redacted] Danièle

7 Côte Carmagnac

69 [redacted]

tel

le 11 Mai 2013

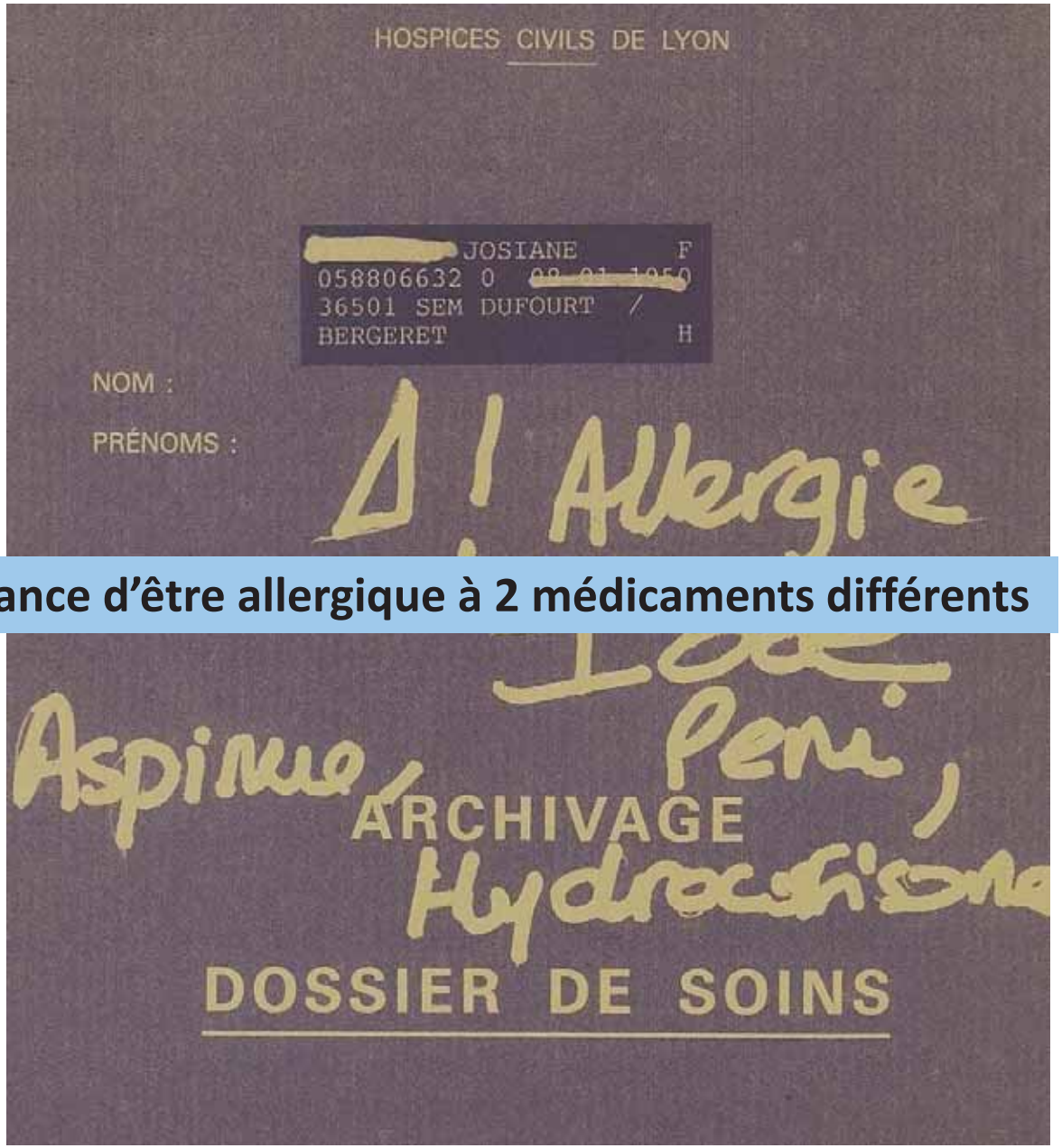
Docteur Nicolas,

Mon fils Yves a rendez-vous le 25 Juin pour des tests. Il est né le 8 janvier 1983, et a fait un urticaire géant au Clamoxyl en 1986, donc on a évité cet antibiotique. Le 22 Décembre dernier, il a fait un oedème de Quincke,

Quand on est allergique à tout, on est allergique à rien

n'avait pris ni clamoxyl, ni érythrogel, ni aucun médicament, et il a refait un oédème de Quincke. J'ai donc noté qu'il avait mangé = du nougat chinois, concombres, tomates, betteraves, magret de canard, sauce au poivre vert, mangues, litchis, comté et pâtes. Il y avait aussi un très gros bouquet de tulipes posé près de lui, avec des jonquilles.

Désolé d'avoir dû changer le rendez-



Aucune chance d'être allergique à 2 médicaments différents

Hypersensitivity reactions

1. Immunology definition

   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

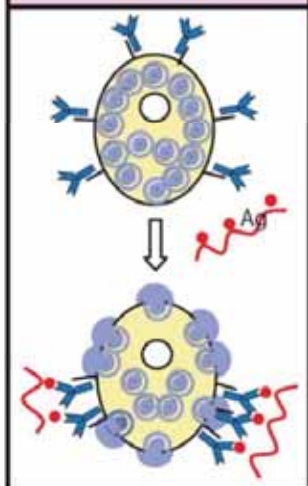
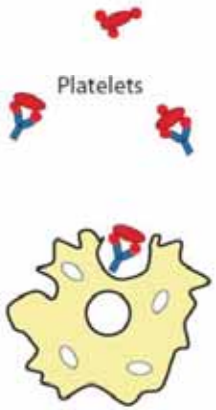
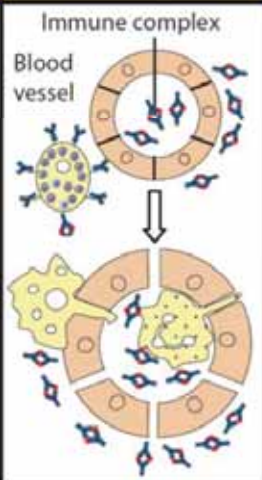
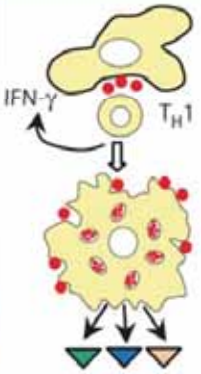
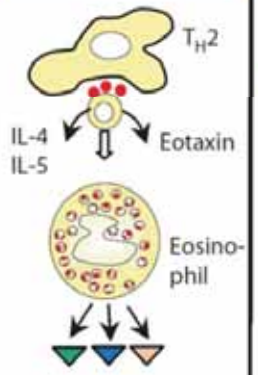
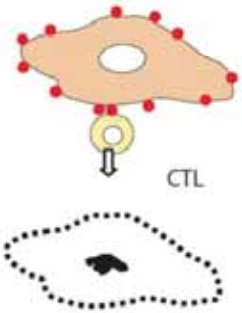
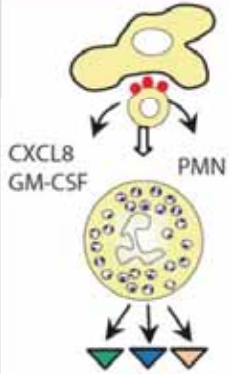
   Hypersensitivity reactions = inappropriate and damaging immune response to a molecule caused by both innate and/or adaptive immunity

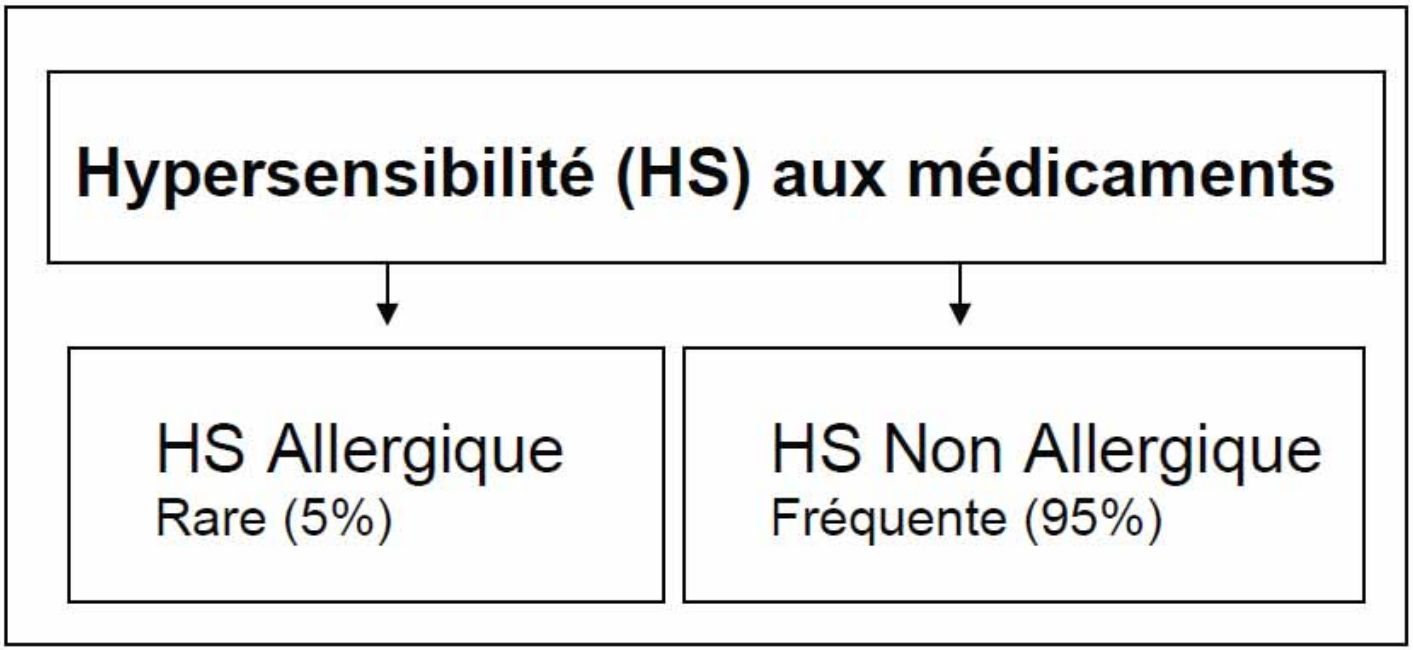
   - Allergic HS

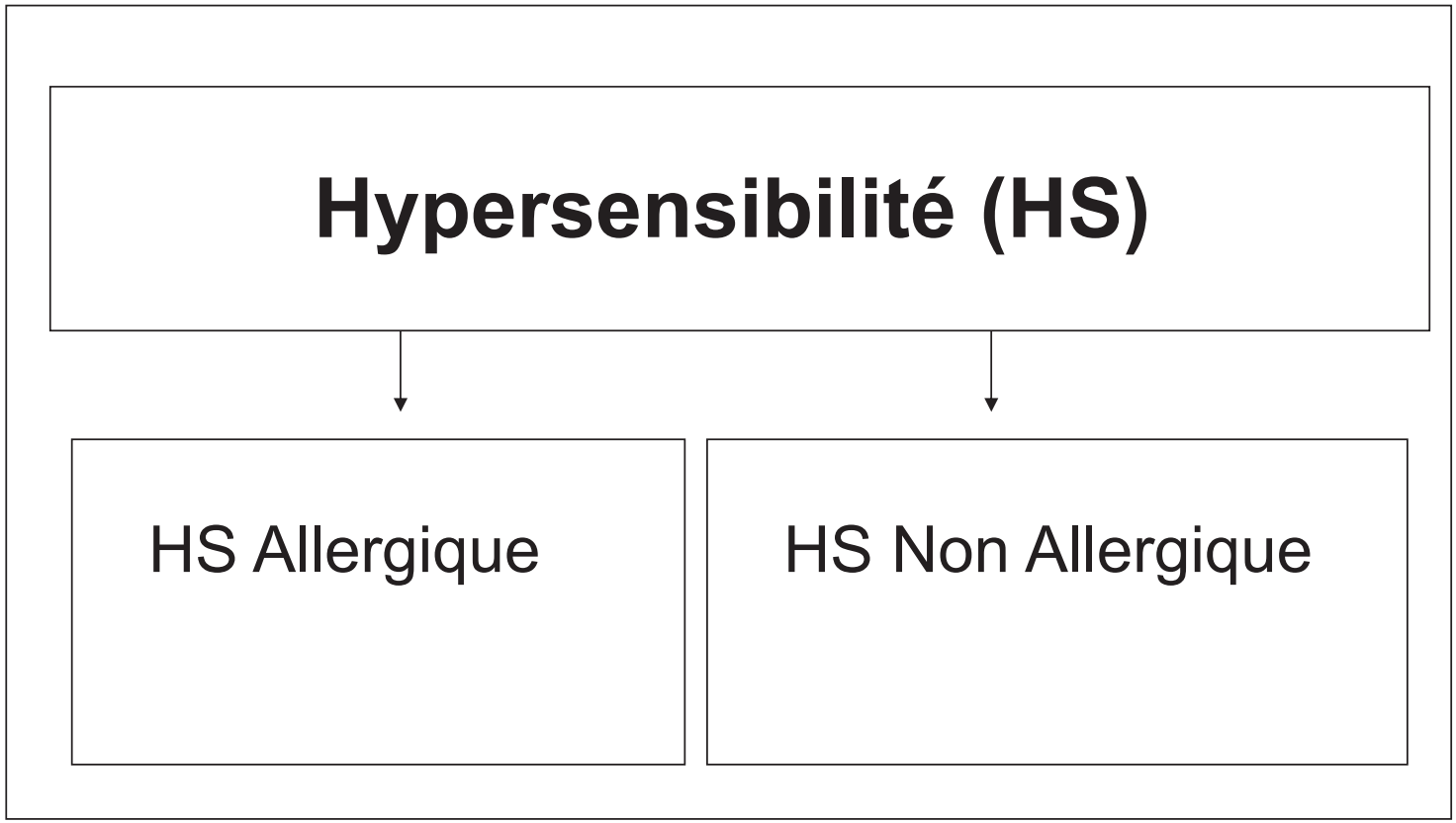
   - Non allergic HS

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	IIFN-γ, TNF-α **Th1/Type 1**	IL-5, IL-4/IL-13 **Th2/Type 2**	Perforin/ granzyme B **Cytotoxic**	**Th17/Type 17**
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
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators


Hypersensibilité (HS) aux médicaments
HS Allergique
Rare (5%)
HS Non Allergique
Fréquente (95%)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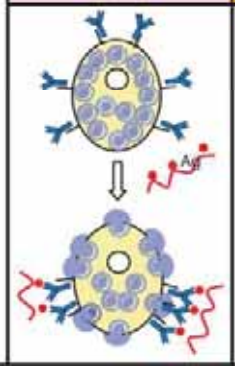
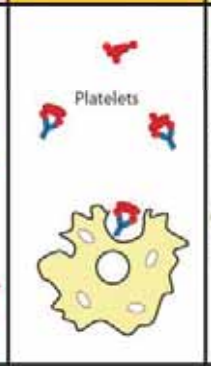
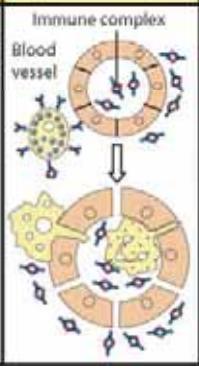
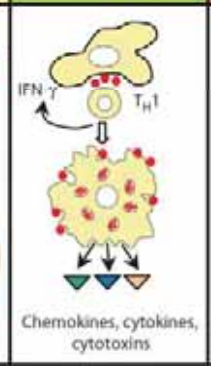
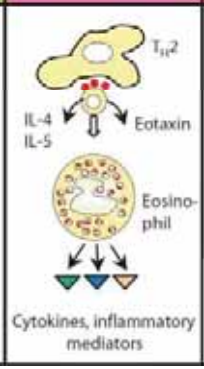
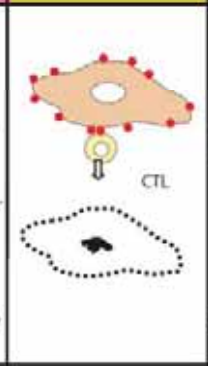
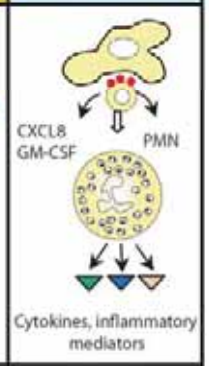
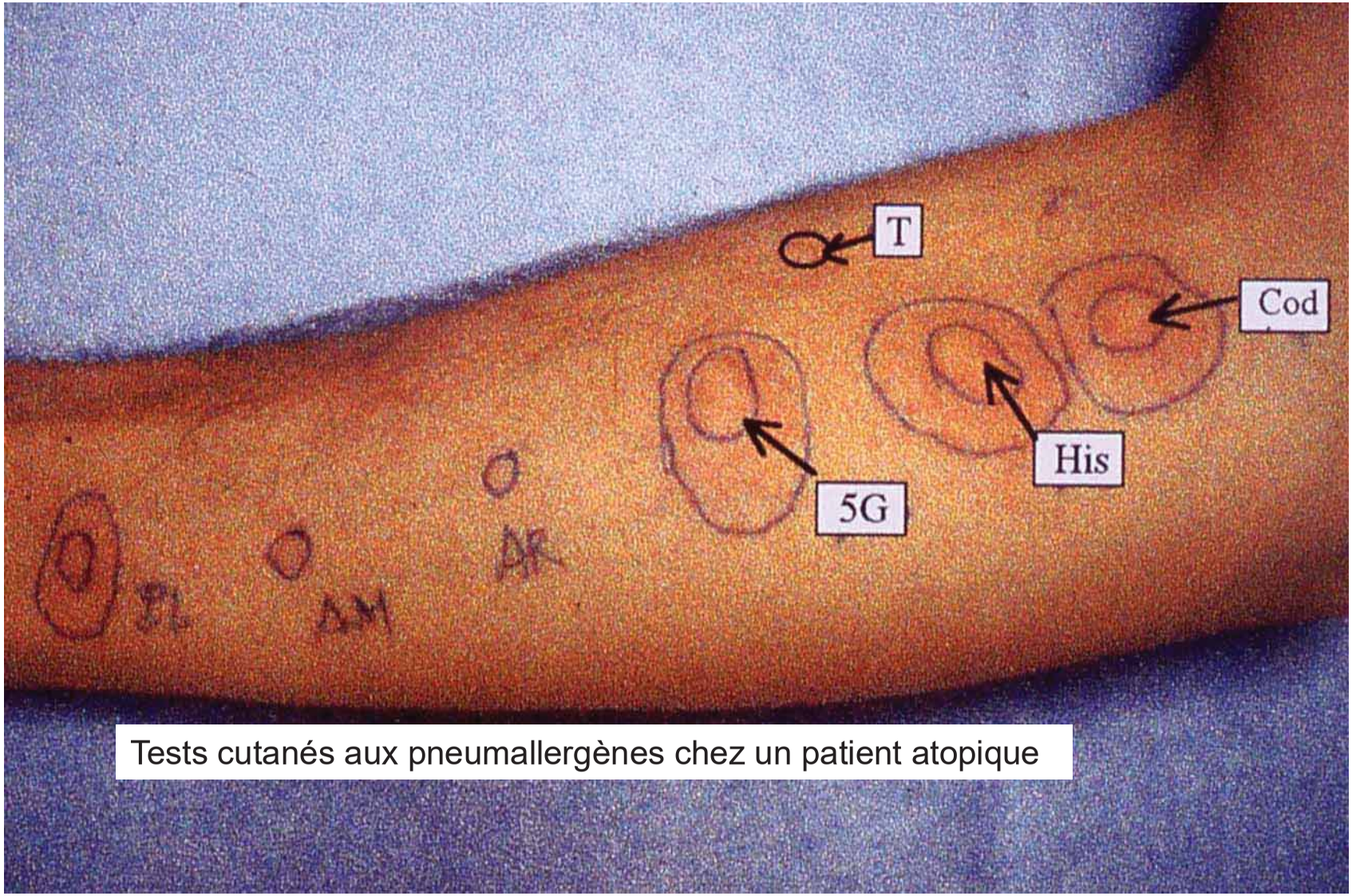
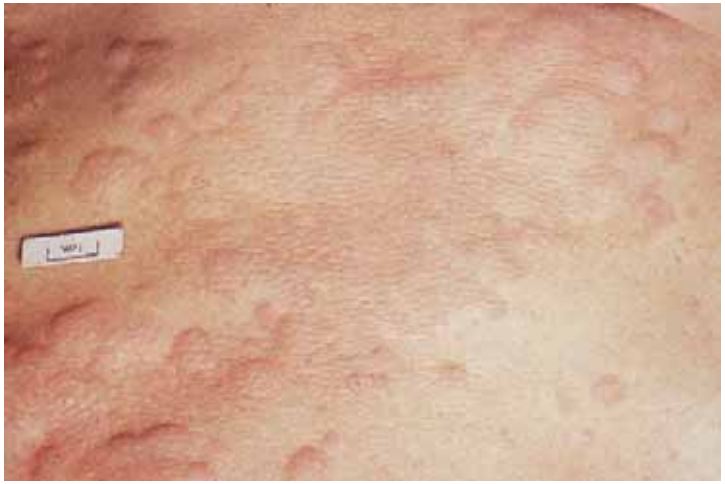
							
				Chemokines, cytokines, cytotoxins	Cytokines, inflammatory mediators		Cytokines, inflammatory mediators
Maladies autoimmunes et allergiques	Anaphylaxie Rhinite allergique Asthme (crise)	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe 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 Pemphigoide 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 aigue généralisée

HSI allergique et non allergique

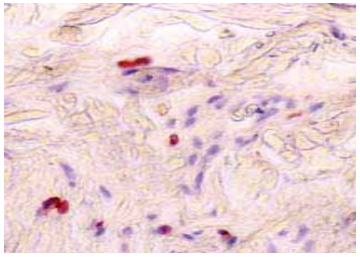


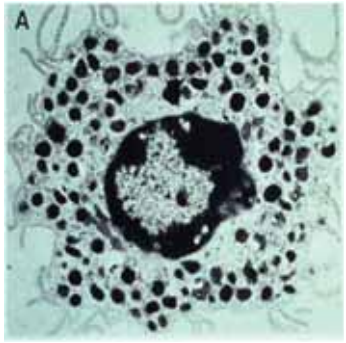
Tests cutanés aux pneumallergènes chez un patient atopique

TYPE I HYPERSENSITIVITY

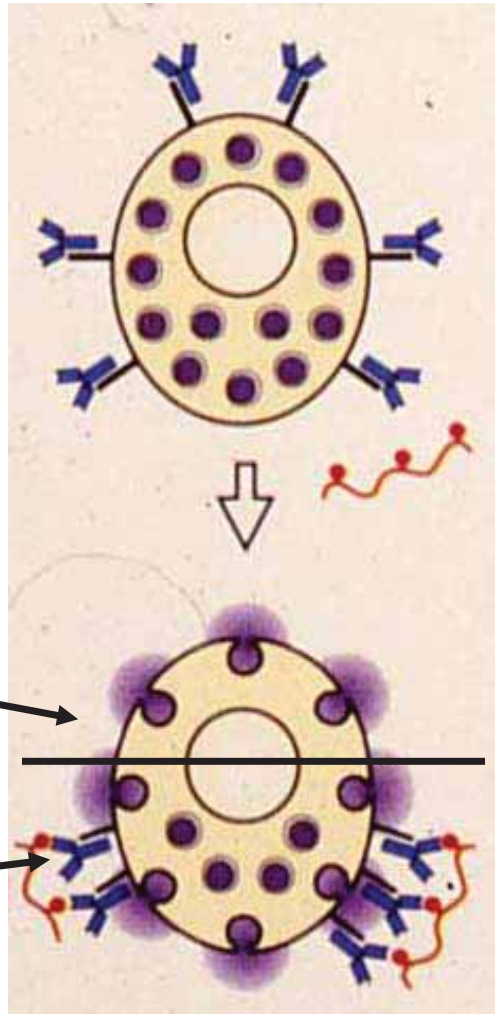


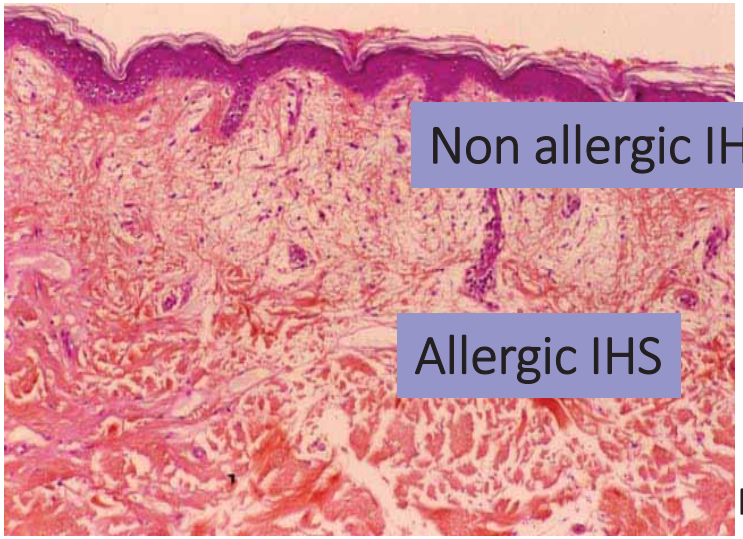
Œdème du derme / Vaisseaux



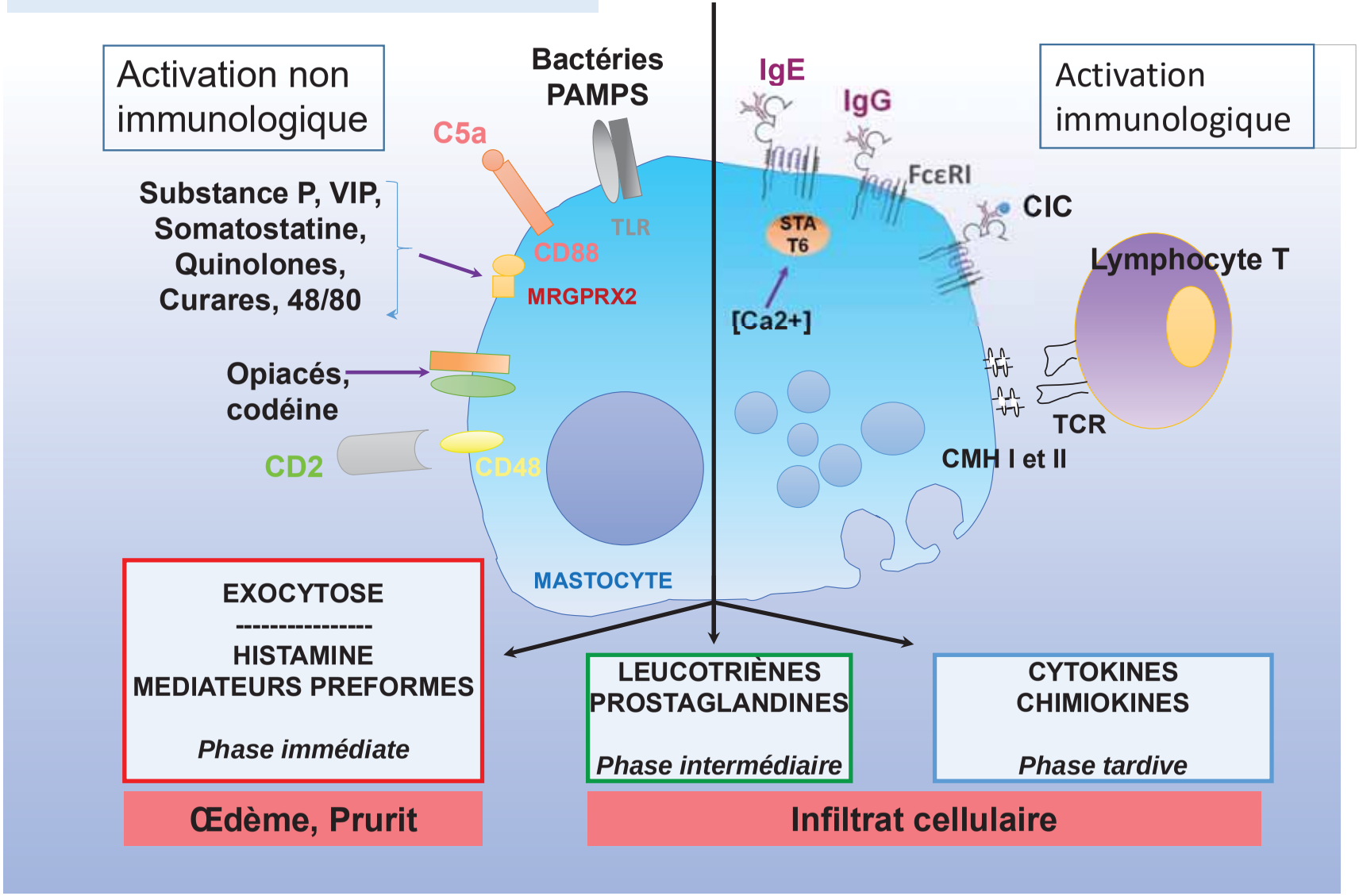


Mastocytes / Histamine





MASTOCYTES
Récepteurs et activation



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doi:10.1038/nature14022

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

Mast cells are primary effectors in allergic reactions, and may have important roles in disease by secreting histamine and various inflammatory and immunomodulatory substances[1,2]. Although they are classically activated by immunoglobulin (Ig)E antibodies, a unique property of mast cells is their antibody-independent responsiveness to a range of cationic substances, collectively called basic secretagogues, including inflammatory peptides and drugs associated with allergic-type reactions[1,3]. The pathogenic roles of these substances have prompted a decades-long search for their receptor(s). Here we report that basic secretagogues activate mouse mast cells *in vitro* and *in vivo* through a single receptor, Mrgprb2, the orthologue of the human G-protein-coupled receptor MRGPRX2. Secretagogue-induced histamine release, inflammation and airway contraction are abolished in Mrgprb2-null mutant mice. Furthermore, we show that most classes of US Food and Drug Administration (FDA)-approved peptidergic drugs associated with allergic-type injection-site reactions also activate Mrgprb2 and MRGPRX2, and that injection-site inflammation is absent in mutant mice. Finally, we determine that Mrgprb2 and MRGPRX2 are targets of many small-molecule drugs associated with systemic pseudo-allergic, or anaphylactoid, reactions; we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

Responsiveness to basic secretagogues is conserved among mammals[4] and is also found in birds[5], indicating an ancient, fundamental role for its mechanism. Many basic secretagogues are endogenous peptides, often linked to inflammation; however, they activate connective tissue mast cells only at high concentrations and independent of their canonical receptors, so another mechanism of stimulation must exist[6]. Several candidate proteins that bind polycationic compounds have been proposed as basic secretagogue receptors[6–9]. Among these, MRGPRX2 has been screened with the most compounds[8,10–14], and short interfering RNA (siRNA) knockdown studies support at least a partial role for *MRGPRX2* in activation by four non-canonical basic secretagogues[11,13]. However, no direct *in vivo* study or knockout model has been employed for any candidate. The investigation of MRGPRX2 in mice is complicated because

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- Récepteur non sélectif
- Tous les mastocytes n'expriment pas MRGPRX2
- Variants avec gain ou perte de fonction de MRGPRX2
- Lie des peptides et molécules aux propriétés physico-chimiques particulières (Cationique, Hydrophobiques)
  - -Peptides toxines
  - -Neuropeptides
  - -Peptides anti-microbiens
  - -Other endogenous peptides: kallicreine
  - -Peptides médicaments
  - -Self-peptides dégradés des protéines

ell-specific receptor crucial reactions

Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

we show that drug-induced symptoms of anaphylactoid responses are significantly reduced in knockout mice; and we identify a common chemical motif in several of these molecules that may help predict side effects of other compounds. These discoveries introduce a mouse model to study mast cell activation by basic secretagogues and identify MRGPRX2 as a potential therapeutic target to reduce a subset of drug-induced adverse effects.

Substance	Mrgprb2 EC_{50}	MRGPRX2 EC_{50}
Compound 48/80	3.7 ± 0.5 μg/ml	470.1 ± 139.6 ng/ml
Substance P	54.3 ± 4.9 μM	152.3 ± 48.0 nM
Cortistatin-14	21.3 ± 0.9 μM	106.7 ± 39.3 nM
PAMP (9-20)	12.4 ± 1.6 μM	166.0 ± 35.7 nM
Mastoparan	24.0 ± 3.6 μM	3.9 ± 0.7 μM
Icatibant	32.5 ± 2.0 μg/ml	15.8 ± 2.7 μg/ml
Cetrorelix	23.4 ± 1.4 μg/ml	221.7 ± 63.1 ng/ml
Sermorelin	29.1 ± 1.2 μg/ml	4.5 ± 0.9 μg/ml
Octreotide	10.0 ± 1.1 μg/ml	6.6 ± 0.7 μg/ml
Leuprolide	152.0 ± 7.1 μg/ml	9.1 ± 0.7 μg/ml
Atracurium	44.8 ± 1.4 μg/ml	28.6 ± 2.4 μg/ml
Rocuronium	22.2 ± 3.3 μg/ml	261.3 ± 14.4 μg/ml
Ciprofloxacin	126.5 ± 5.1 μg/ml	6.8 ± 0.5 μg/ml
Moxifloxacin	14.1 ± 2.1 μg/ml	9.9 ± 0.6 μg/ml
Levofloxacin	807.6 ± 47.1 μg/ml	22.7 ± 0.4 μg/ml
Ofloxacin	225.0 ± 25.4 μg/ml	30.1 ± 1.5 μg/ml

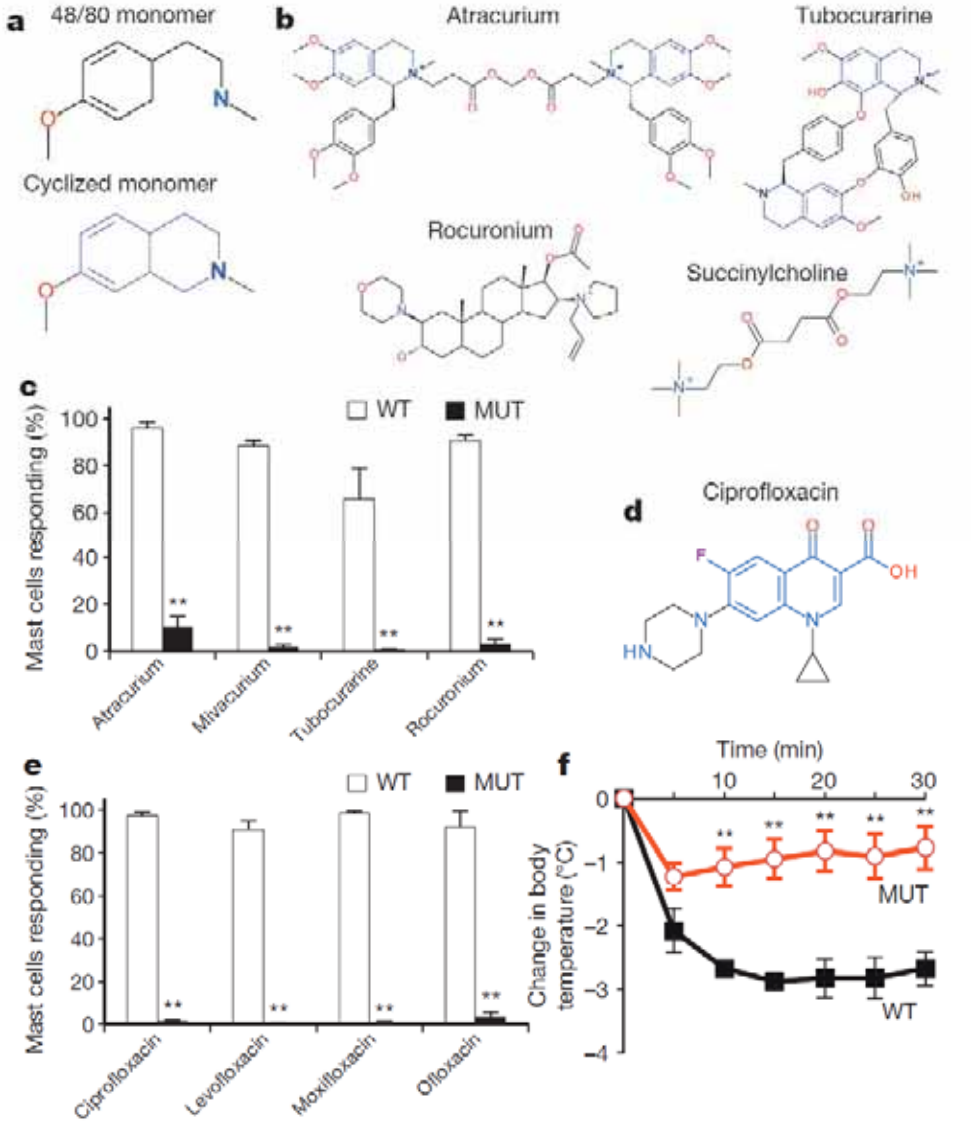

Figure 4 | Mrgprb2 mediates mast cell responsiveness and side effects of small-molecule therapeutic drugs. **a**, Structures of 48/80 and a cyclized variant. The THIQ motif is highlighted in blue. **b**, Structures of representative members of all NMBD classes (see Supplementary Information). THIQ motifs are highlighted in blue. Note that only succinylcholine lacks a bulky hydrophobic group. **c**, Percentage of responding cells from wild-type (WT) and $Mrgprb2^{MUT}$ (MUT) peritoneal mast cells after application of various NMBDs, assayed using Fluo-4 imaging. Concentrations of drugs (in $\mu g\,ml^{-1}$): atracurium, 50; mivacurium, 20; tubocurarine, 30; rocuronium, 500. $n = 3$ mice per genotype; >150 cells counted per substance. **d**, Structure of ciprofloxacin, with the motif common to all fluoroquinolones highlighted in blue. Note the nitrogens close to the quinolone motif. **e**, Percentage of responding cells from wild-type and $Mrgprb2^{MUT}$ peritoneal mast cells after fluoroquinolone application, assayed using Fluo-4 imaging. Concentrations of drugs (in $\mu g\,ml^{-1}$): ciprofloxacin, 200; levofloxacin, 500; moxifloxacin, 160; ofloxacin, 400. $n = 3$ mice per genotype; >150 cells counted per substance. **f**, Changes in body temperature after intravenous injection of ciprofloxacin (1.5 mg in 125 µl saline) at time 0. $n = 4$ mice per genotype. Data are presented as mean ± s.e.m. Two-tailed unpaired Student's *t*-test: $^{*}P < 0.05$, $^{**}P < 0.01$.

MASTOCYTES
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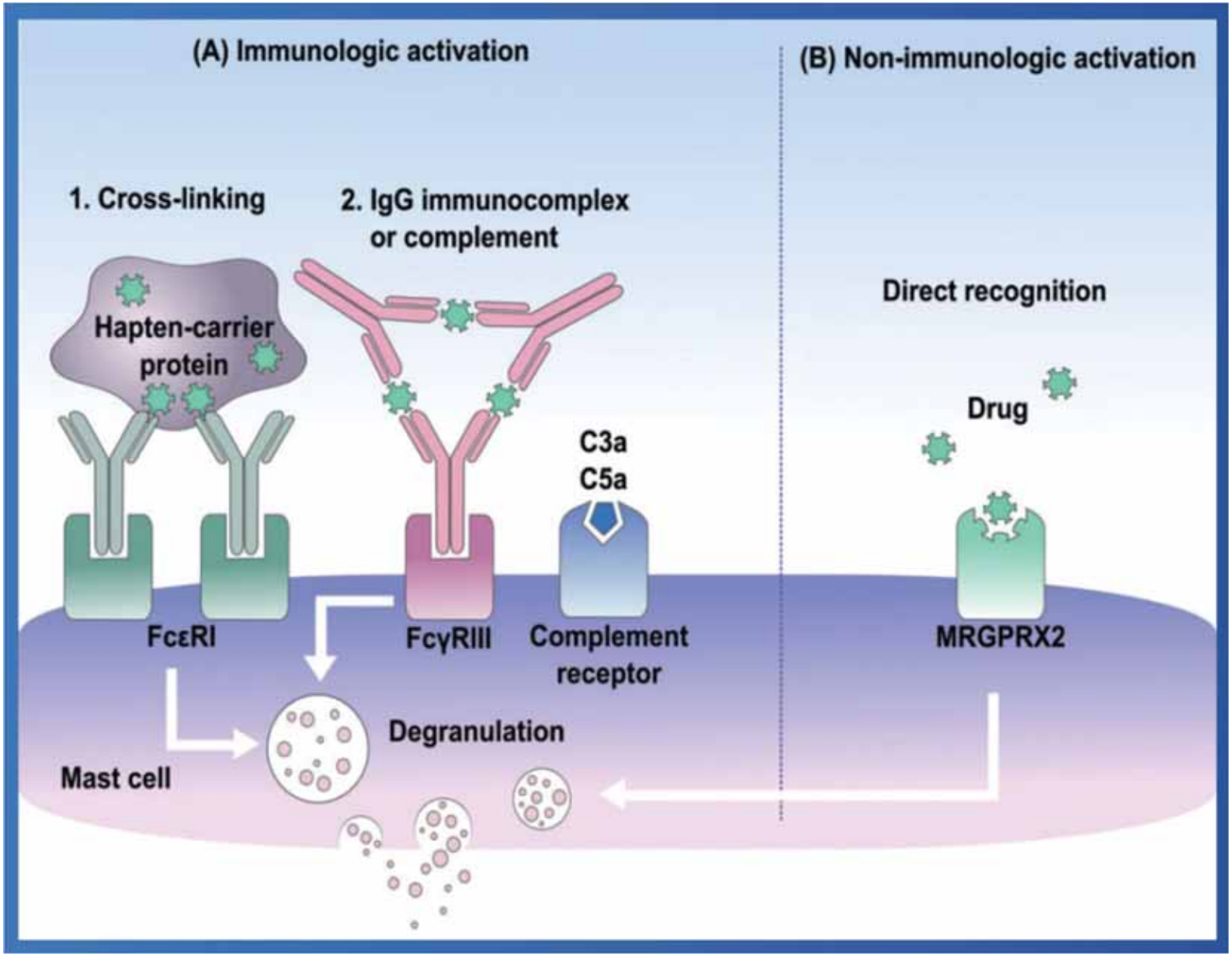
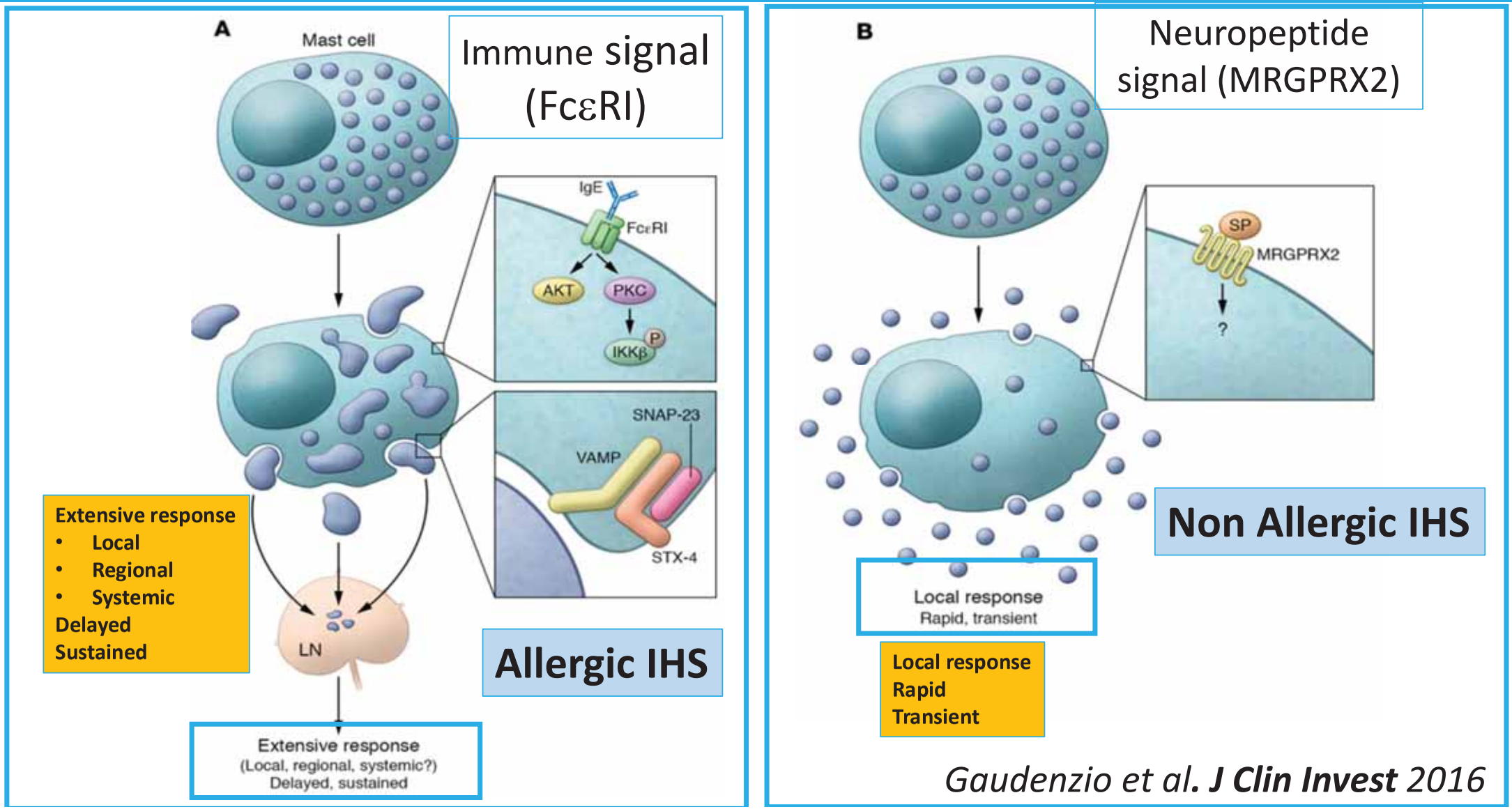


Two fundamental degranulation pathways in mast cells



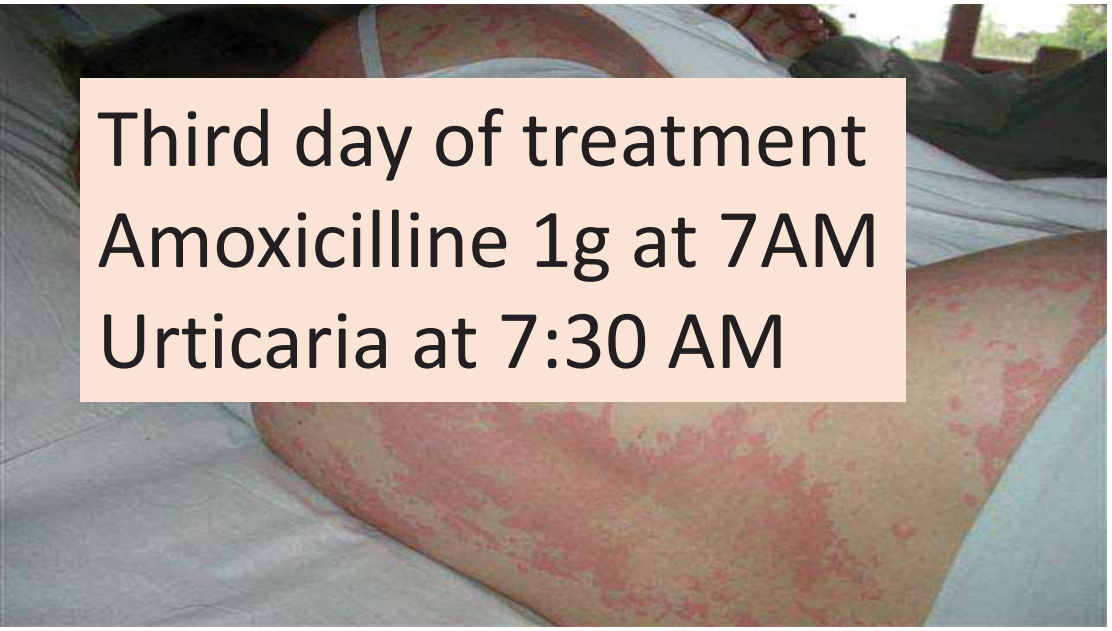
Gaudenzio et al. ***J Clin Invest*** *2016*

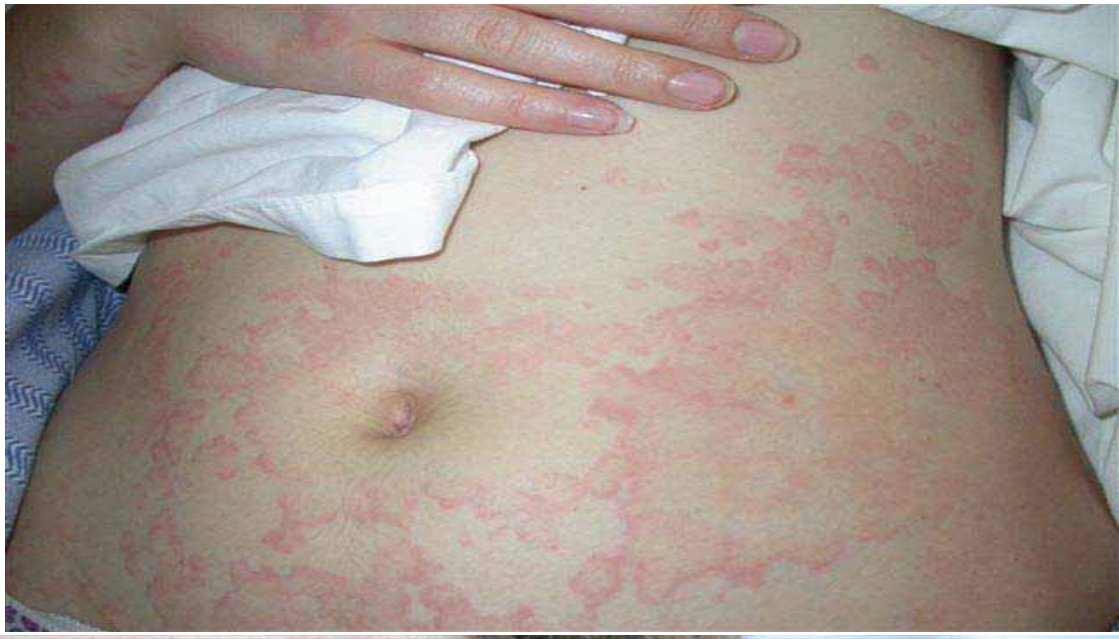
Drug-induced urticaria and angioedema

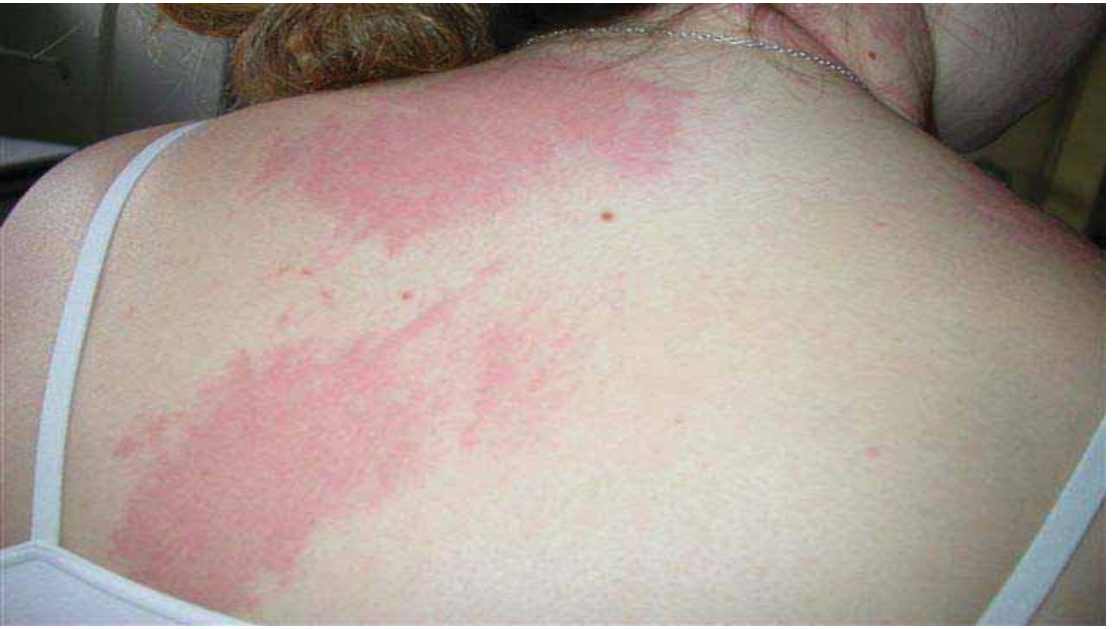
- **Allergic (IgE)**: rares (5%) and exceptionally isolated

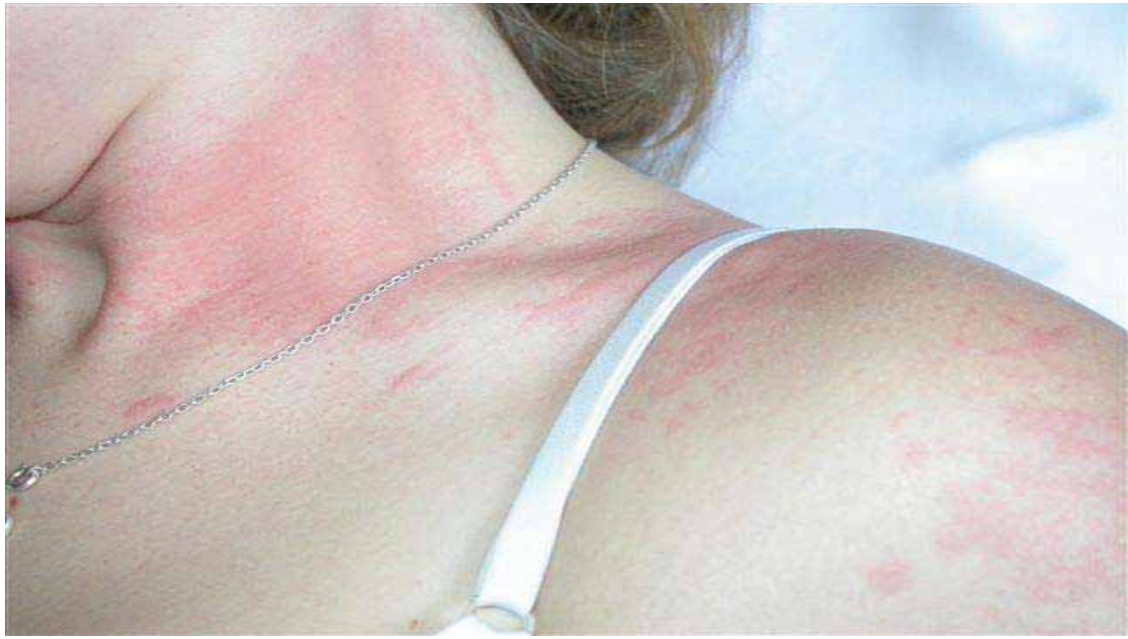
- **Non allergic**: frequent (95%) and almost always benign

- Cousin F, Philips K, Favier B, Bienvenu J**,** Nicolas JF**.** Drug-induced urticaria. **Eur J Dermatol** 2001;11(3):181-7.

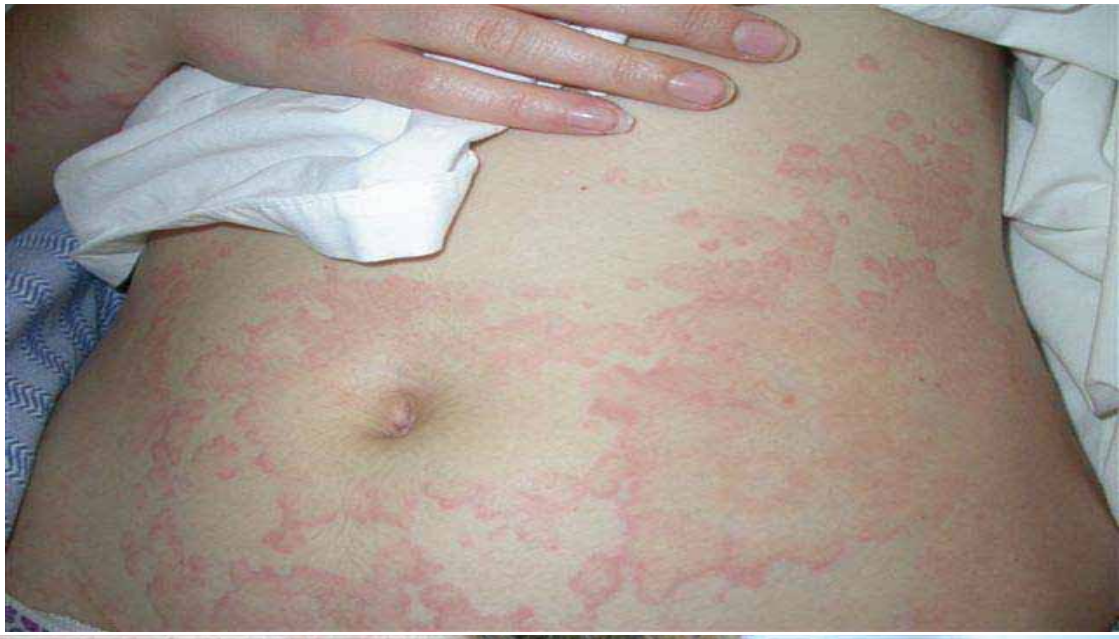

Third day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM

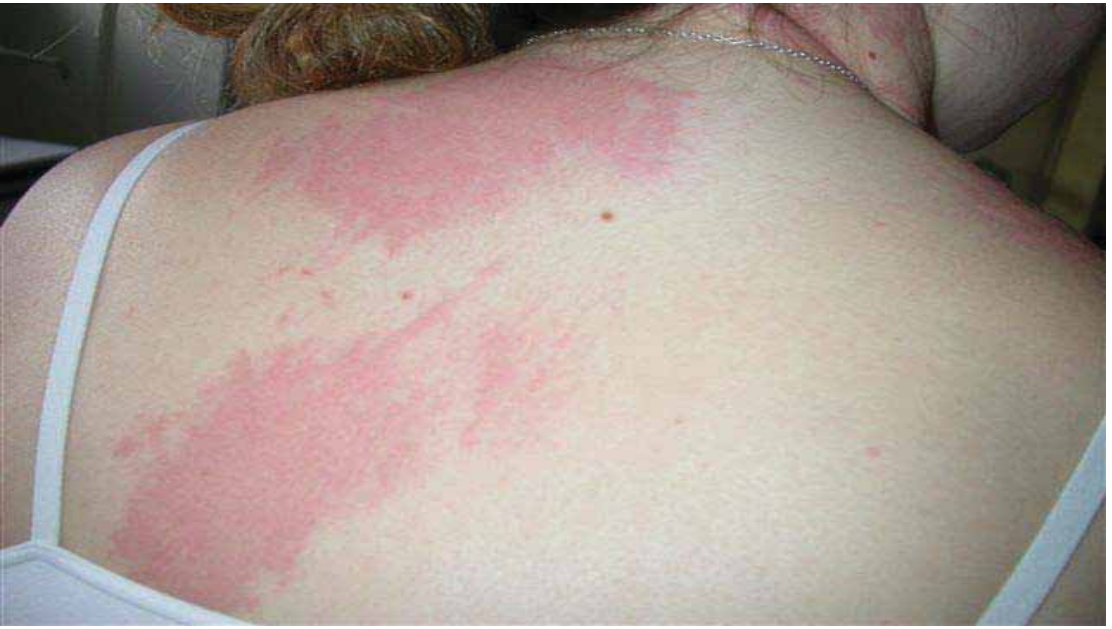


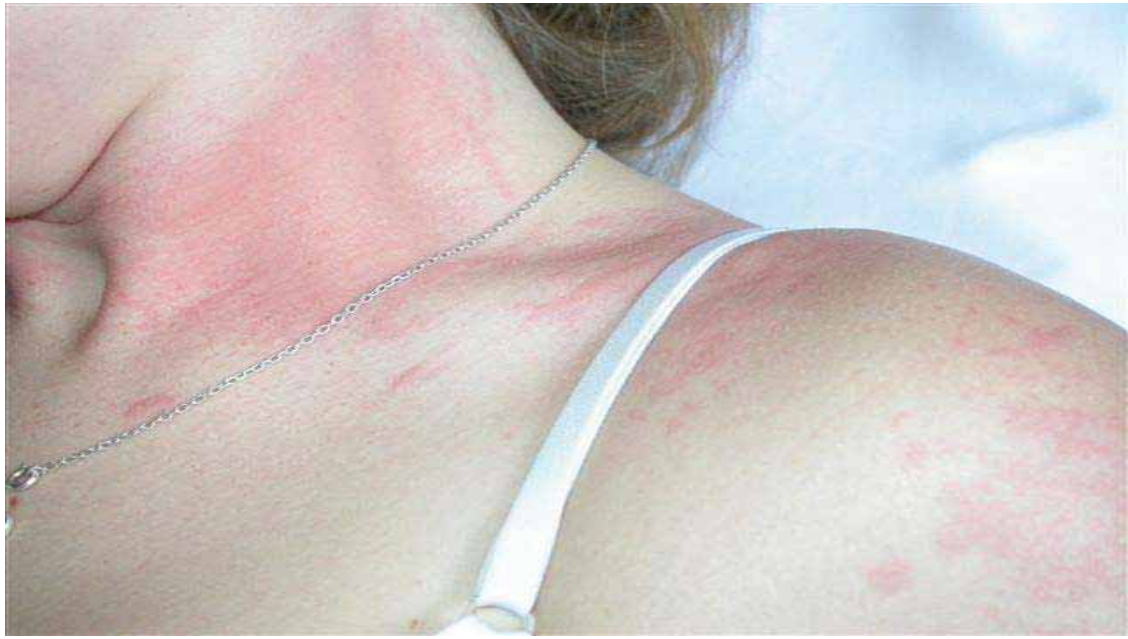


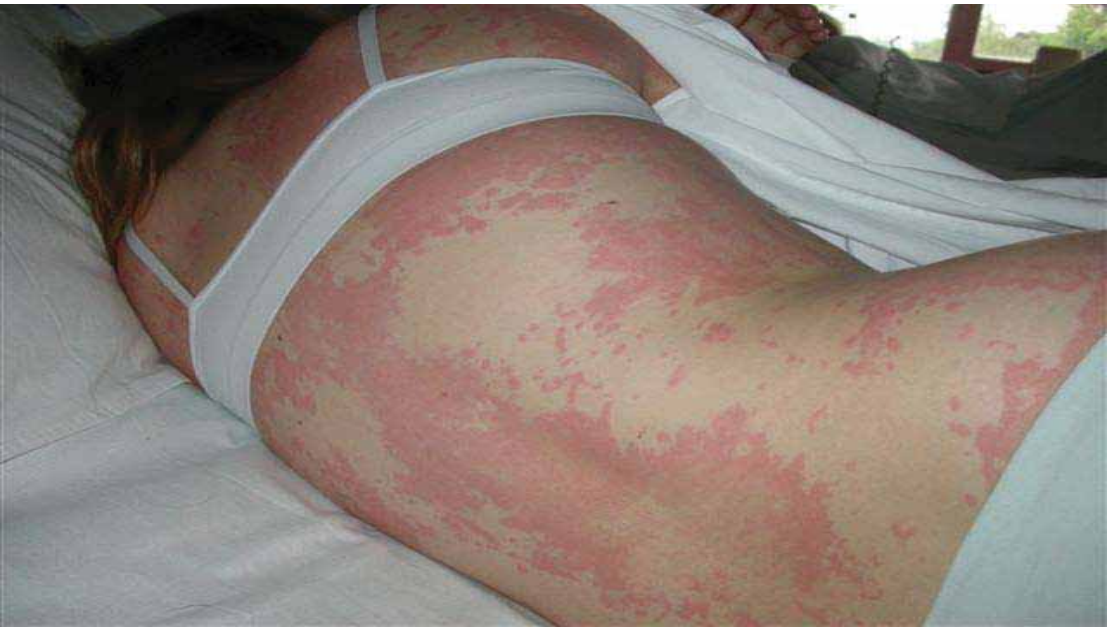


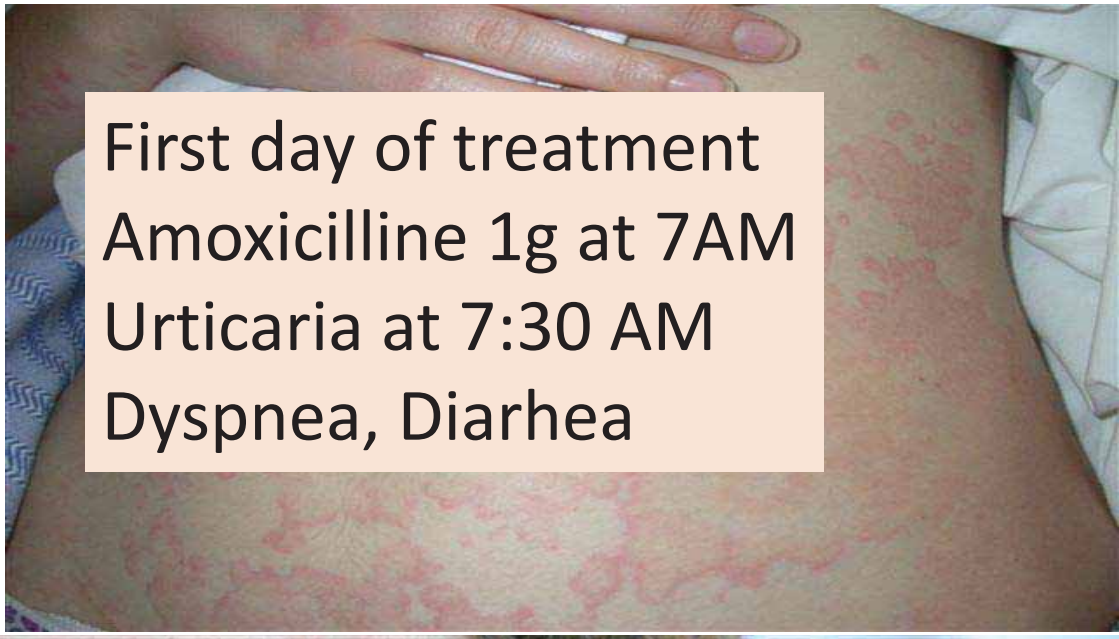

First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 11 AM



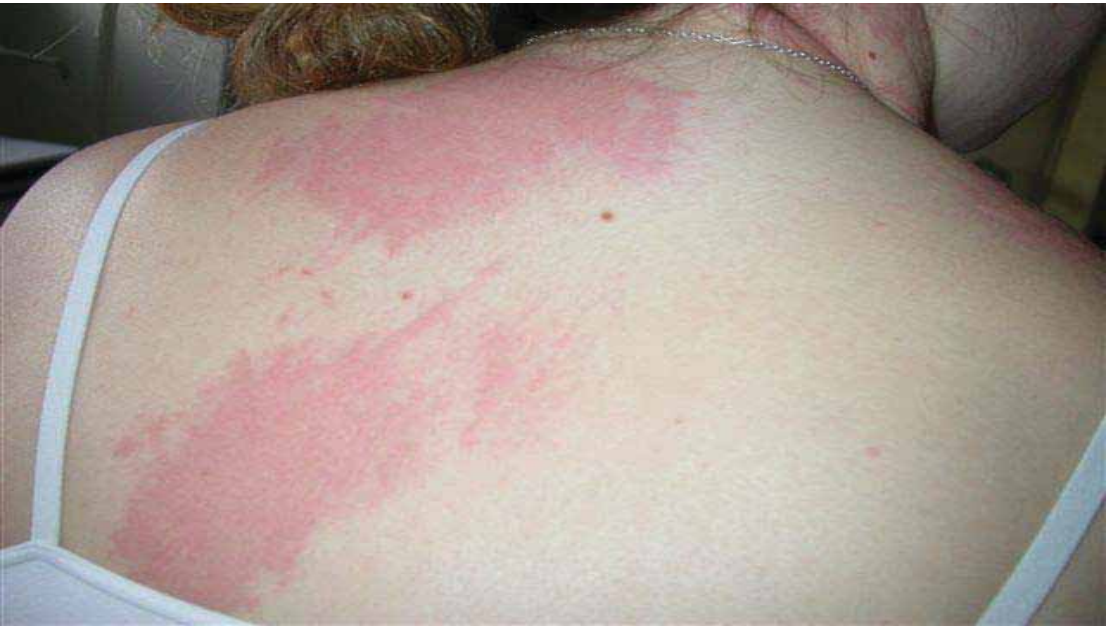


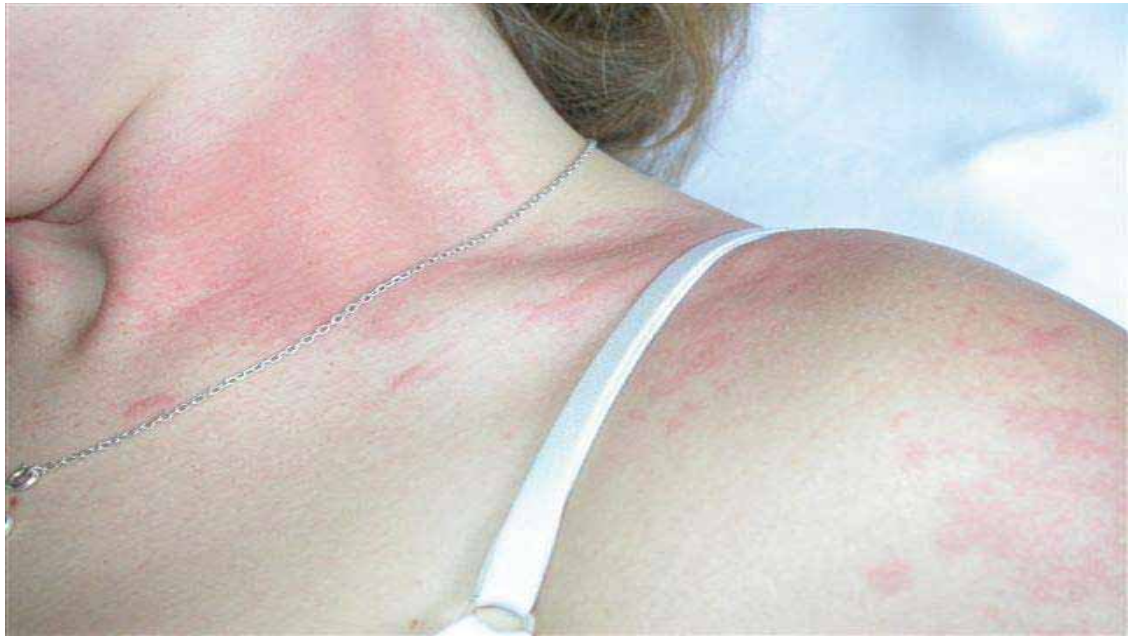


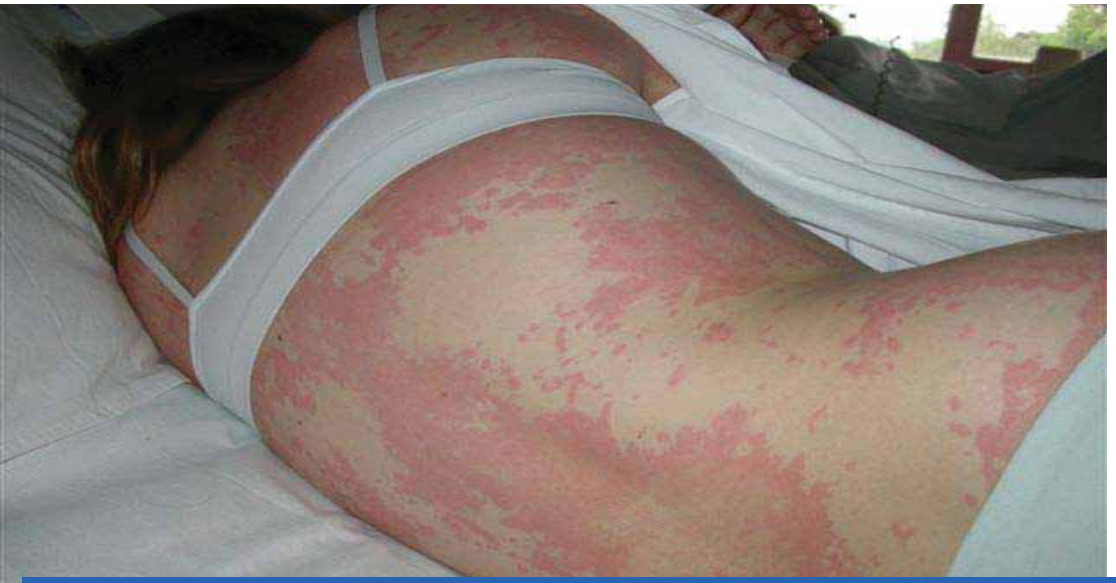


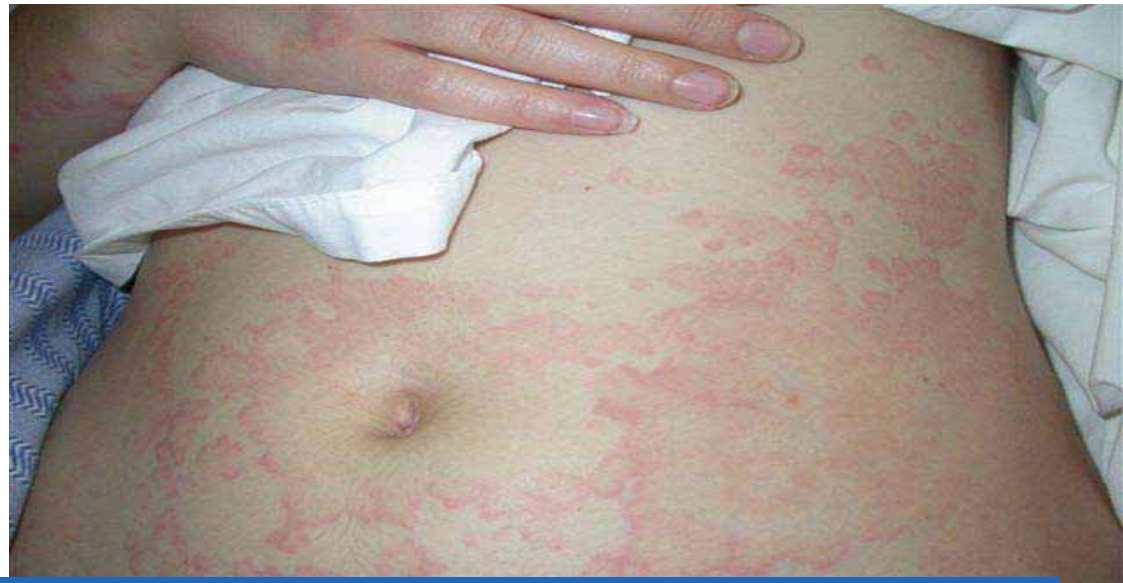


First day of treatment
Amoxicilline 1g at 7AM
Urticaria at 7:30 AM
Dyspnea, Diarhea









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

Hypersensibilités
Classification de Gell & Coombs

Antibody ← → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IIFN-γ, TNF-α **Th1/Type 1**	IL-5, IL-4/IL-13 **Th2/Type 2**	Perforin/ granzyme B **Cytotoxic**	CXCL8, **Th17/Type 17**
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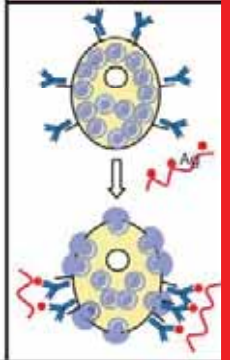
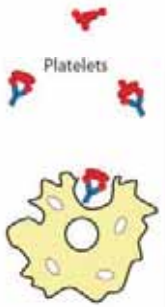
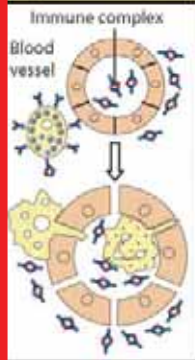
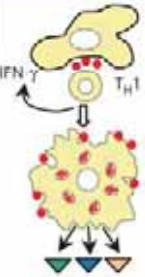
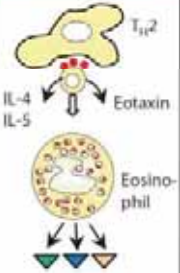
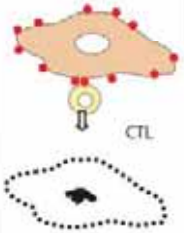
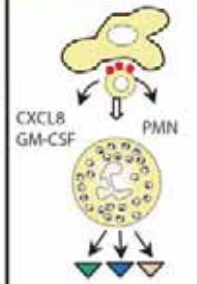
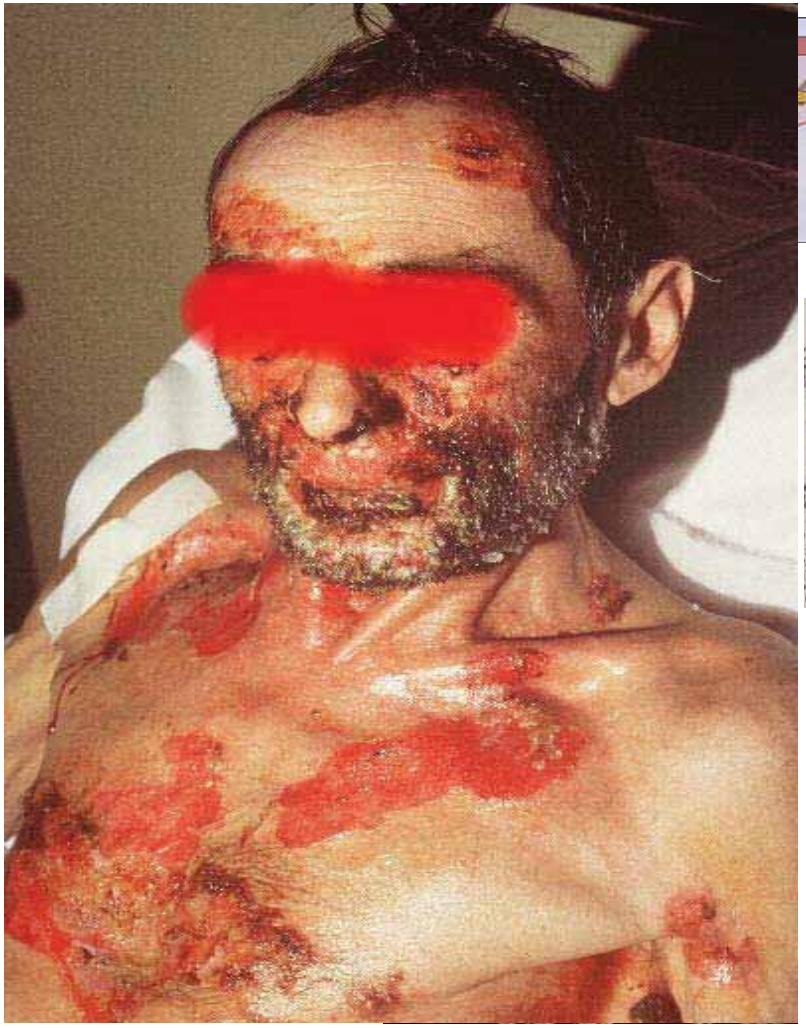
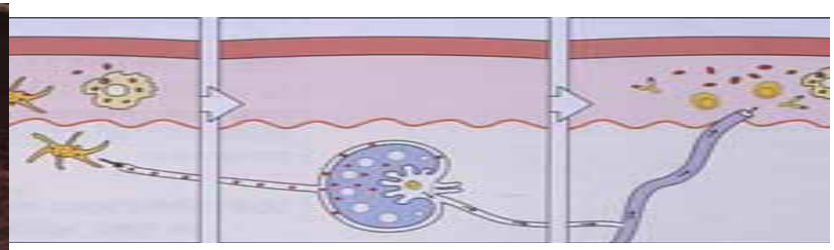
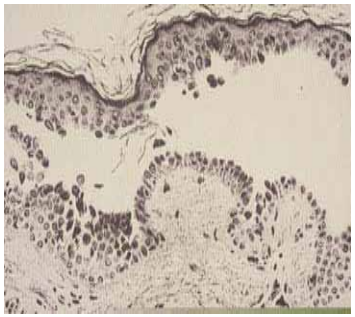
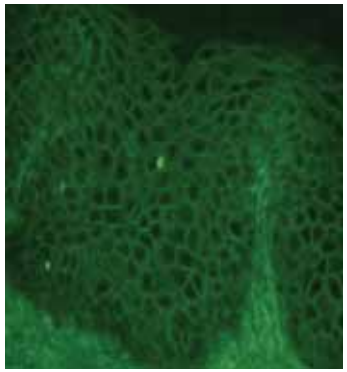
							
Maladies autoimmunes et allergiques	Anaphylaxie Rhinite allergique Asthme (crise)	Réaction transf. Anémie hémol. Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	IDR tuberculine Rejet de greffe Polyarthrite Diabète	Asthme chron. Rhinite chron.	Rejet de greffe Diabète SEP	Polyarthrite Sclérose en plaque Mal. de Crohn
Dermatoses autoimmunes et allergiques	Urticaire contact	Pemphigus Pemphigoide 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 aigue généralisée

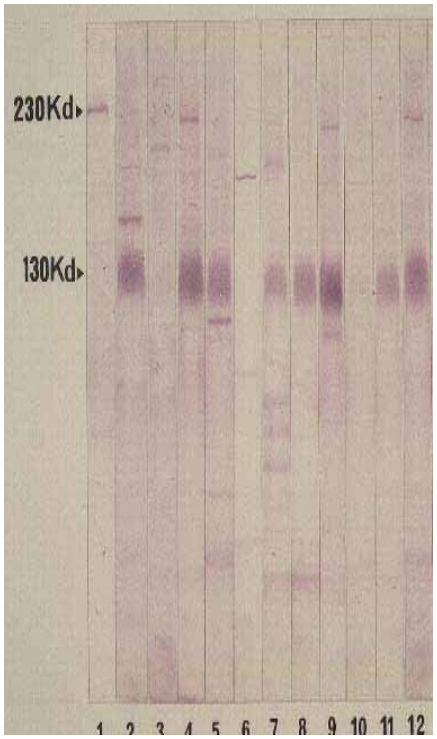
Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS











Hypersensibilités

Classification de Gell & Coombs

Antibody ← → T cells

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
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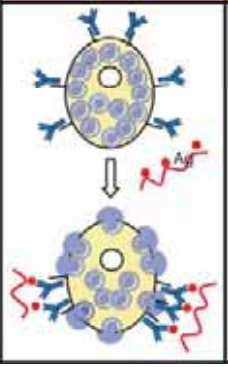
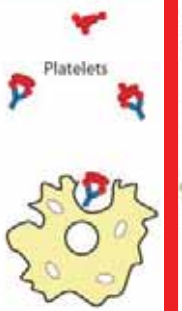
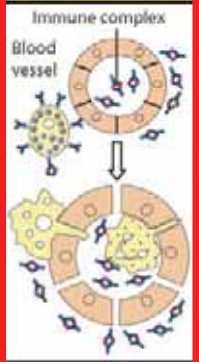
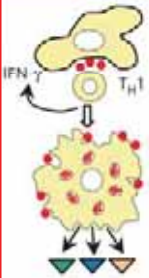
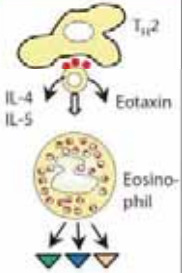
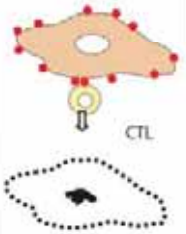
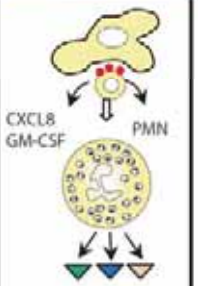
							
	Chemokines, cytokines, cytotoxins	Cytokines, inflammatory mediators	Cytokines, inflammatory mediators				

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

Fig

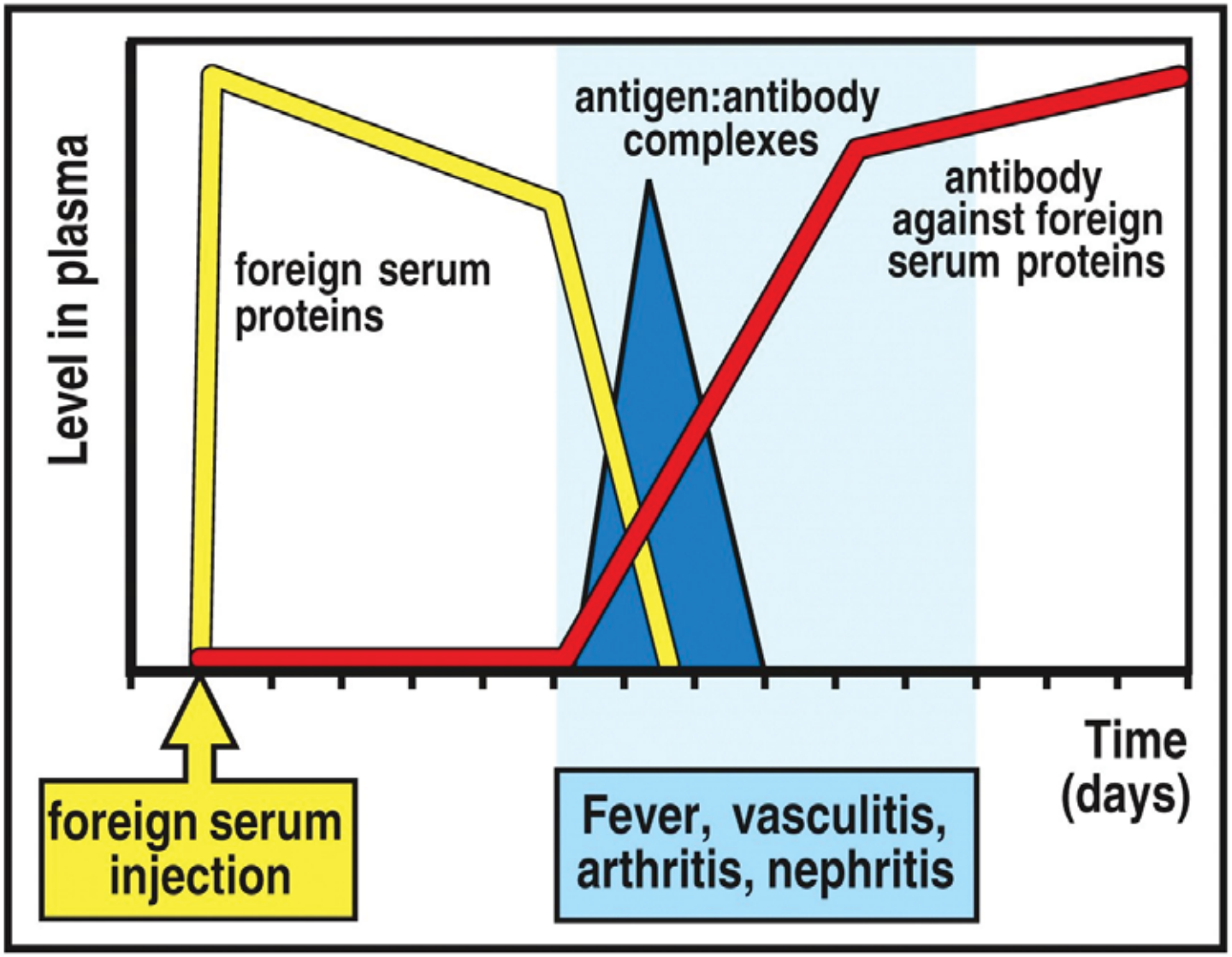
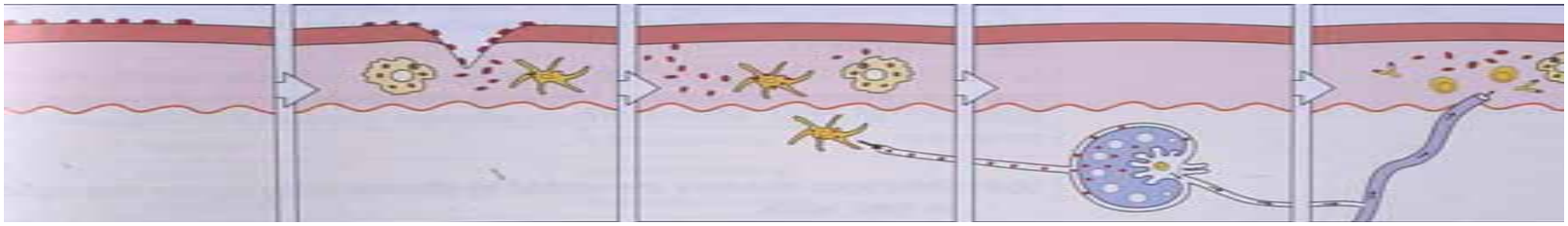
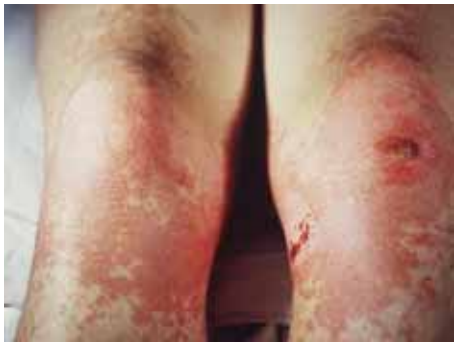
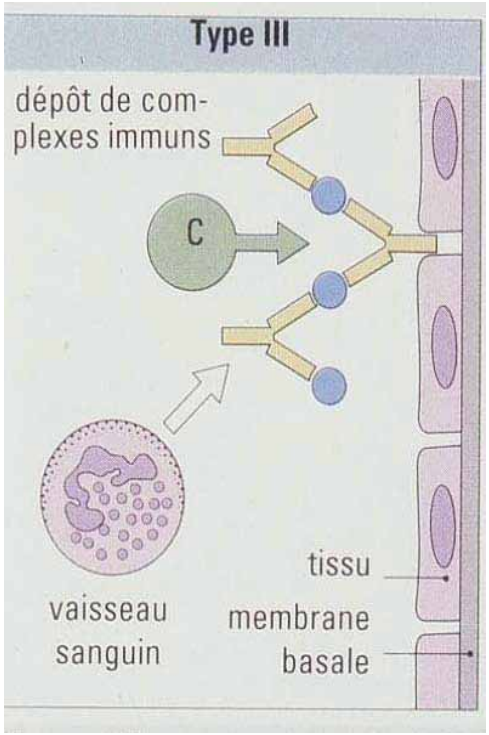


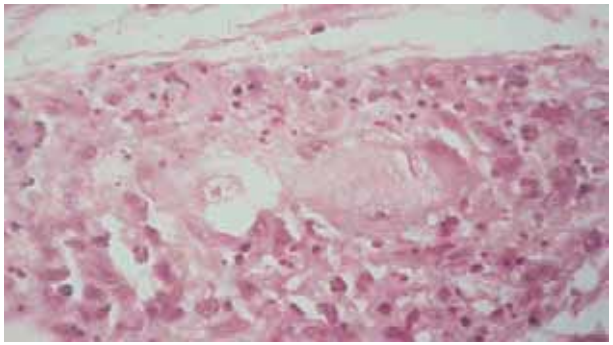
Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

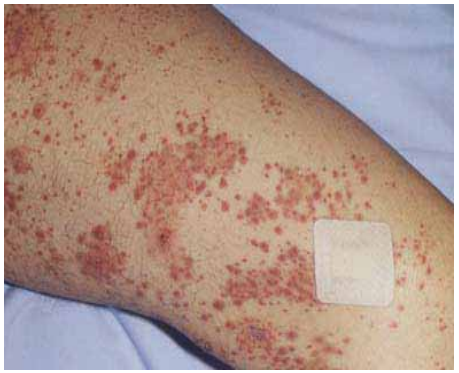
Hypersensibilité de type III due à des complexes immuns
VASCULITES – PURPURA RHUMATOIDE

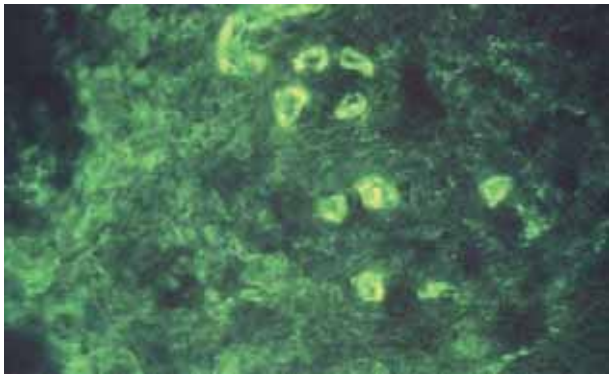






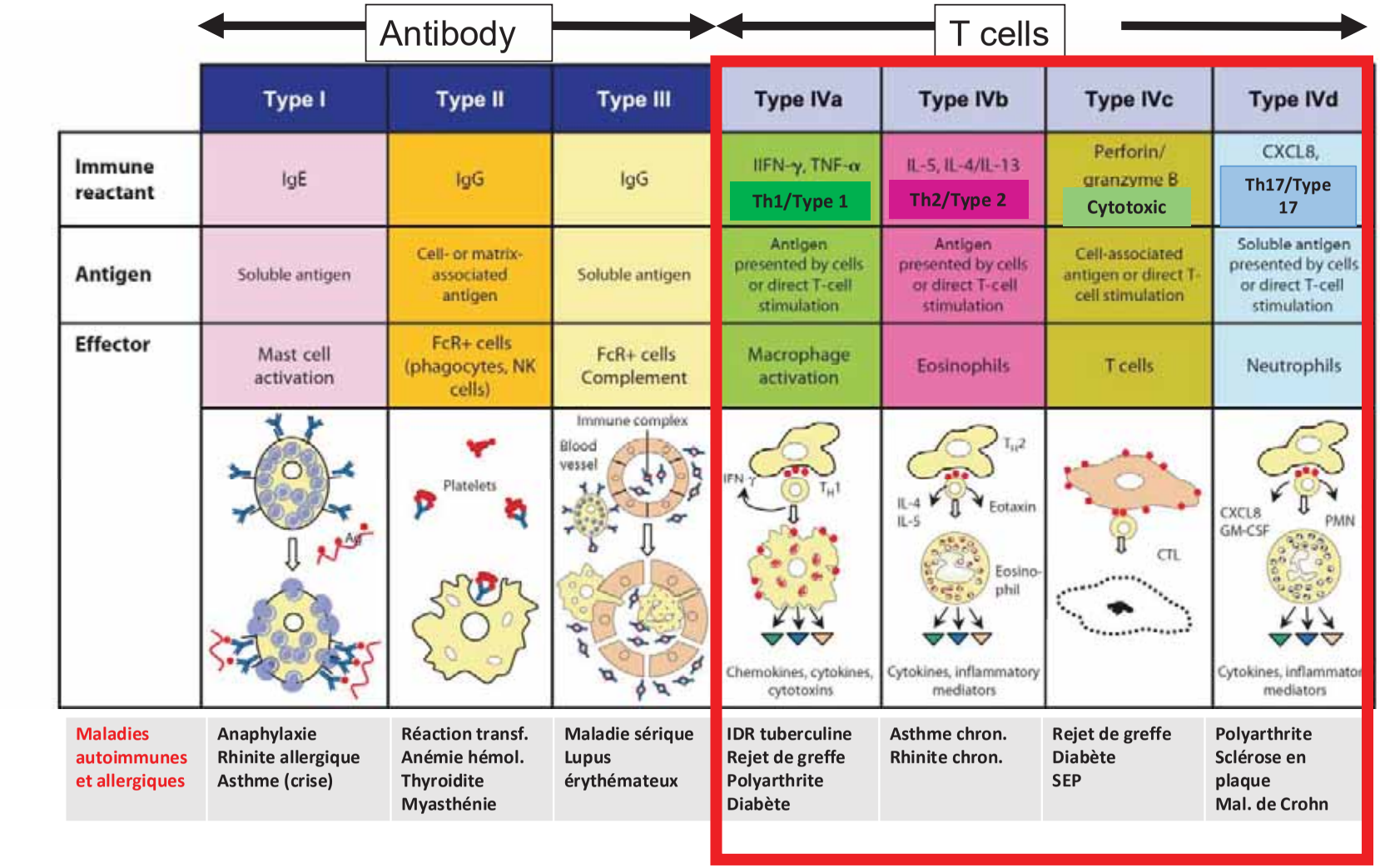






Hypersensibilités

Classification de Gell & Coombs



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

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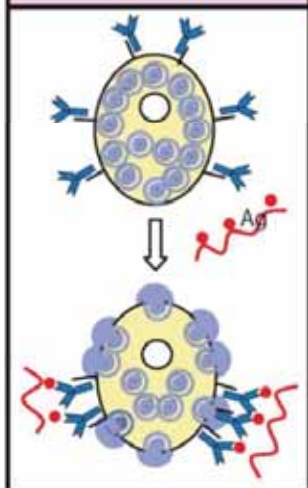
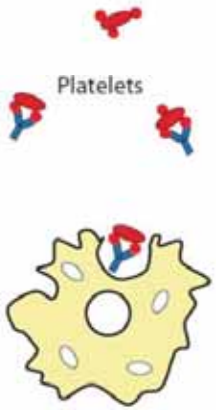
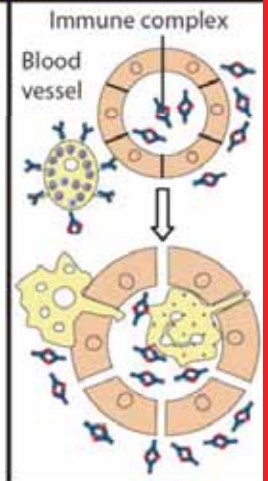
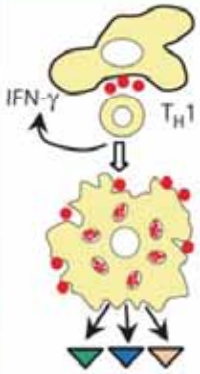
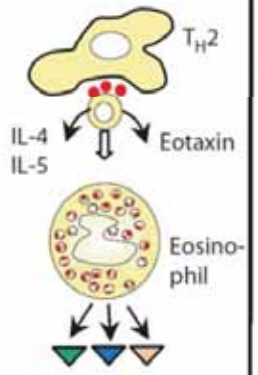
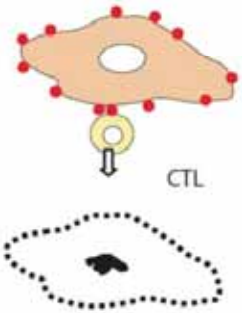
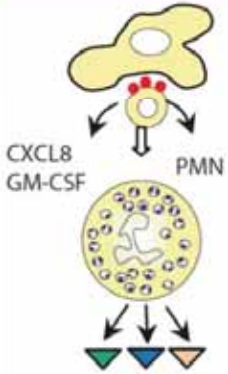
				 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators

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 γt$^+$ 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,

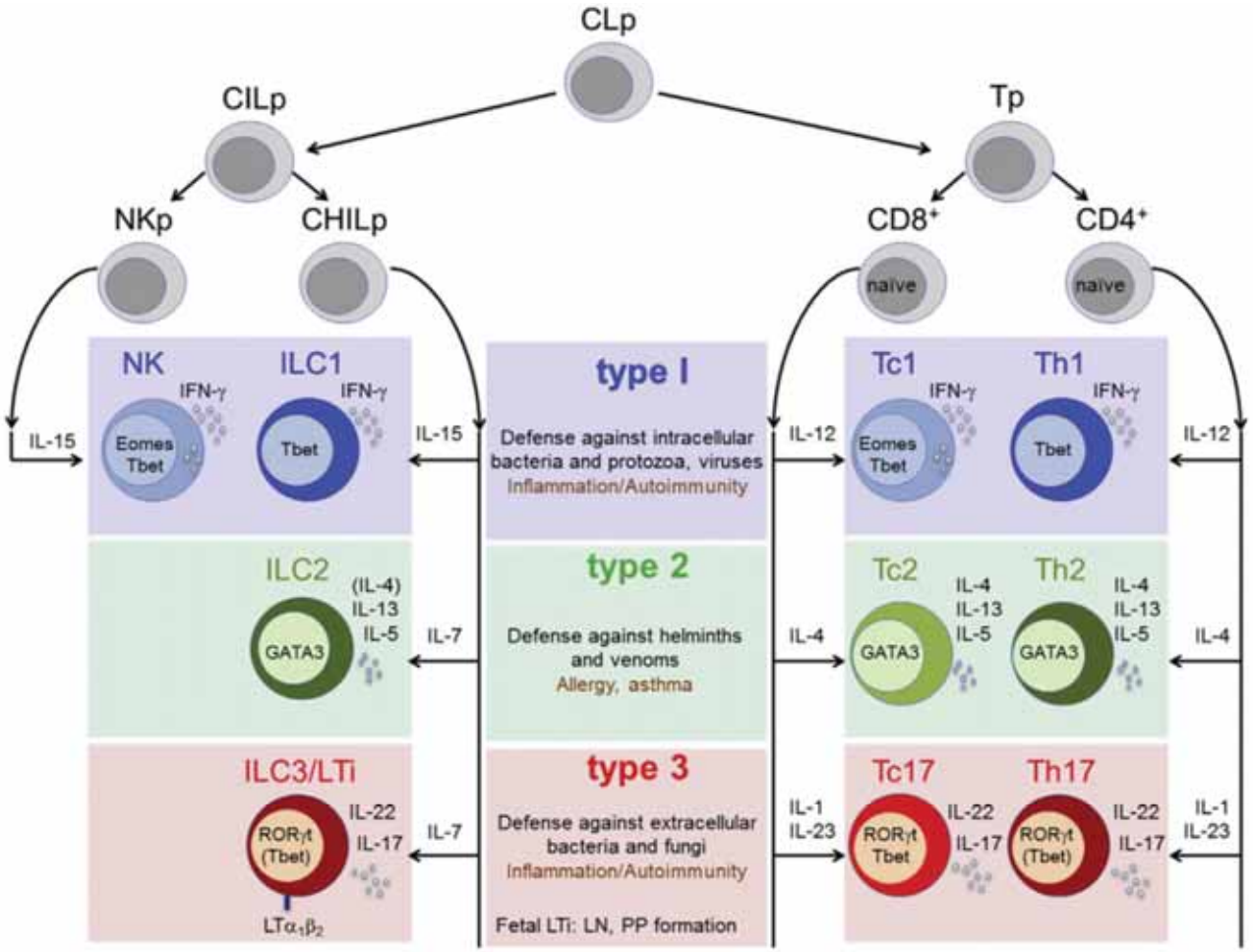
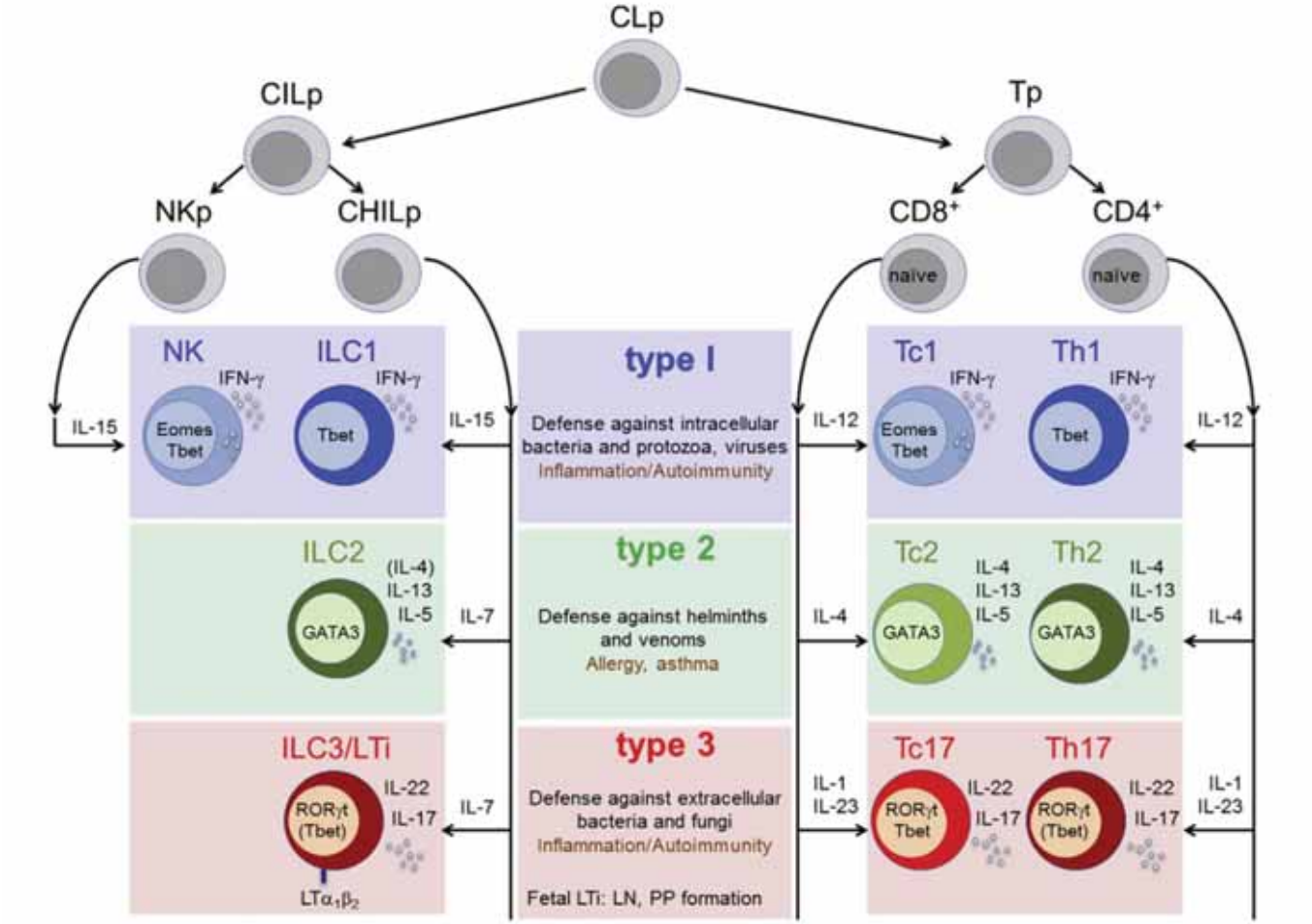


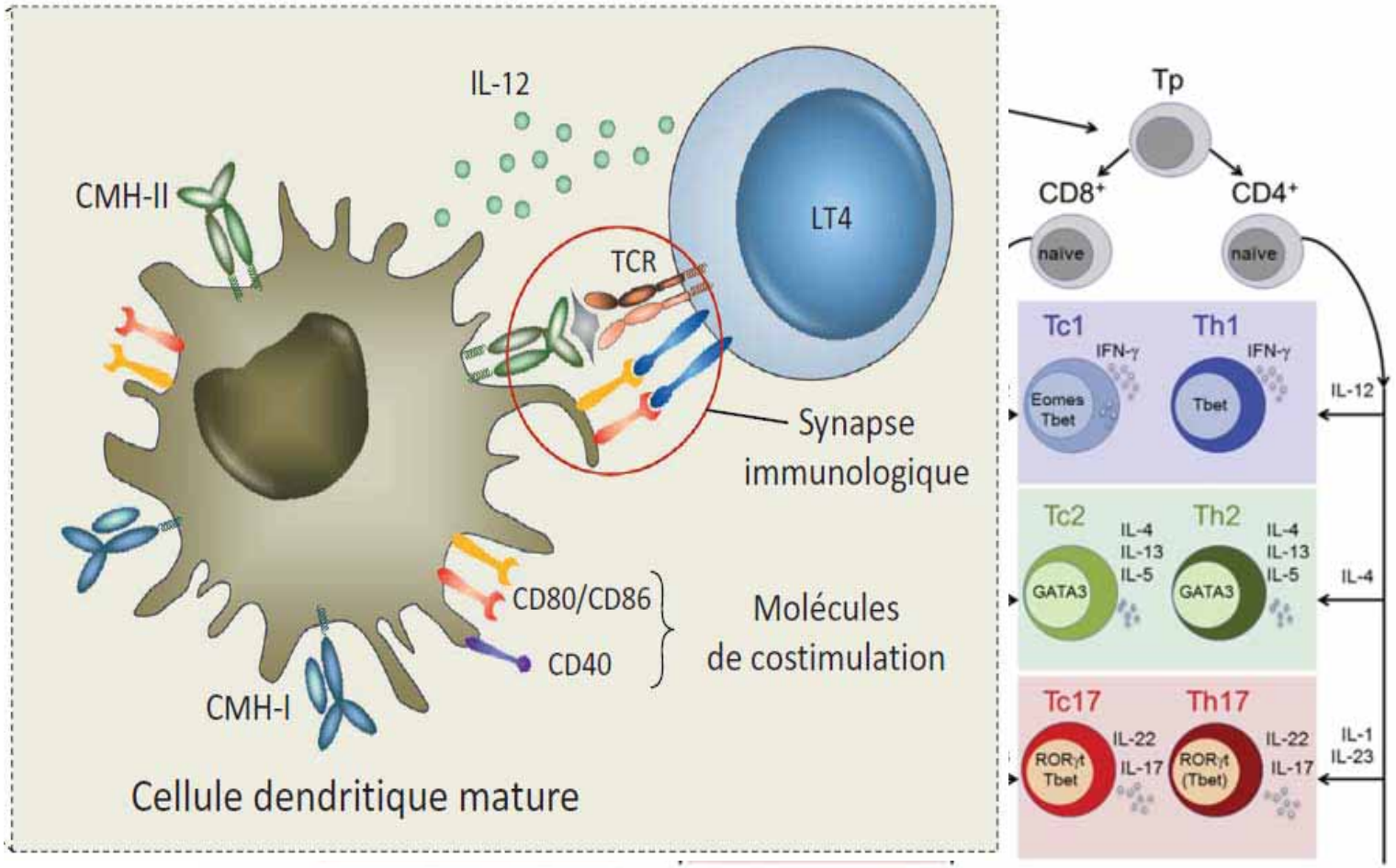
FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and ILC2s, which produce IL-4, IL-5, and IL-13. Type 3 immunity is composed of RORγt *(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 adaptative cell-mediated immunity



Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol. **2015** Mar;135(3):626-35.

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



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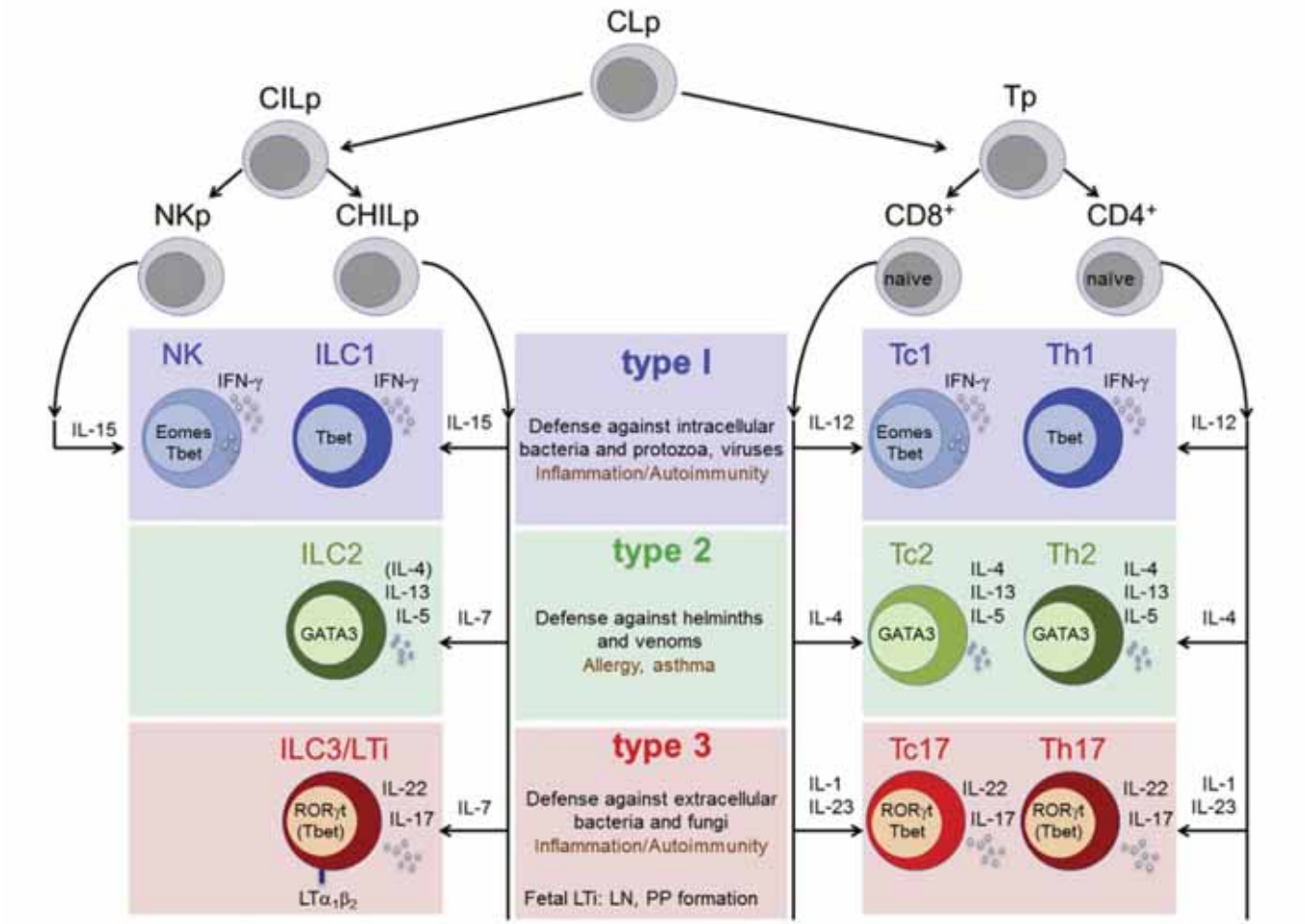

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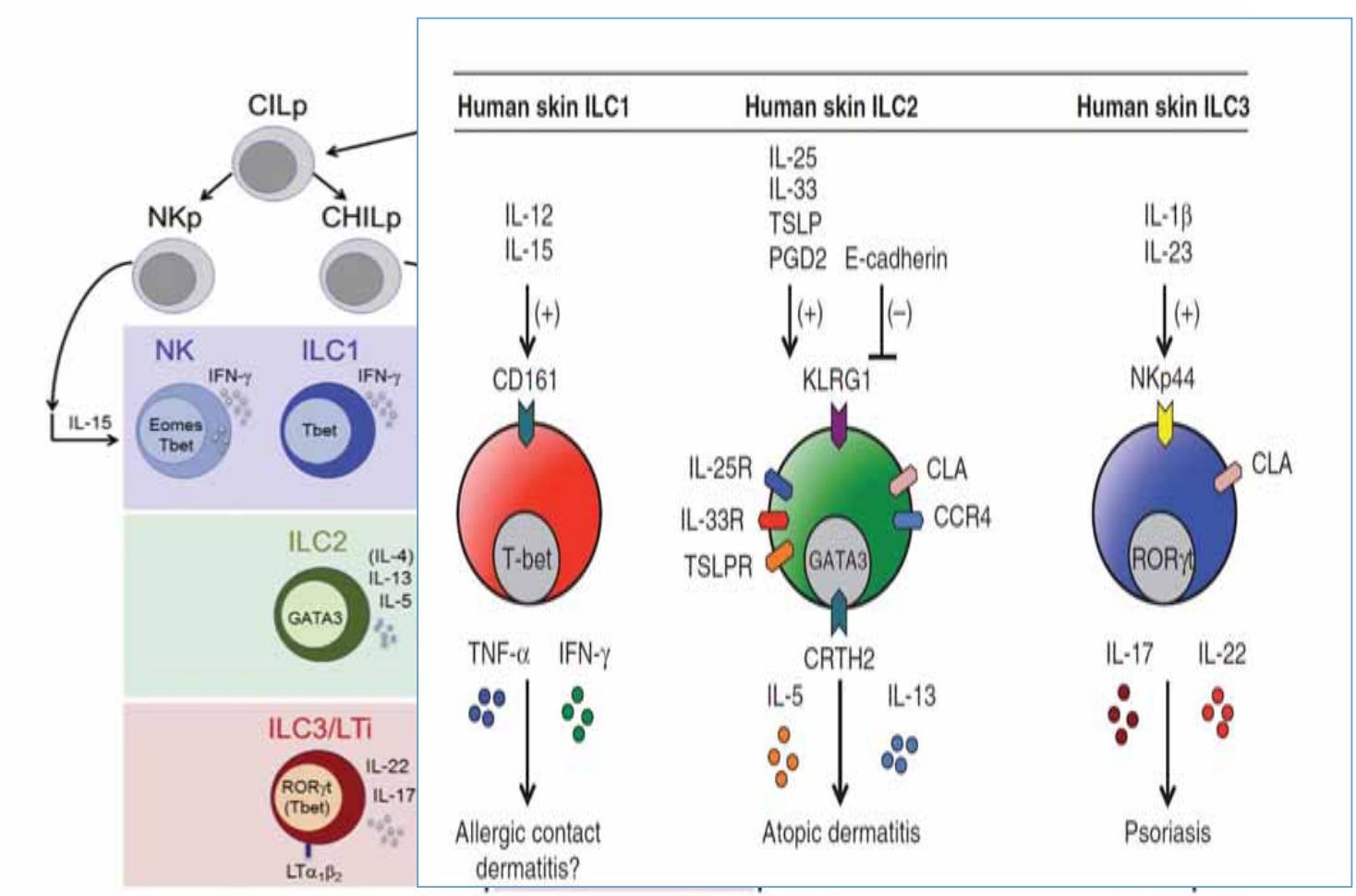

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Type 1 Immunity

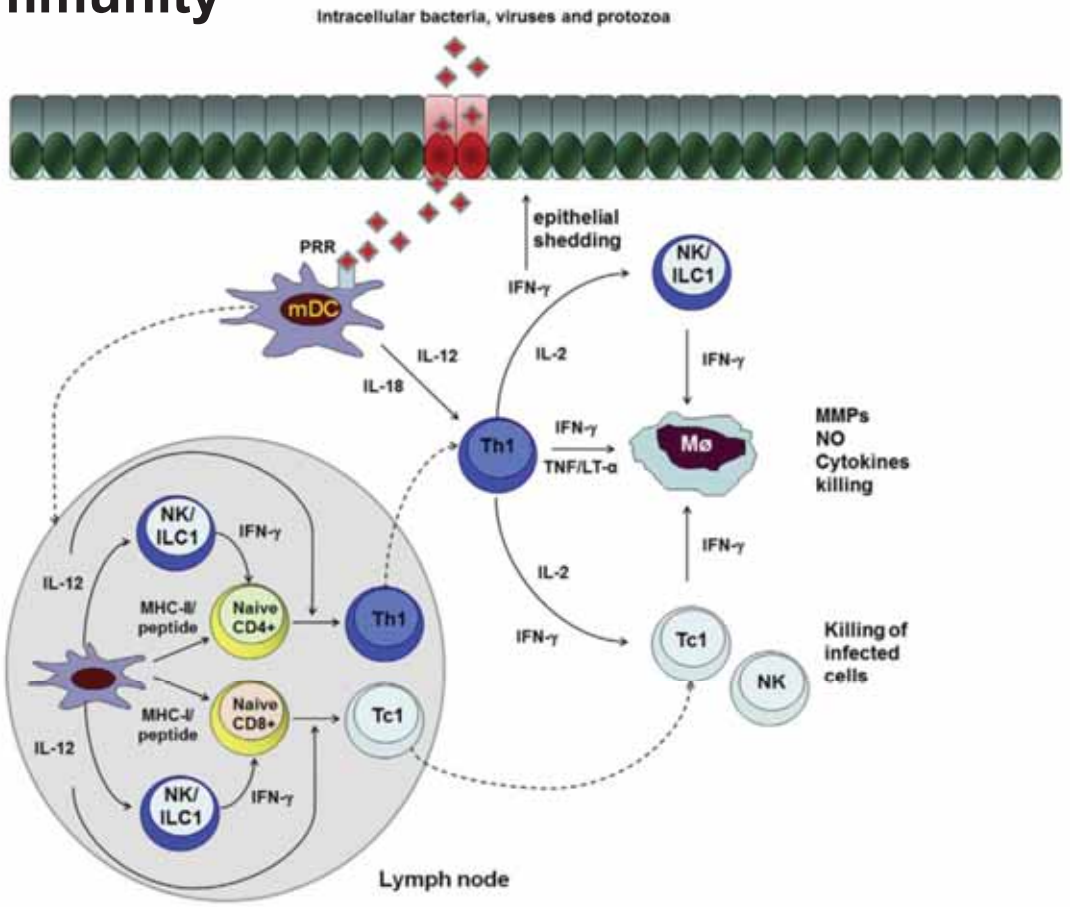


FIG 2. Cells, cytokines, and effectors of type 1 immunity. Intracellular microbes interacting with pathogen recognition receptors *(PRR)* on DCs in the presence of DC-derived IL-12 and IL-18 and of NK/ILC1-derived IFN-γ induce T_H1 or T_C1 development from naive T cells. T_C1 and NK cells kill virus-infected cells. T_H1 cell–, T_C1 cell–, and ILC1-derived cytokines activate MPs to produce the matrix metallopeptidase *(MMPs)*, nitric oxide *(NO)*, and cytokines that allow engulfment and killing of microbial invaders. *mDC*, Myeloid dendritic cell.

Type 2 Immunity

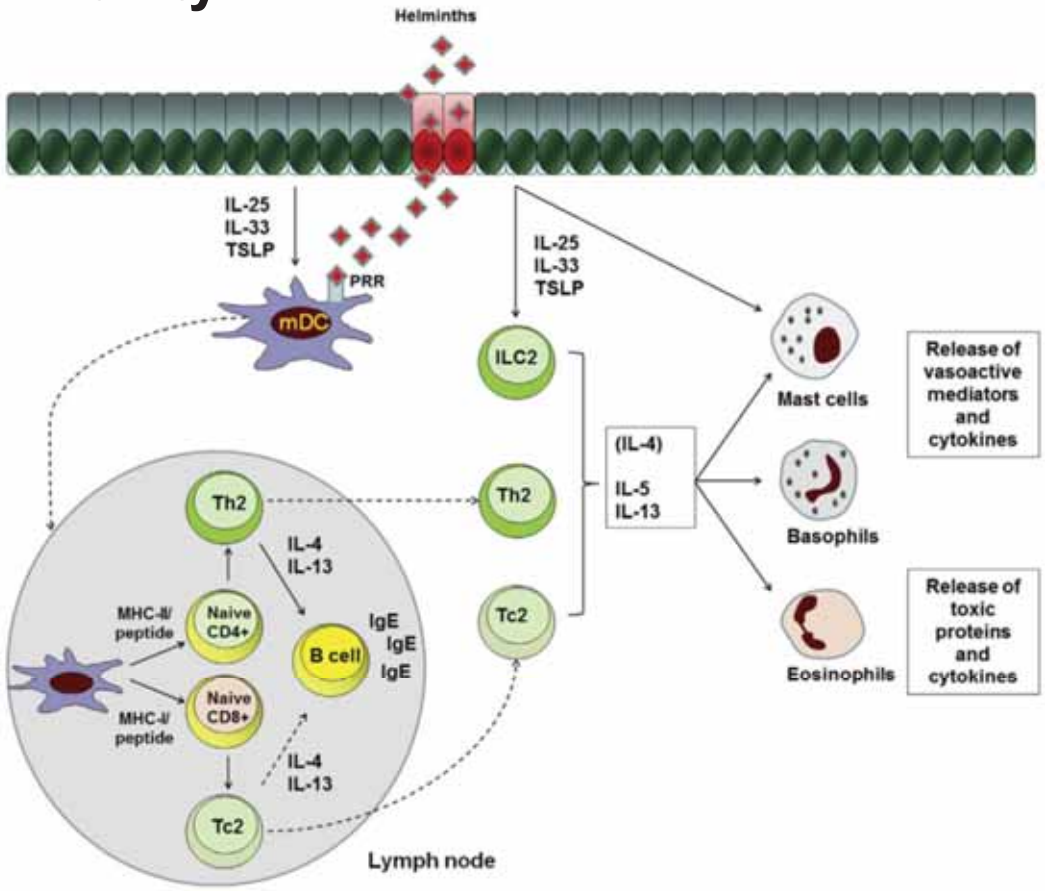


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin *(TSLP)* release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated DCs in the presence of IL-4 induce naive T cells to develop into T_H2 and T_C2 cells producing IL-4, IL-5, and IL-13. IL-4 and IL-13 allow IgE production by B lymphocytes, whereas IL-5 promotes eosinophil recruitment. *mDC*, Myeloid dendritic cell; *PRR*, pathogen recognition receptors.

Type 3/ type 17 Immunity

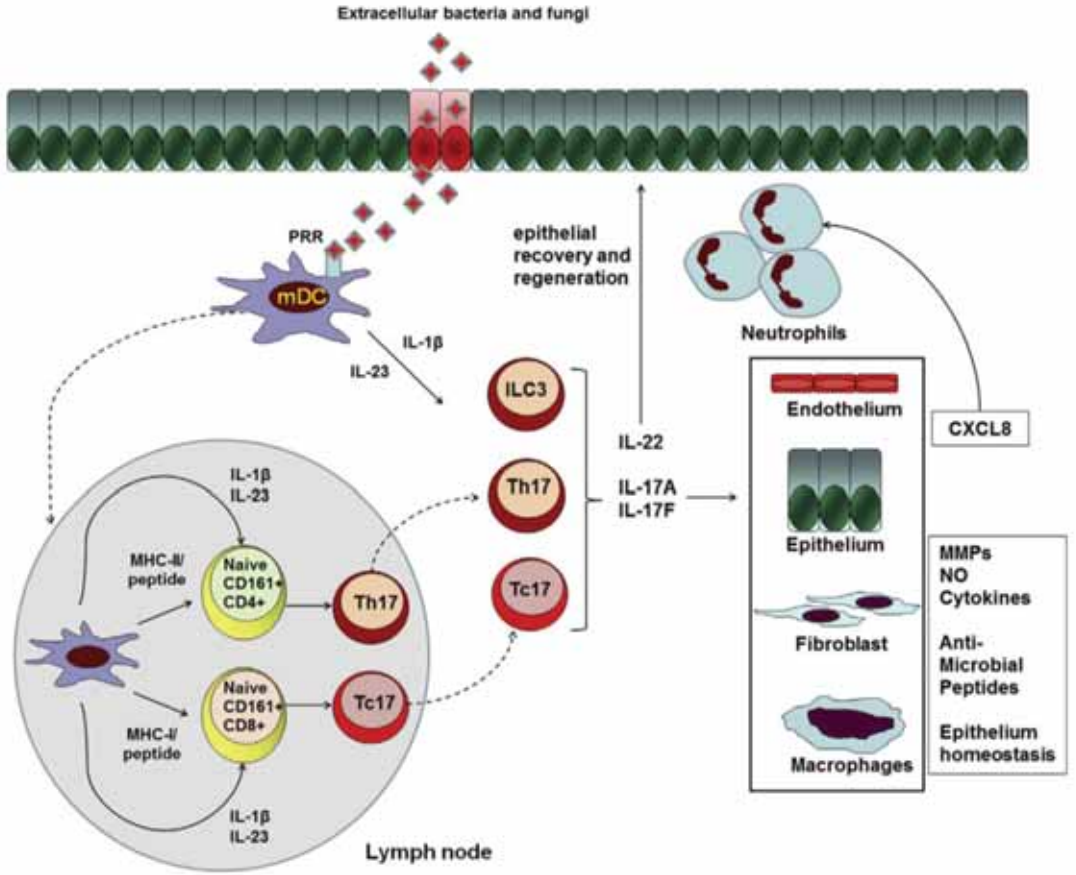
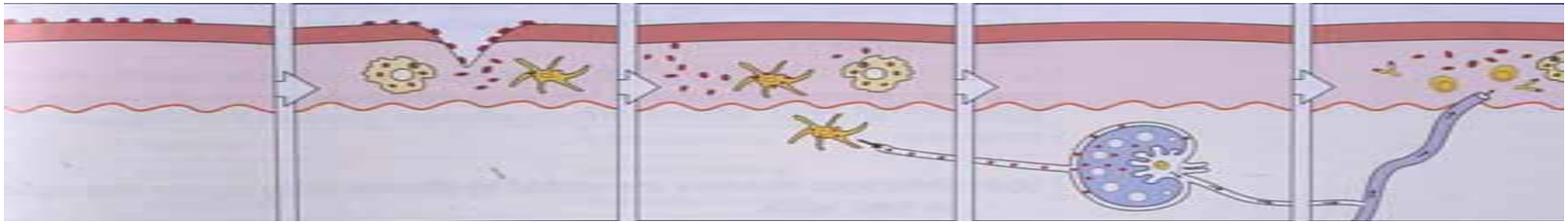
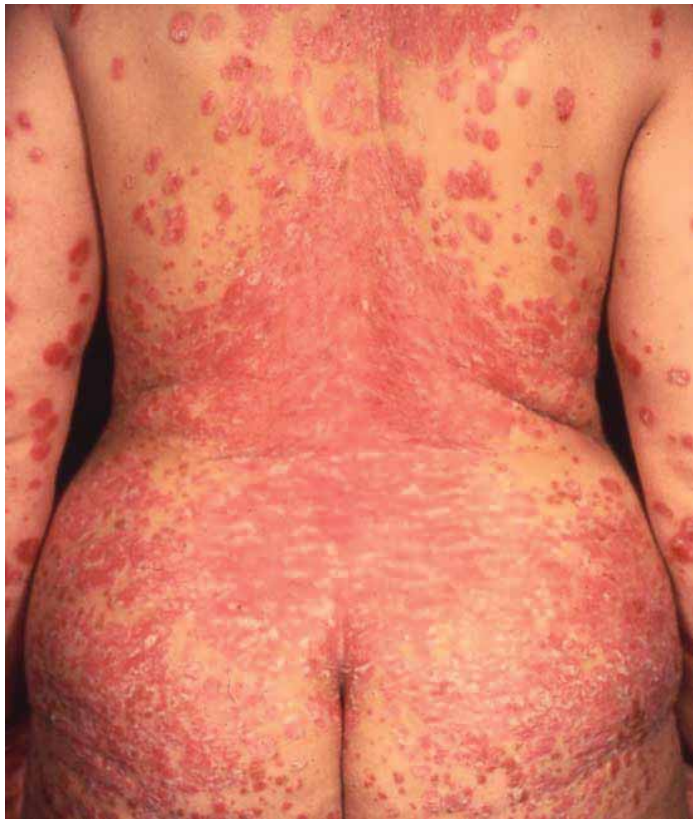


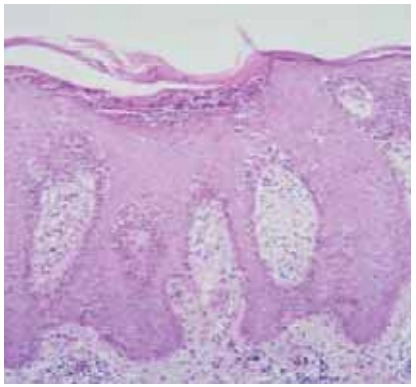
FIG 4. Cells, cytokines, and effectors of type 3 immunity. Extracellular bacteria and fungi induce myeloid dendritic cells *(mDC)* to produce IL-1β and IL-23, which allow T_H17 or T_C17 development from naive $CD161^+$ T cells and trigger cytokine production by ILC3s. IL-17A, IL-17F, and IL-22 from ILC3s and T_H17 and T_C17 cells activate nonimmune and immune cells to produce matrix metallopeptidases *(MMPs)*, nitric oxide *(NO)*, cytokines, antimicrobial peptides, and the neutrophil recruiter CXCL8. IL-22, especially that produced by ILC3s, promotes epithelial proliferation and restrains the gut microflora. *PRR*, Pathogen recognition receptors.

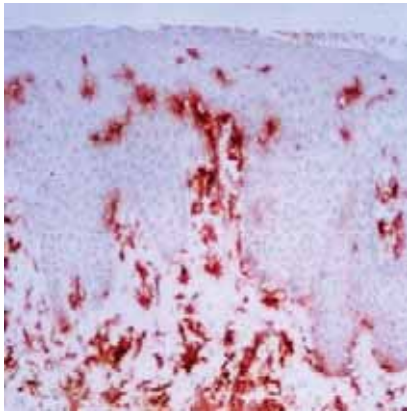
Hypersensibilité de type IV (HS retardée) due à des LT 17
PSORIASIS

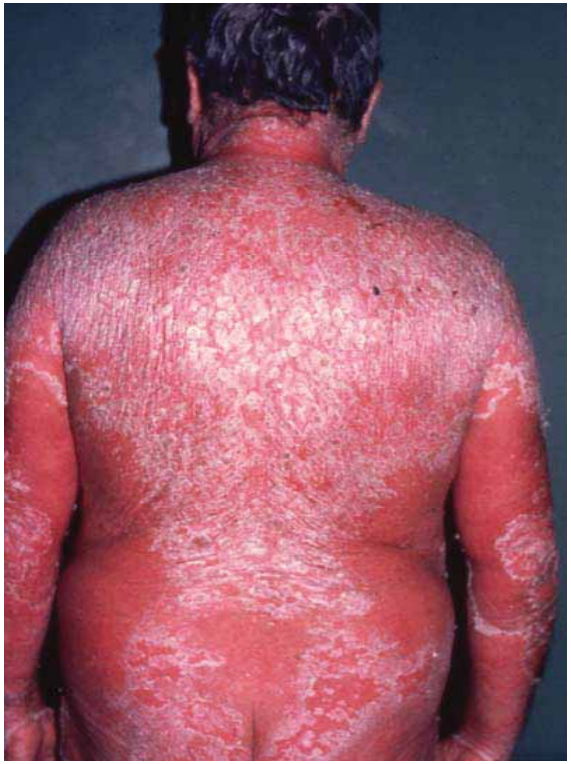
Th17
Type 17





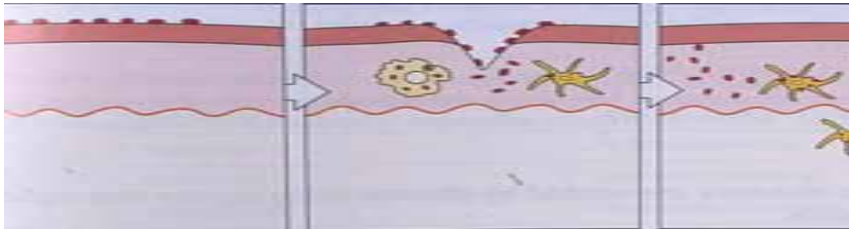


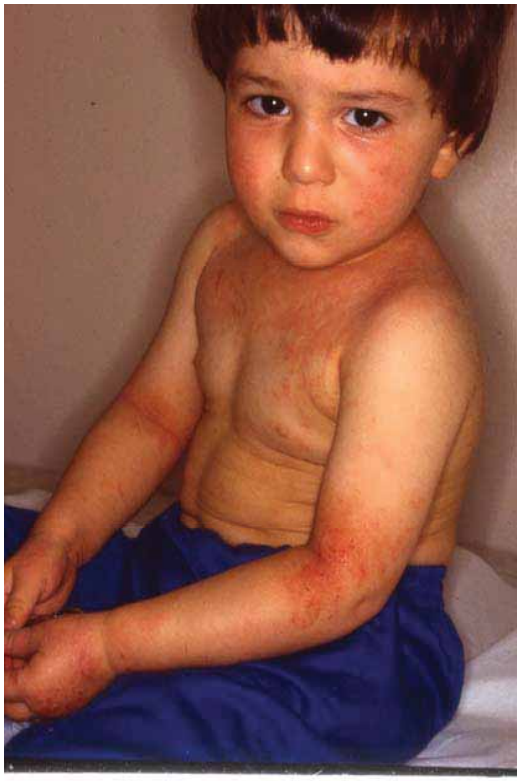


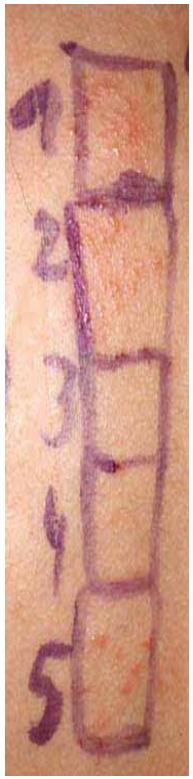


Hypersensibilité de type IV (HS retardée) due à des LT2
DERMATITE ATOPIQUE

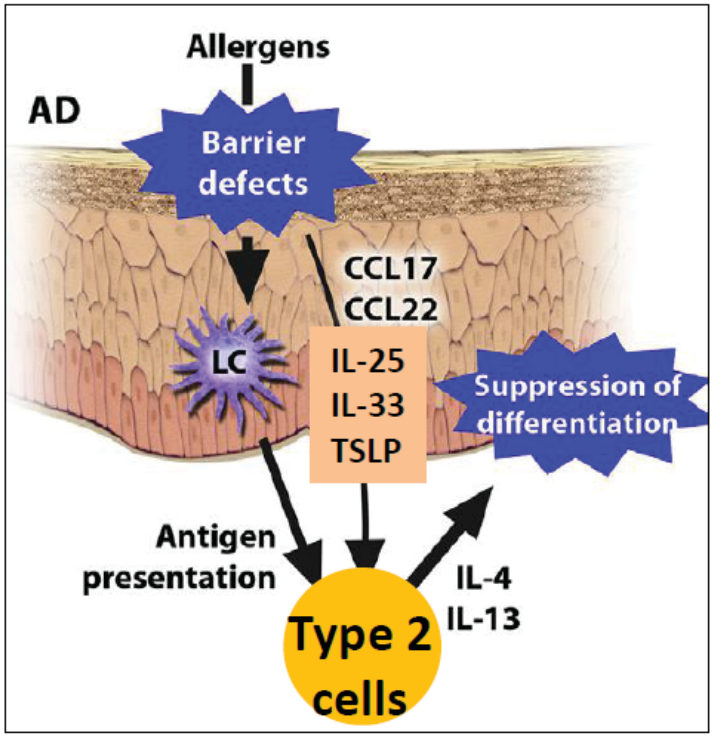
Th2
Type 2







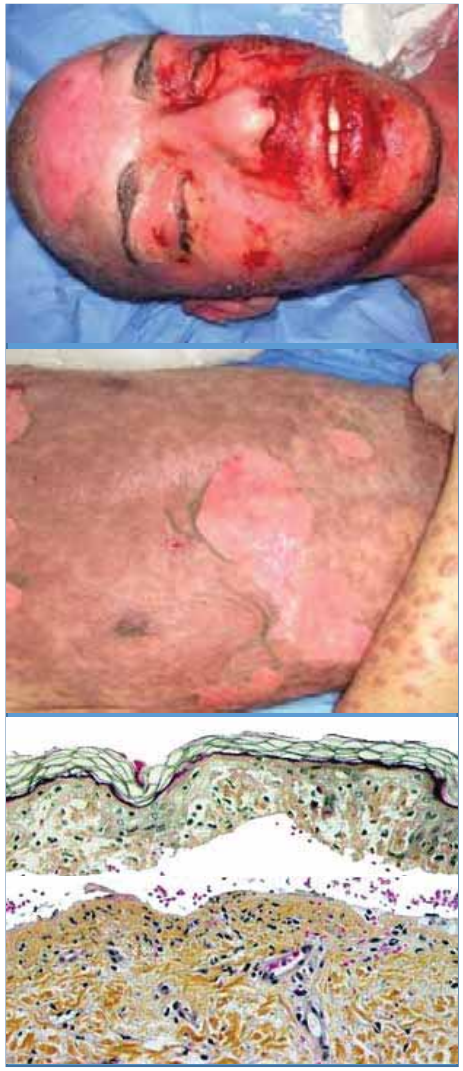
Type 2 phenotype

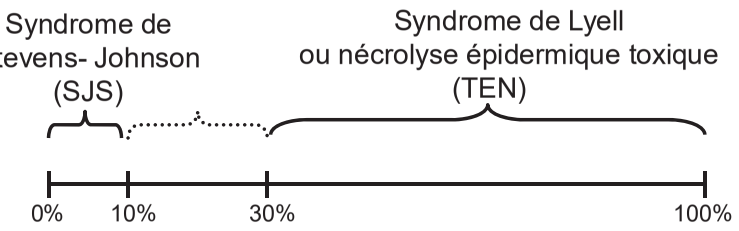


Type 2 inflammation
Type 2 immunity

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

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





- **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, sulfamethoxazole, AINS (oxicams), nevirapine,…
- **Mortalité:** 30-35% (estimée par le SCORTEN)

Exanthèmes médicamenteux et toxidermies sévères

Signes généraux et muqueux imposent l'arrêt immédiat du médicament

Les hypersensibilités retardées aux médicaments peuvent toucher tous les organes mais la peau est certainement celui le plus fréquemment atteint. Elles surviennent quelques heures, jours ou semaines après la prise de médicaments et se manifestent par un exanthème, plus ou moins œdémateux, la survenue de bulles et/ou de décollements cutanés. On parle souvent de « toxidermies » pour décrire ces atteintes cutanées. Le tableau (v. p. 982) donne les caractéristiques des principales toxidermies. Le bilan allergologique qui comprend des tests cutanés (patch-tests et intradermoréactions), des tests biologiques (tests de prolifération et/ou d'activation lymphocytaire) et des tests de réintroduction dans les formes bénignes, permet de différencier hypersensibilité retardée allergique et non allergique et de proposer aux patients des alternatives thérapeutiques.

symptoms) ou une nécrolyse épidermique toxique.

L'évolution est en général favorable en 1 à 4 semaines après arrêt et élimination du médicament, laissant la place à une desquamation sans séquelle.

Tous les médicaments peuvent induire un exanthème, en particulier les antibiotiques et plus spécialement les pénicillines.

Diagnostic différentiel

Dans tous les cas il est important d'éliminer un exanthème infectieux, en particulier viral (infection par le virus de l'immunodéficience humaine [VIH] chez l'adulte jeune ou mononucléose infectieuse),[2] en sachant que l'infection et la fièvre sont des cofacteurs souvent nécessaires au développement d'un exanthème médicamenteux. Cette association infection virale et exanthème aux pénicillines est classique au cours de la primo-infection par le virus d'Epstein-Barr (EBV ou *human herpes virus*-4 [HHV4]).

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BÉNÉDICTE LEBRUN-VIGNES***
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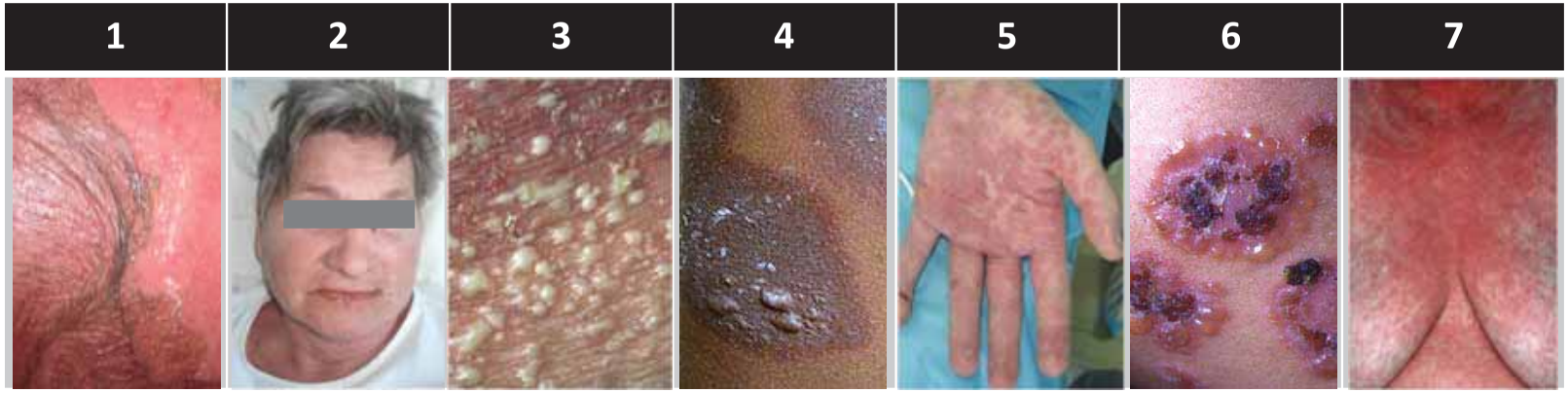
Toxidermies – Drug allergy

Cytotoxic



Severity

Prevalence

SEVERE

1 - TEN: Toxic Epidermal Necrolysis

MODERATE

2 - DRESS: Drug Rash with Eosino &Systemic symptoms

3 - AGEP: Acute Generalized Exanthematous Pustulosis

4 - FDE: Fixed Drug Eruption

5 - Generalized Erythema multiform

6 - Linear IgA Dermatosis

MILD

7 - MPE: Maculo-papular exanthema