Mécanismes immunologiques des allergies

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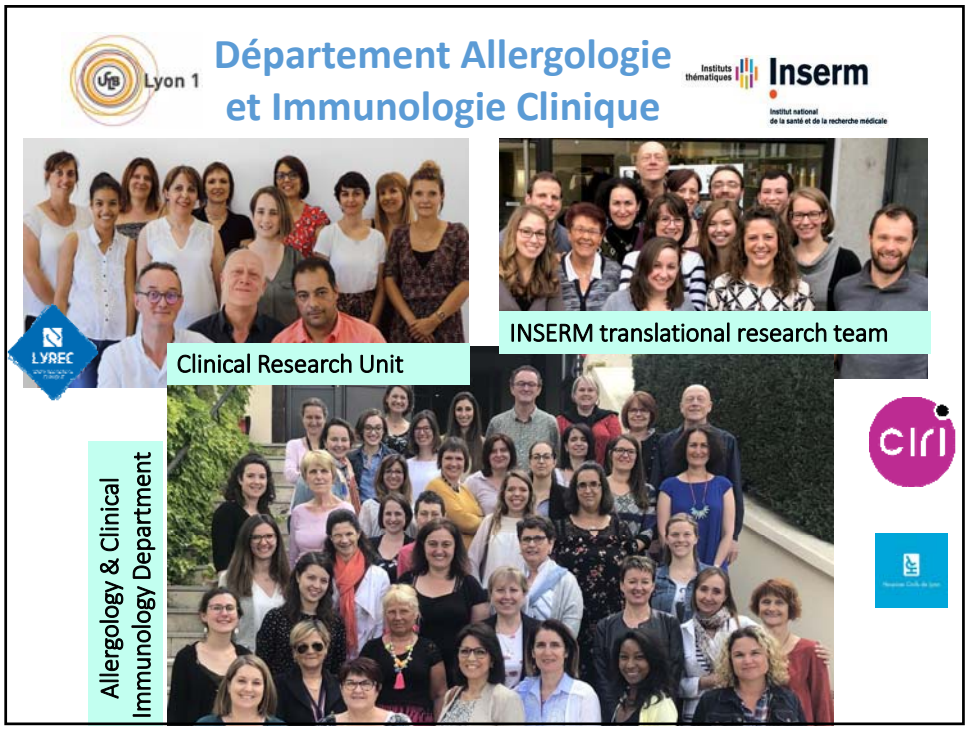


LES HYPERSENSIBILITES

1. Définition immunologique

Maladies dues à des effecteurs de l'immunité spécifique

- M inflammatoires chroniques
- M allergiques
- M autoimmunes

2. Définition allergologique

HS allergique: immunité spécifique (aux Ac et/ou LT)

HS non allergique: immunité innée

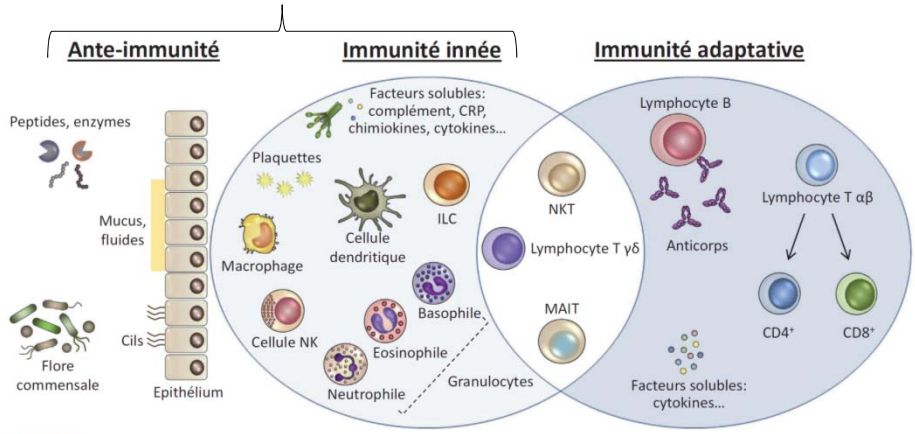


Figure 2.1

Organisation générale du système immunitaire.
Ce schéma illustre l'ensemble des acteurs du système immunitaire, qu'ils fassent partie de l'ante-immunité, de l'immunité innée et/ou adaptative, qu'ils soient de type moléculaire, microbien ou cellulaire.

Hypersensibilité (HS) aux médicaments

HS Allergique	HS Non Allergique
Rare (5%)	Fréquente (95%)

[redacted] Danielle
7 Cote Carmagnac
69
tel [redacted]

le 11 Mai 2013

Docteur Nicolas,

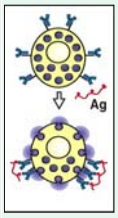
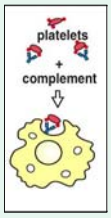
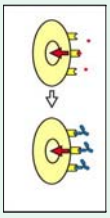
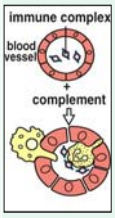
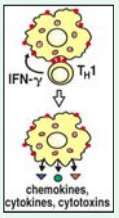
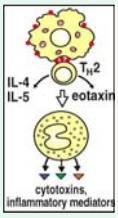
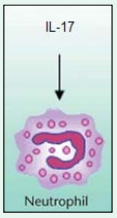
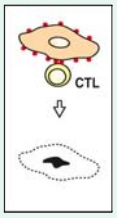
Mon fils Yves a rendez-vous le 25 Juin pour des tests. Il est né le 8 janvier 1983, et a fait un urticaire géant au Clamoxyl en 1986, donc on a évité cet antibiotique. Le 22 Décembre dernier, il a fait un oedème de Quincke,

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

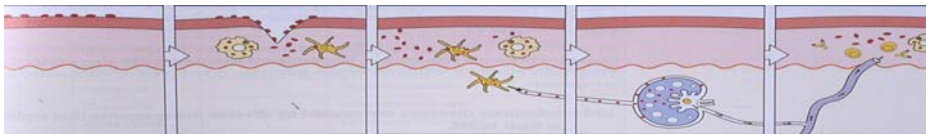
n'avait pris ni clamoxyl, ni érythrogel, ni aucun médicament, et il a refait un oédème de Quincke. J'ai donc noté qu'il avait mangé : du nougat chinois, concombres, tomates, betteraves, magret de canard, sauce au poivre vert, mangues, litchis, comté et pâtes. Il y avait aussi un très gros bouquet de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

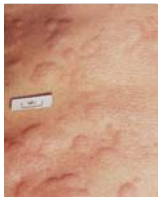
Désolé d'avoir dû changer le rendez-

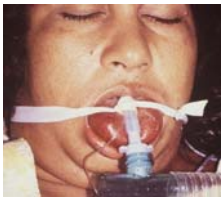
Classification des hypersensibilités immunologiques
Maladies autoimmunes et allergiques

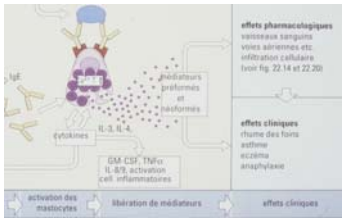
Type I	Type II		Type III	Type IV			
IgE	IgG		IgG	CD4 Th1	CD4 Th2	CD4 Th17	CD8 cytotox.
Antigènes solubles	Ag cellulaires ou matriciels	Récepteur cellulaire	Ag solubles	Ag soluble	Ag soluble		Ag cellulaire
Mastocyte	Complément, Phagocytes, NK	Ac altère la signalisation	Complément, Phagocytes	Macrophage	Eosinophiles	Neutrophiles	Cytotoxicité
							
Rhinite all. Asthme all. Anaphylaxie	Réaction transfus. Anémie hémolytique	Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	(IDR tuberculine) Rejet de greffes Arthrite, Diabète	Asthme all. chr. Rhinite all. chr.	Dommages tissulaires	°Rejet de greffes °Diabète type I
Urticaire de contact	Pemphigus Pemphigoide	Urticaire chronique Pemphigus	Vascularites immunoall.	Psoriasis	Dermatite atopique	Polyarthrite rhumatoïde, Sclérose en plaques, Maladie de Crohn, Infections	Eczéma all.de contact Vitiligo, Pelade
Choc anaphylactique	Cytopénies médicamenteuses		Vascularites	Toxidermies	DRESS		Lyell/SJS

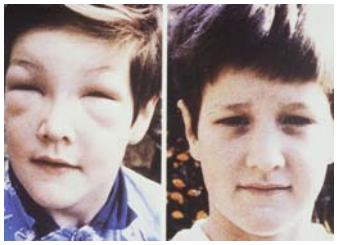
Hypersensibilité de type I due à des IgE spécifiques
ANAPHYLAXIE

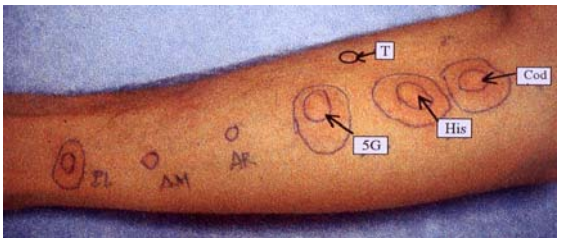


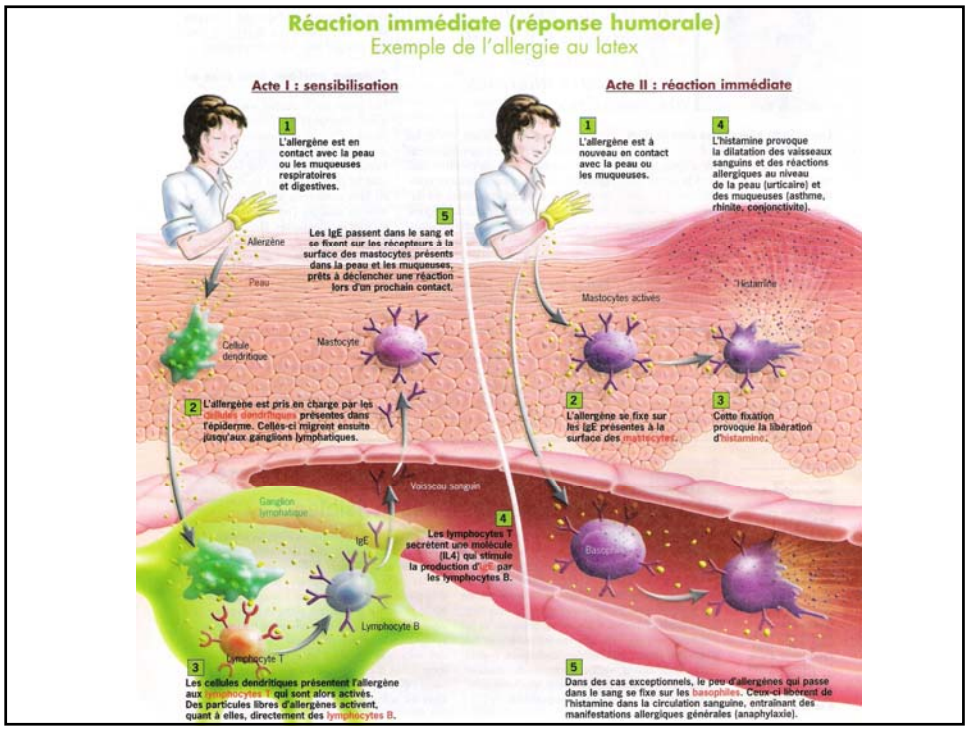




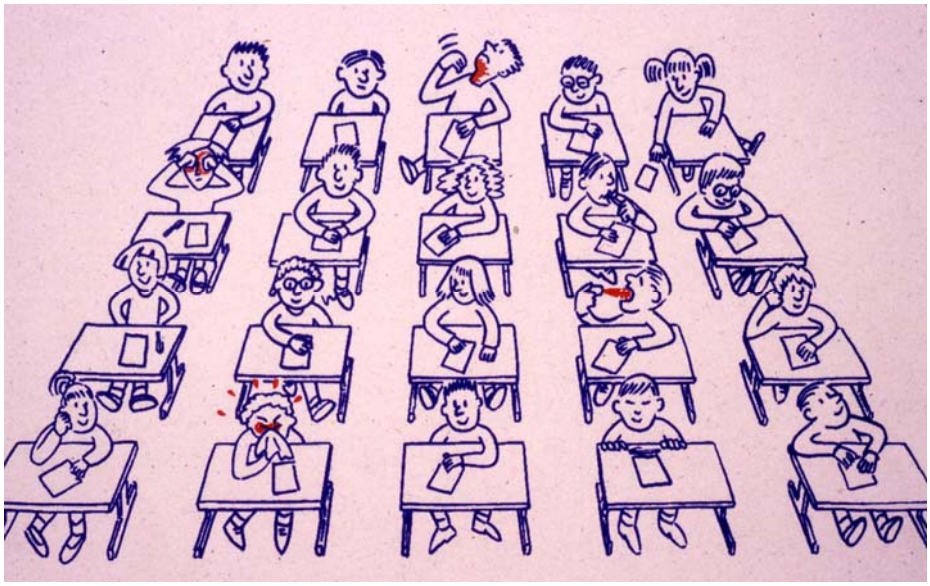




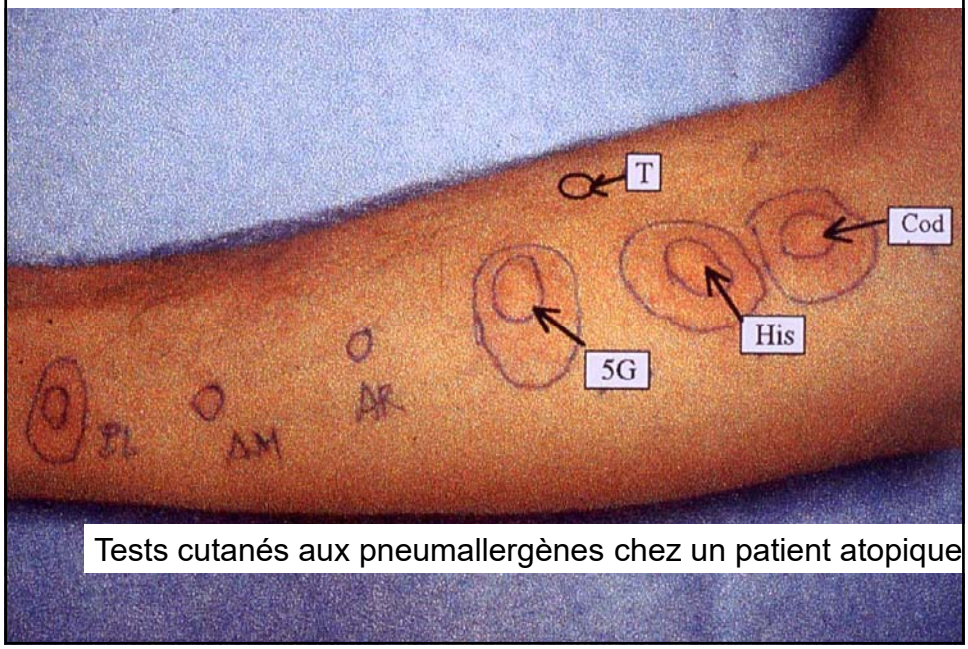




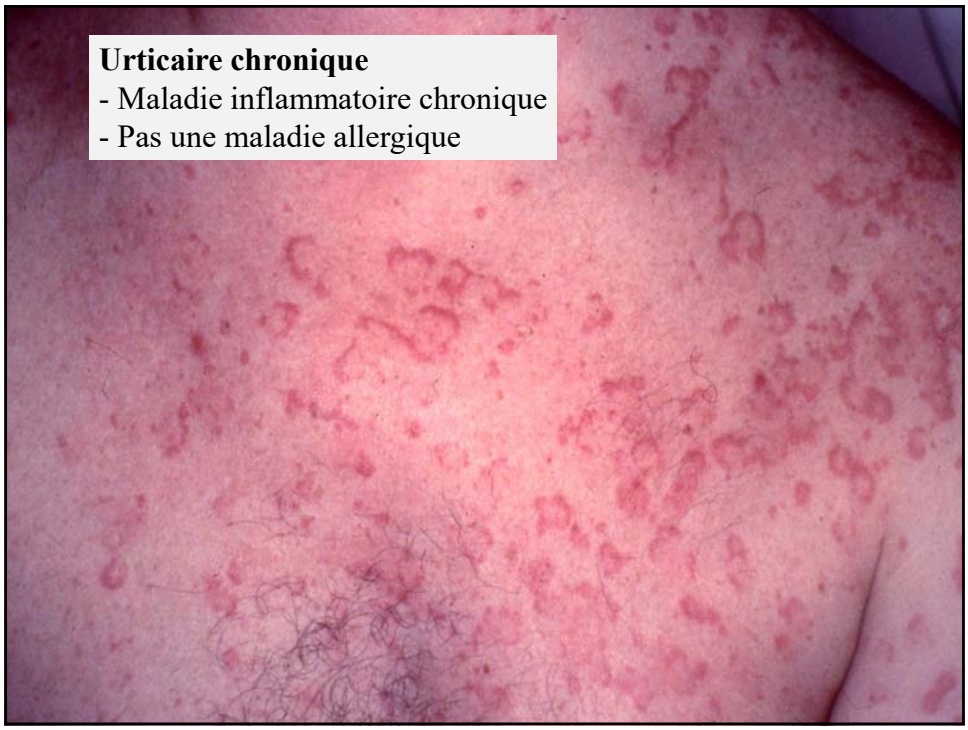
Maladies fréquentes : maladies atopiques



HSI allergique et non allergique

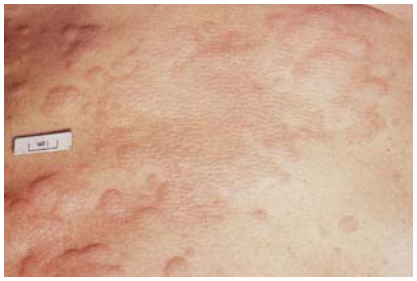


Tests cutanés aux pneumallergènes chez un patient atopique

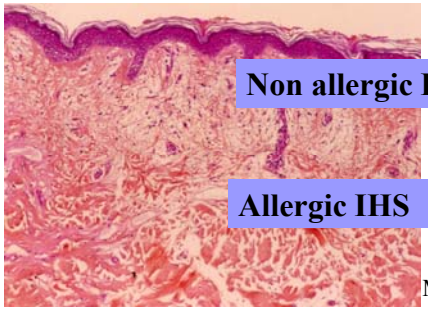


Urticaire chronique
- Maladie inflammatoire chronique
- Pas une maladie allergique

TYPE I HYPERSENSITIVITY

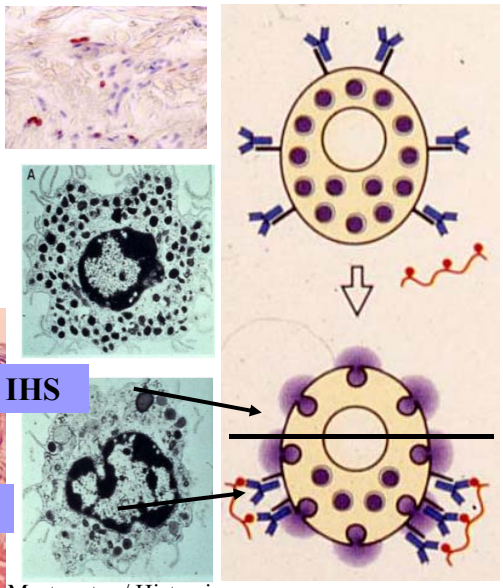


Œdème du derme / Vaisseaux



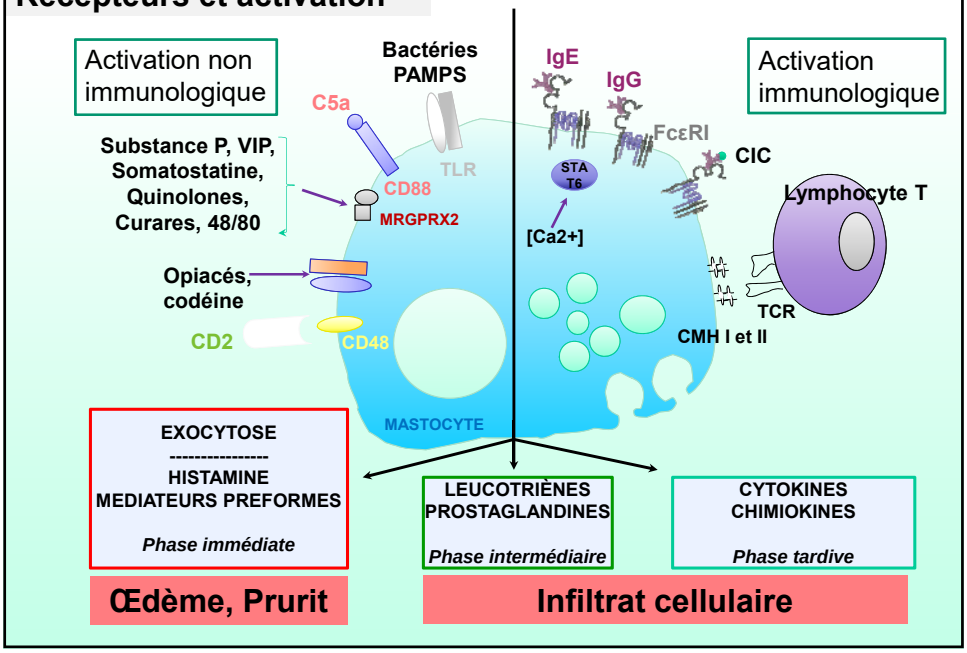
Non allergic IHS

Allergic IHS



Mastocytes / Histamine

MASTOCYTES
Récepteurs et activation



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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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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

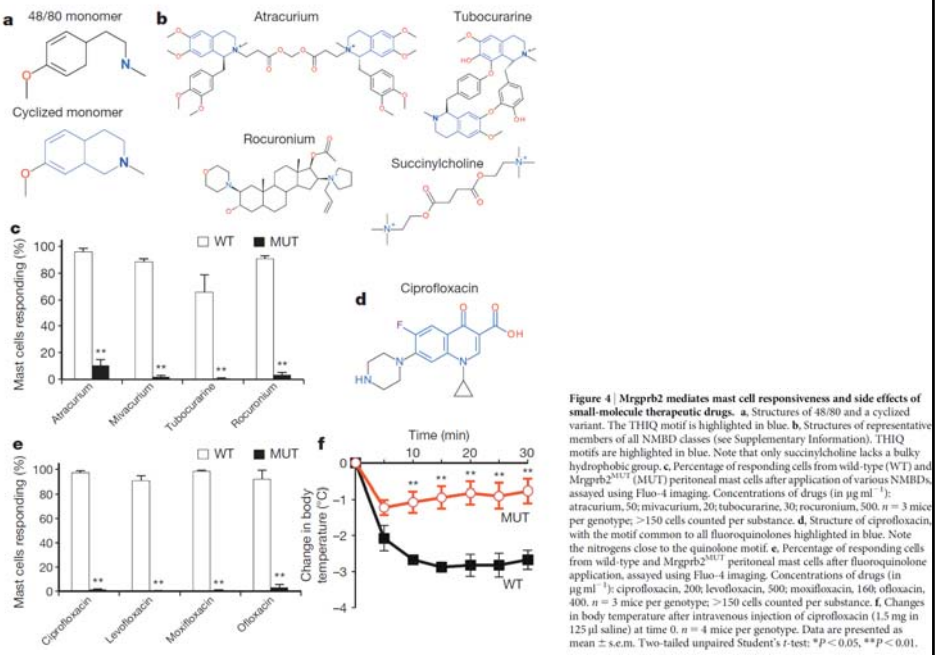
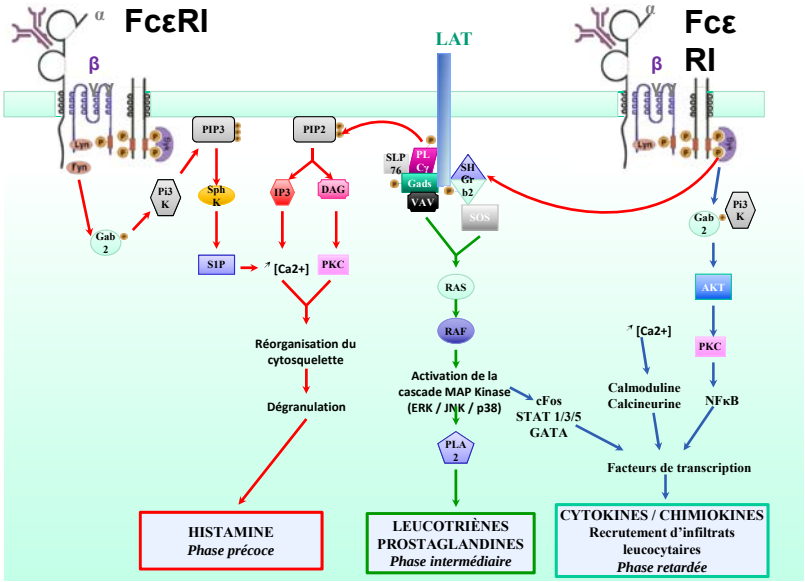
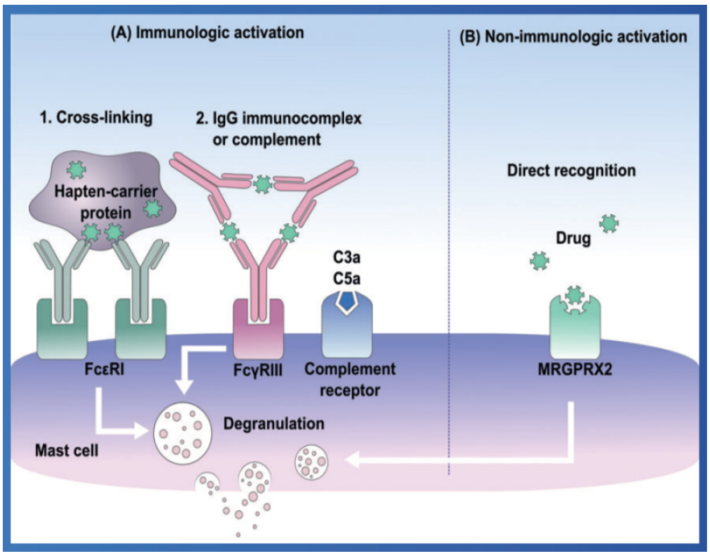


Figure 4 | Mrgprb2 mediates mast cell responsiveness and side effects of small-molecule therapeutic drugs. **a**, Structures of 48/80 and a cyclized variant. The THIQ motif is highlighted in blue. **b**, Structures of representative members of all NMBD classes (see Supplementary Information). THIQ motifs 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 μg 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 μg 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: $^{*}P < 0.05$, $^{**}P < 0.01$.

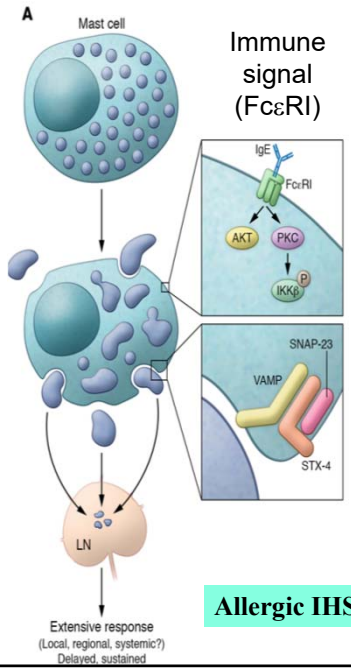
MASTOCYTES
Voies d'activation et signalisation



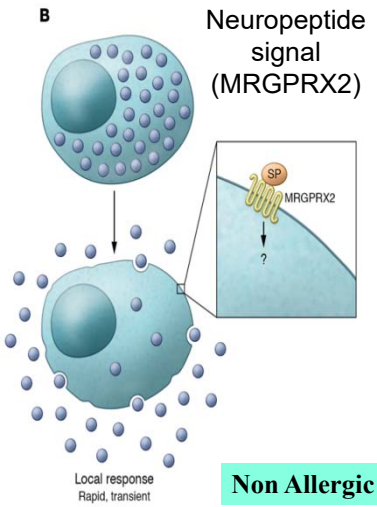
MASTOCYTES
Récepteurs et activation



Two fundamental degranulation pathways in mast cells



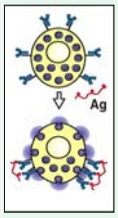
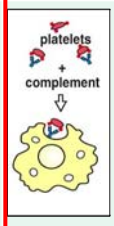
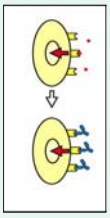
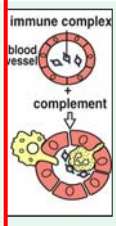
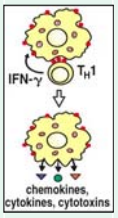
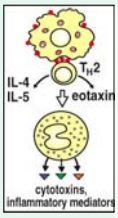
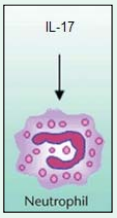
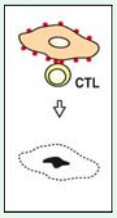
Allergic IHS



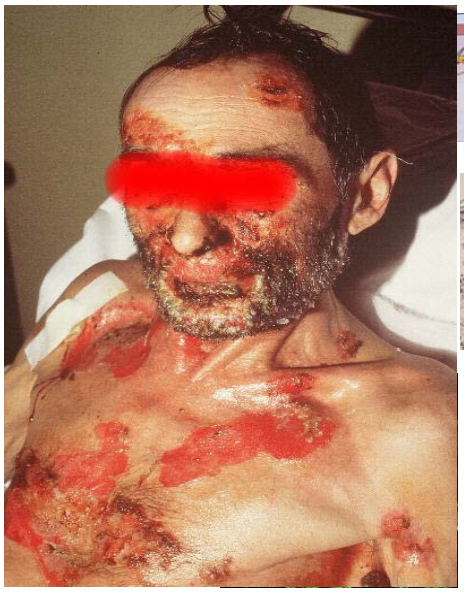
Non Allergic IHS

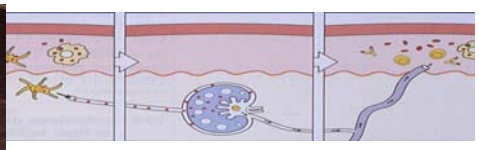
*Gaudenzio et al. **J Clin Invest** 2016*

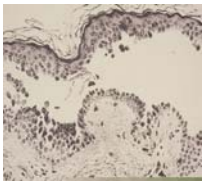
Classification des hypersensibilités immunologiques
Maladies autoimmunes et allergiques

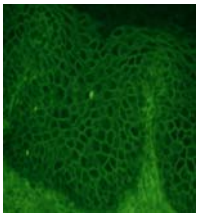
Type I	Type II		Type III	Type IV			
IgE	IgG		IgG	CD4 Th1	CD4 Th2	CD4 Th17	CD8 cytotox.
Antigènes solubles	Ag cellulaires ou matriciels	Récepteur cellulaire	Ag solubles	Ag soluble	Ag soluble		Ag cellulaire
Mastocyte	Complément, Phagocytes, NK	Ac altère la signalisation	Complément, Phagocytes	Macrophage	Eosinophiles	Neutrophiles	Cytotoxicité
							
Rhinite all. Asthme all. Anaphylaxie	Réaction transfus. Anémie hémolytique	Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	(IDR tuberculine) Rejet de greffes Arthrite, Diabète	Asthme all. chr. Rhinite all. chr.	Dommages tissulaires	°Rejet de greffes °Diabète type I
Urticaire de contact	Pemphigus Pemphigoide	Urticaire chronique Pemphigus	Vascularites immunoall.	Psoriasis	Dermatite atopique	Polyarthrite rhumatoïde, Sclérose en plaques, Maladie de Crohn, Infections	Eczéma all.de contact Vitiligo, Pelade
Choc anaphylactique	Cytopénies médicamenteuses		Vascularites	Toxidermies	DRESS		Lyell/SJS

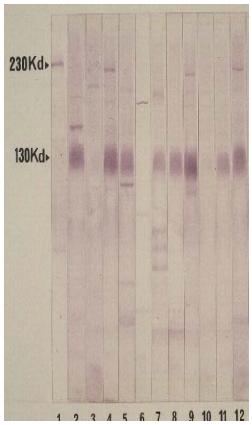
Hypersensibilité de type II due à des IgG spécifiques
PEMPHIGUS











Classification des hypersensibilités immunologiques
Maladies autoimmunes et allergiques

Type I	Type II		Type III	Type IV			
IgE	IgG		IgG	CD4 Th1	CD4 Th2	CD4 Th17	CD8 cytotox.
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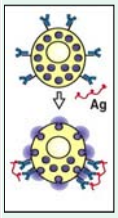
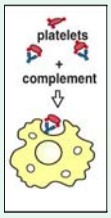
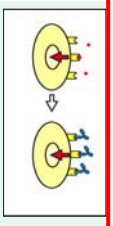
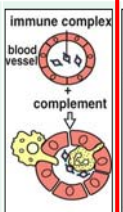
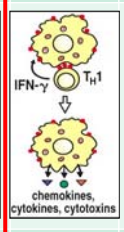
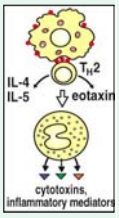
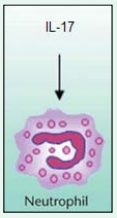
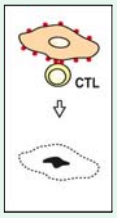
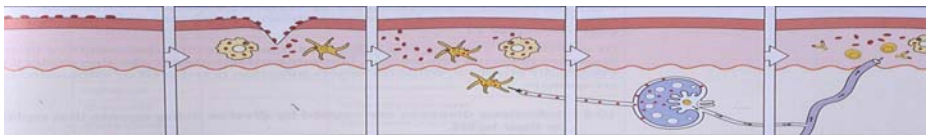
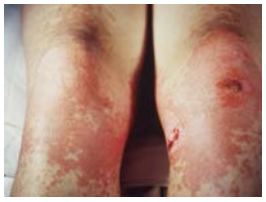
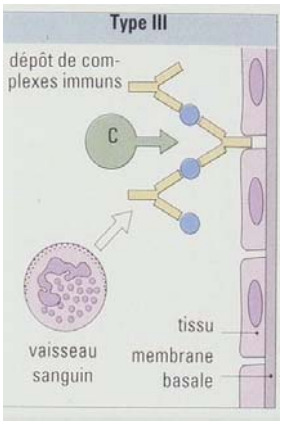
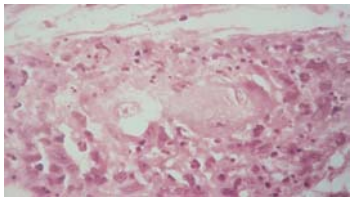
							
Rhinite all. Asthme all. Anaphylaxie	Réaction transfus. Anémie hémolytique	Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	(IDR tuberculine) Rejet de greffes Arthrite, Diabète	Asthme all. chr. Rhinite all. chr.	Dommages tissulaires	°Rejet de greffes °Diabète type I
Urticaire de contact	Pemphigus Pemphigoide	Urticaire chronique Pemphigus	Vascularites immunoall.	Psoriasis	Dermatite atopique	Polyarthrite rhumatoïde, Sclérose en plaques, Maladie de Crohn, Infections	Eczéma all.de contact Vitiligo, Pelade
Choc anaphylactique	Cytopénies médicamenteuses		Vascularites	Toxidermies	DRESS		Lyell/SJS

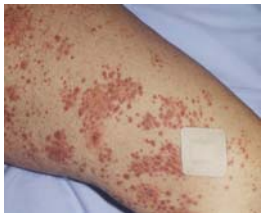
Hypersensibilité de type III due à des complexes immuns
VASCULITES – PURPURA RHUMATOIDE

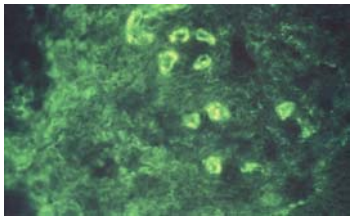












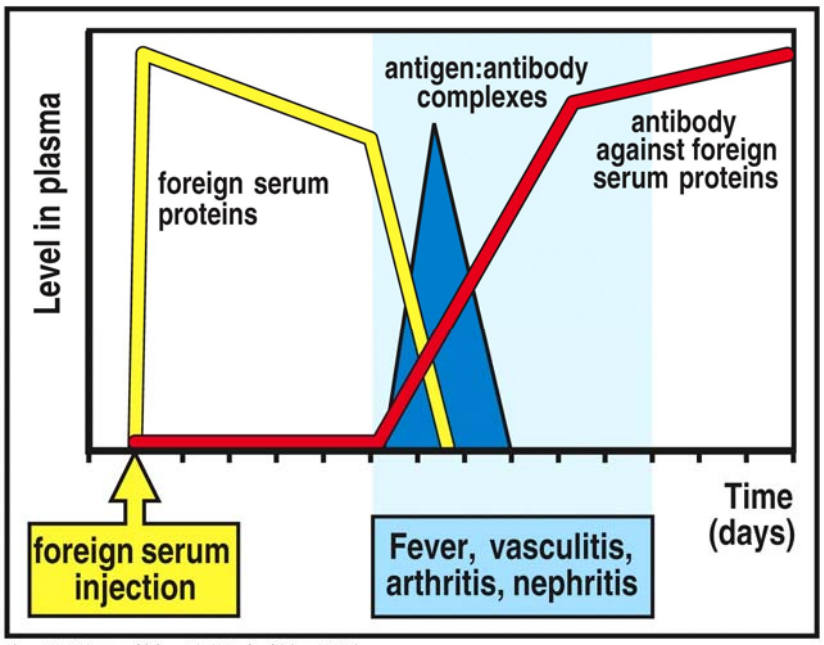


Figure 12-23 Immunobiology, 6/e. (© Garland Science 2005)

Journal of Cutaneous Pathology

Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern

Cuong V. Nguyen and Daniel D. Miller
Department of Dermatology, University of Minnesota, Minneapolis, MN, USA

The diagnosis of serum sickness-like reaction (SSLR) is typically based on clinical findings. Histopathologic examination is often deferred, as these eruptions commonly present in young children, and often to primary care providers. A PubMed literature search revealed only five existing cases of SSLR which describe cutaneous histopathologic features. We report two cases of SSLR, one each to bupropion and orlistat. Skin biopsy findings in both cases showed a neutrophil-predominant urticarial pattern resembling neutrophilic urticaria or neutrophilic urticarial dermatosis. We also provide a summary of the histopathologic findings that can help support a diagnosis of SSLR.

Nguyen & Miller

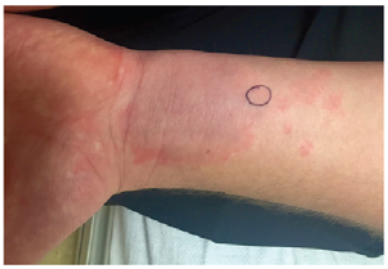


Fig. 1. Urticarial, annular plaques with dusky centers on the ventral forearm.

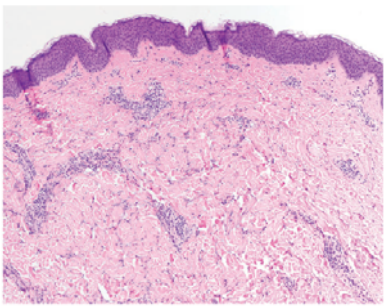


Fig. 2. Superficial and mid-perivascular and interstitial infiltrate (hematoxylin and eosin stain, ×100 magnification).

Classification des hypersensibilités immunologiques
Maladies autoimmunes et allergiques

Type I	Type II		Type III	Type IV			
IgE	IgG		IgG	CD4 Th1	CD4 Th2	CD4 Th17	CD8 cytotox.
Antigènes solubles	Ag cellulaires ou matriciels	Récepteur cellulaire	Ag solubles	Ag soluble	Ag soluble		Ag cellulaire
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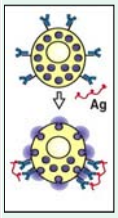	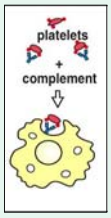	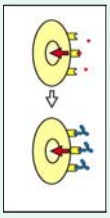	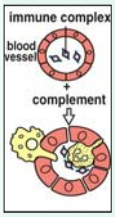	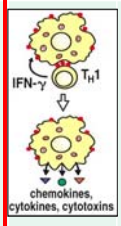	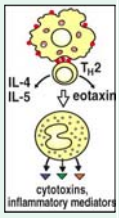	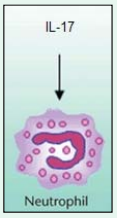	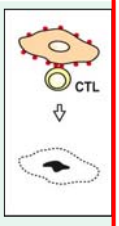
Rhinite all. Asthme all. Anaphylaxie	Réaction transfus. Anémie hémolytique	Thyroidite Myasthénie	Maladie sérique Lupus érythémateux	(IDR tuberculine) Rejet de greffes Arthrite, Diabète	Asthme all. chr. Rhinite all. chr.	Dommages tissulaires	°Rejet de greffes °Diabète type I
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Choc anaphylactique	Cytopénies médicamenteuses		Vascularites	Toxidermies	DRESS		Lyell/SJS

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,

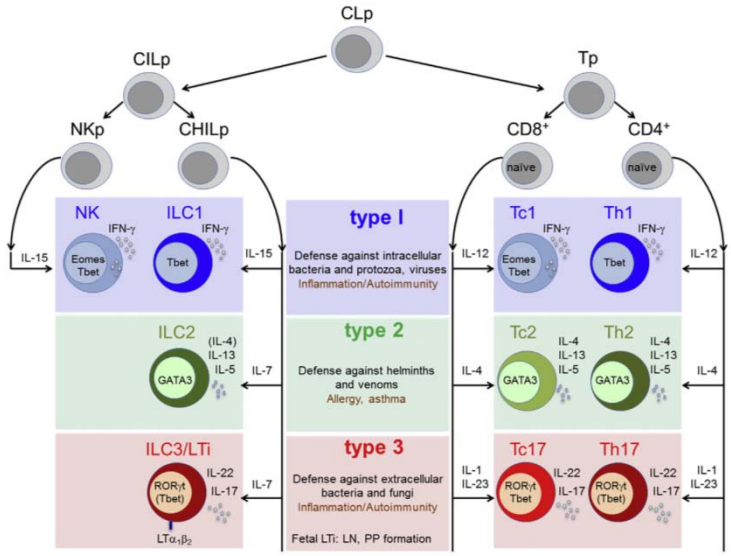


FIG 1. The 3 major types of innate and adaptive cell-mediated effector immunity. Type 1 immunity is composed of T-bet$^+$ IFN-γ–producing CD4$^+$ T_H1 cells and ILC1s and T-bet$^+$Eomes$^+$CD8$^+$ T_C1 and NK cells. Type 2 immunity is composed of GATA-3$^+$CD4$^+$ T_H2 cells, CD8$^+$ T_C2 cells, and 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.

Type 1 Immunity

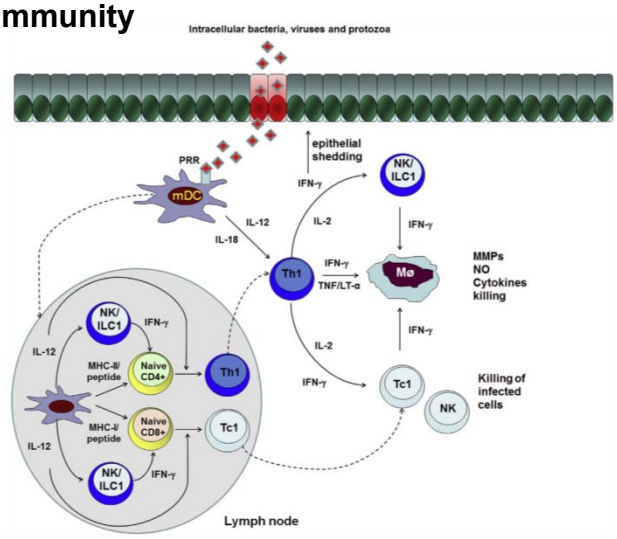


FIG 2. Cells, cytokines, and effectors of type 1 immunity. Intracellular microbes interacting with pathogen recognition receptors *(PRR)* on DCs in the presence of DC-derived IL-12 and IL-18 and of NK/ILC1-derived IFN-γ induce T_H1 or T_C1 development from naive T cells. T_C1 and NK cells kill virus-infected 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

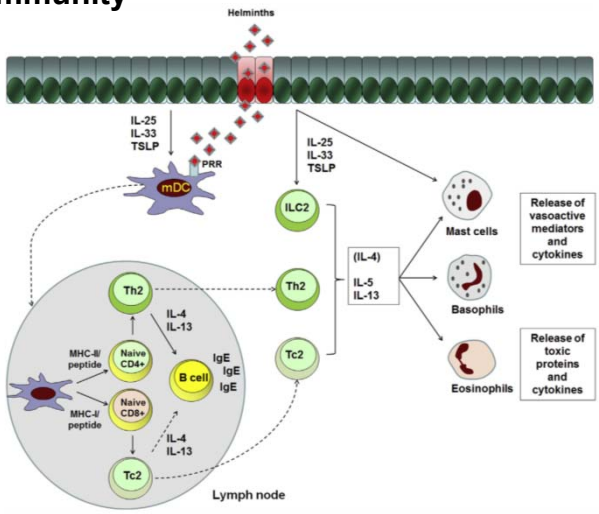


FIG 3. Cells, cytokines, and effectors of type 2 immunity. Helminths induce IL-25, IL-33, and thymic stromal lymphopoietin *(TSLP)* release by epithelial cells, which might directly activate mast cells, eosinophils, basophils, and ILC2s to produce IL-5, IL-13, and perhaps small amounts of IL-4. Activated 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

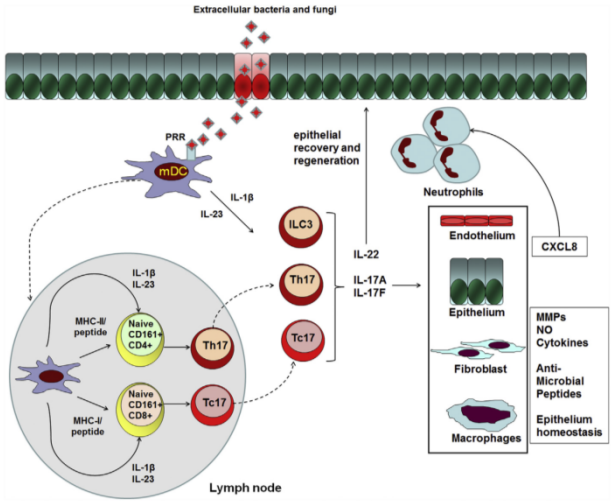
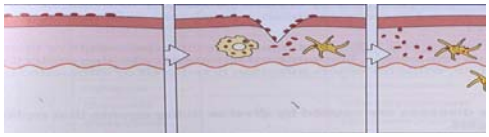
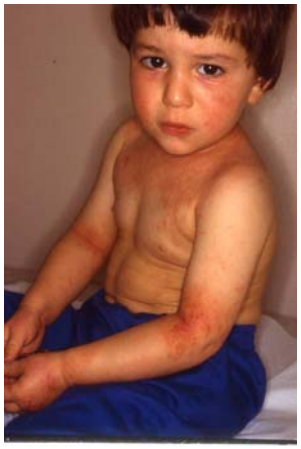
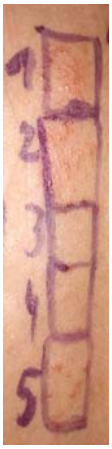


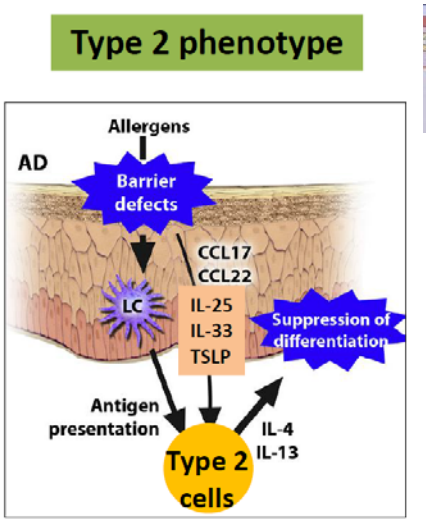
FIG 4. Cells, cytokines, and effectors of type 3 immunity. Extracellular bacteria and fungi induce myeloid dendritic cells *(mDC)* to produce IL-1β and IL-23, which allow T_H17 or T_C17 development from naive $CD161^+$ T cells and trigger cytokine production by ILC3s. IL-17A, IL-17F, and IL-22 from ILC3s 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.

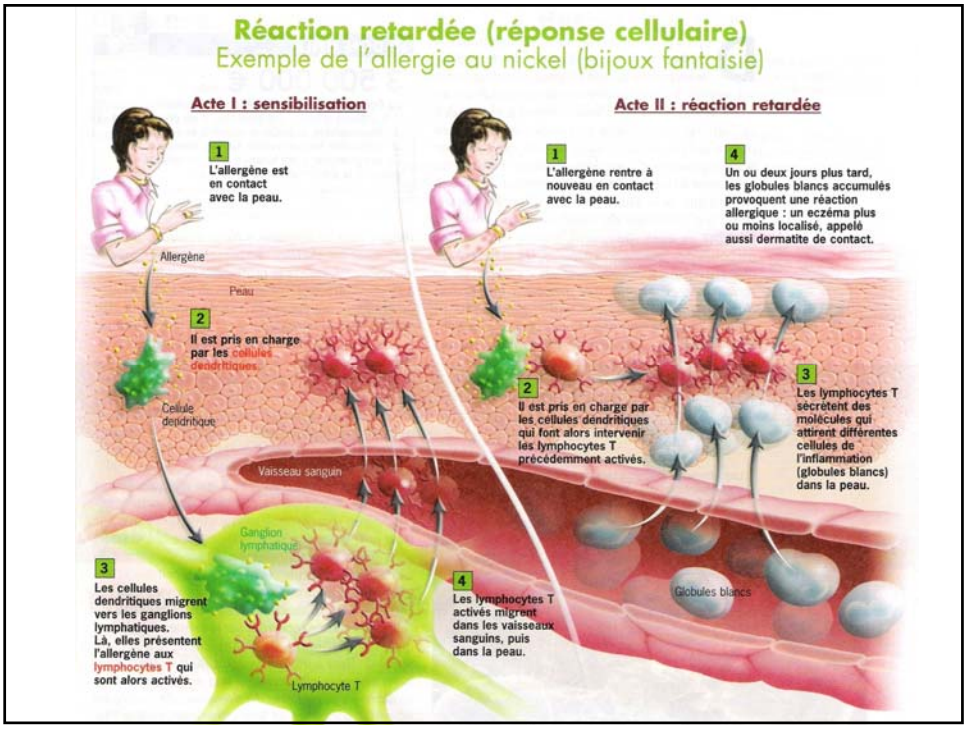
Hypersensibilité de type IV (HS retardée) due à des LT
DERMATITE ATOPIQUE



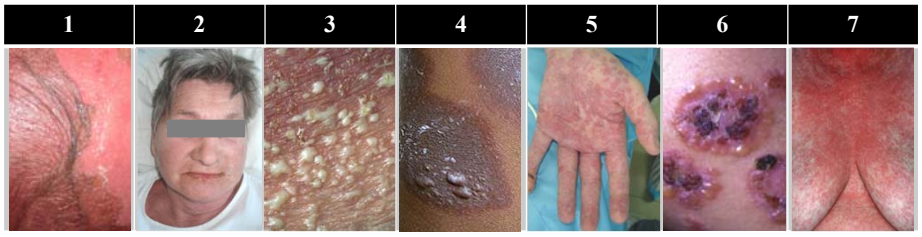








Toxidermies



Severity

Prevalence

SEVERE

1 - TEN: Toxic Epidermal Necrolysis

MODERATE

2 - DRESS: Drug Rash with Eosino &Systemic symptoms

3 - AGEP: Acute Generalized Exanthematous Pustulosis

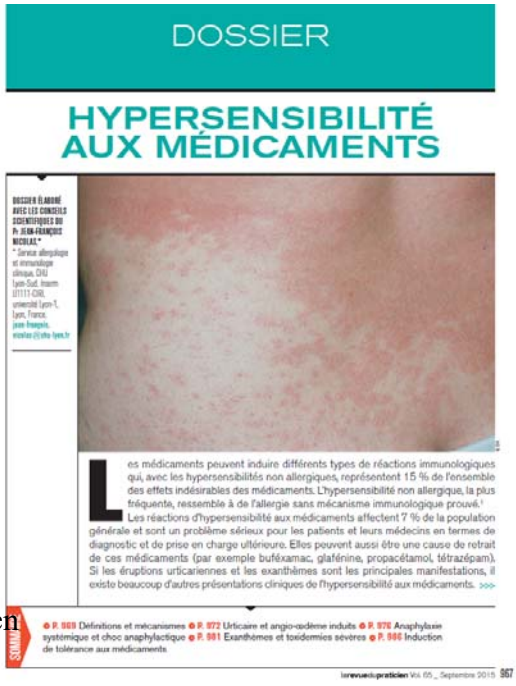
4 - FDE: Fixed Drug Eruption

5 - Generalized Erythema multiform

6 - Linear IgA Dermatosis

MILD

7 - MPE: Maculo-papular exanthema



DOSSIER

HYPERSENSIBILITÉ AUX MÉDICAMENTS

Les médicaments peuvent induire différents types de réactions immunologiques qui, avec les hypersensibilités non allergiques, représentent 15 % de l'ensemble des effets indésirables des médicaments. L'hypersensibilité non allergique, la plus fréquente, ressemble à de l'allergie sans mécanisme immunologique prouvé.[1] Les réactions d'hypersensibilité aux médicaments affectent 7 % de la population générale et sont un problème sérieux pour les patients et leurs médecins en termes de diagnostic et de prise en charge ultérieure. Elles peuvent aussi être une cause de retrait de ces médicaments (par exemple buféxamac, glafénine, propacétamol, tétrazépam). Si les éruptions urticariennes et les exanthèmes sont les principales manifestations, il existe beaucoup d'autres présentations cliniques de l'hypersensibilité aux médicaments. >>>

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