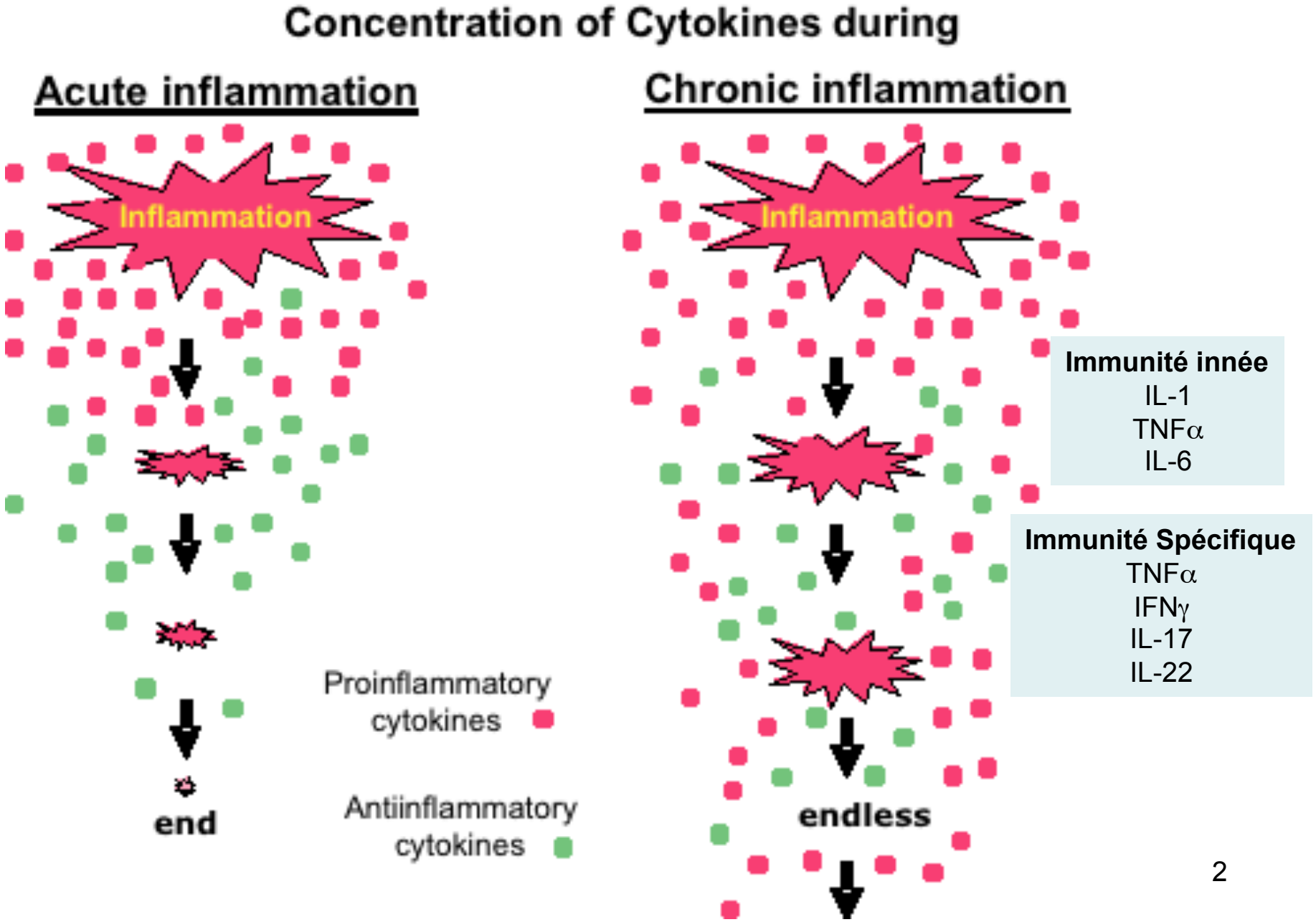
LES MALADIES INFLAMMATOIRES

Classification et physiopathologie

Jean-François NICOLAS, Frédéric BERARD

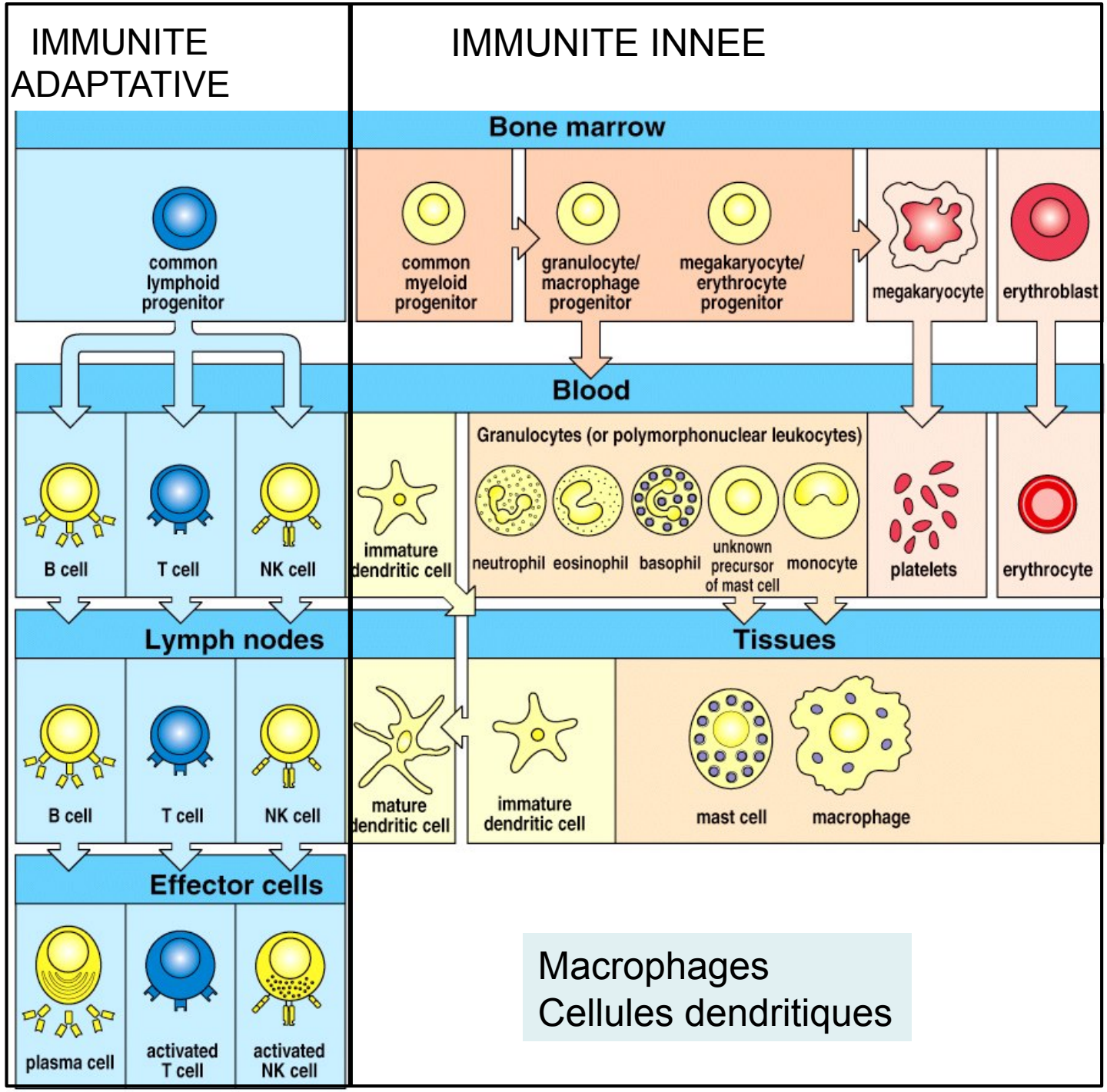
Université Lyon1, INSERM U 1111-CIRI,
CHU Lyon-Sud

Inflammation aigüe versus inflammation chronique



Immunité innée
IL-1
TNFα
IL-6

Immunité Spécifique
TNFα
IFNγ
IL-17
IL-22


IMMUNITE ADAPTATIVE
IMMUNITE INNEE
Bone marrow
common lymphoid progenitor
common myeloid progenitor
granulocyte/ macrophage progenitor
megakaryocyte/ erythrocyte progenitor
megakaryocyte
erythroblast
Blood
Granulocytes (or polymorphonuclear leukocytes)
B cell
T cell
NK cell
immature dendritic cell
neutrophil
eosinophil
basophil
unknown precursor of mast cell
monocyte
platelets
erythrocyte
Lymph nodes
Tissues
B cell
T cell
NK cell
mature dendritic cell
immature dendritic cell
mast cell
macrophage
Effector cells
plasma cell
activated T cell
activated NK cell
Macrophages
Cellules dendritiques

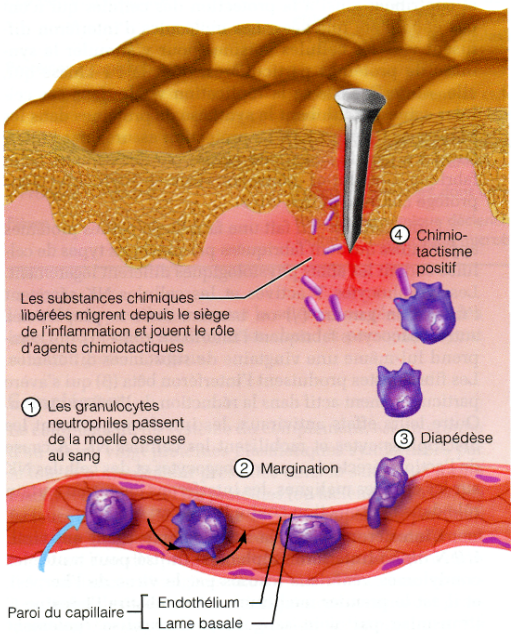
PLAN

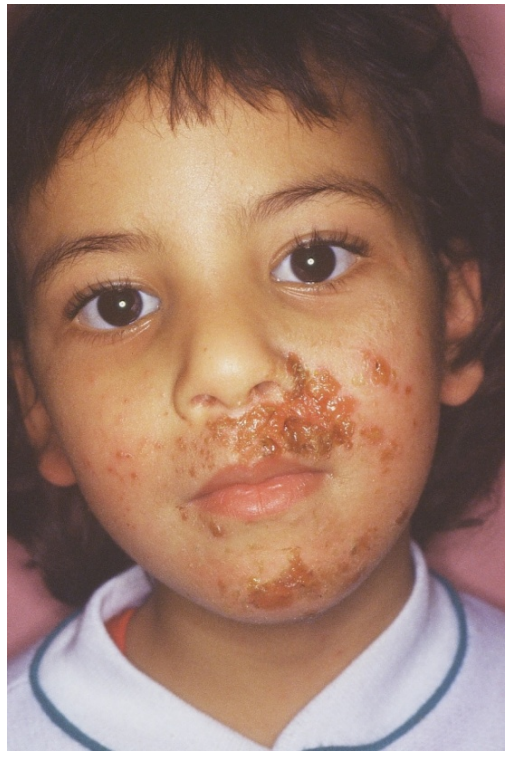
- **Inflammation** = mise en jeu de l'immunité innée et adaptative
  - Immunité adaptative: lymphocytes T et B
  - Immunité innée: leucocytes et toutes les cellules de l'organisme
- **Inflammation physiologique**
  - **Réponse immunitaire**
  - Réponse physiologique aux agressions
  - Ex: cicatrisation; guérison d'une infection
- **Inflammation pathologique: Maladies**
  - autoinflammatoires
  - inflammatoires chroniques

  } Immunité innée

  - autoimmunes
  - allergiques

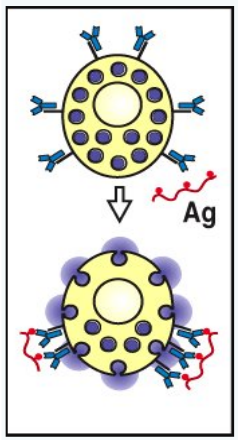
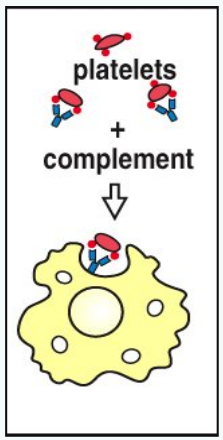
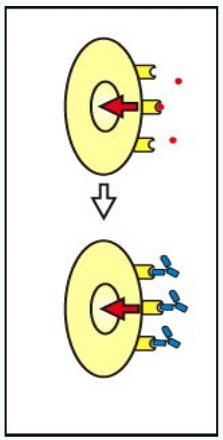
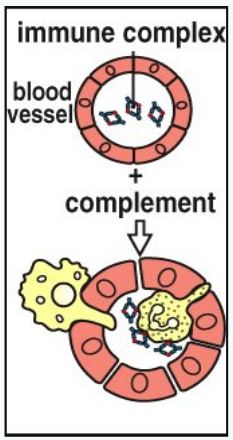
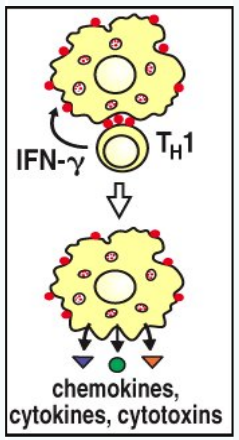
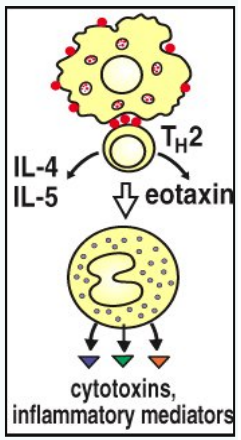
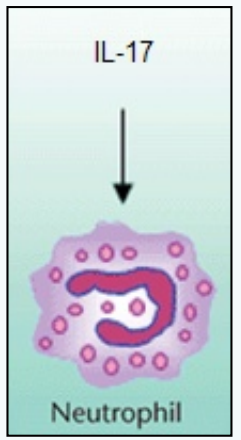
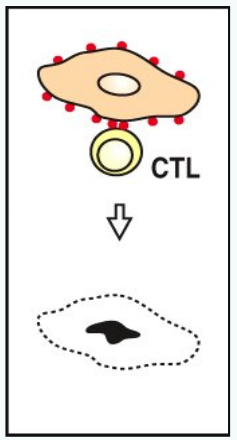
  } Immunité adaptative





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, Psoriasis, Maladie de Crohn, Infections**	**Eczéma all.de contact Vitiligo, Pelade**
Choc anaphylactique	**Cytopénies médicamenteuses**		**Vascularites**	**Toxidermies**	**DRESS**		**Lyell/SJS**

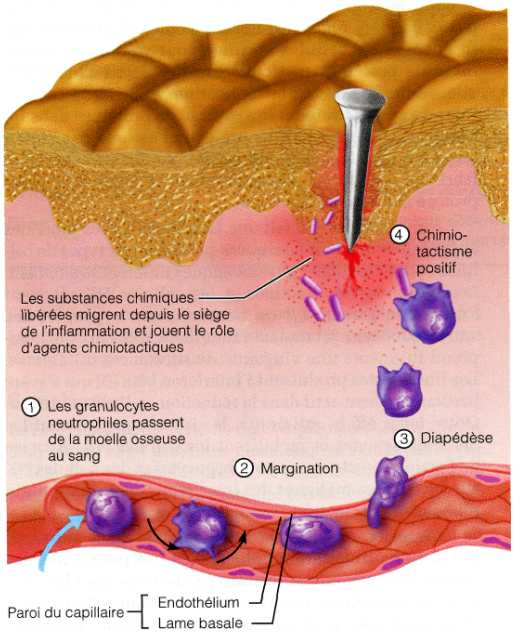
PLAN

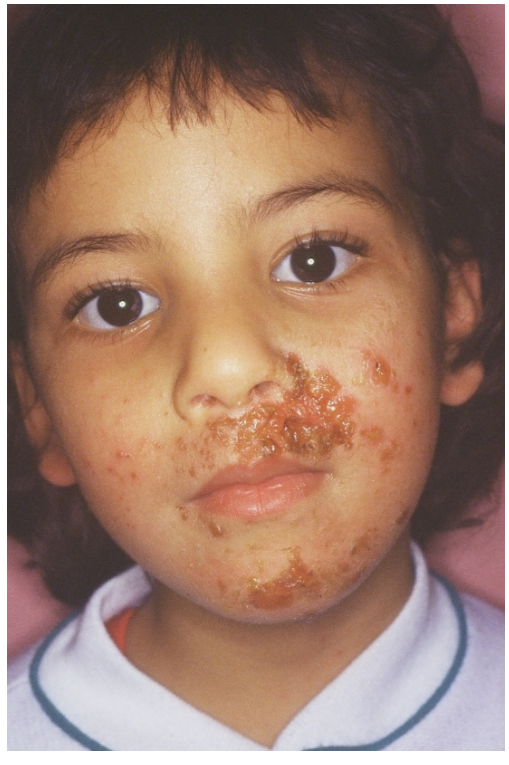
- **Inflammation** = mise en jeu de l'immunité innée et adaptative
  - Immunité adaptative: lymphocytes T et B
  - Immunité innée: leucocytes et toutes les cellules de l'organisme
- **Inflammation physiologique**
  - **Réponse immunitaire**
  - Réponse physiologique aux agressions
  - Ex: cicatrisation; guérison d'une infection
- **Inflammation pathologique: Maladies**
  - autoinflammatoires
  - inflammatoires chroniques

  } Immunité innée

  - autoimmunes
  - allergiques

  } Immunité adaptative





Les macrophages et cellules dendritiques:

Cellules initiatrices de l'inflammation

Signaux de danger
-Microbiens
-Non microbiens

Cytokines primaires

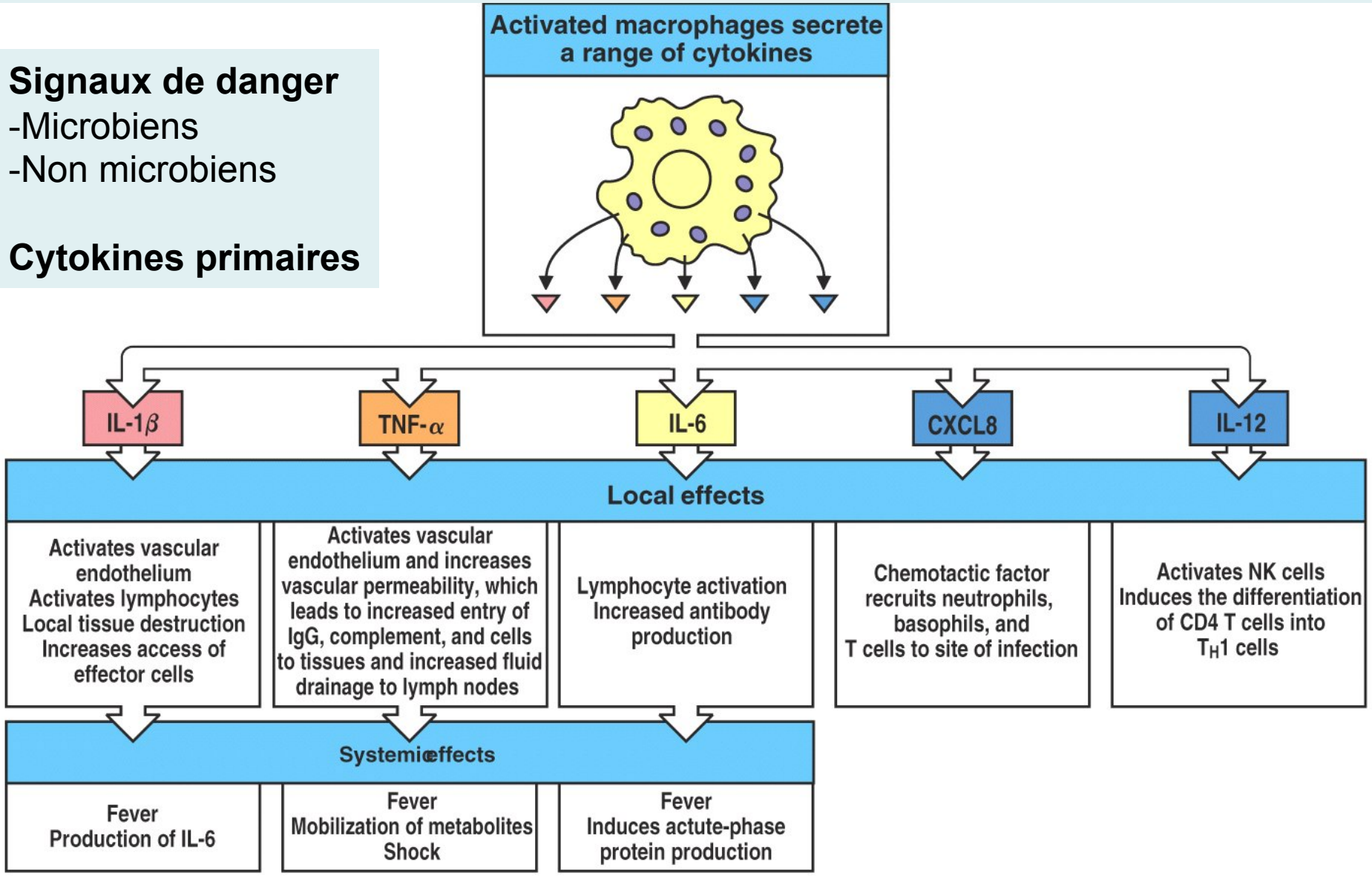


Figure 2-39 Immunobiology, 6/e. (© Garland Science 2005)

Signal de danger et IL-1:

Voies de signalisation de l'immunité innée

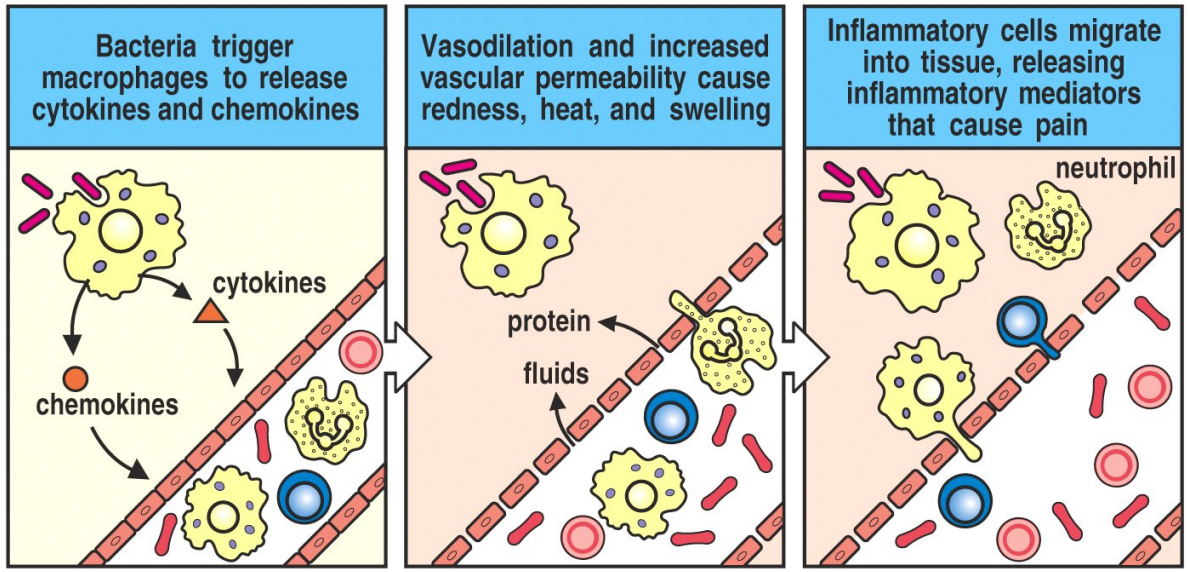
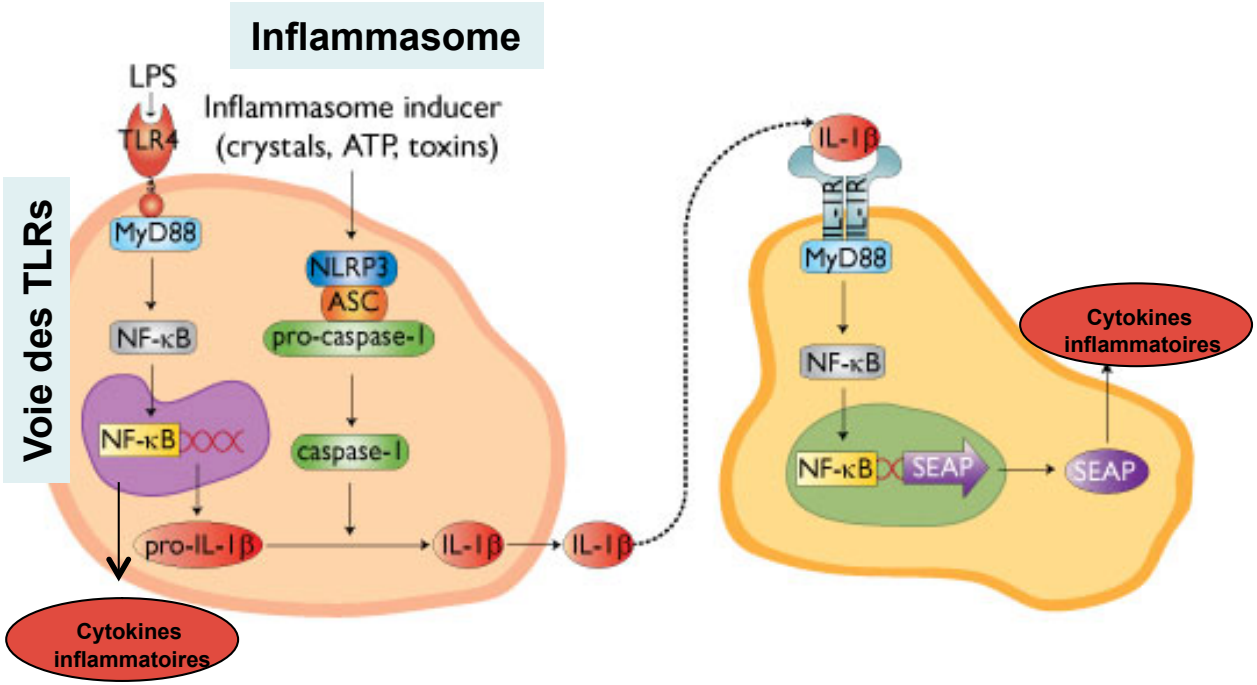


Figure 1-12 Immunobiology, 6/e. (© Garland Science 2005)



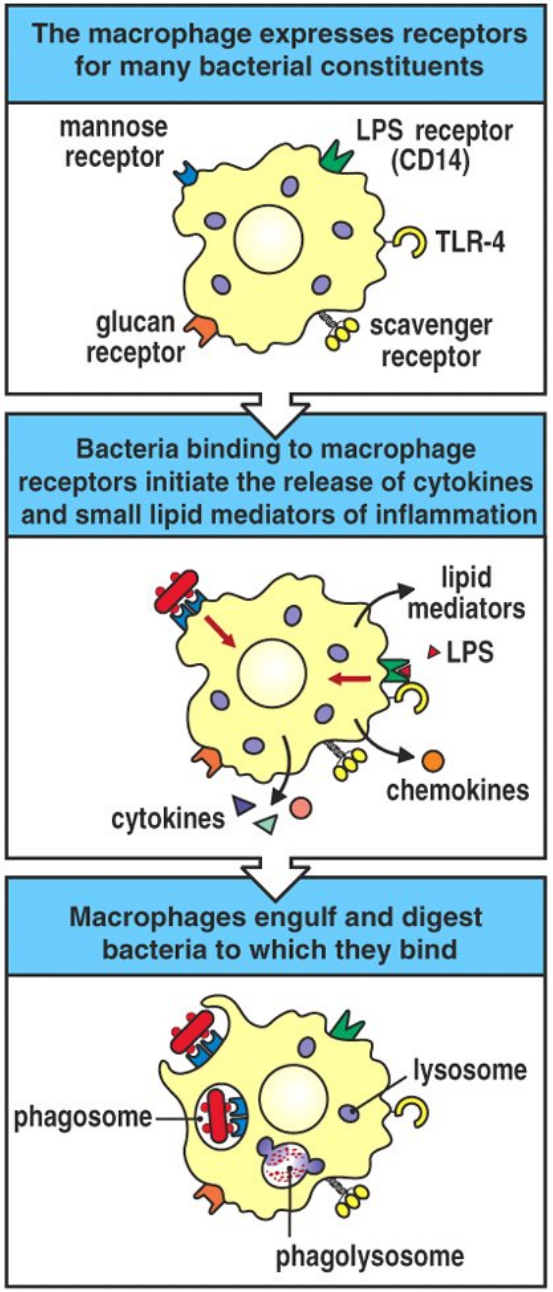
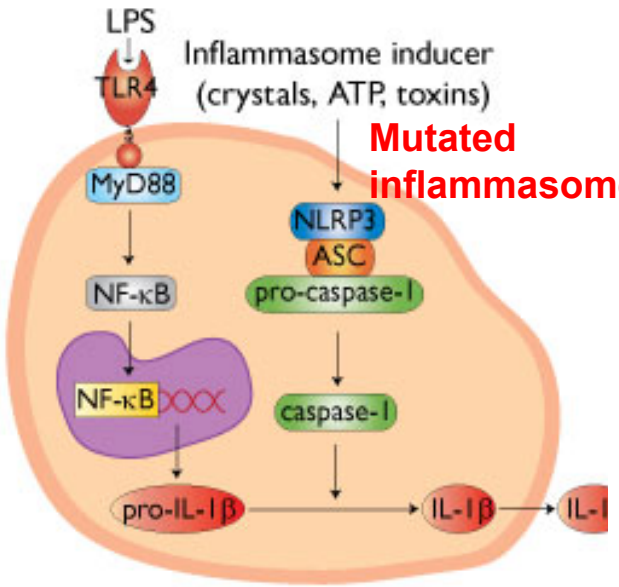


Figure 2-5 Immunobiology, 6/e. (© Garland Science 2005)

Maladies autoinflammatoires familiales

• Hyperproduction d'IL-1

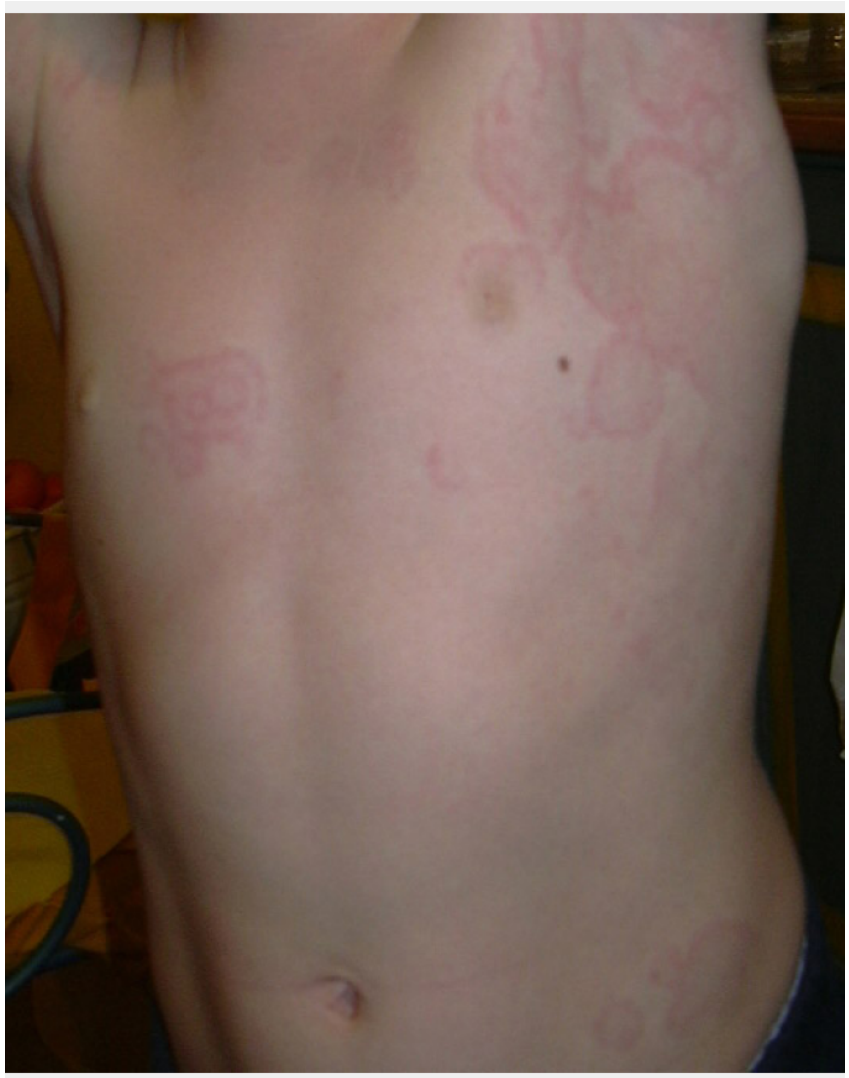
• Mutations des gènes impliqués dans les voies de signalisation de l'immunité innée
• Mutations « gain de fonction »
• Traitement: bloquer l'effet de l'IL-1 par anticorps ou par antagonistes du récepteur

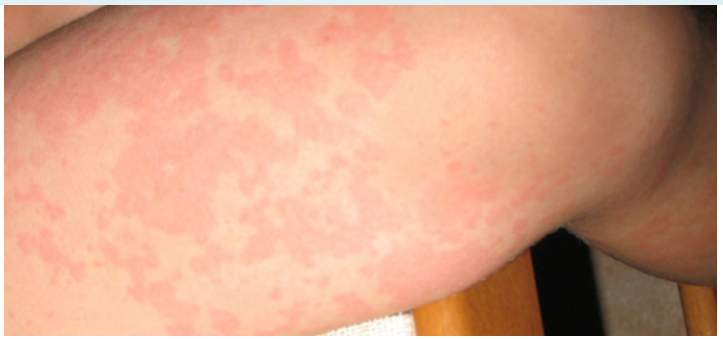


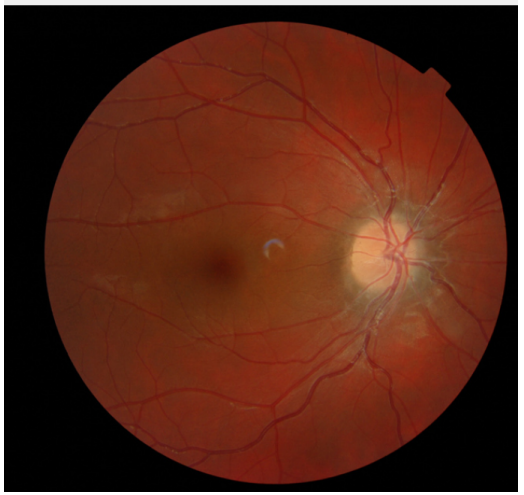
Disease*	Gene	Protein	Inheritance pattern
Familial Mediterranean fever (FMF)	*MEFV*	Pyrin	Autosomal recessive or gene-dosage-dependent autosomal dominant
Tumour necrosis factor-associated periodic syndrome (TRAPS)	*TNFRSF1A*	Tumour necrosis factor receptor 1	Autosomal dominant with dependence on the wild-type allele
Hyper IgD syndrome	*MVK*	Mevalonate kinase	Autosomal recessive
Cryopyrin-associated periodic syndromes (FCAS, MWS and NOMID)	*NLRP3*	NLRP3	Autosomal dominant
Blau syndrome‡	*NOD2*	NOD2	Autosomal dominant
PAPA syndrome	*PSTPIP1*	PSTPIP1	Autosomal dominant
Deficiency of IL-1 receptor antagonist (DIRA)	*IL1RN*	IL-1 receptor antagonist	Autosomal recessive
Deficiency of IL-36 receptor antagonist (DITRA)	*IL36RN*	IL-36 receptor antagonist	Autosomal recessive
Familial psoriasis (PSORS2) and CARD14-mediated pustular psoriasis (CAMPS)	*CARD14*	Caspase-recruitment domain-containing protein 14	Autosomal dominant
CANDLE syndrome, Nakajo–Nishimura syndrome and JMP syndrome	*PSMB8*	PSMB8 immunoproteasome subunit	Autosomal recessive

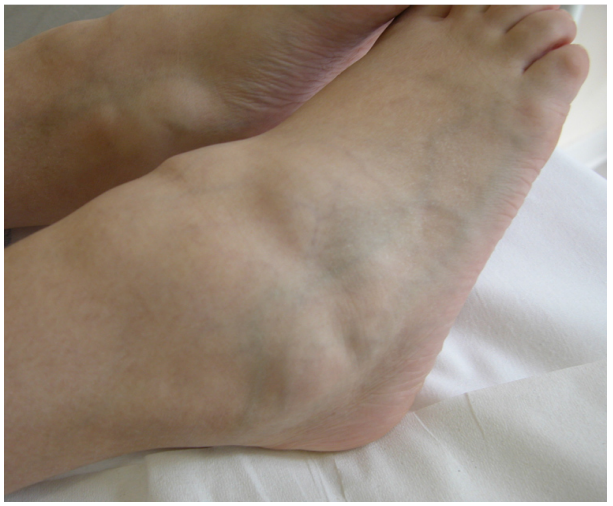
Maladies autoinflammatoires familiales

- Hyperproduction d'IL-1
- Maladies systémiques touchant différents organes



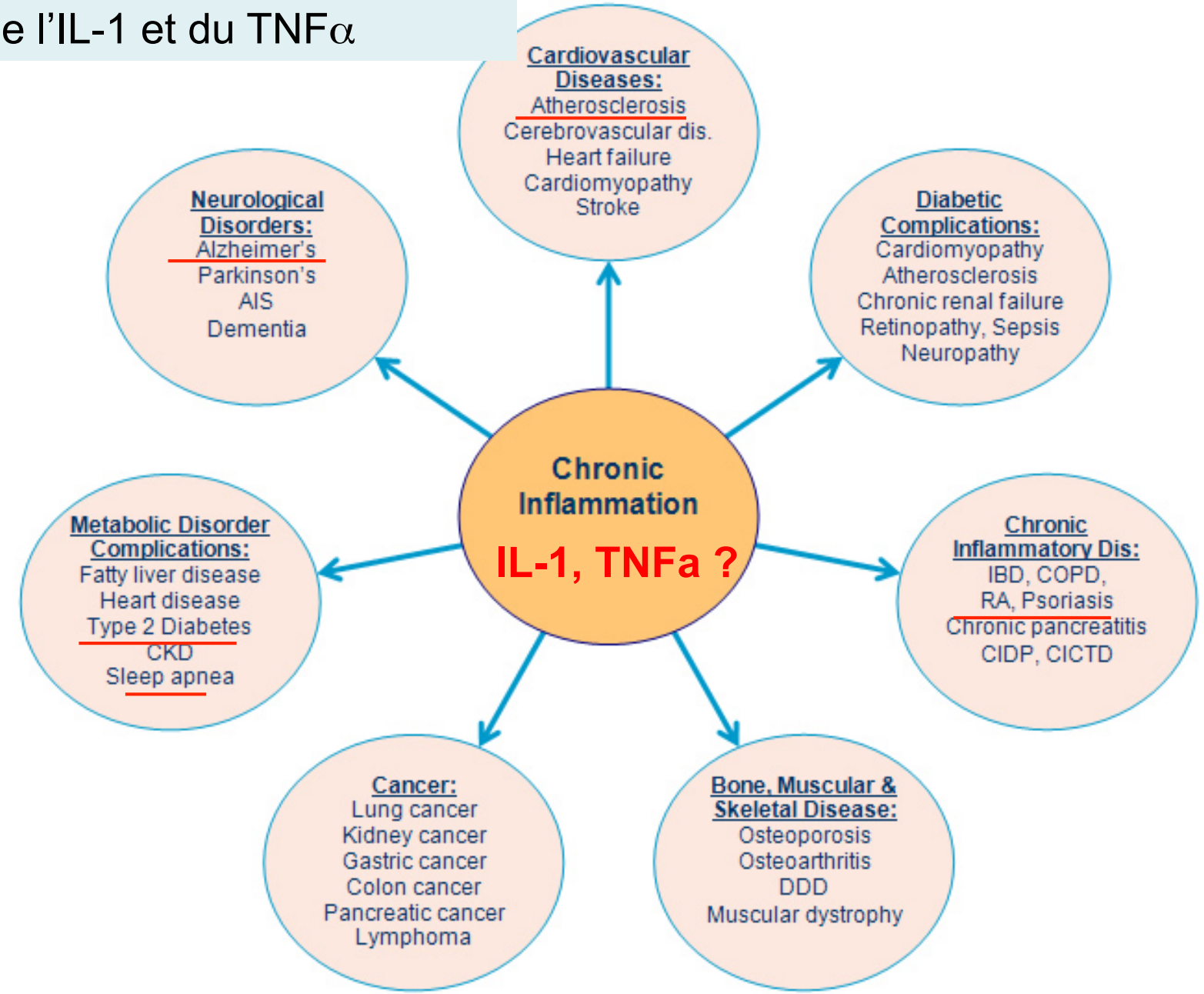




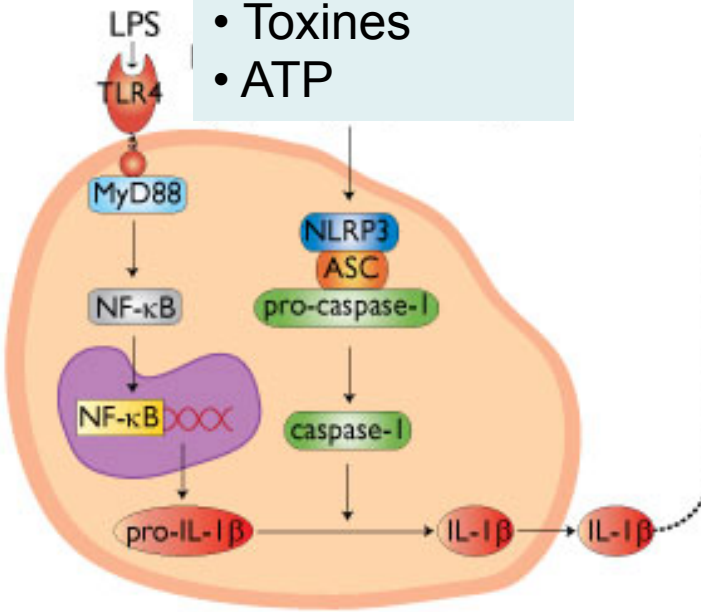


Maladies inflammatoires chroniques

- Dérégulation de l'immunité innée
- Rôle de l'IL-1 et du TNFα



- Cristaux (Asbestos, alum, Cholesterol, silice, acide urique),
- Chimiques
- Toxines
- ATP



Box 1 | **Examples of conditions treated with IL-1 blockade**

Joint, bone and muscle diseases*

- Rheumatoid arthritis; ankylosing spondylitis
- Erosive osteoarthritis of the hand
- Recurrent multifocal osteomyelitis
- Traumatic knee injury; relapsing polychondritis

Hereditary systemic autoinflammatory diseases*‡

- Familial Mediterranean fever (FMF)
- Cryopyrin-associated periodic syndrome (CAPS)
- TNF receptor-associated periodic syndrome (TRAPS)
- Hyper-IgD syndrome (HIDS)
- Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)
- Deficiency of interleukin-1 (IL-1) receptor antagonist (DIRA)

Systemic inflammatory diseases*

- Systemic juvenile idiopathic arthritis
- Adult-onset Still's disease
- Schnitzler syndrome
- Behçet's disease
- PFAPA
- SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome
- Macrophage activation syndrome

Common inflammatory diseases*

- Gout; pseudogout
- Type 2 diabetes
- Hidradenitis suppurativa
- Systolic heart failure; cardiac remodelling
- Dry eye syndrome
- Pustular psoriasis; neutrophilic dermatoses

*See Supplementary information S1 (table) for a referenced and expanded list. ‡See TABLE 2.

Anti-IL-1 et diabète

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D., Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.

ABSTRACT

BACKGROUND

The expression of interleukin-1–receptor antagonist is reduced in pancreatic islets of patients with type 2 diabetes mellitus, and high glucose concentrations induce the production of interleukin-1β in human pancreatic beta cells, leading to impaired insulin secretion, decreased cell proliferation, and apoptosis.

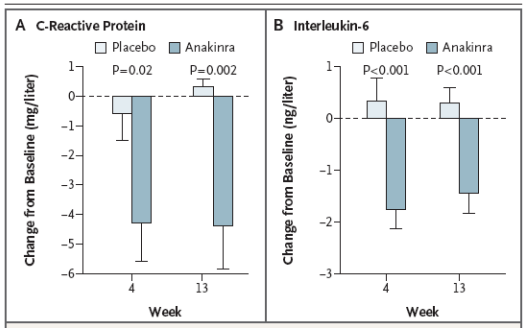


Figure 4. Markers of Systemic Inflammation.
The average absolute differences between baseline and 4 and 13 weeks in each study group are shown for levels of circulating C-reactive protein (Panel A) and interleukin-6 (Panel B). In the placebo group, the analysis included 35 patients at week 4 and 33 at week 13. In the anakinra group, the analysis included 34 patients at weeks 4 and 13. The I bars indicate standard errors.

The NEW ENGLAND JOURNAL of MEDICINE

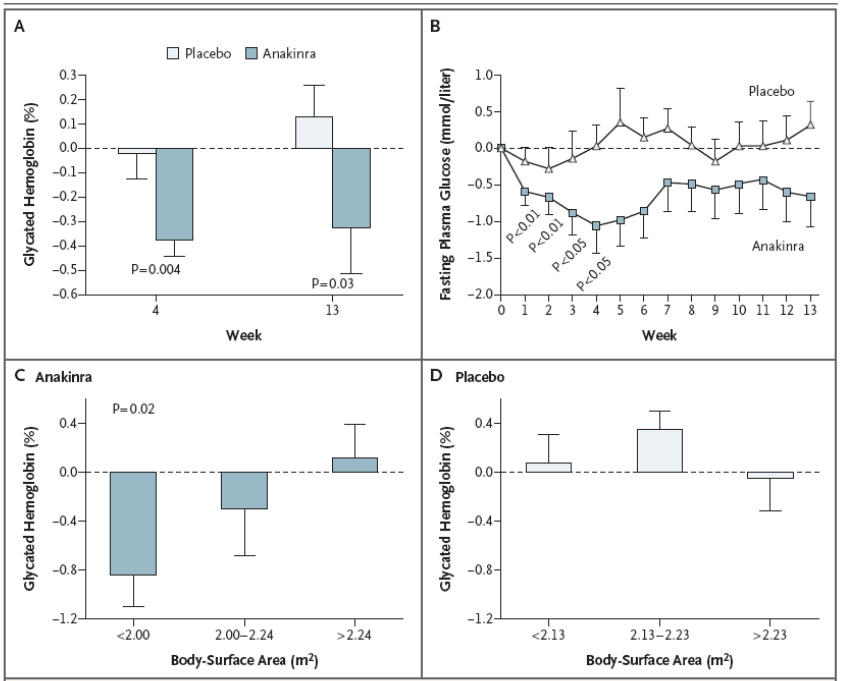


Figure 2. Changes in Glycated Hemoglobin and Fasting Plasma Glucose Levels during the 13-Week Study Period.
Panel A shows the average absolute difference in glycated hemoglobin levels between baseline and 4 and 13 weeks in each study group. Panel B shows the average absolute differences in fasting plasma glucose levels between the baseline value and weekly measurements performed by the patients at home during the 13-week study period. Panels C and D show the average absolute differences in glycated hemoglobin levels at 13 weeks in each study group stratified into thirds according to body-surface area. In the placebo group, the analysis included 35 patients at week 4, 34 at week 5, and 33 at week 13. In the anakinra group, the analysis included 34 patients at each weekly measure. The I bars indicate standard errors.

Maladies inflammatoires
classification et physiopathologie

Maladie	Exemple	Immunité	Effecteurs	Physiopathologie	Classification
IMMUNITE SPECIFIQUE					
Allergiques	Asthme Eczéma	Adaptative	Ac et lymphocytes T	-Réponse immune spécifique -Allergènes	Gell & Coombs
Auto-immunes	Diabète I Thyroidites SEP	Adaptative	Ac et lymphocytes T	-Réponse immune spécifique -Auto-antigènes	Gell & Coombs
IMMUNITE INNEE					
Auto-inflammatoires	FMF Muckle-Wells	Innée	Cytokines IL-1	-Maladies génétiques rares -Mutations inflammasome	?
Inflammatoires chroniques	Psoriasis Diabète gras Athérosclérose Alzheimer Urticaire chronique ?	Innée	Cytokines IL-1 IL-17 TNF	-Maladies fréquentes -Dérégulation de l'immunité innée -Inflammasome ?	?

Allergologie et Immunologie Clinique – CHU Lyon-Sud

www.allergolyon.org

SEMINAIRE ALLERGOLYON 2015

Mercredi 21 au Samedi 24 janvier 2015

Ecole Normale Supérieure de Lyon

PROGRAMME

- **Peau et Immunité (mercredi 21 janvier)**
- **Allergie aux médicaments (jeudi 22 janvier)**
- **Immuno-Dermatologie (vendredi 23 janvier)**
- **Best of Allergologie (samedi 24 janvier)**

www.allergolyon.org

Equipe 14 – INSERM U1111

Service Allergologie
et Immunologie Clinique Lyon-Sud

Unité de recherche clinique
Lyon-Sud