Defects in INNATE IMMUNITY

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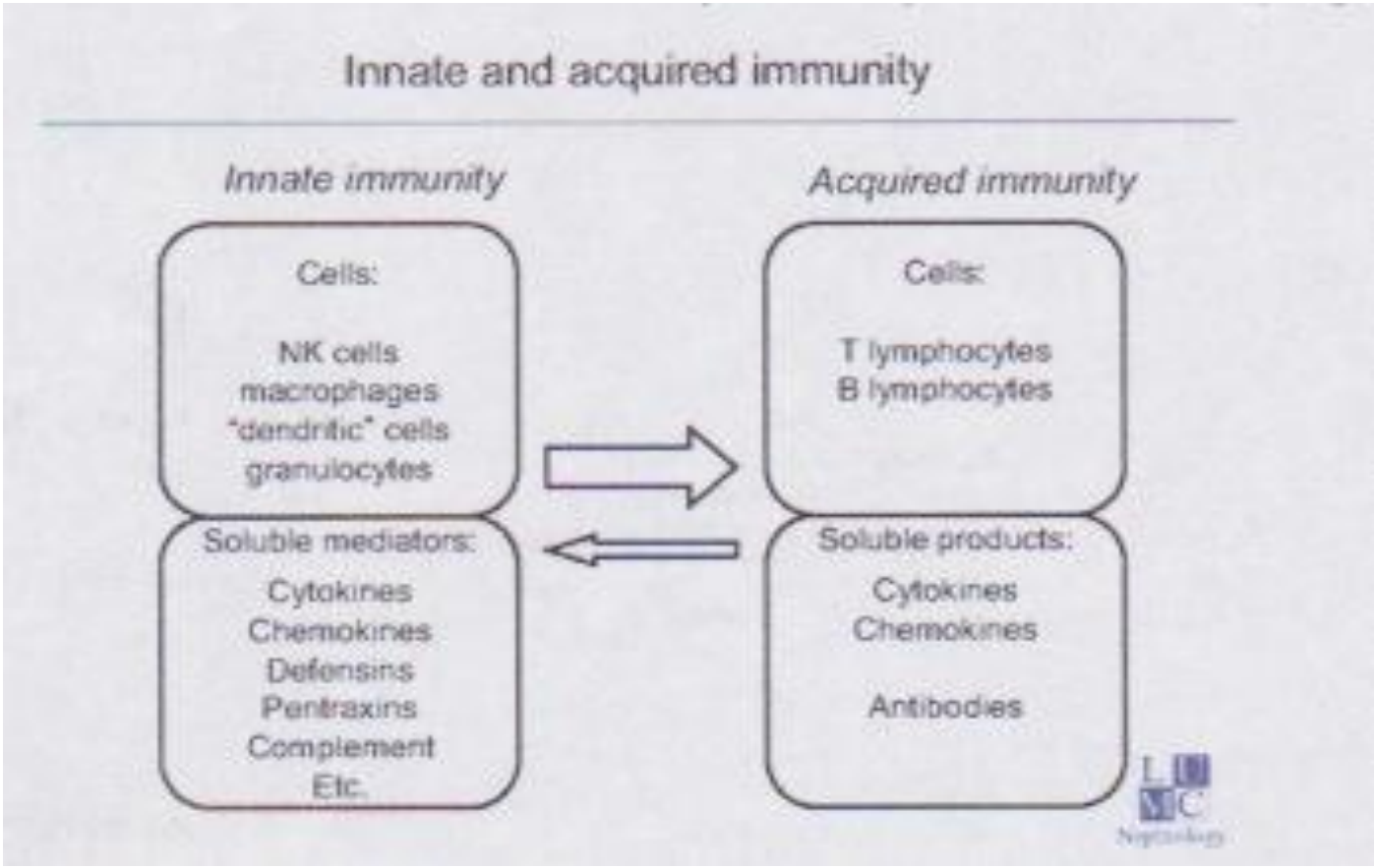
Definition in a Dictionary of Science:

INNATE = present at birth, inherited



MR Daha 2011

Differences between Innate and Acquired Immunity

Innate: non-specific, present at birth, quick response. Dendritic cells, phagocytes, mastocytes … are the main cells responsible.They produce inflammatory cytokines (IL-1, IL-6, etc)

Acquired: developed after meeting the antigen, highly specific, it takes some time to develop, lymphocytes are the main cells responsible (T and B). They produce antibodies, cytotoxic cells and cytokines (IL-2 , IFNγ, etc)

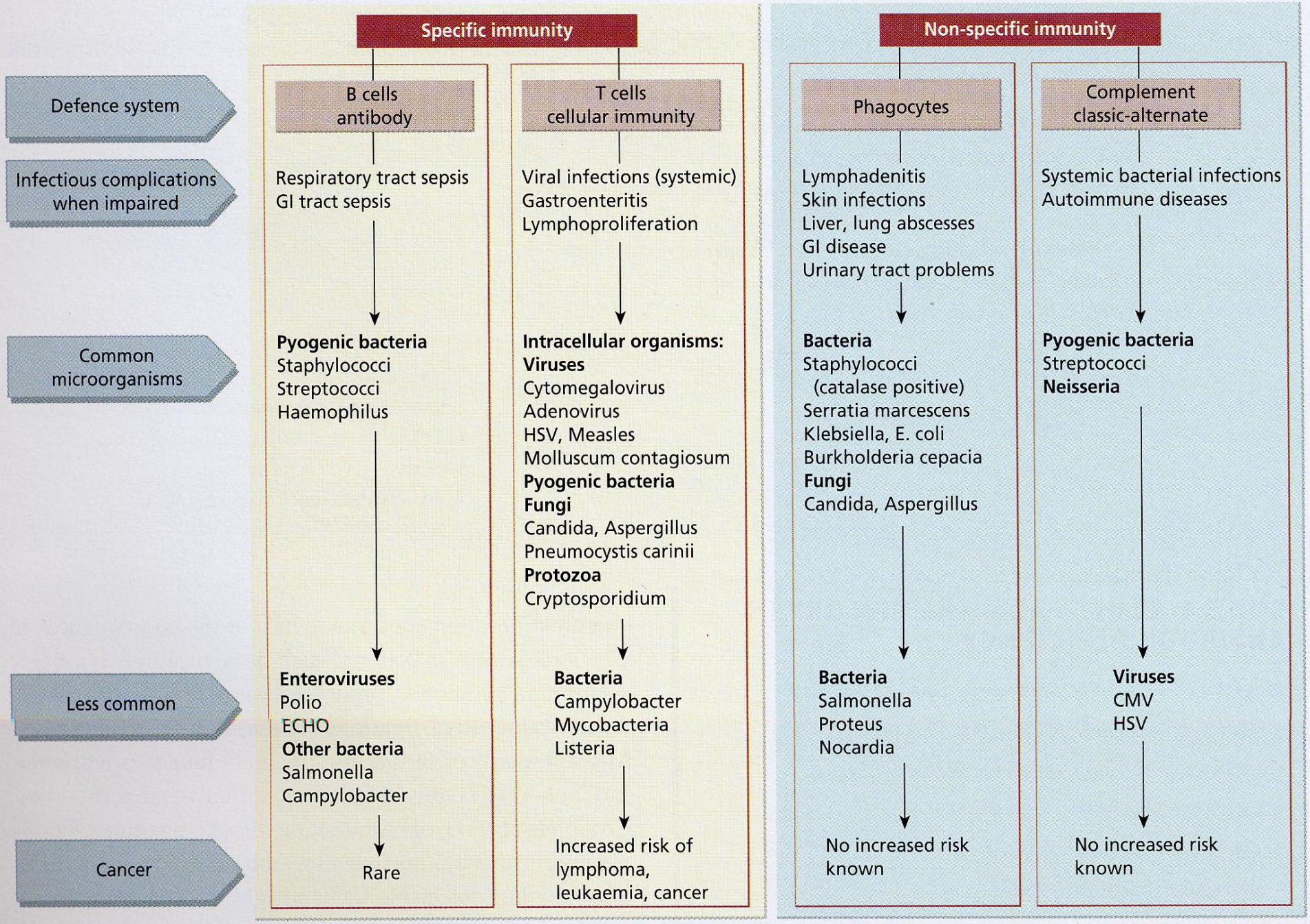
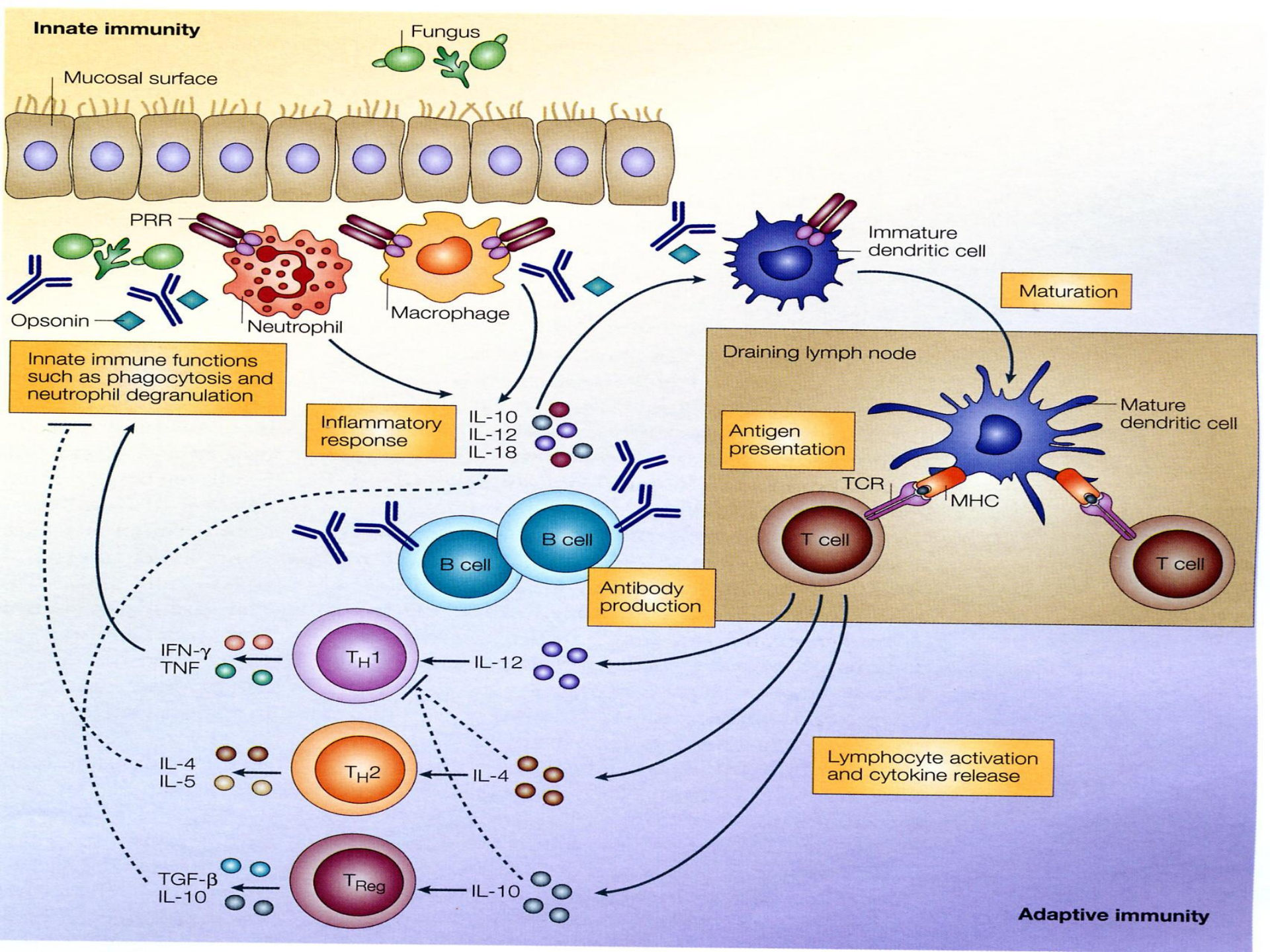


Fig. 3.2 Defects in immunity suggested by infections with certain organisms. GI, gastrointestinal; HSV, herpes simplex virus.


Innate immunity
Fungus
Mucosal surface
PRR
Opsonin
Neutrophil
Macrophage
Immature dendritic cell
Maturation
Innate immune functions such as phagocytosis and neutrophil degranulation
Inflammatory response
IL-10
IL-12
IL-18
Draining lymph node
Antigen presentation
Mature dendritic cell
TCR
MHC
T cell
T cell
B cell
B cell
Antibody production
IFN-γ
TNF
T_H1
IL-12
IL-4
IL-5
T_H2
IL-4
Lymphocyte activation and cytokine release
TGF-β
IL-10
T_{Reg}
IL-10
Adaptive immunity

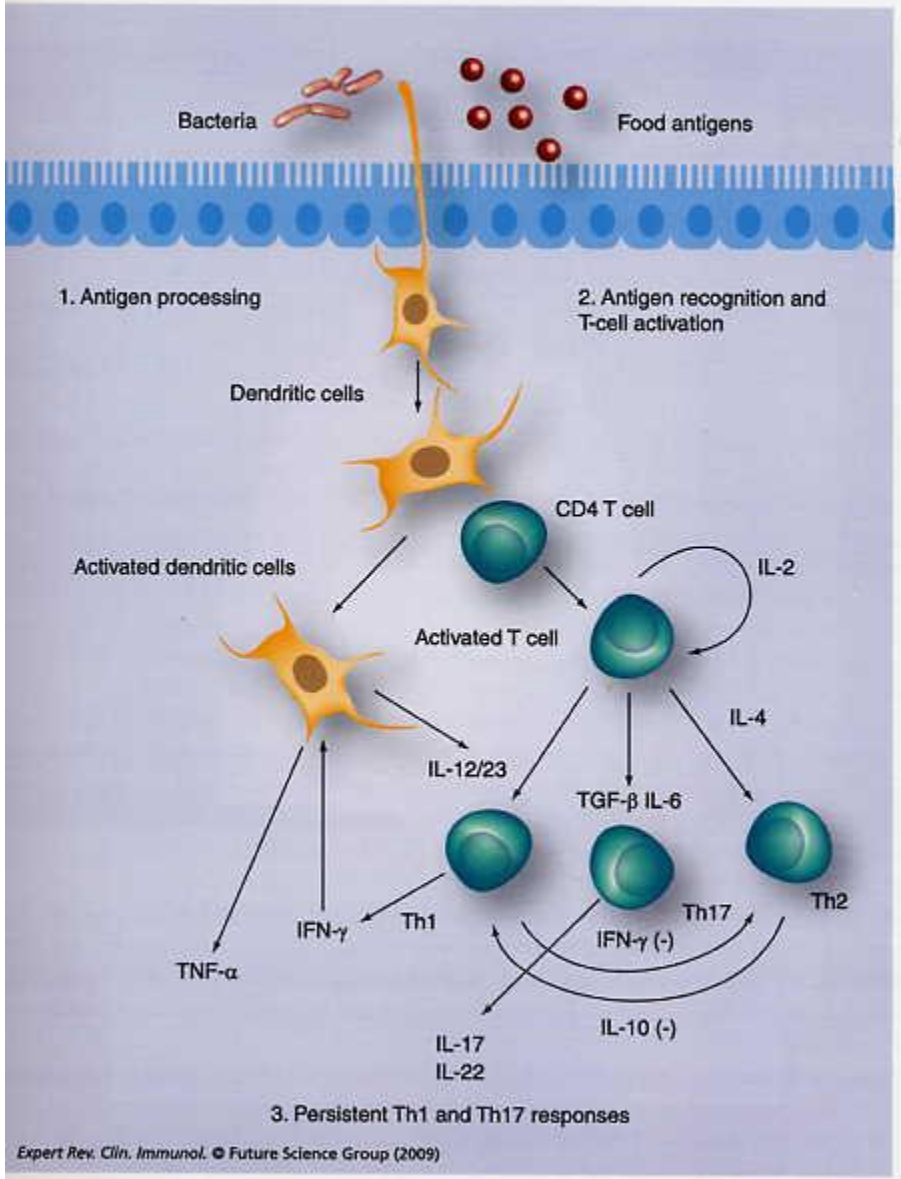
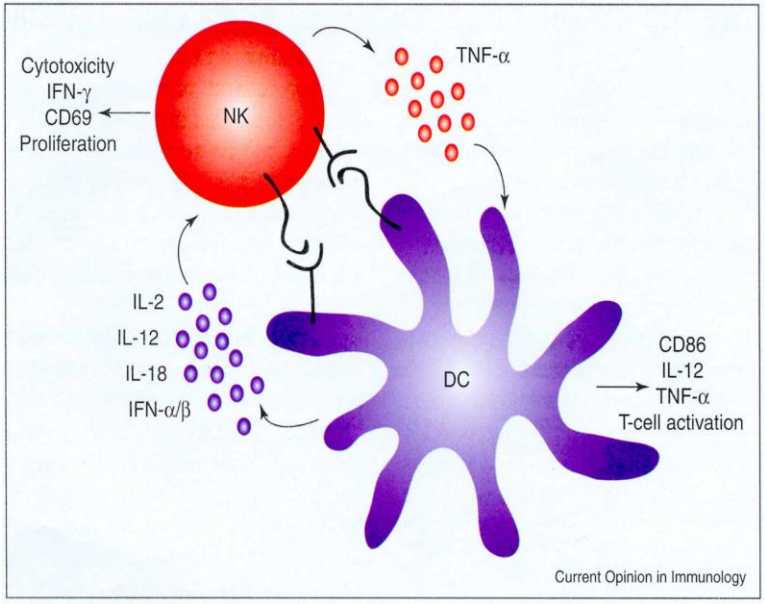


Figure 2. Luminal antigens are recognized and processed by dendritic cells. Antigen-presenting cells activate CD4+ T cells, which differentiate into Th1 and Th17 cells. Deregulated mucosal immune responses result in excessive Th1 and Th17 responses that contribute to chronic inflammation during inflammatory bowel disease.

Dendritic cells are Ag-presenting and processing cells, and cytokine " producers"



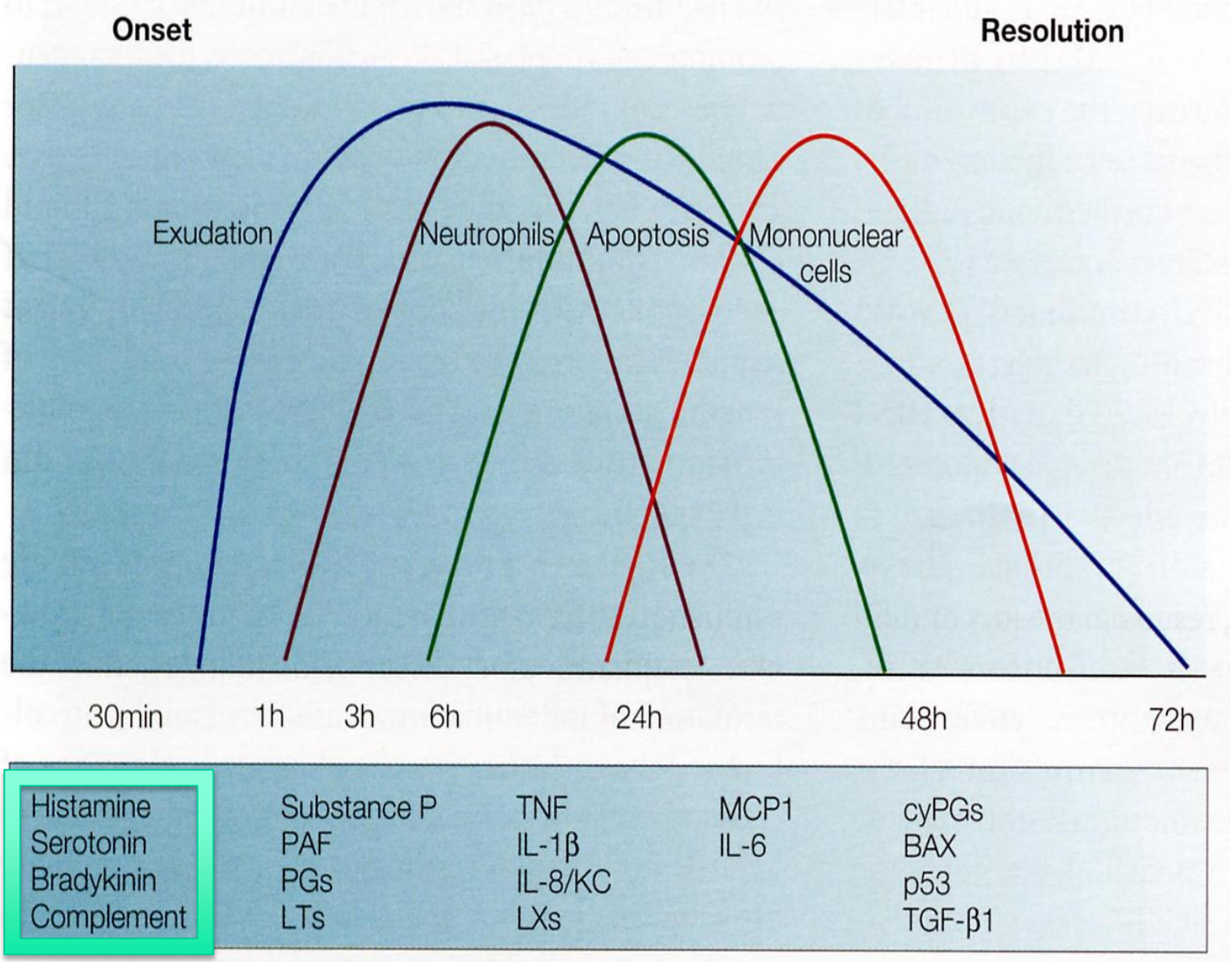
Definition of INFLAMMATION

“is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens (infectious agents), damaged cells or irritants “

Is the first immune response, non-specific, initiated by cells already present in the tissues (dendritic cells, macrophages…) producing inflammatory cytokines. It manifests with local redness, pain, swelling…The increased vascular permeability permits plasma proteins and other cells to be present at the injury site and, if the inflammation is persistent, produce fever, loss of function and general malaise.

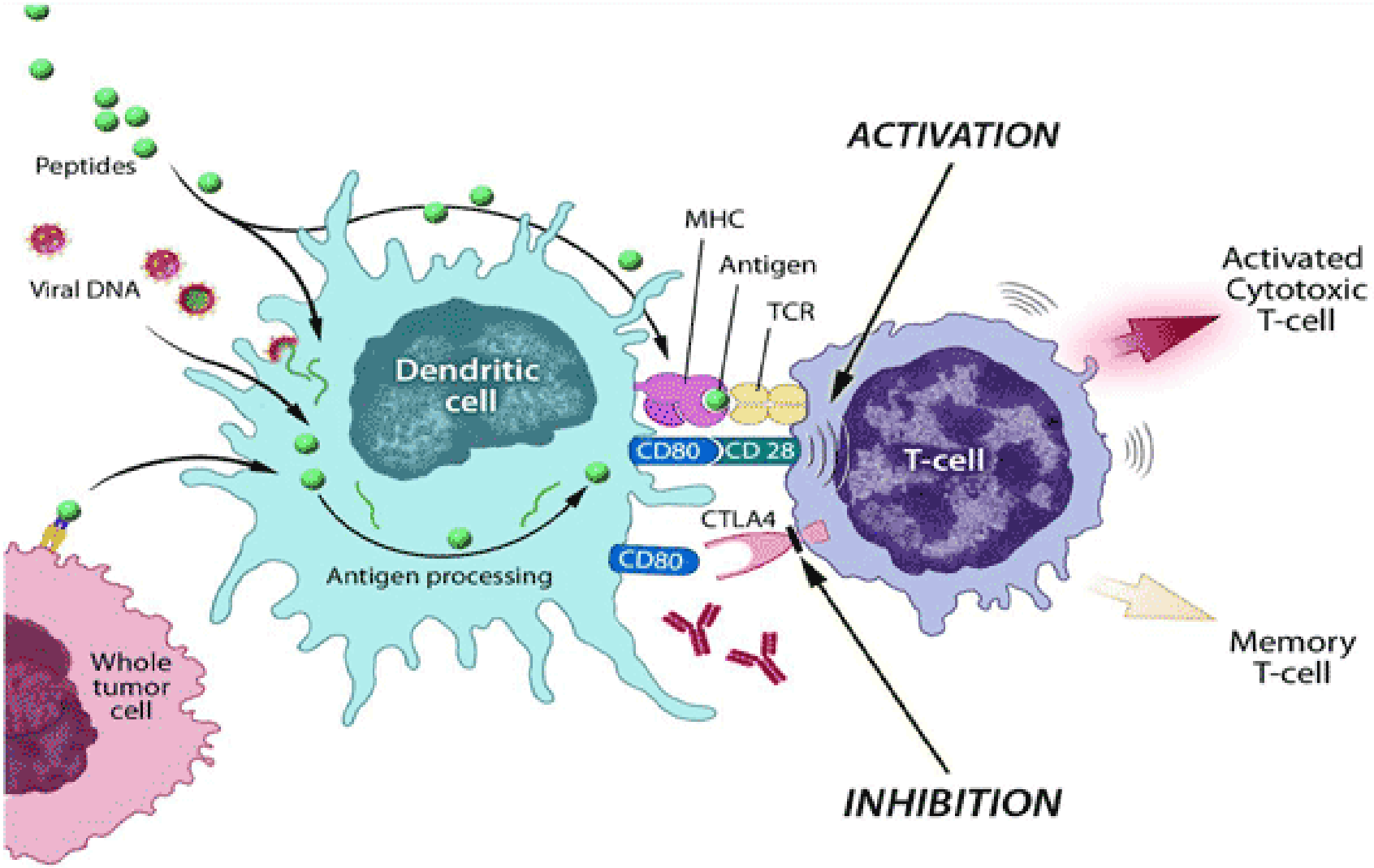
The result of this response is the activation of the acquired immune response, through the “presentation” of antigens (e.g. specific proteins of the pathogens) to T and B cells which will be activated, proliferate and produce cytotoxic cells and antibodies.

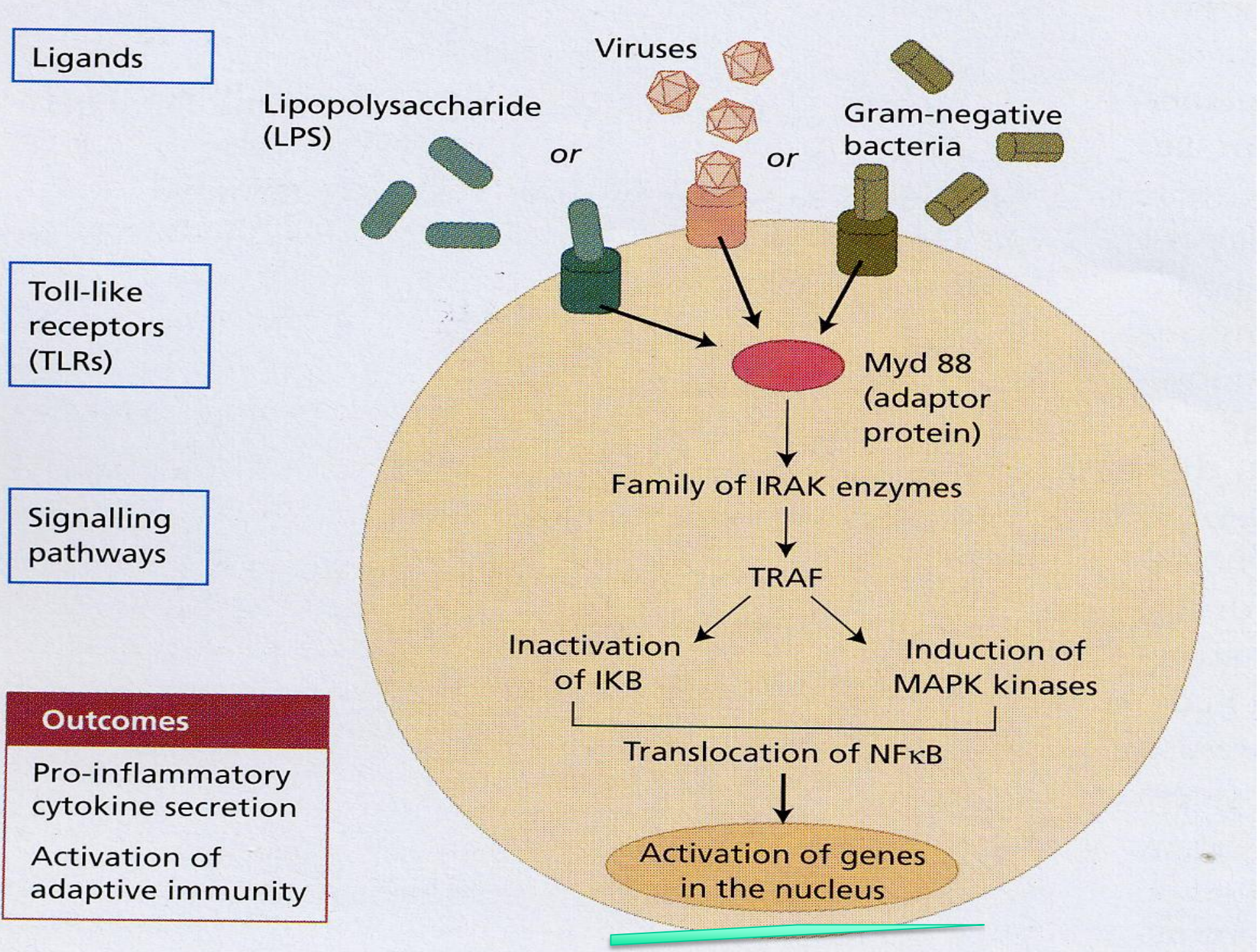
Thus, we know now that the innate response is essential for the complete elimination of aggressions.



Sequence of the inflammation and cytokines produced before the lymphocytes arrive

Signalling between cells is essential. Cells of the innate immune response are initiators of T-cell activation




Ligands
Toll-like receptors (TLRs)
Signalling pathways
Outcomes
Pro-inflammatory cytokine secretion
Activation of adaptive immunity
Lipopolysaccharide (LPS)
or
Viruses
or
Gram-negative bacteria
Myd 88 (adaptor protein)
Family of IRAK enzymes
TRAF
Inactivation of IKB
Induction of MAPK kinases
Translocation of NFκB
Activation of genes in the nucleus

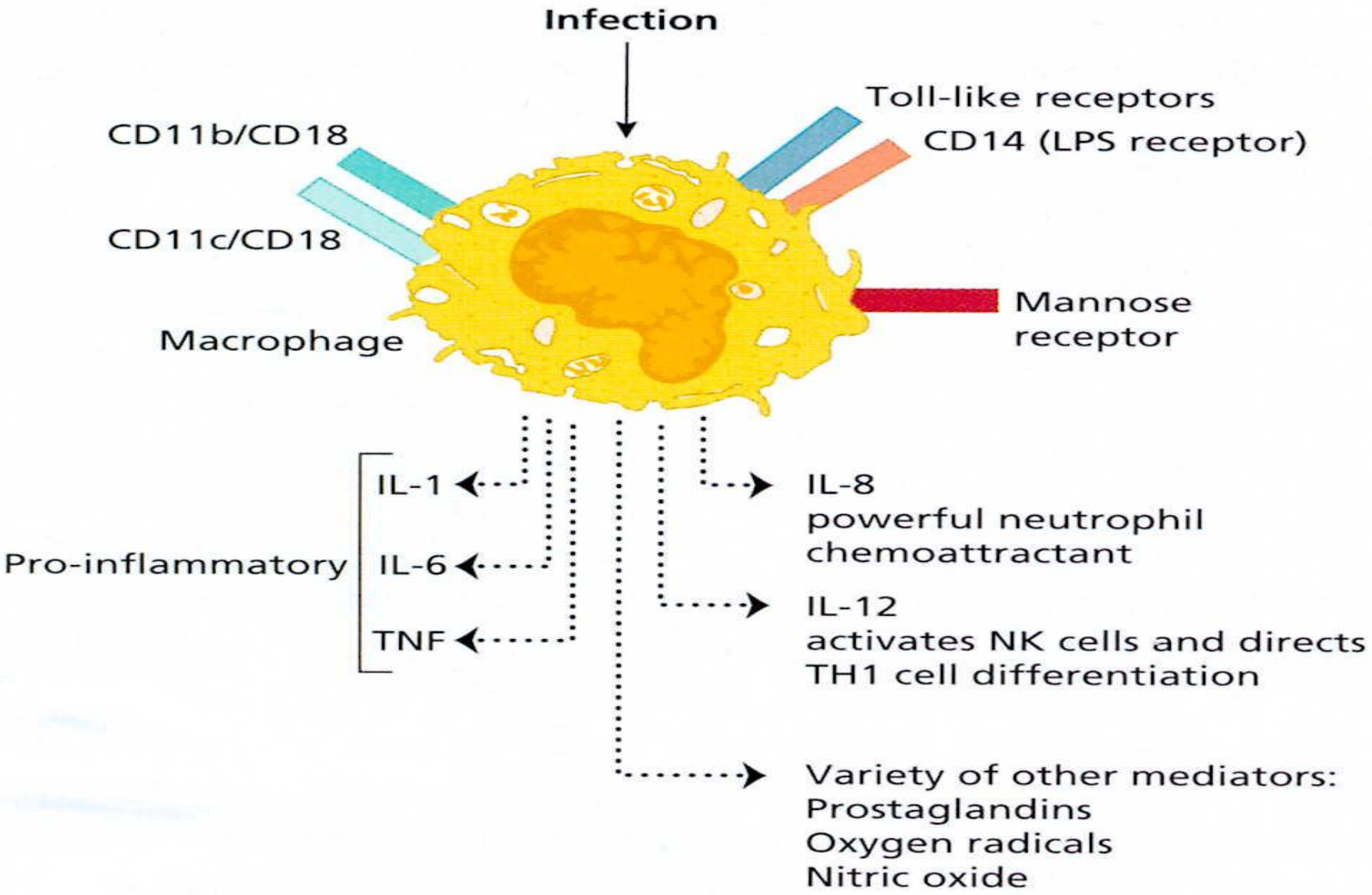
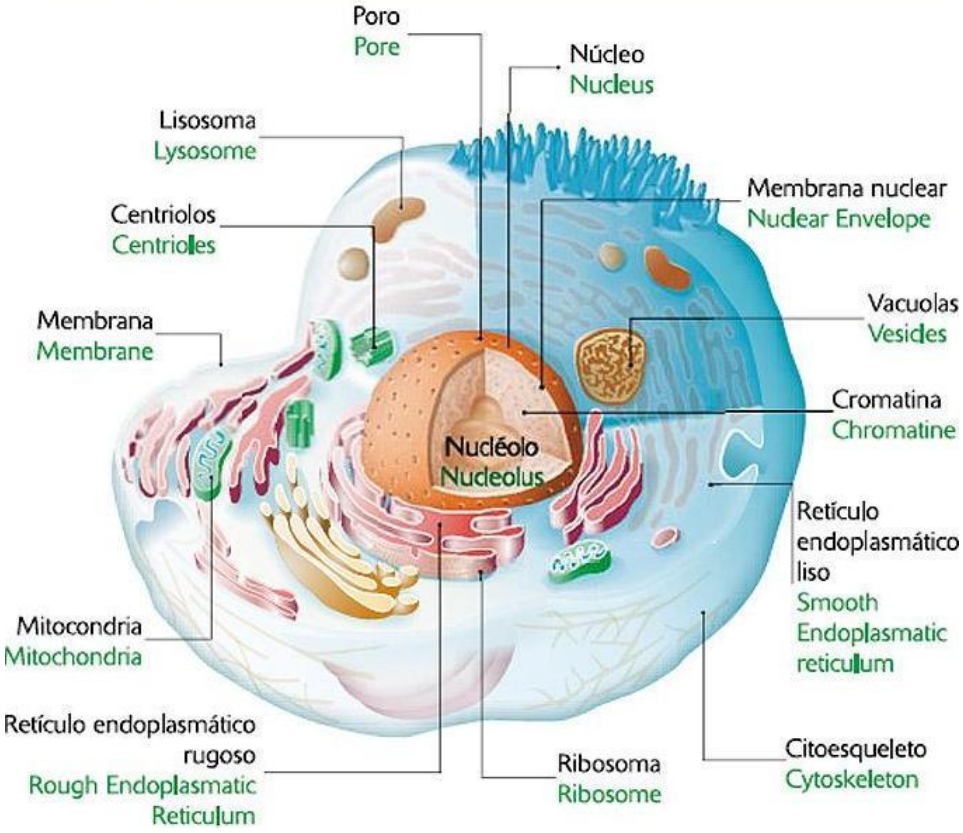
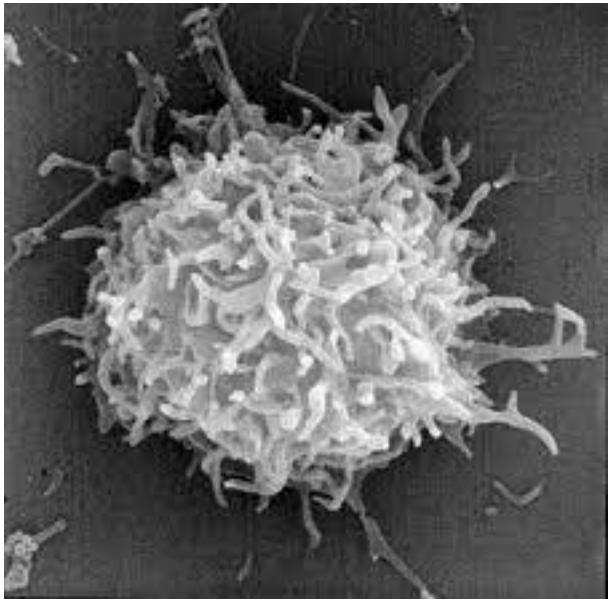


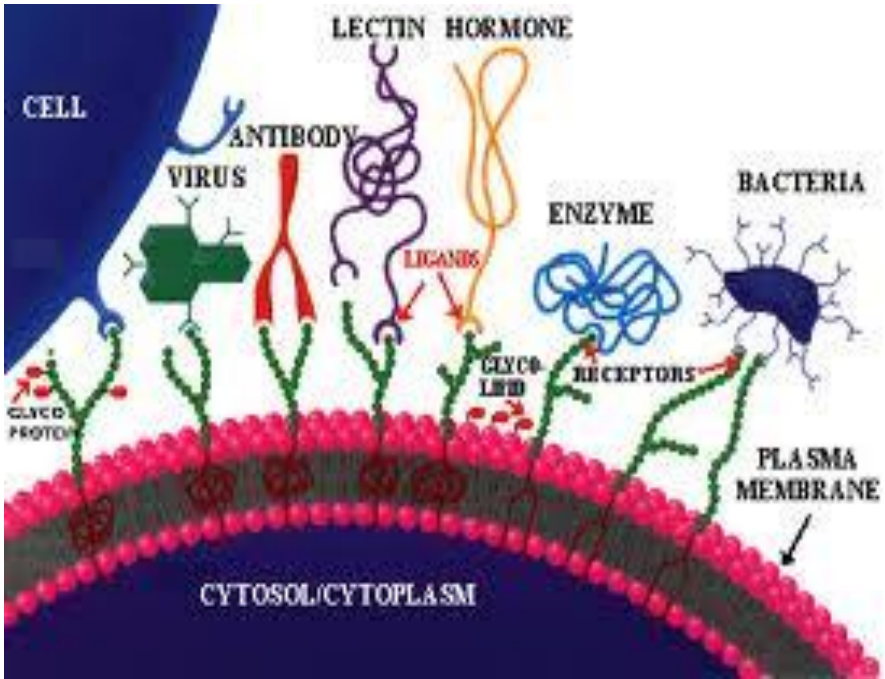
Fig. 2.3 Role of the macrophage in host defence.

Essentials Clin Immunol 5ªed H.Chapel 2006

Célula eucariota animal / Eukaryote animal cell







Satellite dish

Toll receptors are the main immunologic mechanisms in the fly to fight infections. The parallel receptors in the membrane of the innate immune response cells in humans are called Toll-like receptors: TLR

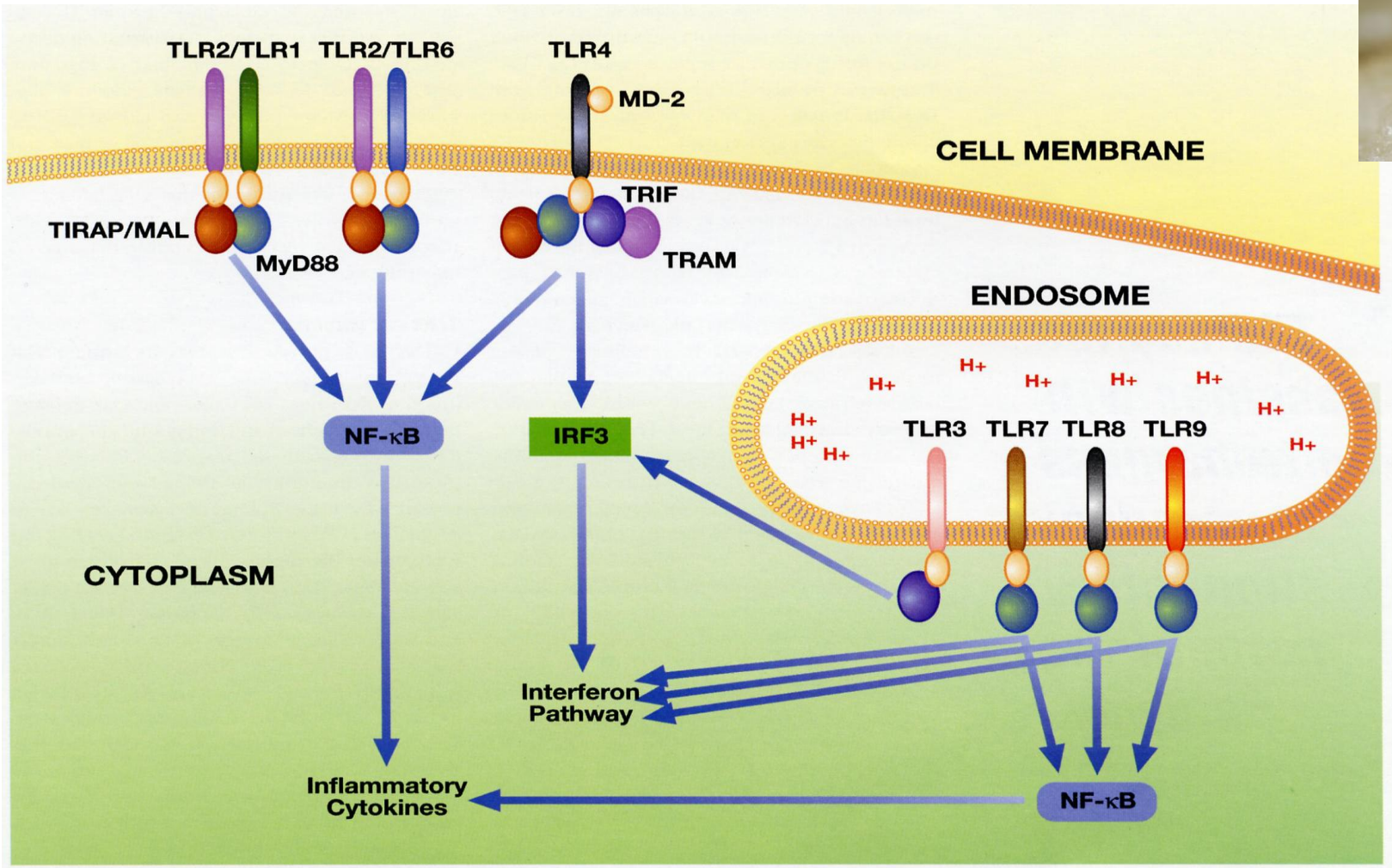
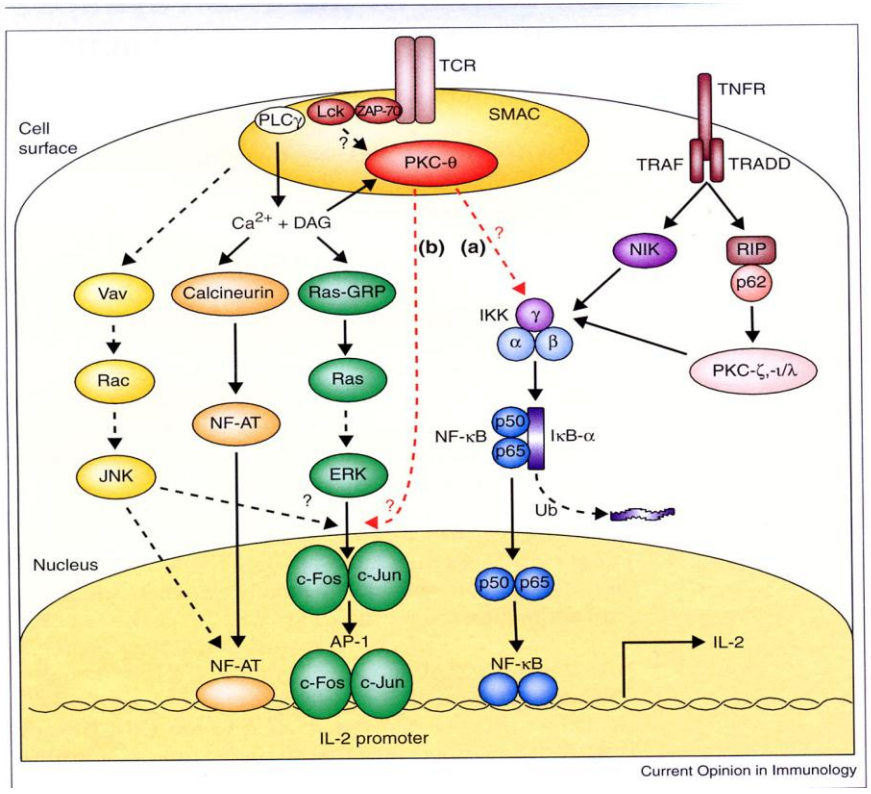


Figure 1. TLR signaling pathways. *TLRs are transmembrane proteins that act alone or in heterologous pairs to detect invading microbes, triggering signaling pathways that ultimately lead to the release of inflammatory cytokines through the NF-κB pathway or the release of interferons through the IRF3 pathway. TLRs can localize to the cell membrane or endosomes and can differ in terms of the adaptor molecules (circles) that relay their intracellular signals. Some of the adaptor molecules have been characterized (MyD88, TRIF, TRAM, TIRAP/MAL), but others remain undefined (adapted from Boehme and Compton,* J. Virol. **78**, *7867, 2004).*

Any defect in the complex machinery, results in a “stop or malfunction”



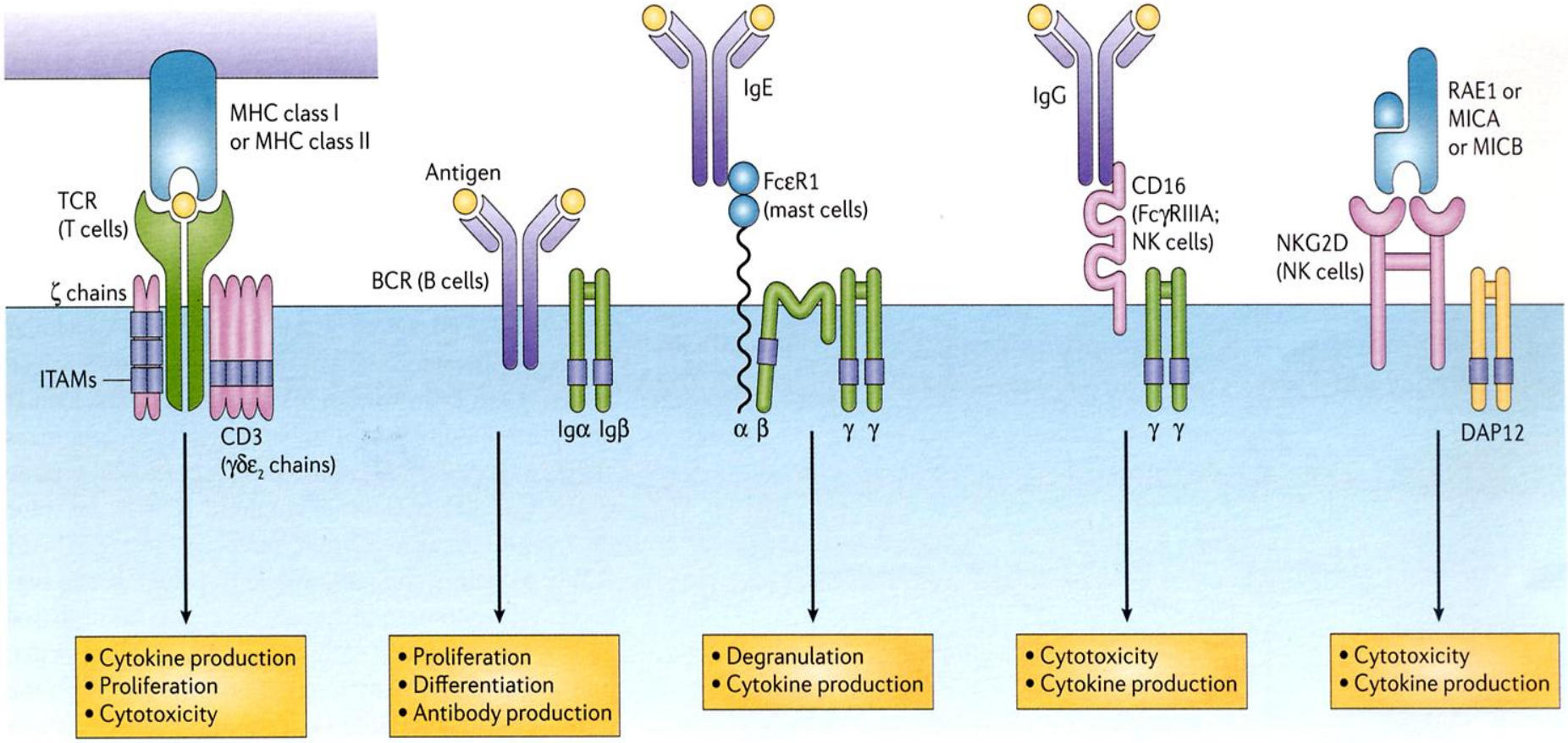
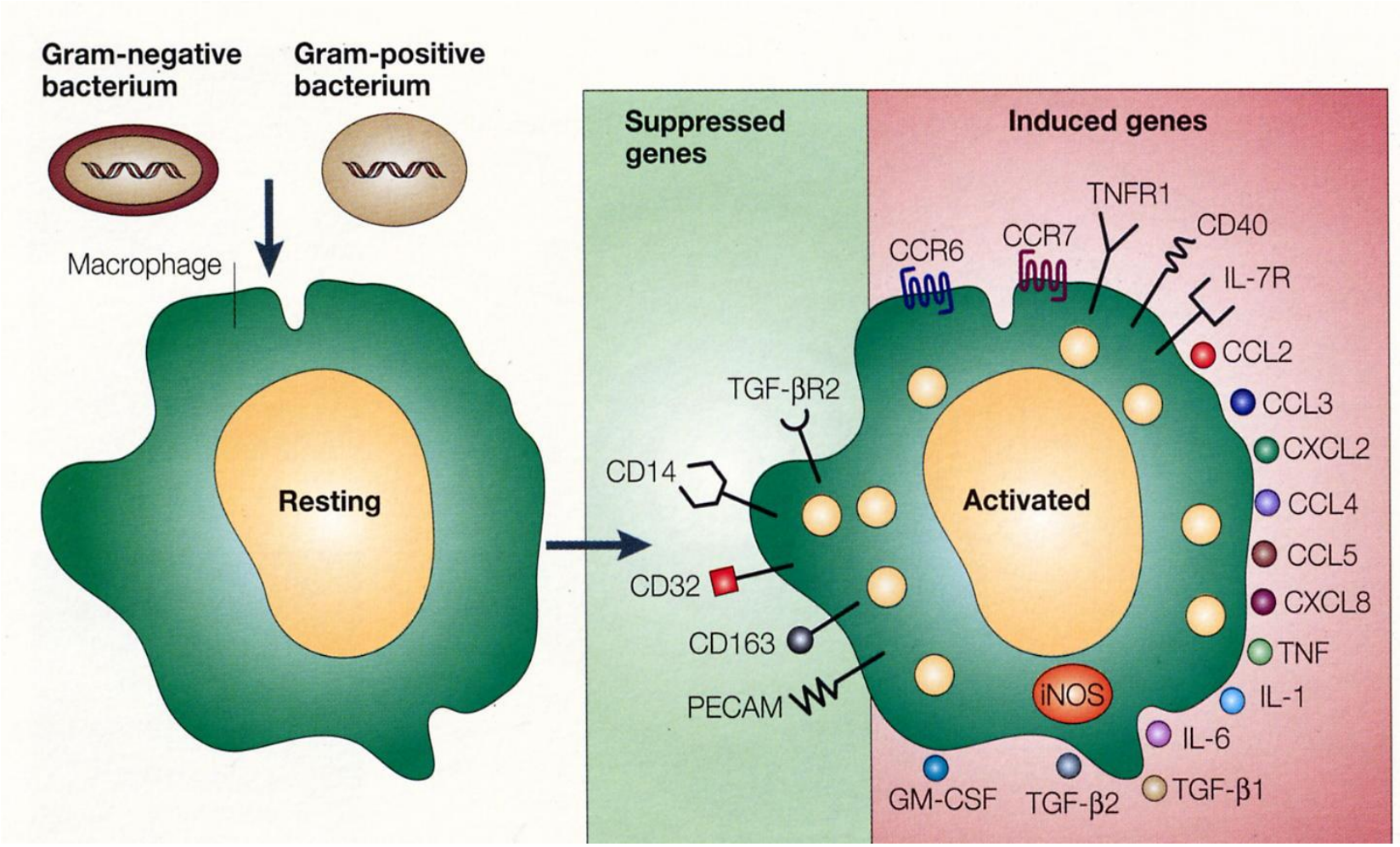


Figure 1 | **Immunoreceptors and their functions.** A schematic representation of the main types of activating immunoreceptors expressed in immune cells is shown. The ligand-binding subunits and signalling subunits, which contain immunoreceptor tyrosine-based activation motifs (ITAMs), are depicted. ITAMs are indicated as purple bars. Ligands are indicated at the top of the schematic; the responses elicited by ligation of the receptors are specified at the bottom. Igα, immunoglobulin-α; BCR, B-cell receptor; DAP12, DNAX activation protein 12; FcεRI, high-affinity receptor for IgE; FcγRIIIA (or CD16), low-affinity Fc receptor for IgG type A; IgE, immunoglobulin E; MICA, MHC-class-I-polypeptide-related sequence A; NK, natural killer; NKG2D, natural-killer group 2, member D; RAE1, retinoic acid early transcript 1; TCR, T-cell receptor.

The number of receptors in the cell membrane, usually quite a few, increases after activation



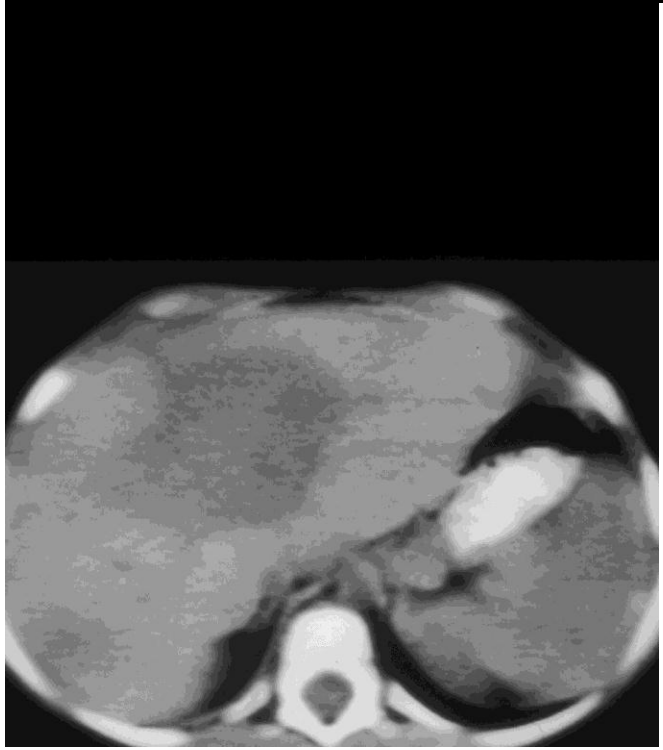
Complement defects :

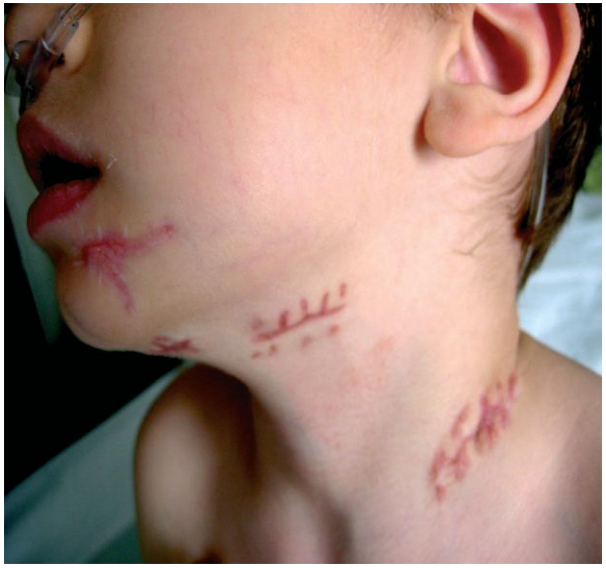
- Repeated bacterial infections
- SLE (autoimmune disease with defects in the elimination of immune complexes)
- Hereditary angioedema (defect in the regulation of the complement activation leading to persisten inflammation)

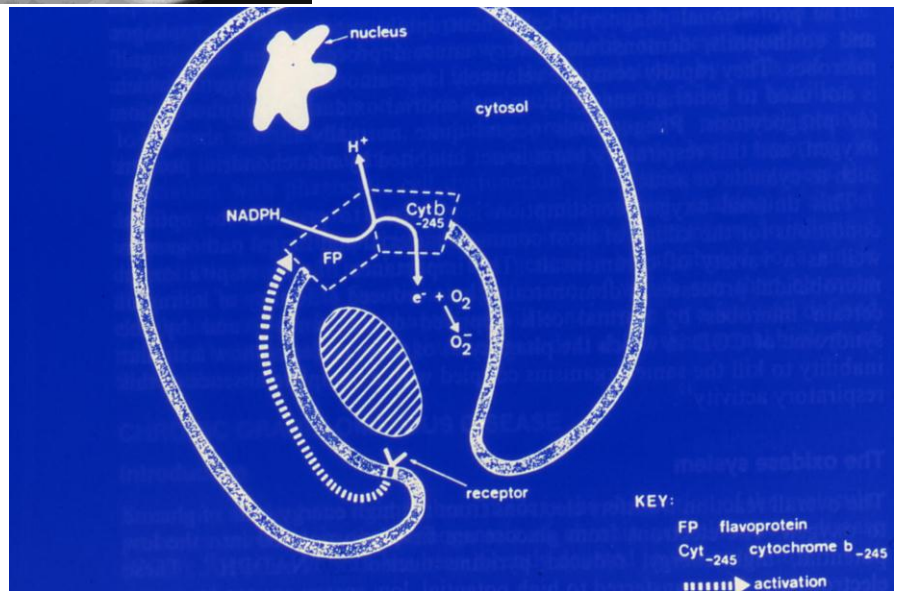
Table 7.1. Inheritance and therapeutic intervention in phagocyte function disorders[a]

Disease	*Inheritance*	*Treatment*	*Defective Characteristics*
Quantitative Phagocytic Disorder			
Reticular dysgenesis (lack of stem cells)	AR	BMT	Aberrant marrow environment
Kostmann syndrome (agranulocytosis)	AR	BMT	Growth or differentiation arrest
Cyclic neutropenia	Unknown	G-CSF Danazole?	Abnormal hormone regulation
Qualitative Phagocyte Disorders			
Adhesion defects (see Chapter 30)			
LAD-1	AR, Chr. 21	BMT	Deficiency of CD18 molecule
LAD-2	AR	—	Deficiency of sialyl Lewis X
Juvenile periodontitis	AD?	Oral hygiene	GP 110 glycoprotein defect
Chemotaxis defects			
Actin dysfunction	AR	—	Defects in actin assembly
Job syndrome	unknown	IFNγ/Vitamin C?	Hyper-IgE; T cell defect? PMN chemotactic defect
Respiratory burst activity disorders			
CGD (see Chapter 29)	AR, XR	IFNγ/BMT gene therapy?	Deficiency of any component of NADPH oxidase: gp91 phox, p22 phox, p47 phox or p67 phox
G6PD deficiency (severe)	XR	—	NADPH production defect in affected leukocytes
Glutathione synthetase deficiency	AR	Vitamin E, N-acetylcysteine	NADPH regeneration defect
Myeloperoxidase deficiency	AR, Chr. 17	Ketoconazole	Myeloperoxidase deficiency
Degranulation defects			
Specific granule deficiency	AR	—	Defective granule content with leukocyte chemotactic defects
Chediak-Higashi syndrome (see Chapter 31)	AR Chr. 1	BMT	Defective granular transport

Staphylococcal abscesses and adenitis in CGD patients







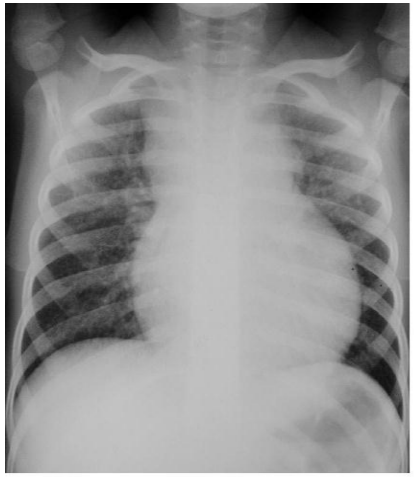
Defects in the molecules of the oxidative pathway

A lot of research work on the acquired immune response in front of infections, has been developed during many years, and shown to be very useful for understanding PID´s.

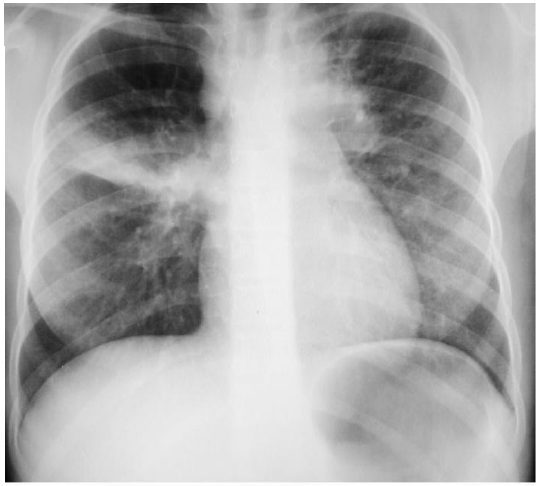
However, in recent years,description of new defects in the innate immune response have shown important pathogenic mechanism against many more infections.
Some of these new PID´s are, perhaps, no so severe, but probably more frequent than we think.

AN EXAMPLE:

A girl with normal Ig´s, complement levels and antibody production. Normal T and B cells and neutrophils……



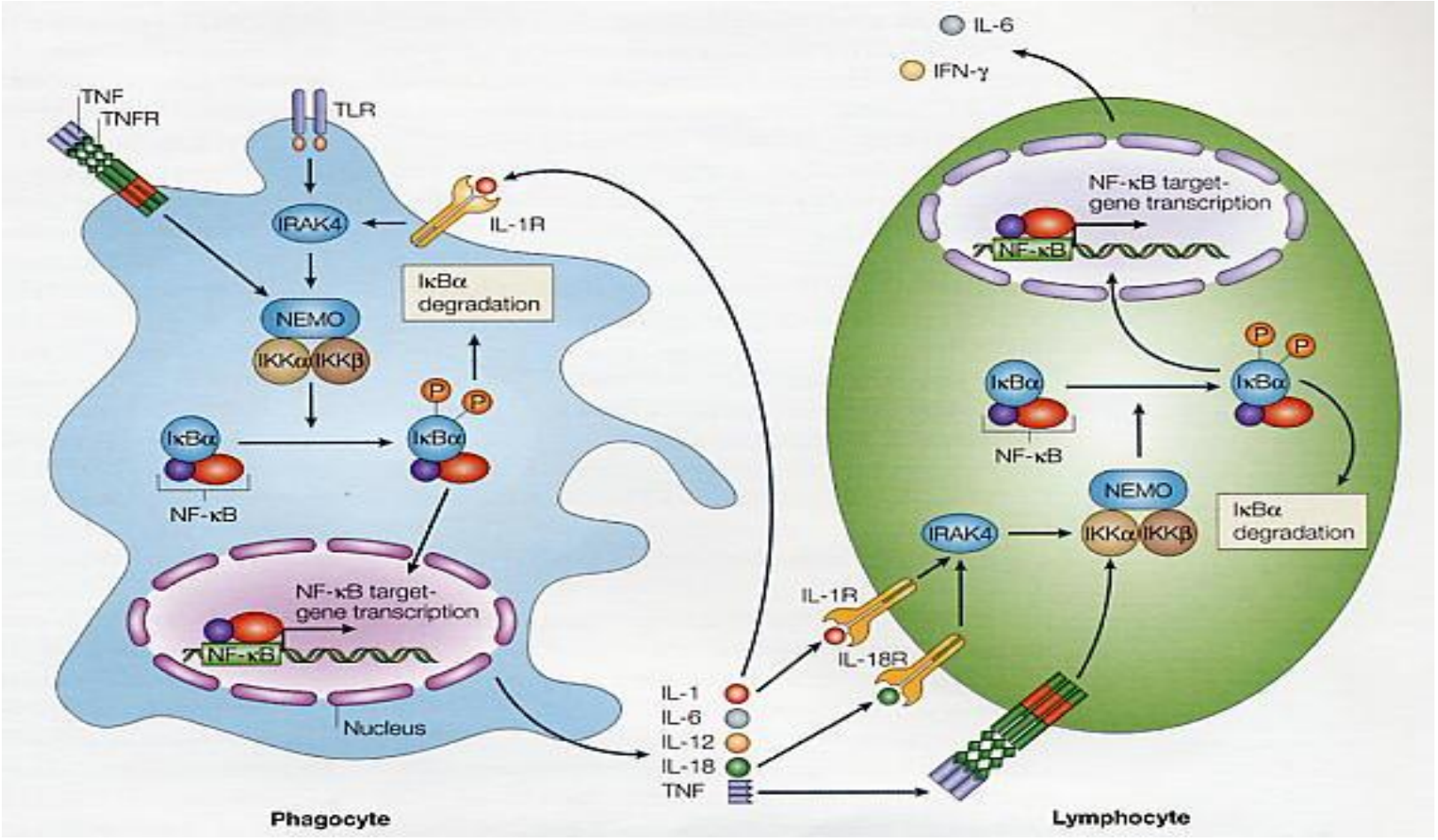
5-year-old girl. Fever, HEM, cardiomegaly, respiratory distress
Diagnosis miliary Tb
Previous Salmonella infection



10-year-old sister.
Bronchogenic Tb

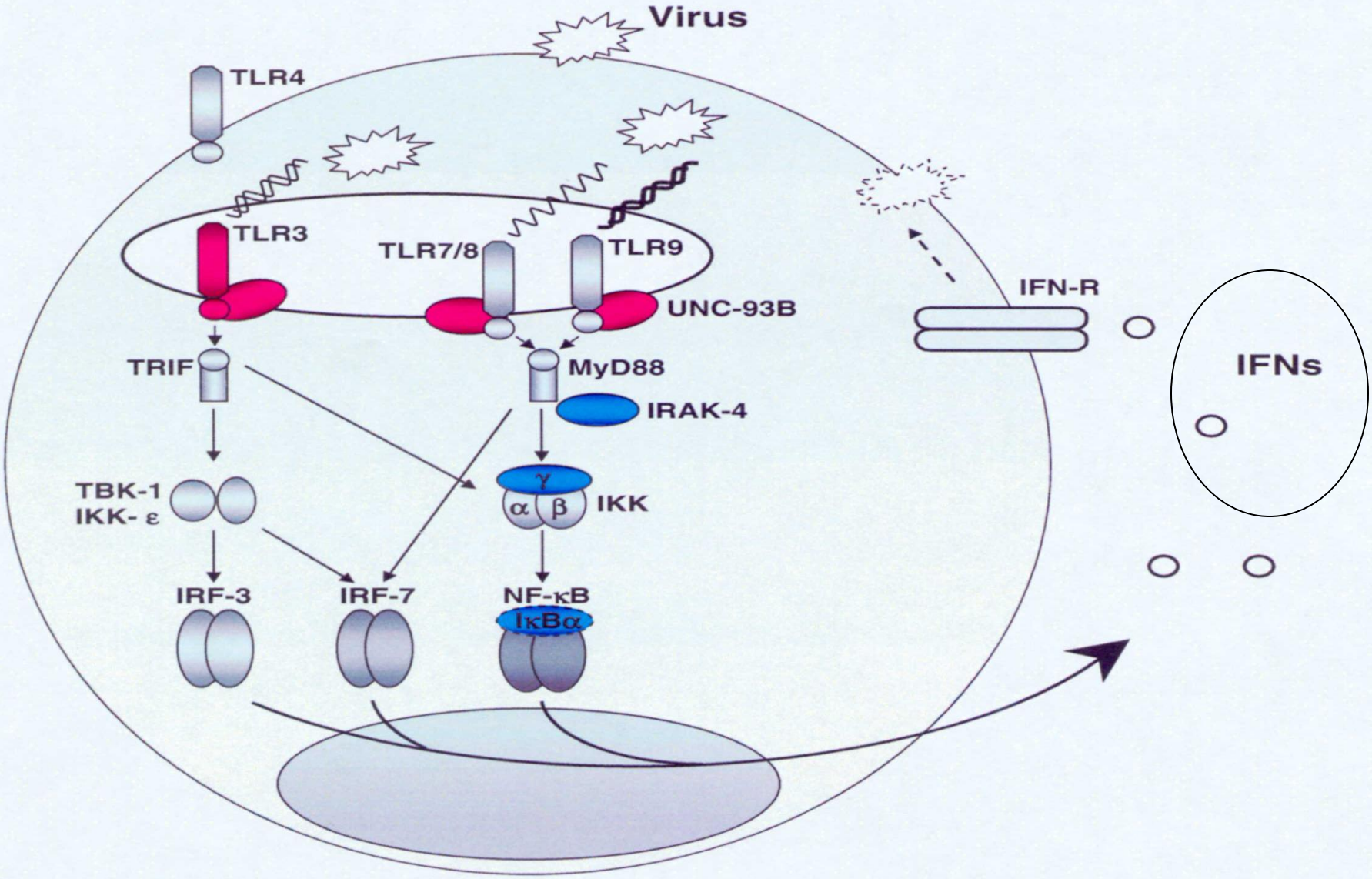
IL-12 (β1) receptor deficiency
Parents heterozygous
I. Caragol et al. Clin. Infect Dis 2003

Anti-mycobacterial response: IL-12/IFNγ pathway



IRAK4 defects = severe pyogenic infections (Pneumococcus septicaemia)

More than 420 cases diagnosed of mutations in the IL-12/INγ pathway



Severe herpes infections in TLR3 deficiency

Therapies for Innate IR defects:

- use of BMT in congenital neutropenia, CGD, etc and probably for severe defects of the receptors or intracellular signalling proteins of the innate response cells (always with an HLA compatible donor)

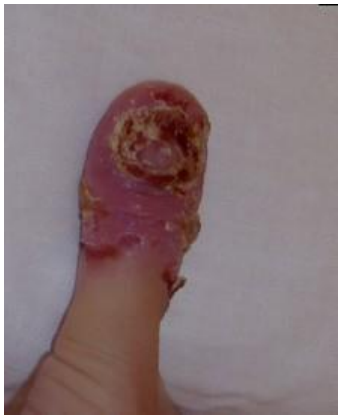
- use of inhibitors of inflammation

- use of IFNγ in severe cases of IL-12/IFNγ pathway defects. etc

NEW genes in the last 5 years

- Immunodeficiency syndromes predisposing to cutaneous viral infections: 4 different genes
- *Sex-linked ID due to…*
- ID predisposing to mucocutaneous candidiasis and /or other fungal infections (IL-17 and others)
- *Hypomorphic SCID*
- Increased susceptibility to herpes simplex encephalitis

TA Fleisher. AAAAI 2012



And, probably, some more !!