# Natural killer cells and other innate lymphoid cells

Prof. Giovanni Bernardini 12 Novembre 2024

# Today's topics

End of T helper effector cell differentition

An introduction to innate lymphoid cells functional and phenotypic diversity

NK cells: a population of cytotoxic innate lymphoid cells

NK cells: mode of recognition and of self tolerance

# Specializzazione della risposta immunitaria

## L'esempio del differenziamento di linfociti T helper

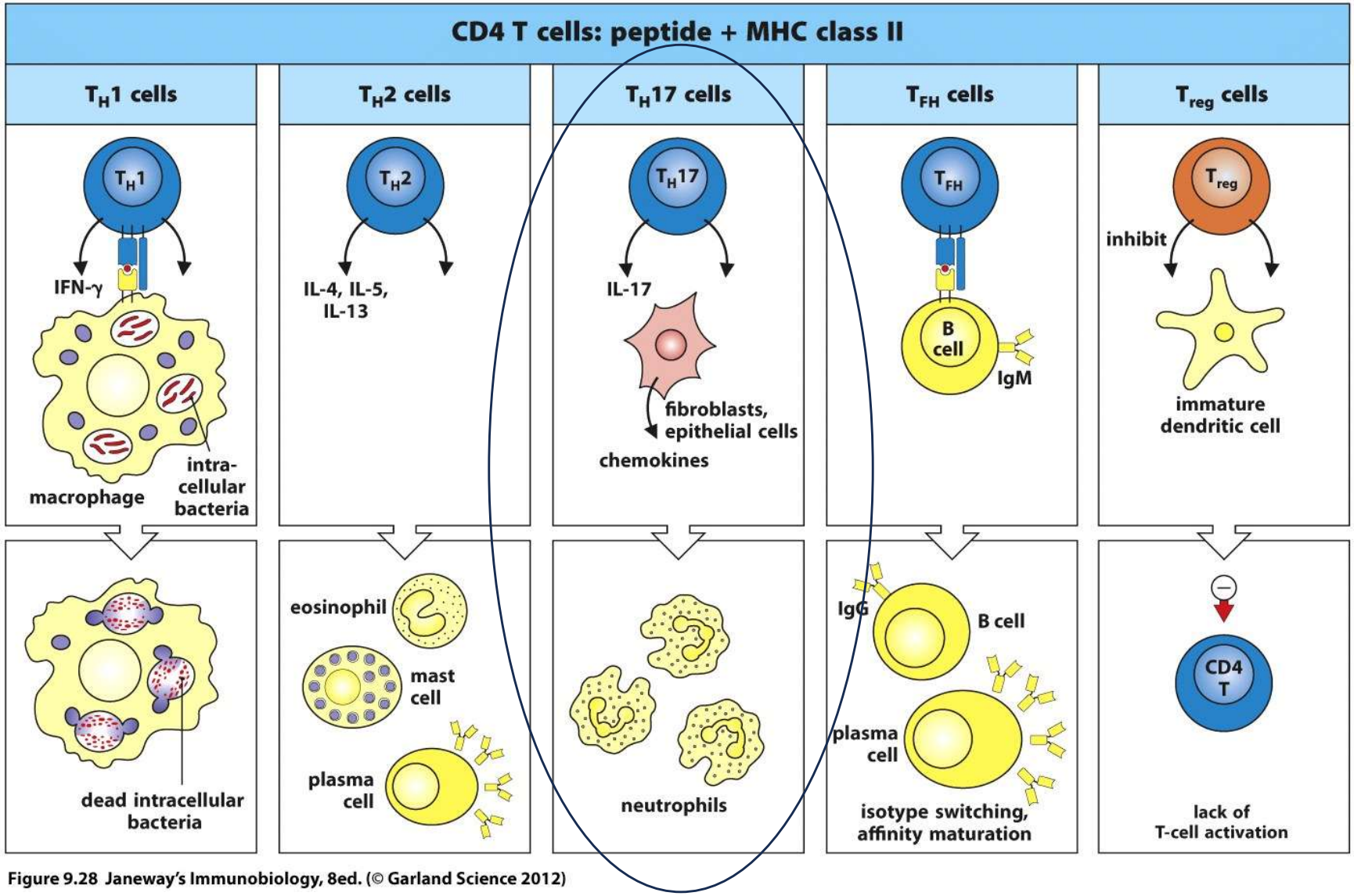
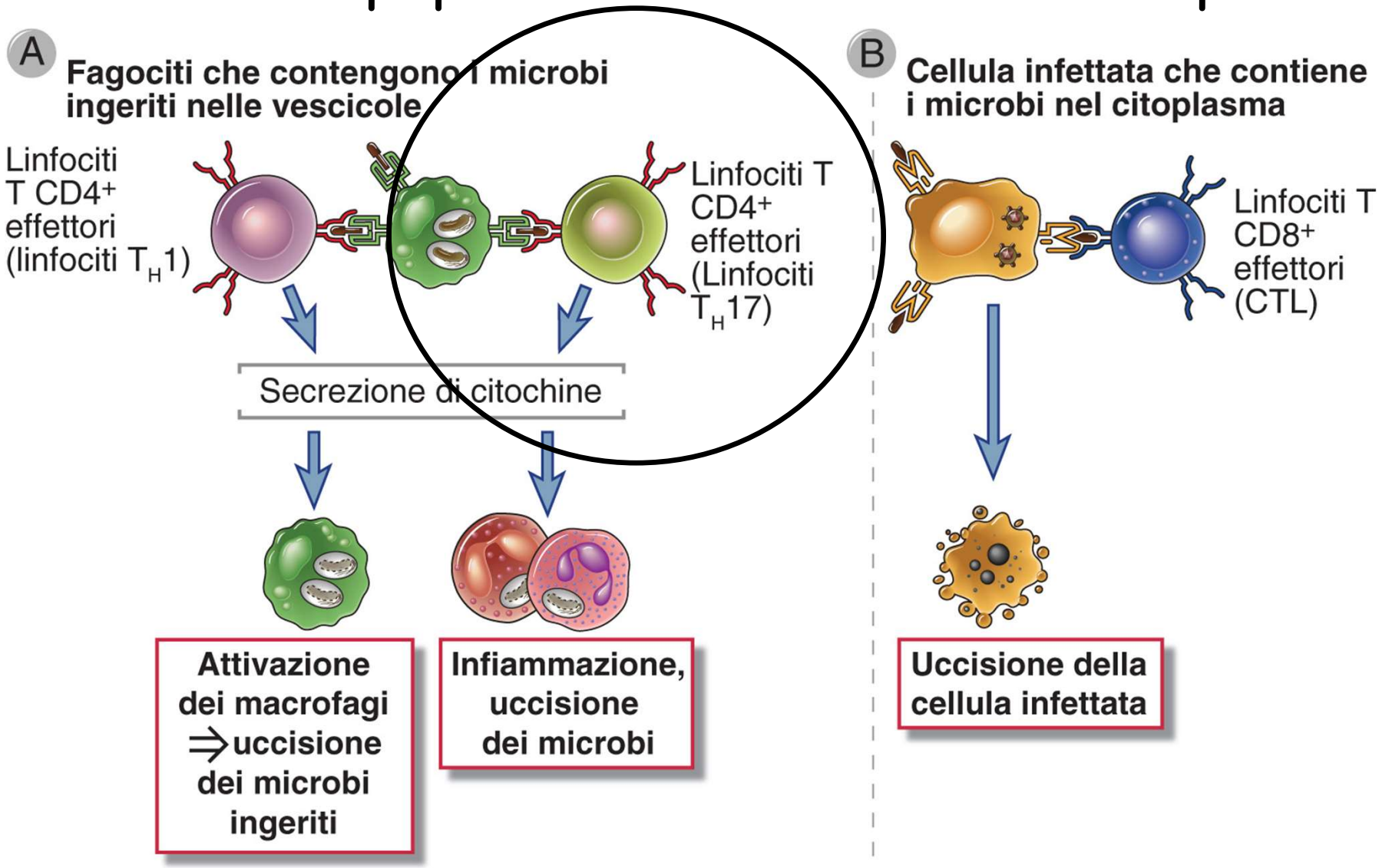



Figure 9.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# In alcuni tipi di risposta cellulo-mediata è richiesta un'altra popolazione di linfociti T helper

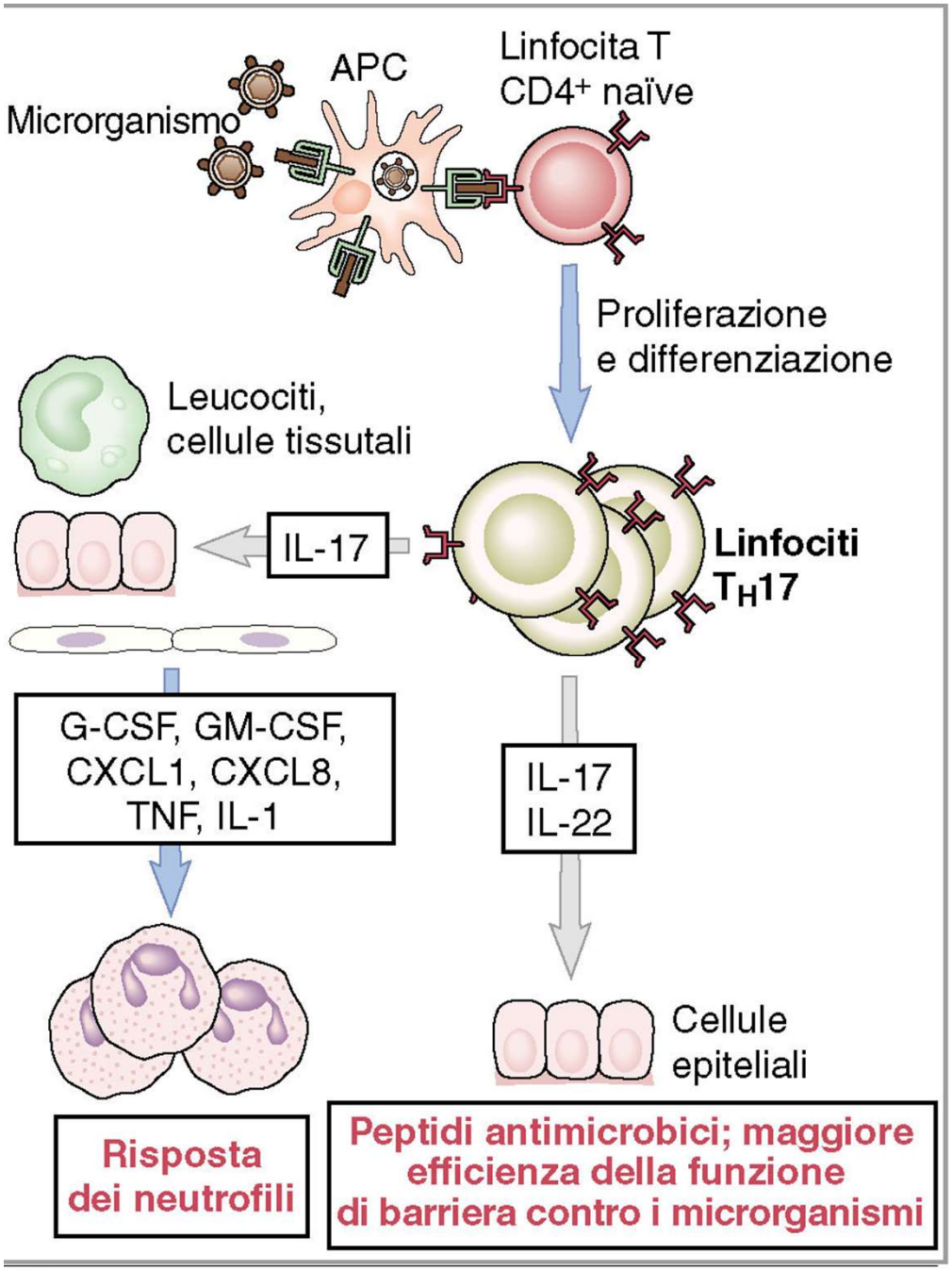



gr1.jpg

Immunologia cellulare e molecolare 7 ed

Risposte immunitarie dei linfociti T. A. I linfociti T CD4<sup>+</sup> riconoscono gli antigeni dei microrganismi extracellulari o fagocitati e producono citochine che stimolano l'attività microbicida e proinfiammatoria dei fagociti. Anche i linfociti CD8<sup>+</sup> possono contribuire a questi processi secernendo citochine. B. I CTL CD8<sup>+</sup> riconoscono gli antigeni peptidici di origine microbica associati a molecole MHC di classe I. Queste cellule sono importanti per combattere i microbi che risiedono nel citoplasma delle cellule infettate provocandone la morte.

# I linfociti Th17




gr16.jpg

Le basi dell'immunologia - 3 Ed. aggiornata

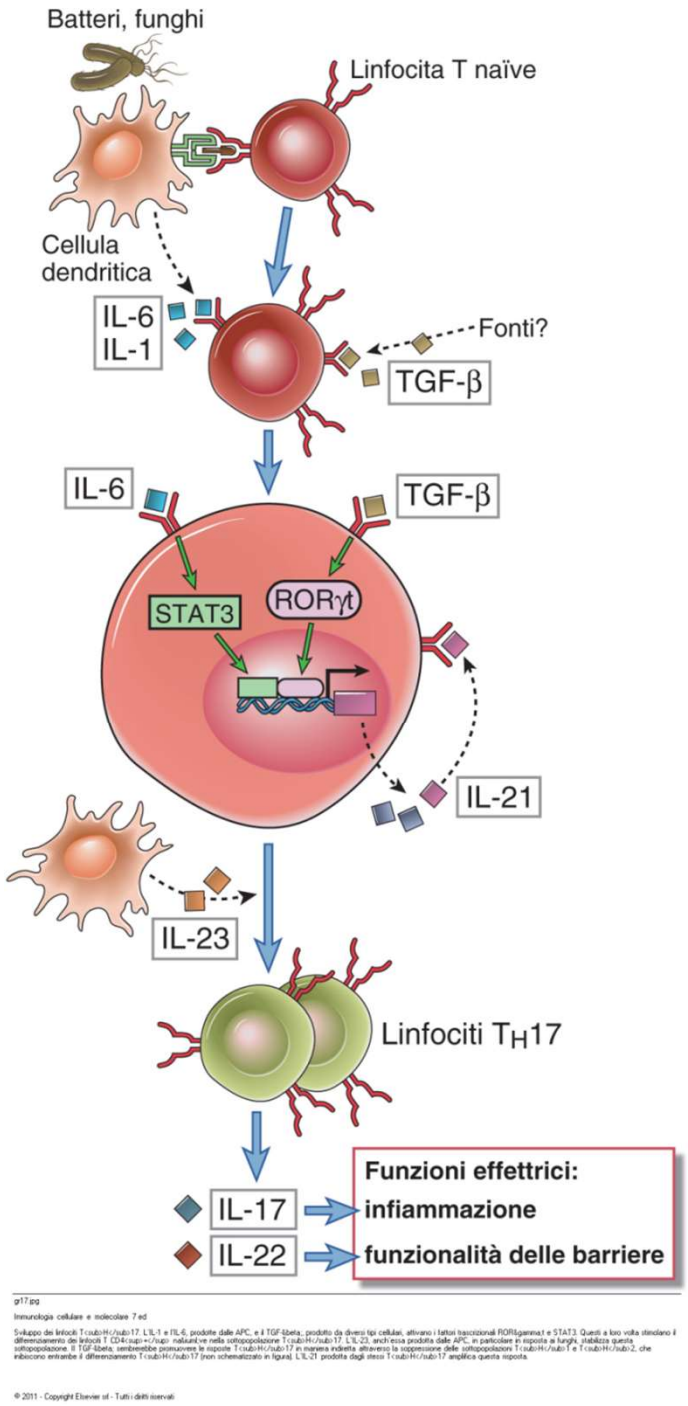
- Sono posizionati in maniera da attaccare funghi e batteri secernendo fattori che attirano e attivano neutrofili
- Proteggono le superfici esterne e interne (cute e intestino) contro batteri extracellulari e funghi

- Esprimono preferenzialmente il recettore per chemochine CCR6 che lega la chemochina CCL20 prodotta da cellule tissutali durante certi tipi di infezioni batteriche e fungine.

# TH17 Decision Making

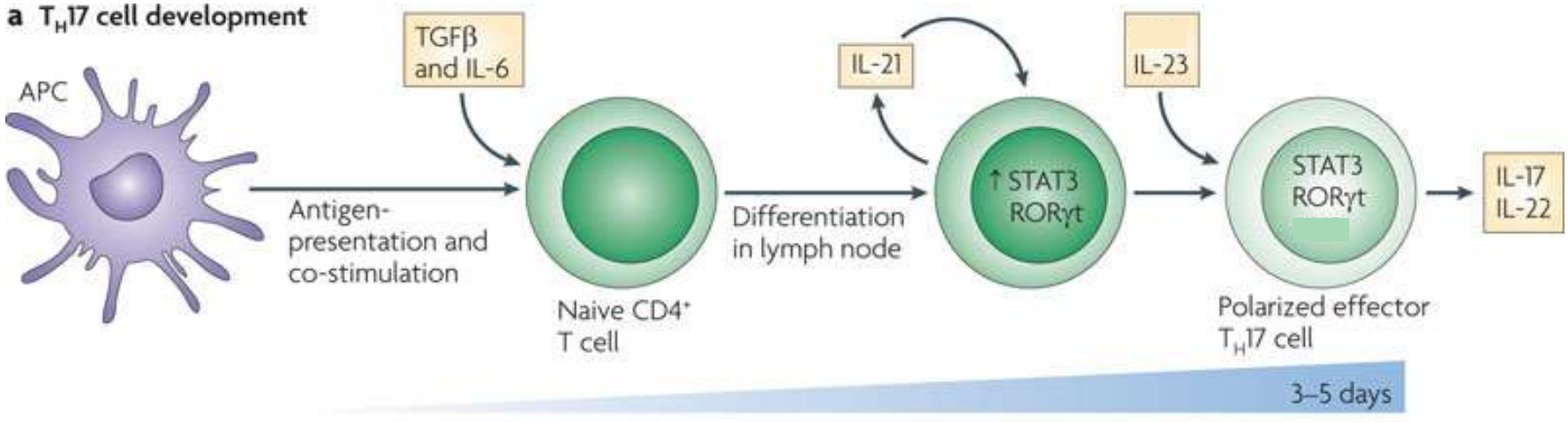
INDUZIONE e INDIRIZZAMENTO

AMPLIFICAZIONE




retinoic acid receptor-related orphan receptor-γt (RORγt)

# I linfociti Th17




INDUZIONE e INDIRIZZAMENTO

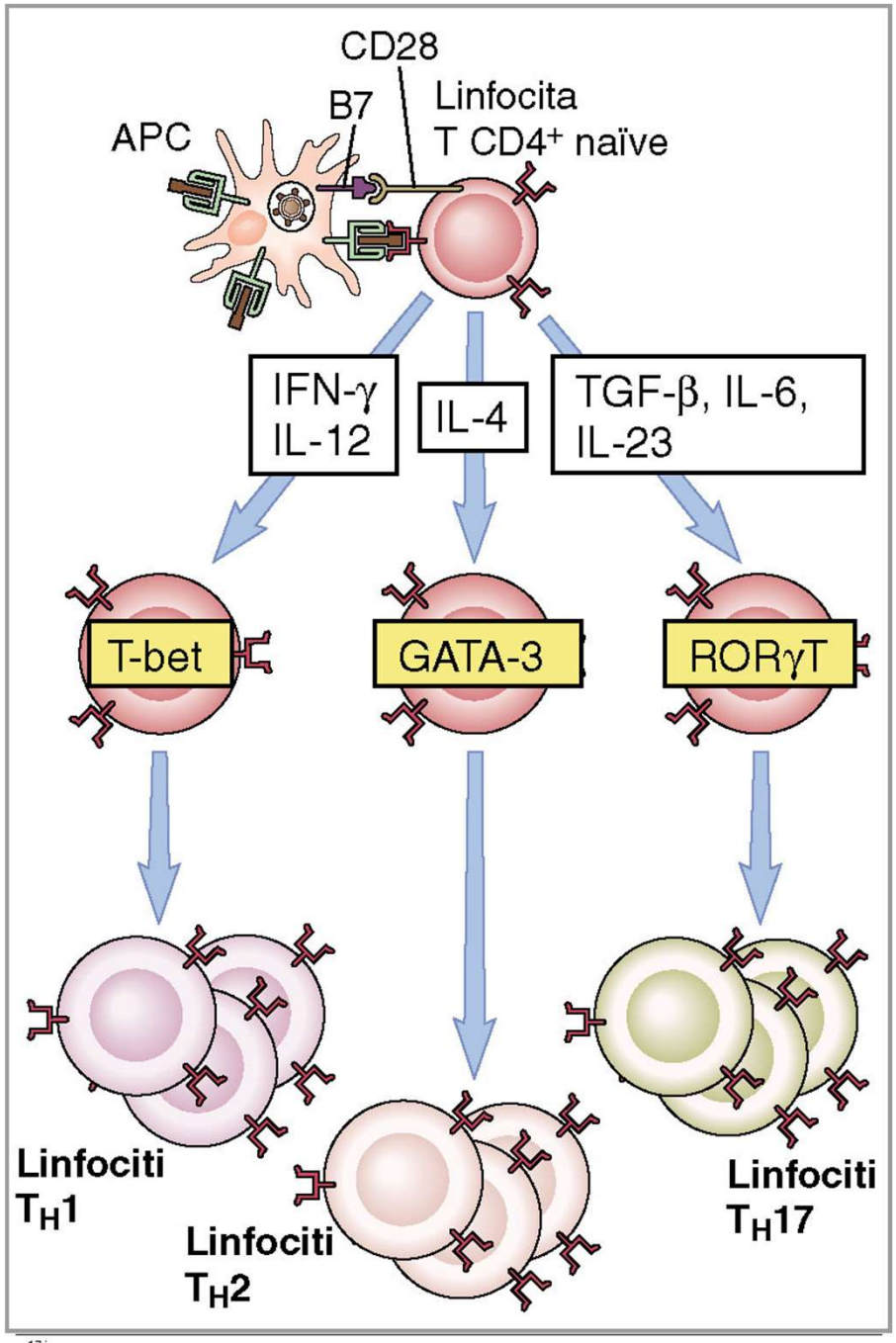
AMPLIFICAZIONE

- **Si generano da linfociti T naive esposti a TGF-β in presenza di IL-6**

- **I linfociti rispondono esprimendo il fattore trascrizionale RORγt e STAT3 e la citochina IL-21**

- **I fattori di trascrizione attivano la sintesi di IL-17 e del recettore di membrana per IL-23 (che consente la proliferazione delle cellule Th17)**

# Generazione di sottopopolazioni di linfociti T CD4+




Attivazione cellulare

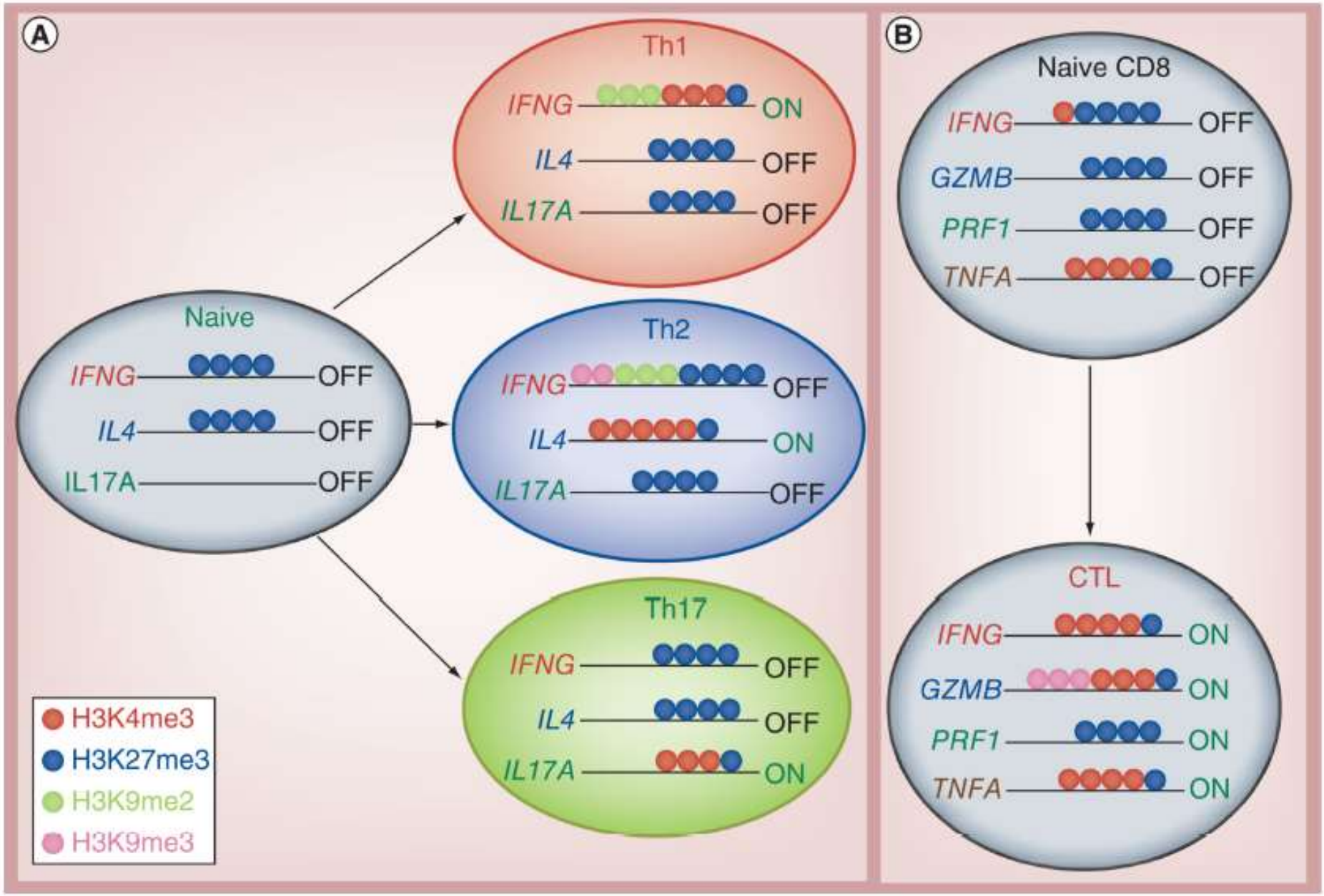
Risposta a citochine

Induzione dell'espressione o attivazione di fattori di trascrizione

Differenziamento

# Come fanno le citochine a orientare il differenziamento dei Linfociti T?

I diversi fattori di trascrizione associati alle diverse popolazioni di linfociti T determinano e le modificazioni della cromatina nei loci genici delle citochine (es. metilazione o acetilazione istonica) e l'espressione delle citochine


A
Naive
IFNG OFF
IL4 OFF
IL17A OFF
Th1
IFNG ON
IL4 OFF
IL17A OFF
Th2
IFNG OFF
IL4 ON
IL17A OFF
Th17
IFNG OFF
IL4 OFF
IL17A ON
H3K4me3
H3K27me3
H3K9me2
H3K9me3
B
Naive CD8
IFNG OFF
GZMB OFF
PRF1 OFF
TNFA OFF
CTL
IFNG ON
GZMB ON
PRF1 ON
TNFA ON

# Rilevamento OPIS

| | | | Corso di Studi | Modulo | Insegnamento |
|---|---|---|---|---|---|
| 6Y7IJARZ | 2025 | 0 | BIOTECNOLOGIE (29887) | IMMUNOLOGIA I (1051487_2) | IMMUNOLOGIA (1051487) |

1. **Prima del log-in è utile disattivare il blocco "pop up" del browser**
2. **Dalla *home page* di uniroma1 https://www.uniroma1.it selezionare:** STUDENTI
3. **Cliccare sul pulsante «Mobile» (procedura più rapida)**


**Log-in** **2/2**

**Inserire codice OPIS → Questionario**

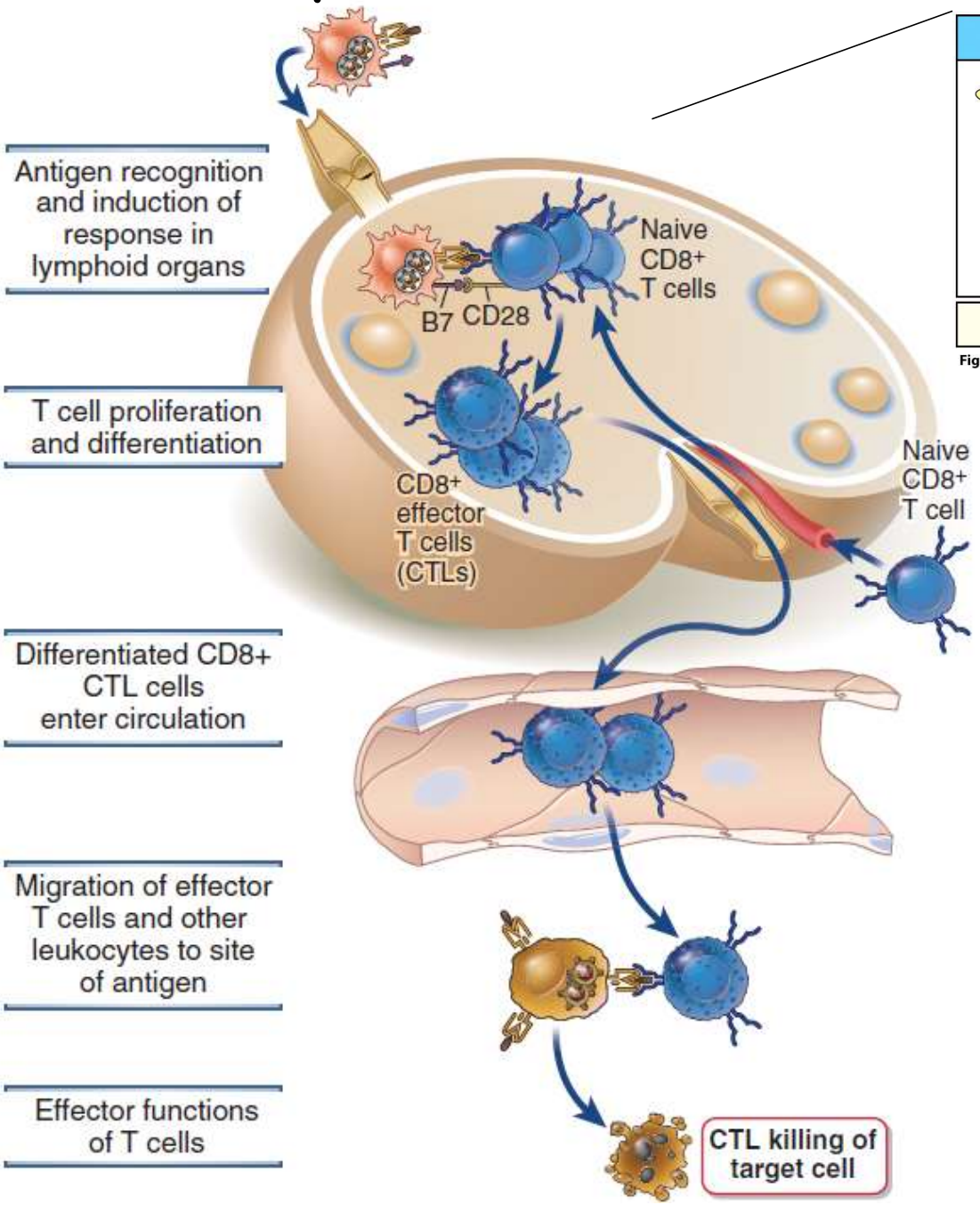
1. **Inserire il codice OPIS fornito dal docente**
2. **Una volta inserito il codice selezionare** vai al questionario
3. **Quindi si sarà indirizzati al questionario da compilare**


4. **Per accedere all'area riservata agli studenti di InfoStud è necessario autenticarsi tramite SPID/CIE**

Peripheral lymphoid organ

Site of infection

# Cytotoxic T cell development



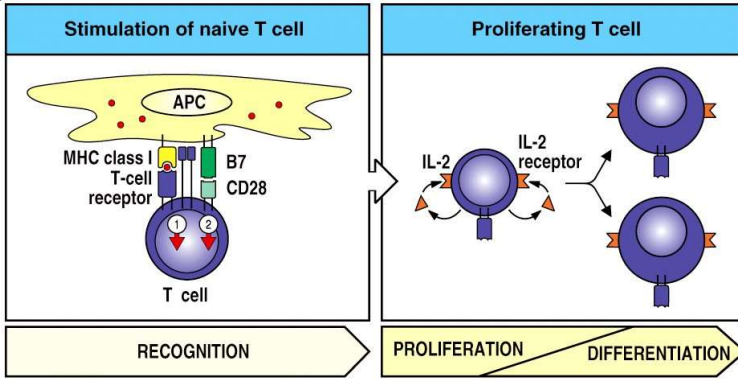



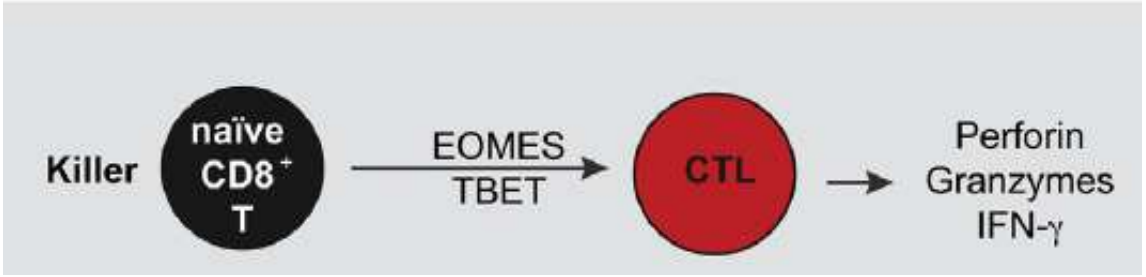

Figure 8-22 Immunobiology, 6/e. (© Garland Science 2005)

The molecular events in CTL differentiation involve transcription of genes encoding proteins, including **perforin** and **granzymes**, whose function is to kill target cells.
These proteins are loaded into numerous modified lysosomes (called granules) during differentiation

**The transcription factors** of the T-box family eomesodermin (**EOMES**) and TBX21 (**T-bet**) contribute to the high level of expression of **perforin, granzymes, and some cytokines, especially IFN-γ** in CTLs.

This is true also for innate lymphoid cells, i.e.the **natural killer (NK) cells**

2 major cytotoxic lymphocyte populations:

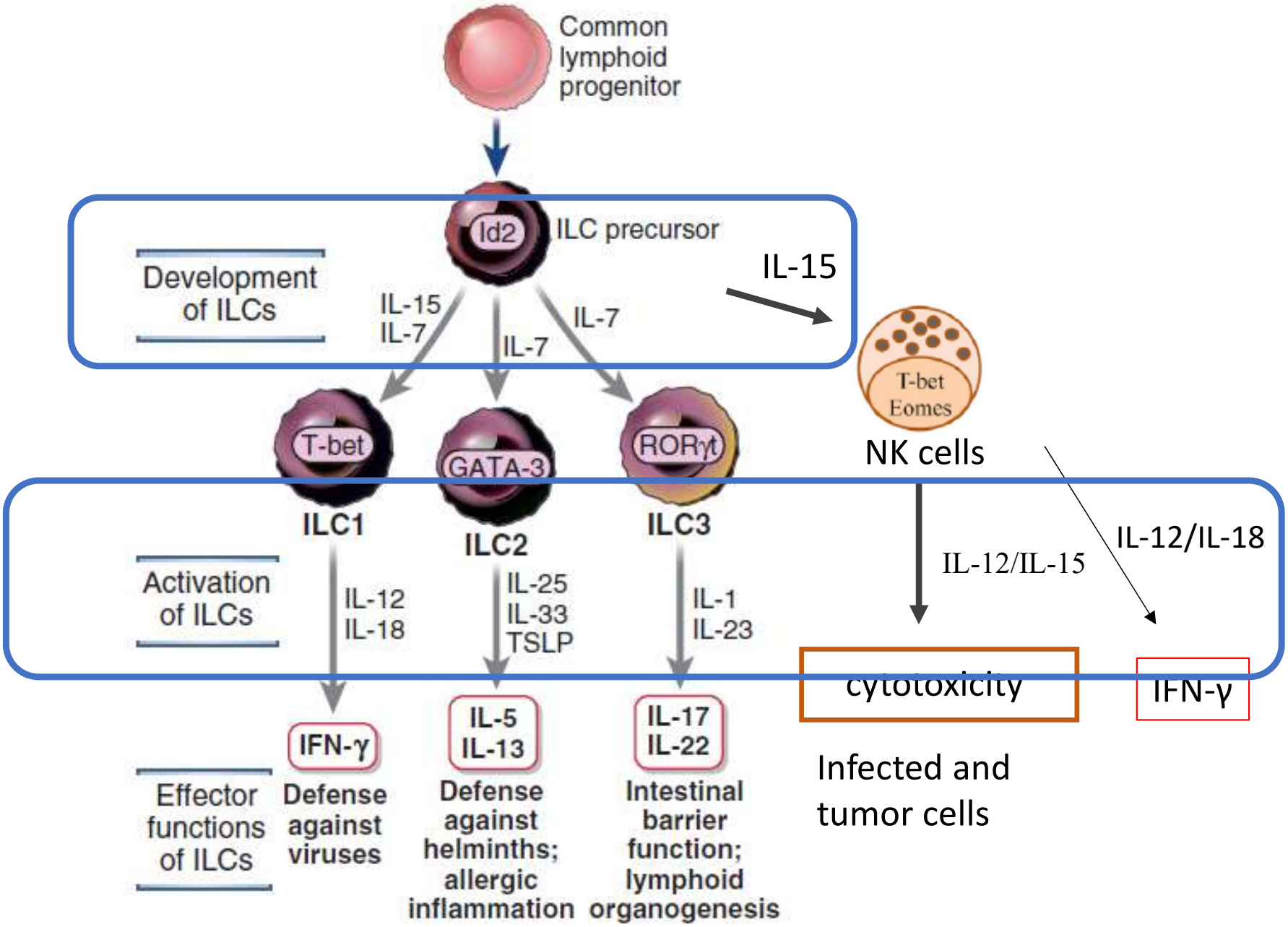



❑ $CD8^+$ T lymphocytes CTL


❑Natural Killer cells NK

Different mechanisms for target cell recognition

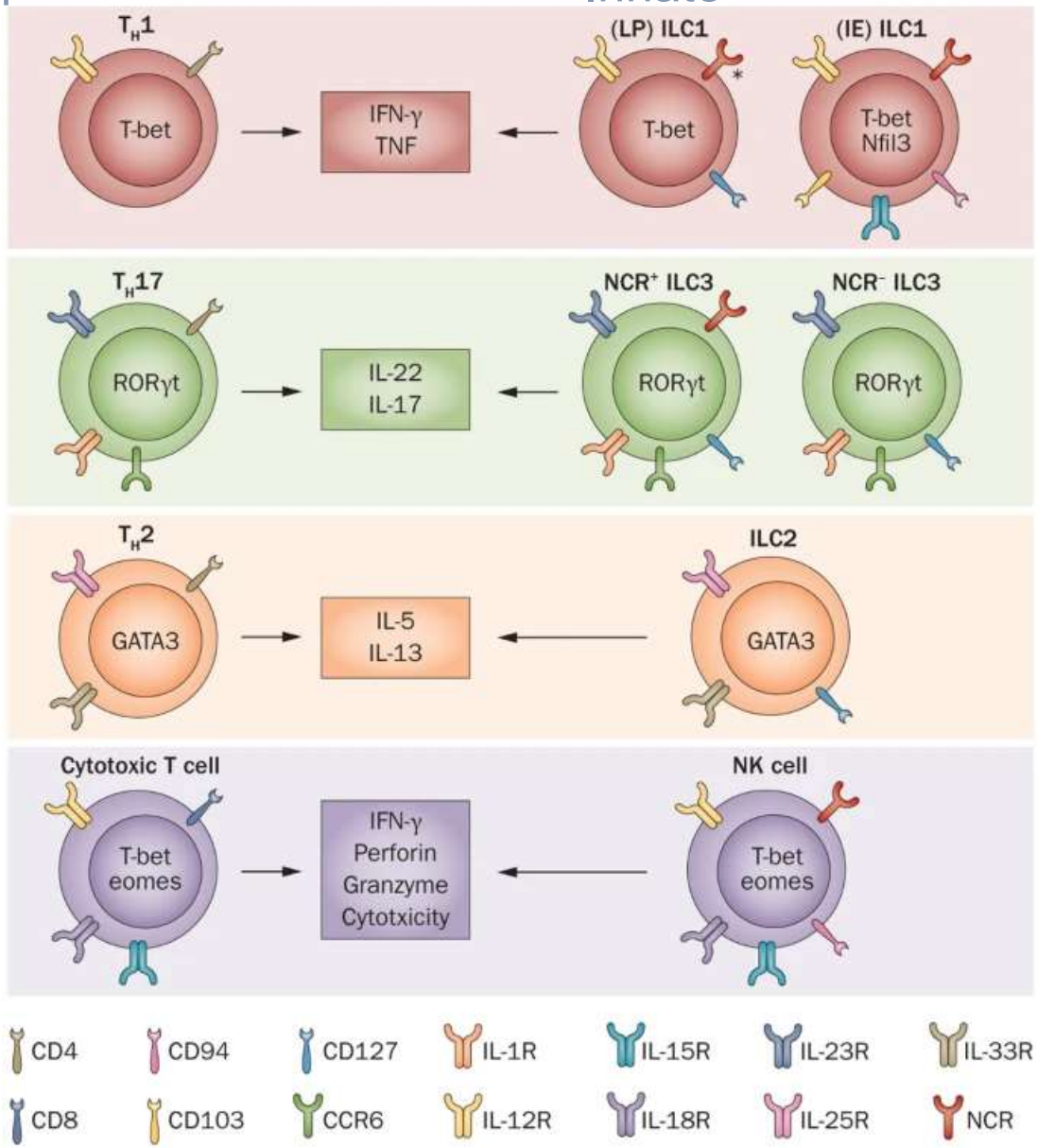
# Cytokine-producing and cytotoxic innate lymphoid cells (ILC)



# The expanding family of ILCs

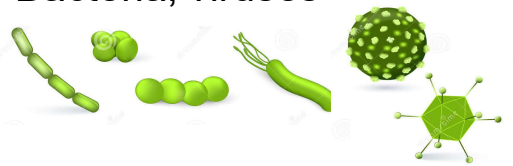
Adaptive T cell

Innate ILC




Nature Reviews | Gastroenterology & Hepatology

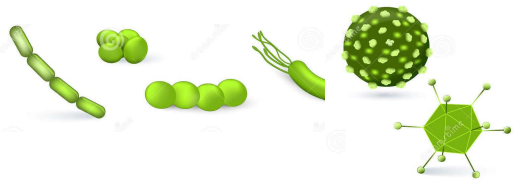
Intracellular pathogens
Bacteria, viruses



Extracellular bacteria
and fungi

Extracellular pathogens
Parasites, worms

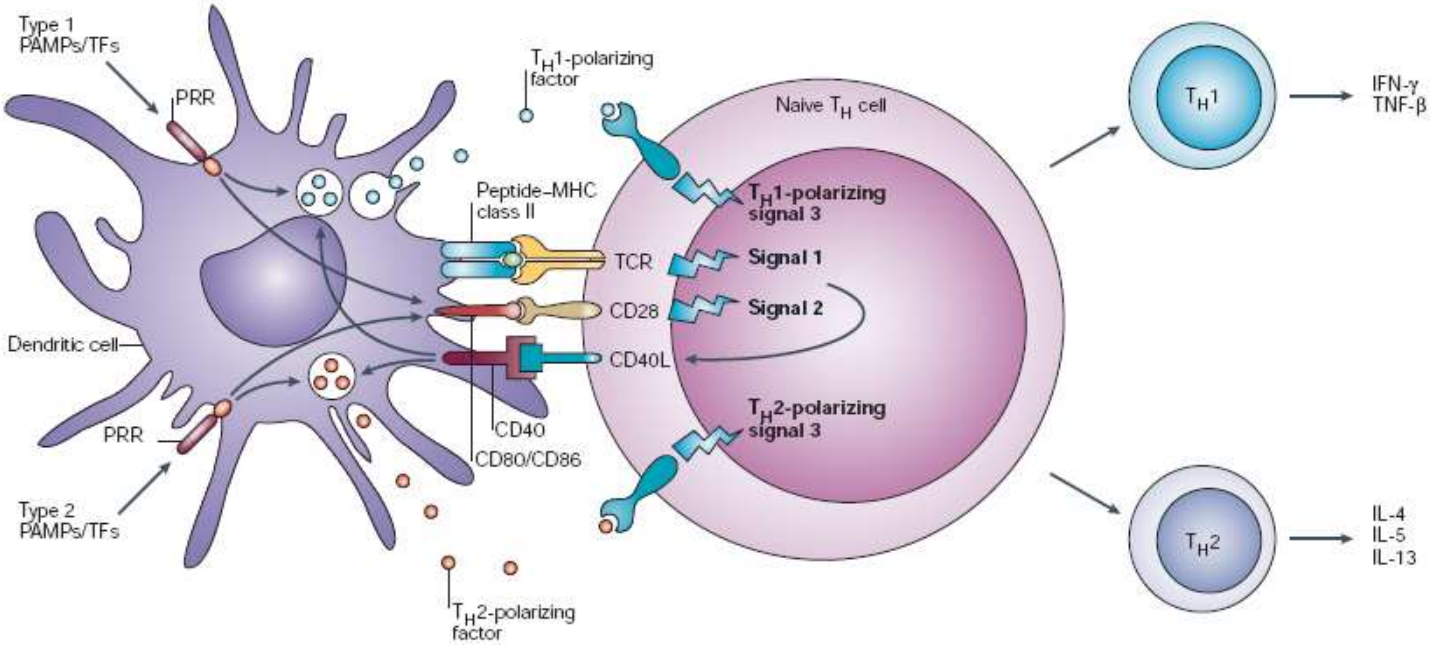
Intracellular pathogens
Bacteria, viruses



# *Adaptive vs. Innate Lymphocytes*

1. *T cell receptor (TCR)*
2. *Co-stimulation*
3. *Cytokines*

# *Adaptive vs. Innate Lymphocytes*




*Days / Weeks*

# TH1/TH2/Th17 Decision Making

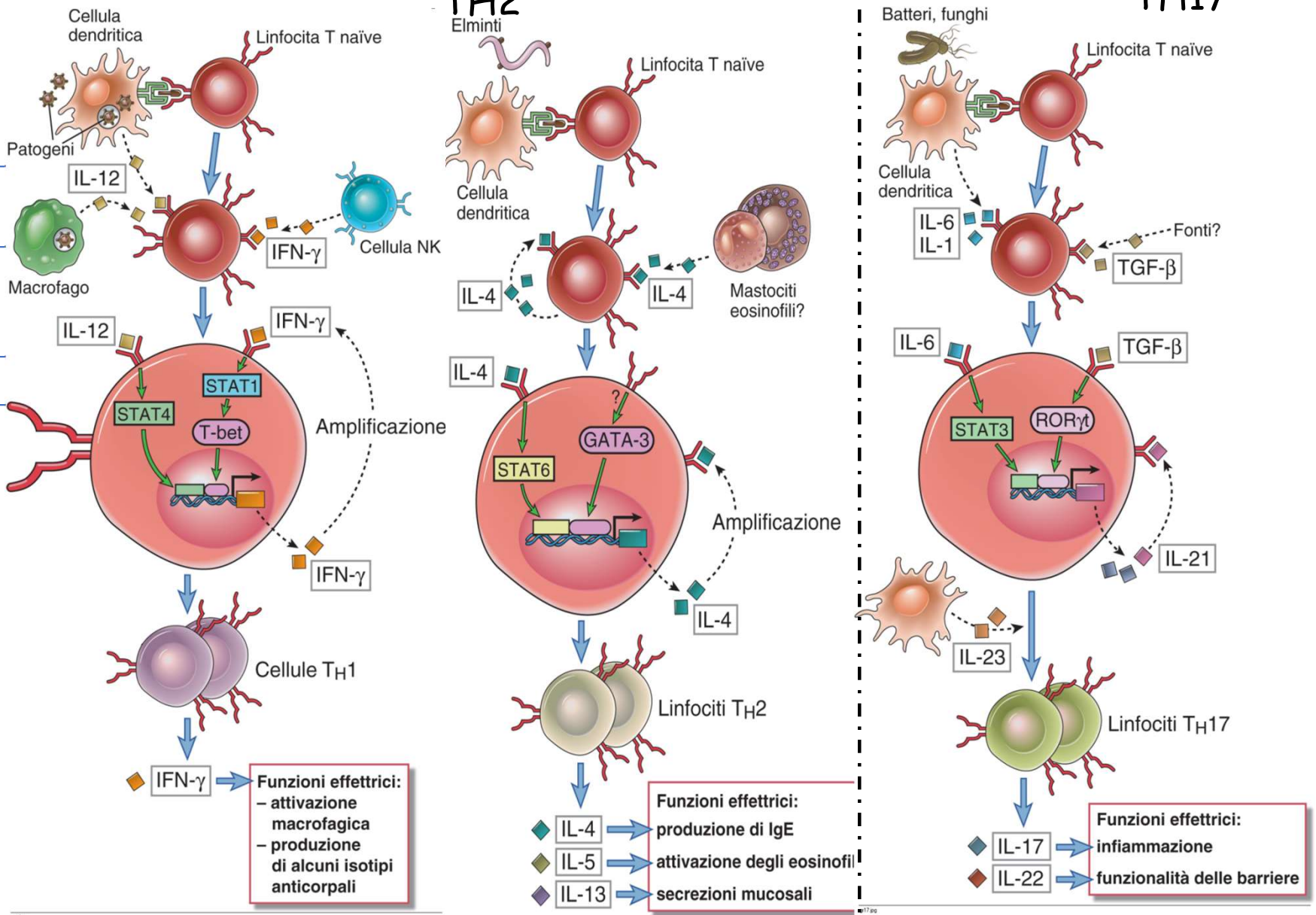
TH1

TH2

TH17

INDUZIONE e INDIRIZZAMENTO

AMPLIFICAZIONE

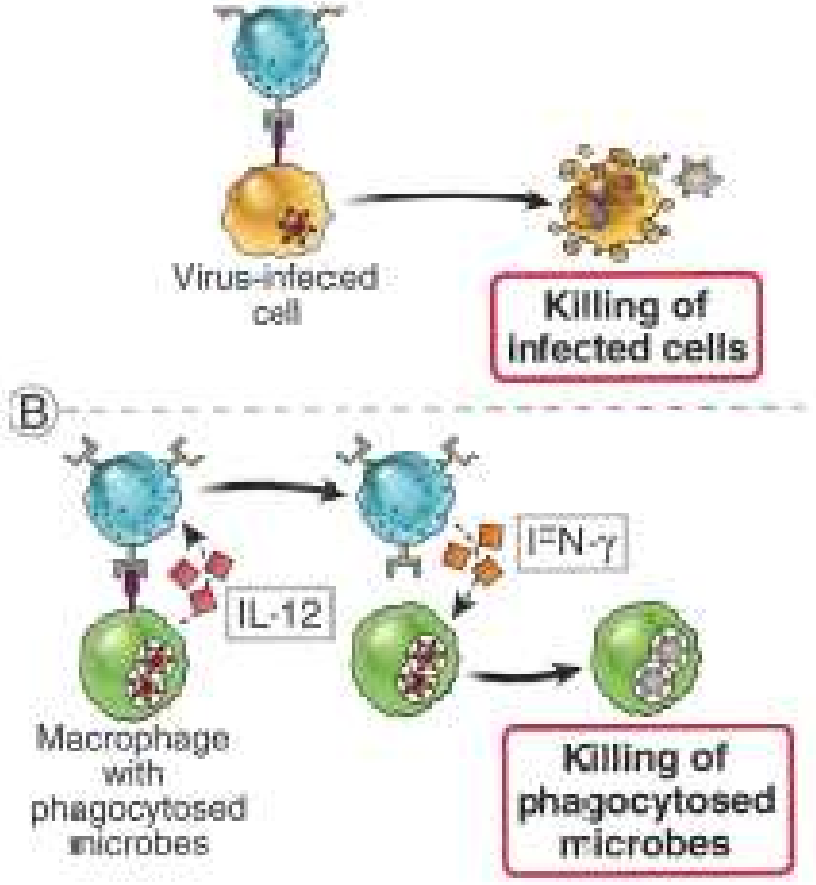


# *Adaptive vs. Innate Lymphocytes*

1. *TCR*
2. *Co-stimulation*
3. *Cytokines*

*Hours!!!*

# Natural killer cells are citotoxic cells able to recognize infected or stressed cells




The "natural killer" designation derives from the fact that their major function is killing infected cells (similarly to CTLs), and they are ready to do so after development, without further differentiation (hence natural).

In addition, NK cell–derived IFN-γ increases the capacity of macrophages to kill phagocytosed bacteria, similarly to IFN-γ produced by T cells

# *The expanding family of ILCs*

Type 1 ILC

Innate


NK cells


ILC1

Adaptive


CTL

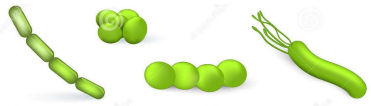

Th1

**Cytotoxic**

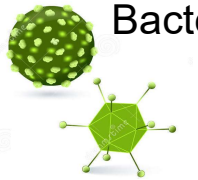
Granzymes,
Perforin
IFN-gamma

**Type I**

IFN-gamma, TNF-alpha,
CCL3-5



Intracellular pathogens
Bacteria, viruses



## Differences and similarities with T cells

- Cytokine production
- Killing properties
- Tissue localization

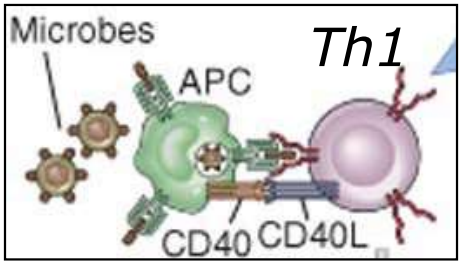
# Type 1 ILCs maintain tissue homeostasis and prompt immune responses

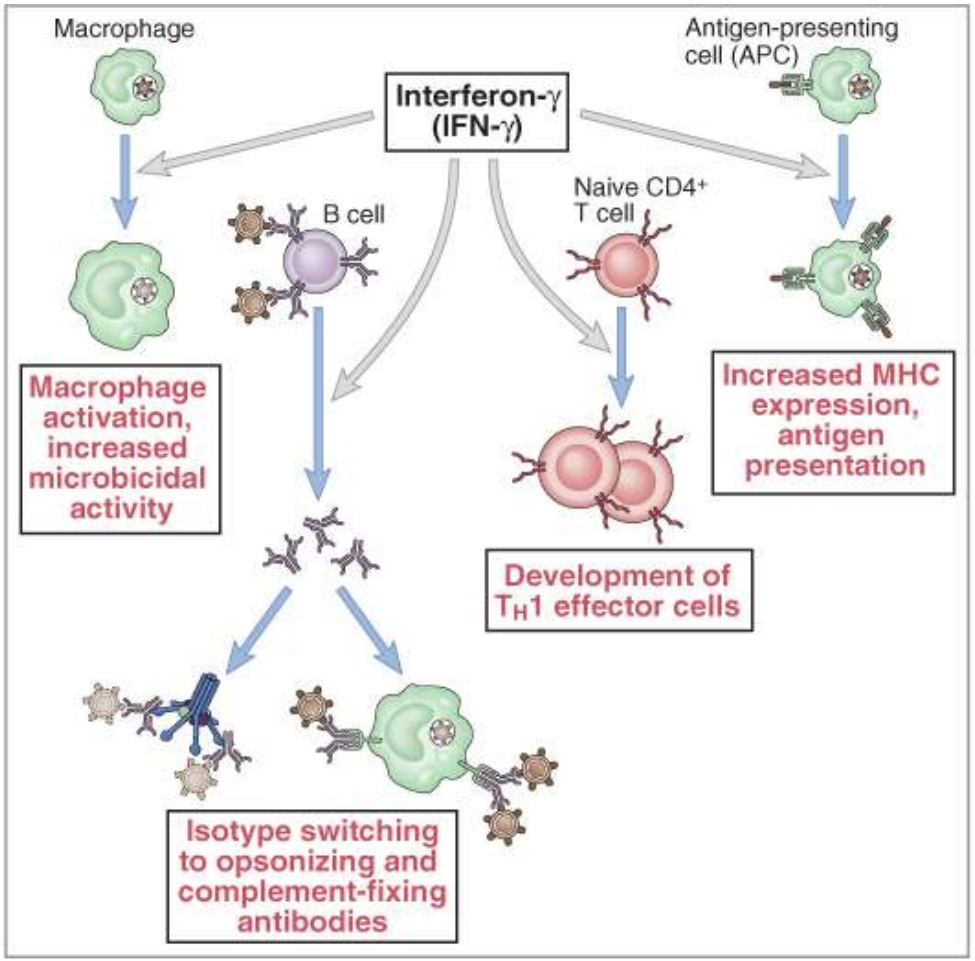
**Circulating** NK cells: cell–cell contact receptors enabling them to patrol, scan and assess health-status of host cells.

**Tissue-resident** ILCs: assess the *status quo* by sensing secreted environmental signals including cytokines, metabolites, and (neuro) peptides.

# Why do different IFN-gamma-producing and cytotoxic lymphocytes exist?

*L'interferone gamma è la principale citochina responsabile dell'attivazione dei macrofagi*



# Why do different IFN-gamma-producing and cytotoxic lymphocytes exist?

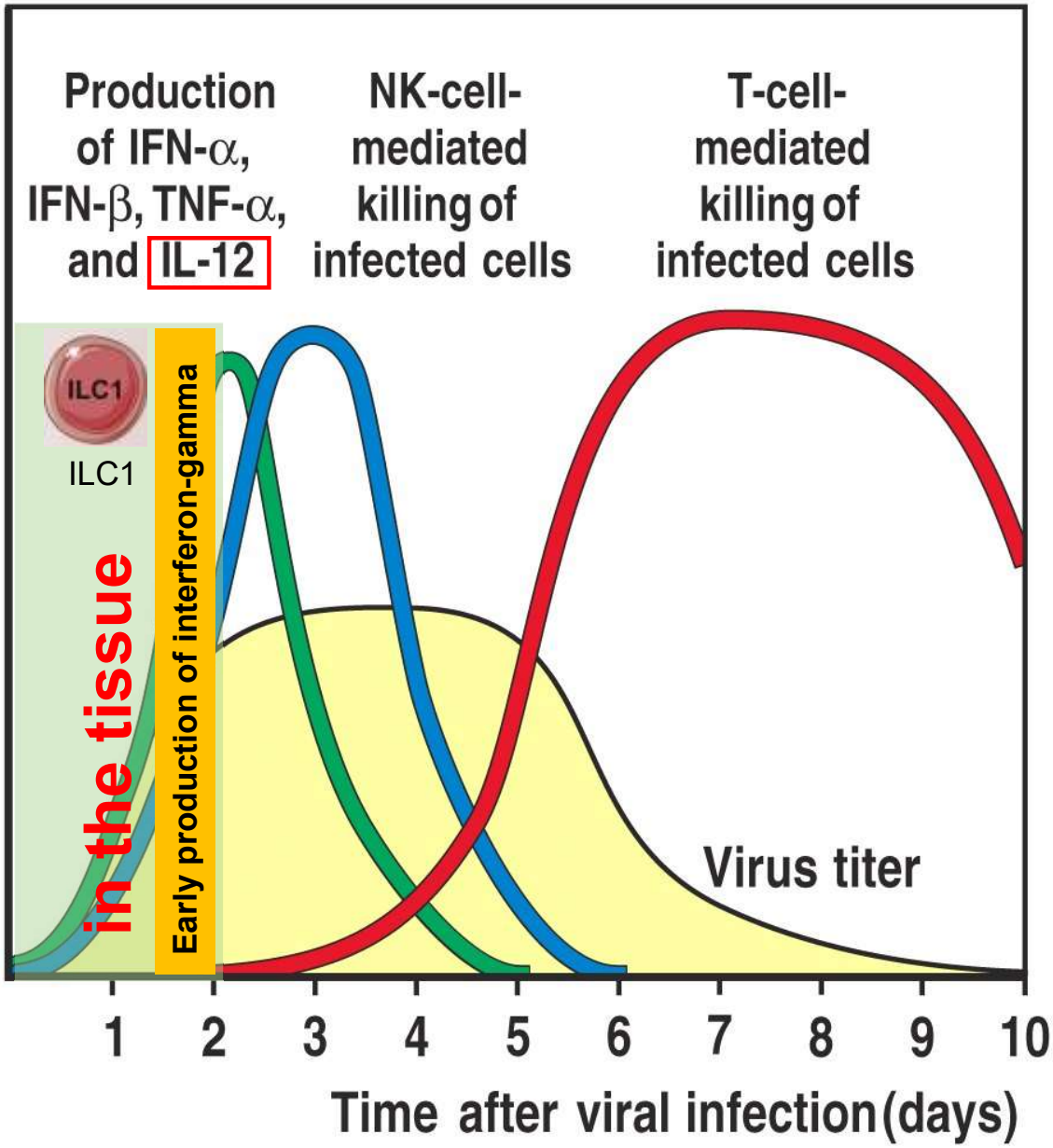


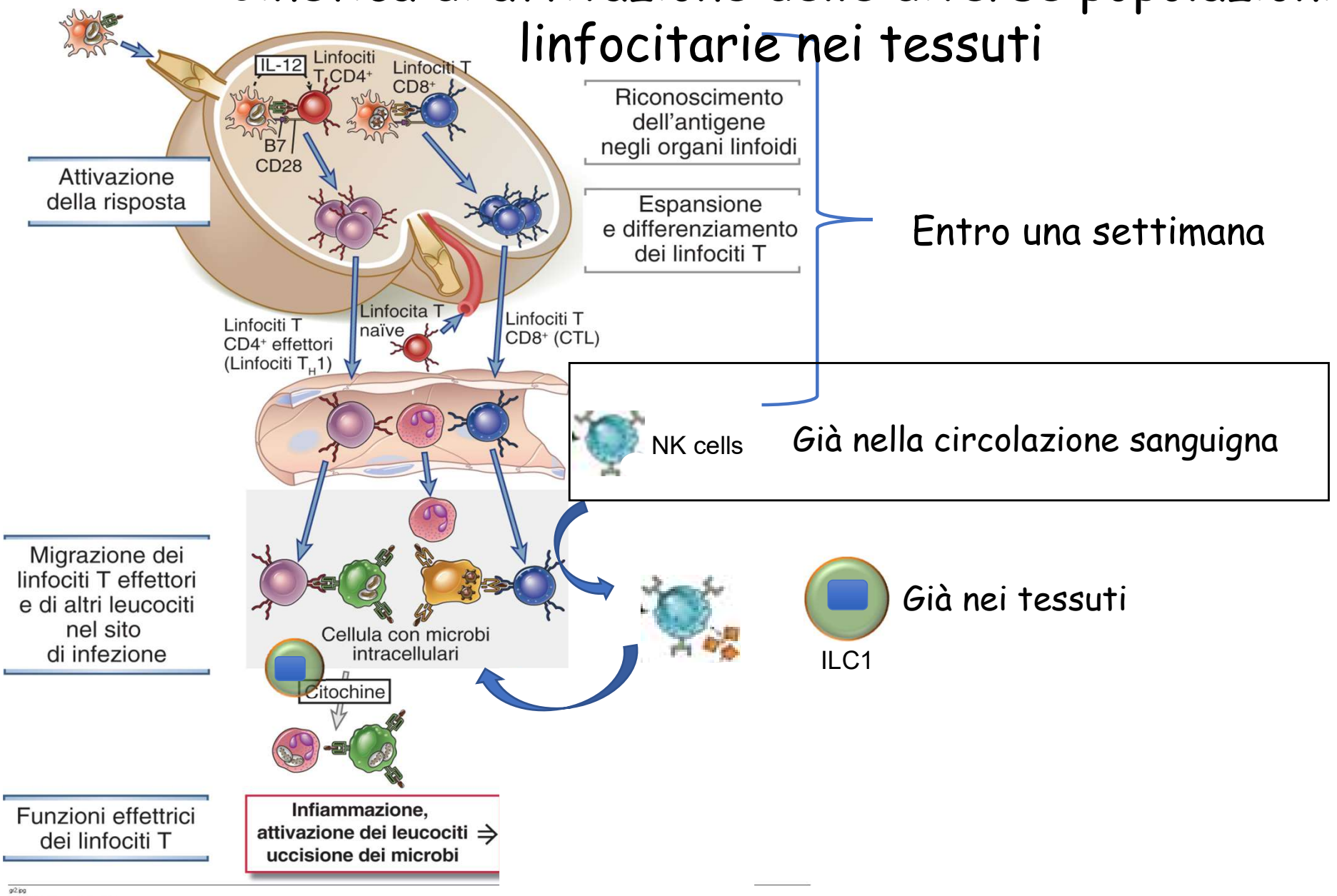

Figure 2-49 Immunobiology, 6/e. (© Garland Science 2005)

**Complementary strategies in the defense against intracellular pathogens!**

**ILC1 are tissue resident cells!!**

**The different cell types participate to the immune response at different time**

# Cinetica di attivazione delle diverse popolazioni linfocitarie nei tessuti




Entro una settimana

gr2.jpg

Immunologia cellulare e molecolare 7 ed

I induzione e fasi effettrici dell'immunità cellulo-mediata. Induzione della risposta: negli organi linfoidi secondari i linfociti T CD4<sup>+</sup> e CD8<sup>+</sup> riconoscono i peptidi derivati dagli antigeni proteici e presentati dalle cellule dendritiche. I linfociti T sono quindi stimolati a proliferare e a differenziarsi in cellule effettrici o della memoria, per poi entrare in circolo. Migrazione dei linfociti T effettori e di altri leucociti verso il focolaio d'infezione: i linfociti T effettori e altri leucociti migrano nei vasi sanguigni verso i tessuti periferici legandosi alle cellule endoteliali che sono state attivate da citochine prodotte a livello dei tessuti infettati. Funzioni effettrici dei linfociti T: i linfociti T effettori riconoscono l'antigene nei tessuti infettati secernendo citochine che reclutano ancora più leucociti e stimolano i fagociti a eradicare l'infezione. Anche i CTL migrano nei tessuti periferici e uccidono le cellule infettate.

# *The expanding family of ILCs*

Innate

Adaptive


NK cells


ILC1


ILC2


CTL

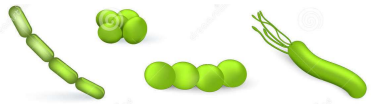

Th1


Th2

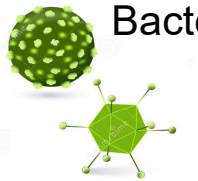
**Cytotoxic**
Granzymes,
Perforin

**Type I**
IFN-g, TNF-a,
CCL3-5

**Type II**
IL-4, IL-5, IL-13

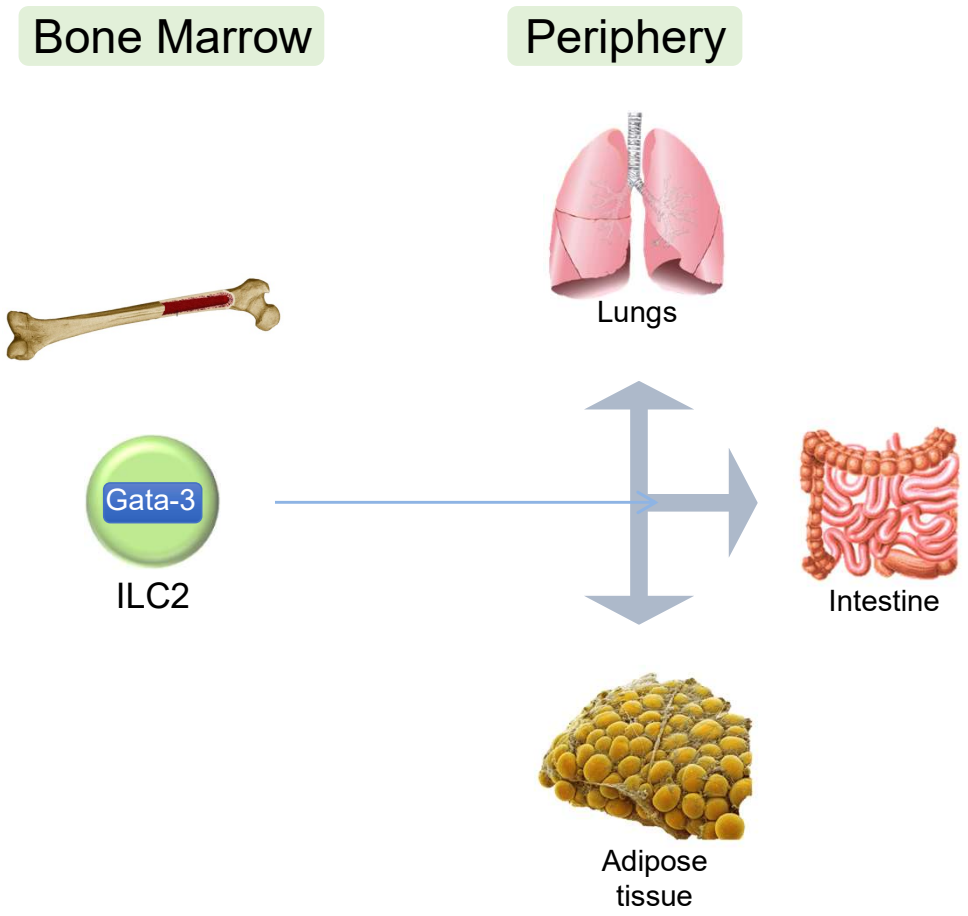


Intracellular pathogens
Bacteria, viruses



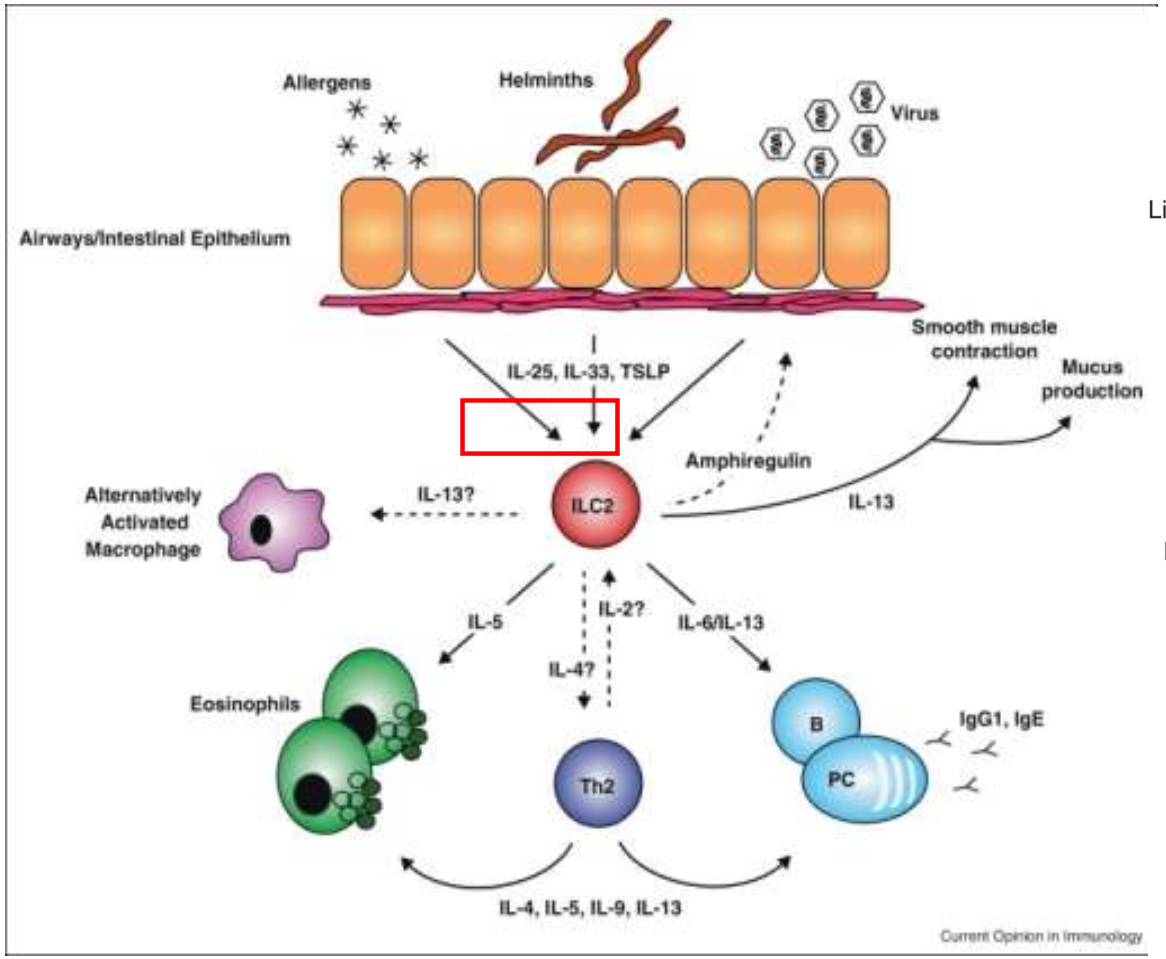
Extracellular pathogens
Parasites, worms

# *Natural Helper Nuocytes ILC2*

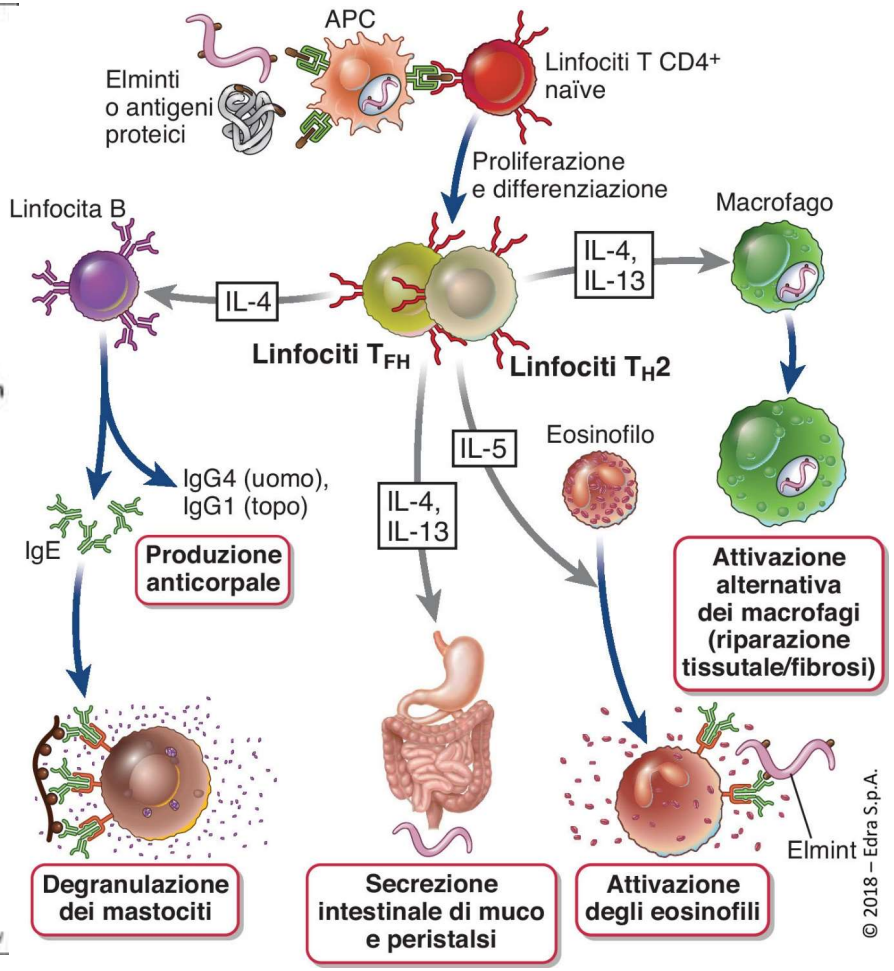


# *ILC2*

## ILC2 activation is fast




## Th2 cells require activation in secondary lymphoid organs



# The expanding family of ILCs

Innate

T-bet
Eomes
NK cells

T-bet
ILC1

Gata-3
ILC2

Rorγt
Lti-like

Rorγt
T-bet
NCR+ILC3

Adaptive

T-bet
Eomes
CTL

T-bet
Th1

Gata-3
Th2

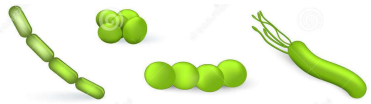
Rorγt
Th17

**Cytotoxic**
Granzymes, Perforin

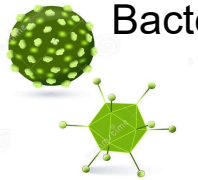
**Type I**
IFN-g, TNF-a, CCL3-5

**Type II**
IL-4, IL-5, IL-13

**Type III**
IL-17, IL-22

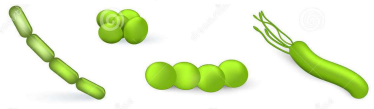


Intracellular pathogens
Bacteria, viruses

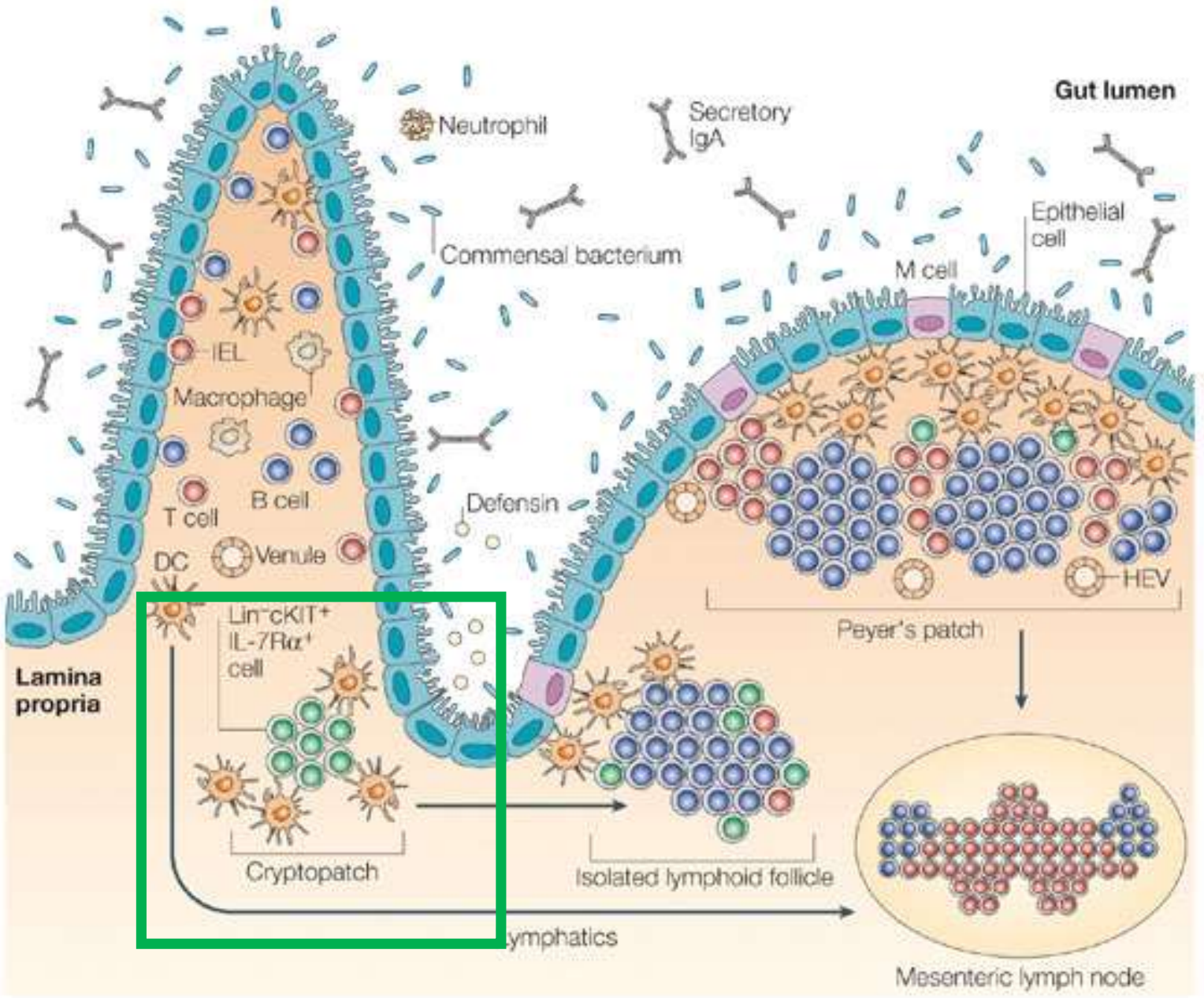


Extracellular pathogens
Parasites, worms

Extracellular bacteria and fungi



# ILC3 are distributed in small lymphoid aggregates

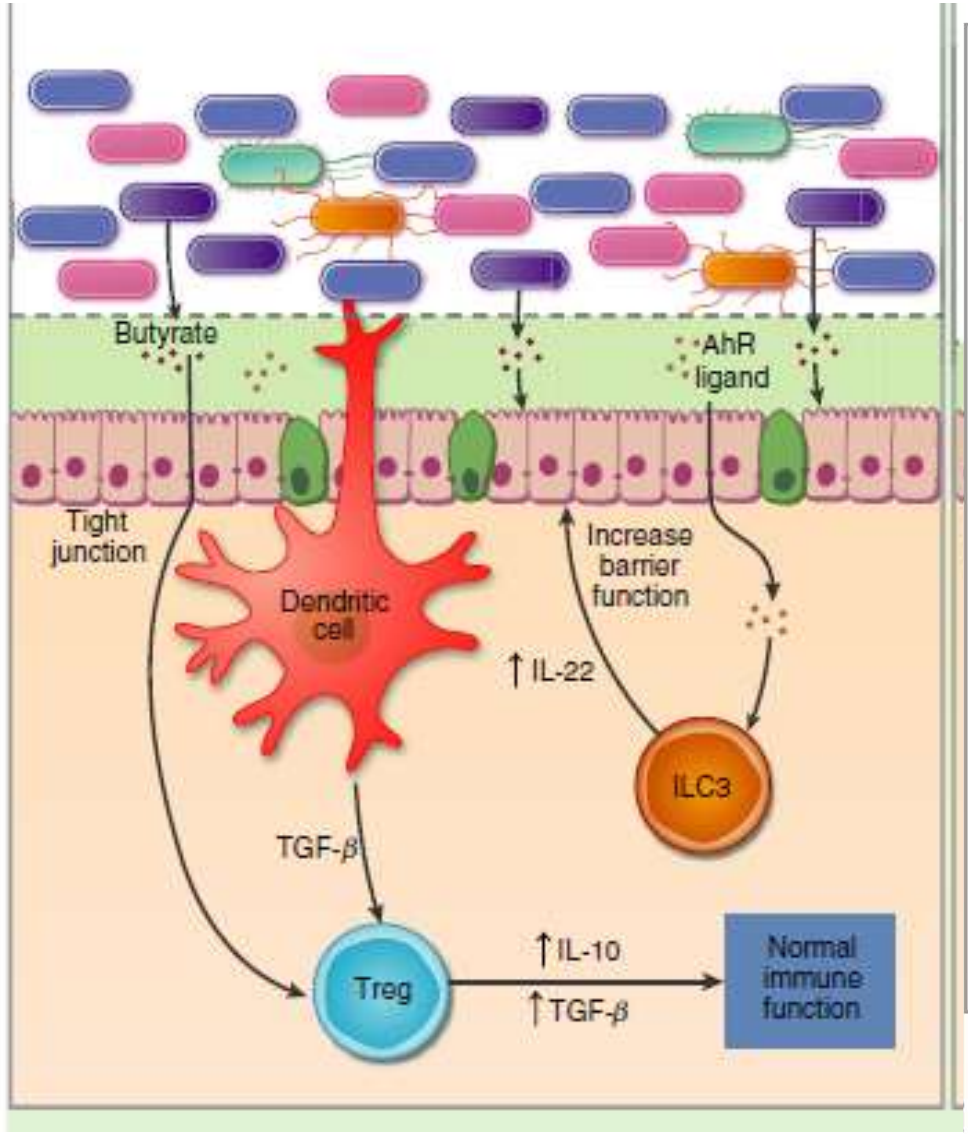


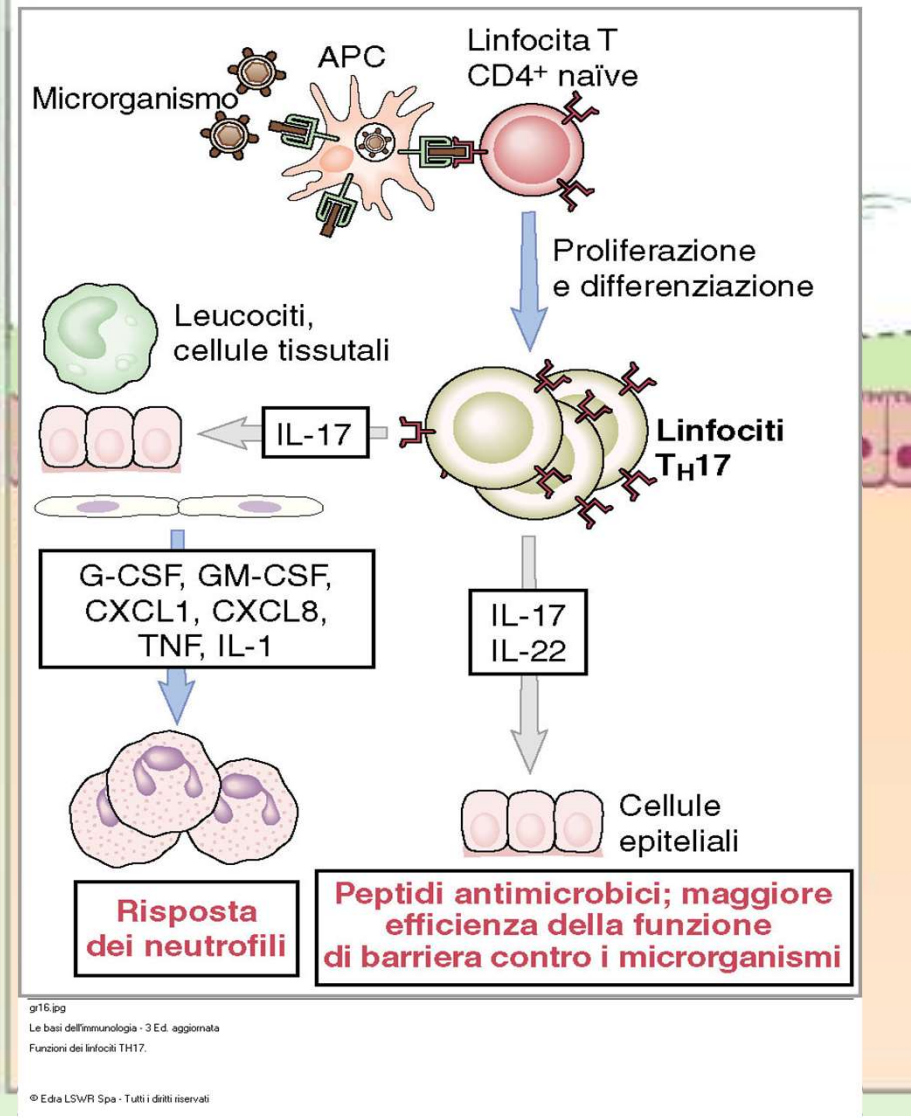

ILC3 si trovano in piccoli aggregati linfoidi sotto la lamina propria intestinale

Nature reviews. Immunology 5(5):413-20

Nature Reviews | Immunology

# ILC3 orchestrate intestinal homeostasis




Production of IL-17A and IL-22 can act
epithelial cells to promote inflammation, innate immunity
and regulate intestinal barrier function.

*ILC development?*

*no requirement of infection*

# *Factors involved in ILC development?*

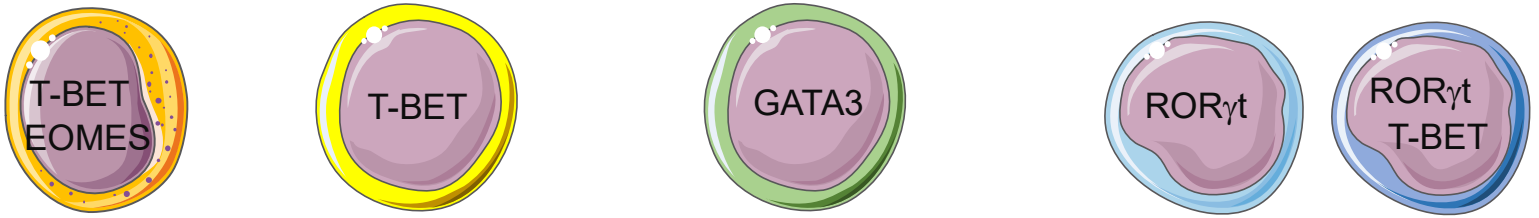
## *Lineage-defining transcription factors (LDTF)*

*Determinano il differenziamento di specifiche popolazioni linfocitarie e ne stabiliscono l'identità regolando l'accessibilità in siti specifici*

# *ILC development starts in the bone marrow and often terminates in peripheral tissues*


Multipotent ILC precursors:
α-lymphoid, ILCp, ChILP


NKp ILC1p ILC2p ILC3p




NK cells ILC1 ILC2 LTi-like NCR+ILC3

**Cytotoxic**
Granzymes, Perforin

**Type I**
IFN-γ, TNF-α, CCL3-5

**Type II**
IL-4, IL-5, IL-13

**Type III**
IL-17, IL-22

# NATURAL KILLER CELLS: FUNCTIONS AND MECHANISMS OF RECOGNITION

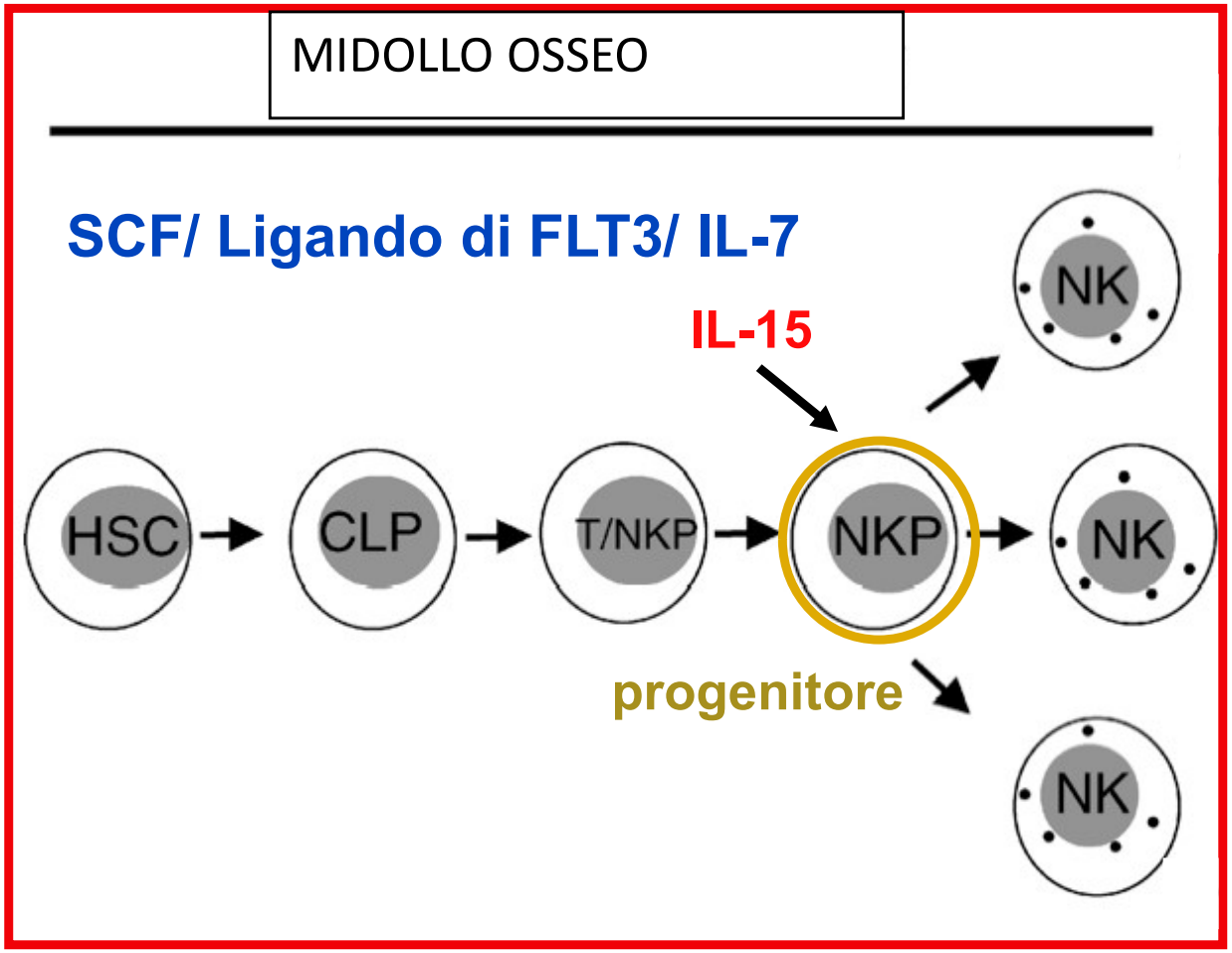
# NK CELL FACTS

- Human natural killer (NK) cells are CD3-CD56+ cells that originate in the bone marrow

- NK cell activation is controlled by a balance between activating and inhibitory signals elicited by antigen-independent interactions with other cells

- NK cells also express various cytokine receptors, notably the receptors for interleukin 12 (IL12), IL15 and IL21, which deliver mitogenic signals

# Le citochine e lo sviluppo delle cellule NK umane

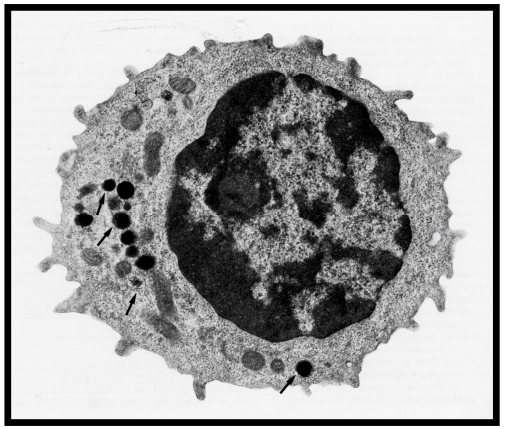



**La citochina IL-15 è il maggior fattore di differenziazione delle cellule NK!!!**

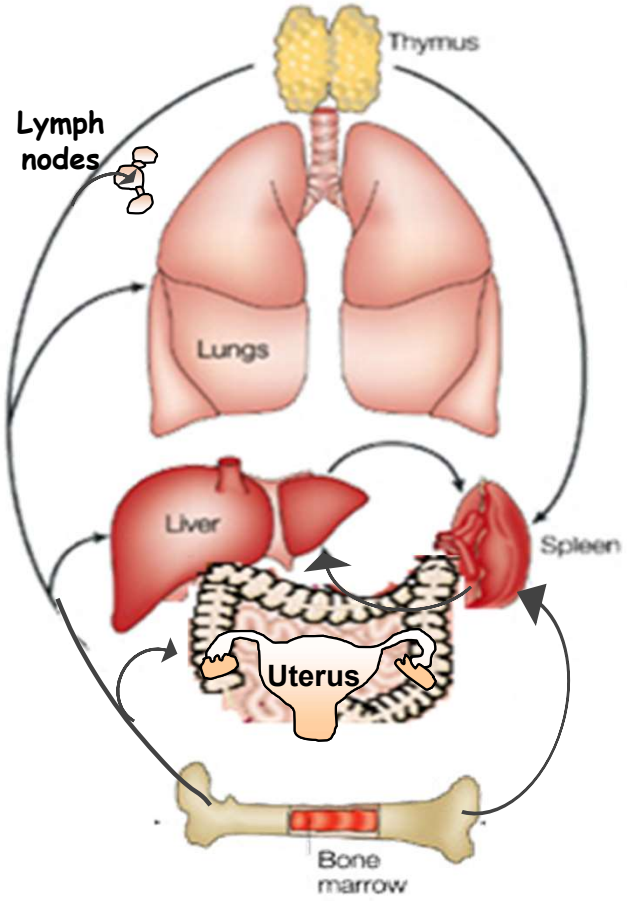
Il contatto diretto e le citochine/fattori di crescita prodotti dalle cellule stromali sono fondamentali per lo sviluppo delle cellule NK nel midollo osseo

**SCF, il ligando di Flt3 e IL-7 prodotti dalle cellule stromali promuovono la sopravvivenza ed inducono l'espressione sui precursori delle cellule NK del recettore per l'IL-15, una citochina fondamentale per la loro maturazione.**

# Natural Killer cells(NK)



**Phenotype:** $CD56^{+}TCR/CD3^{-}$




- Blood circulation

- Lymphoid organs
  (bone marrow, spleen lymphnodes),

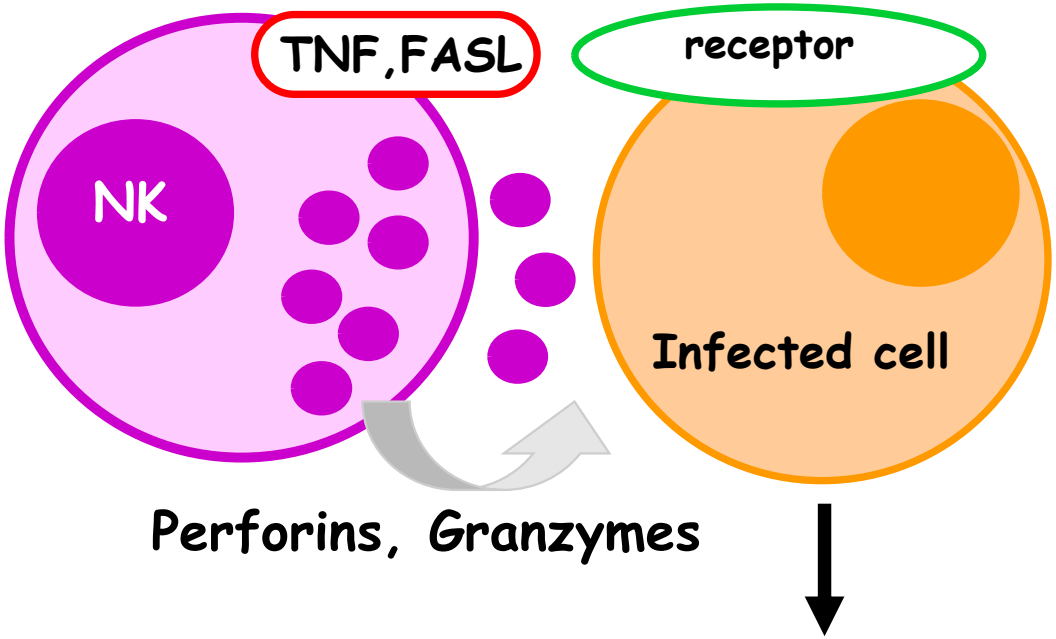
  And non-lymphoid organs
  (Liver, Lung, intestine, uterus)

**Rapidly recruited in tissues:**

- infection
- tumor growth

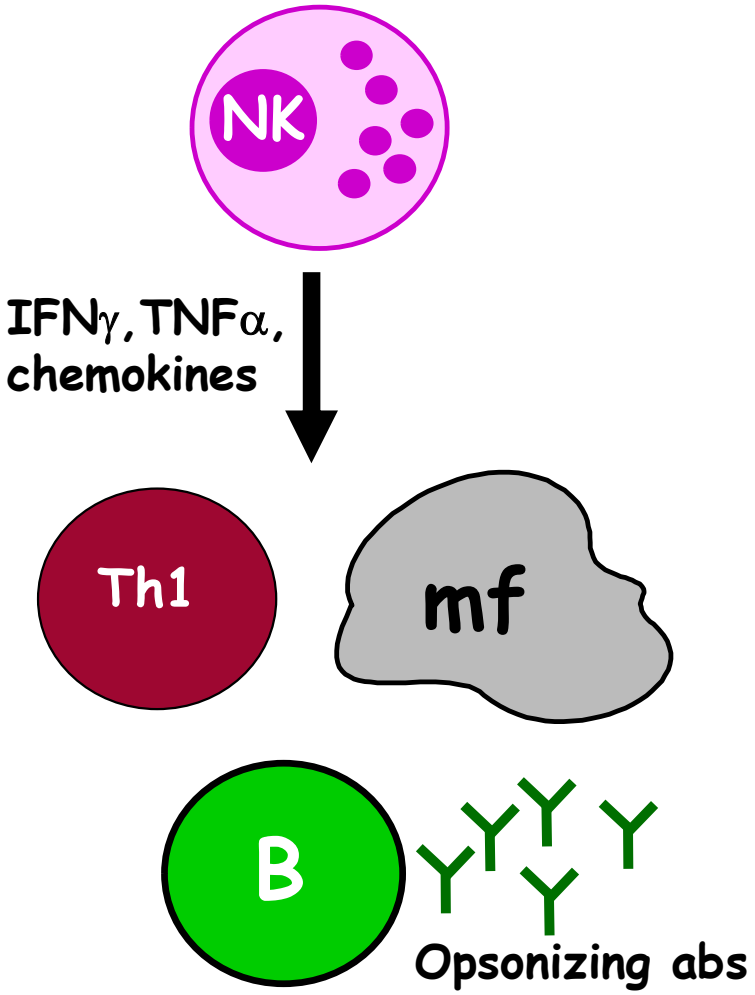
# Effector and Immunoregulatory functions of NK cells

## EFFECTOR FUNCTIONS




Cytotoxic activity

## Immunoregulatory functions




Cytokine and chemokine productions

# Signals are dispatched to NK cells by a variety of surface receptors

(1) killer immunoglobulin-like receptors **(KIRs),** which generally deliver **inhibitory** cues via immunoreceptor tyrosine-based inhibitory motifs (**ITIMs**);

(2) C-type lectin receptors, such as the **immunosuppressive** receptor Natural killer group2A, NKG2A) and **the immunostimulatory** receptor NKG2D

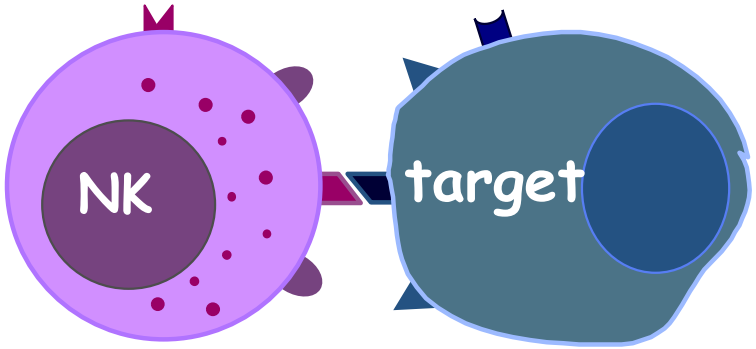
(3) **natural cytotoxicity receptors (NCR),** such as NCR1 (best known as NKp46) and NCR2 (best known as NKp44), which deliver activating stimuli via immunoreceptor tyrosine-based activation motifs (ITAMs)

(4) others….

# NK cell cytotoxic functions

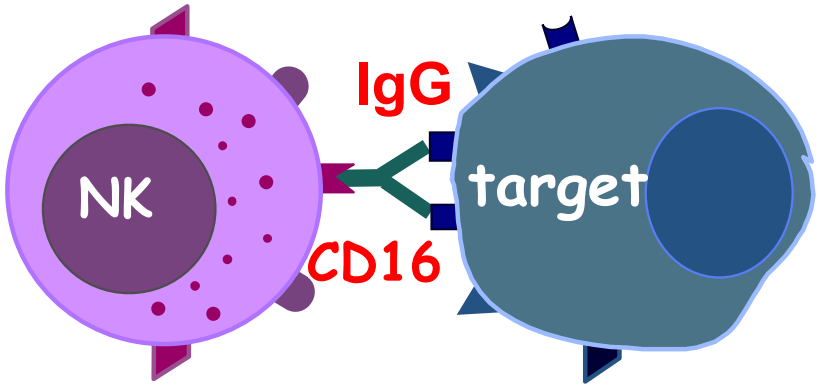
- ➢Natural cytotoxiciy
  - constitutive
  - no MHC-restriction

*against:*
Tumor cells
virus infected cells




➢Antibody dependent cellular cytotoxicity (ADCC)

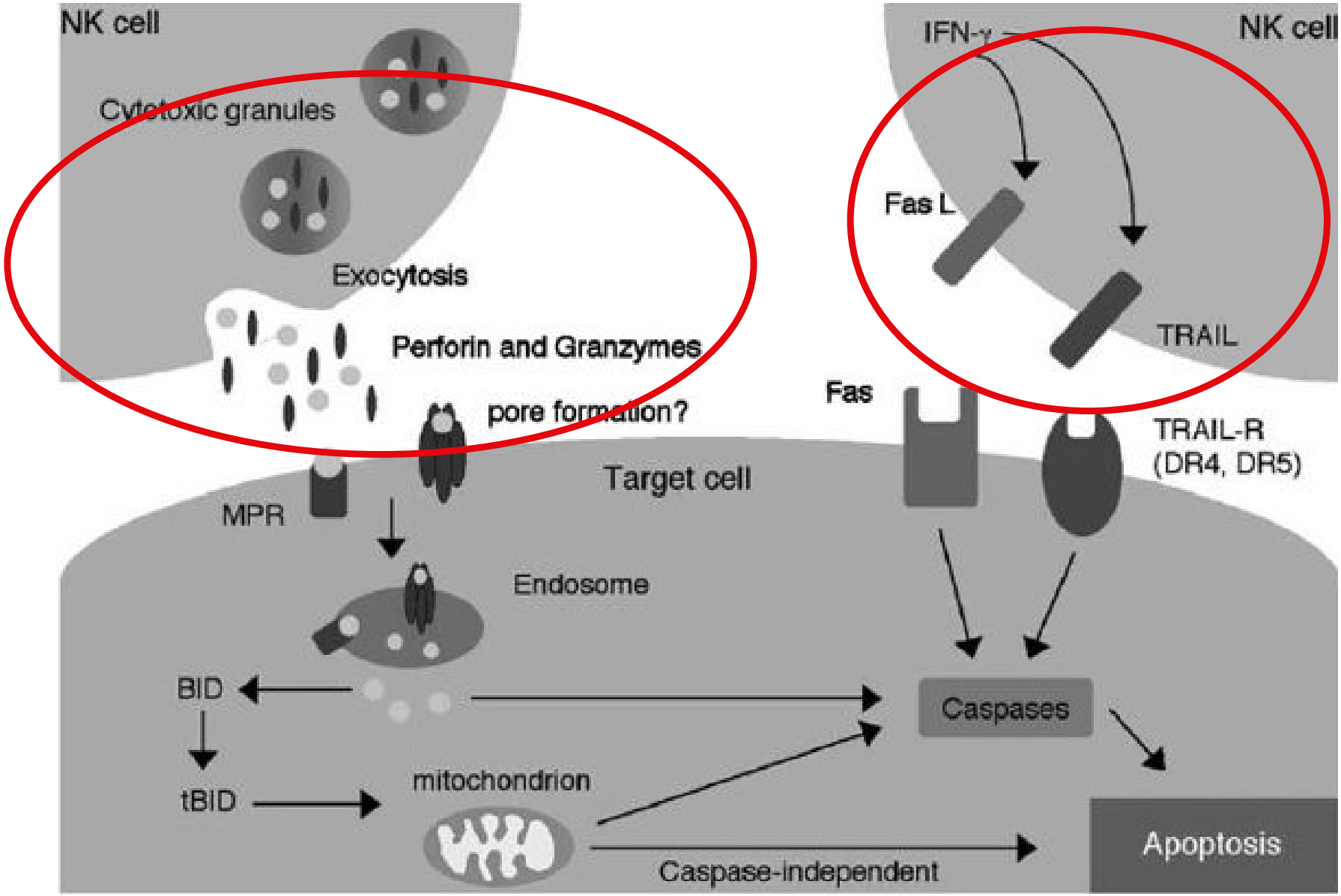
Against: cells coated by IgG (tumor and virus infected cells)



# What's in CTL and NK cytotoxic granules?

| Protein in lytic granules of cytotoxic T cells | Actions on target cells |
|---|---|
| Perforin | Polymerizes to form a pore in target membrane |
| Granzymes | Serine proteases, which activate apoptosis once in the cytoplasm of the target cell |
| Granulysin | Induces apoptosis |
| **Proteoglycans (serglycine)** | **a structural role and a protective function** |

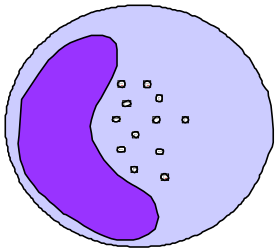
# Molecular mechanisms of NK cell cytotoxicity




Same mechanisms for CTL

TNF-related **apoptosis**-inducing ligand (**TRAIL**)

# NATURAL CYTOTOXICITY



## NK CELLS:

## TARGET CELL RECOGNITION

## And

## TOLERANCE TO SELF

NK CELL CYTOTOXIC ACTIVITY RESULTS FROM A BALANCED ACTIVATION OF

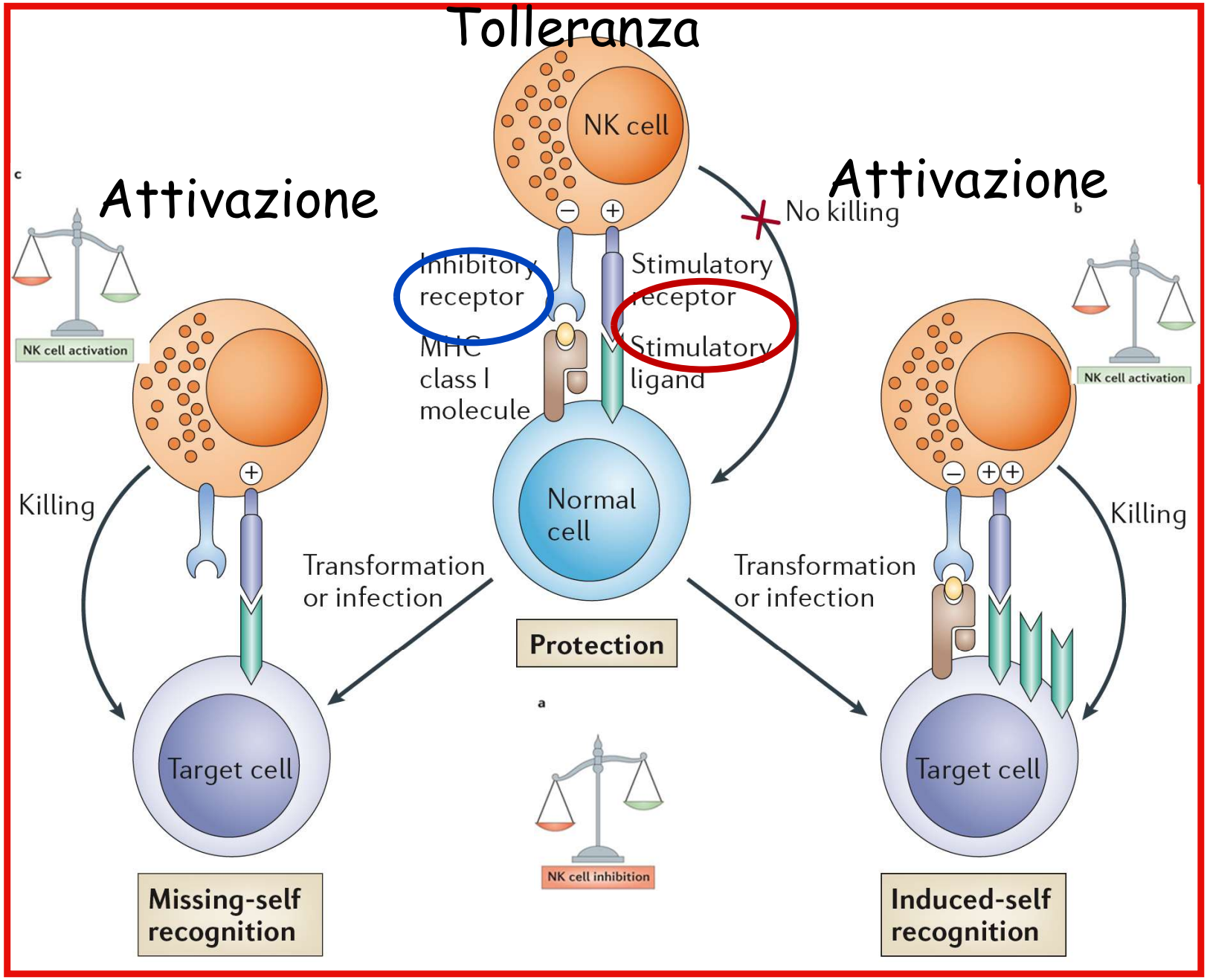
ACTIVATING receptors and

INHIBITORY receptors

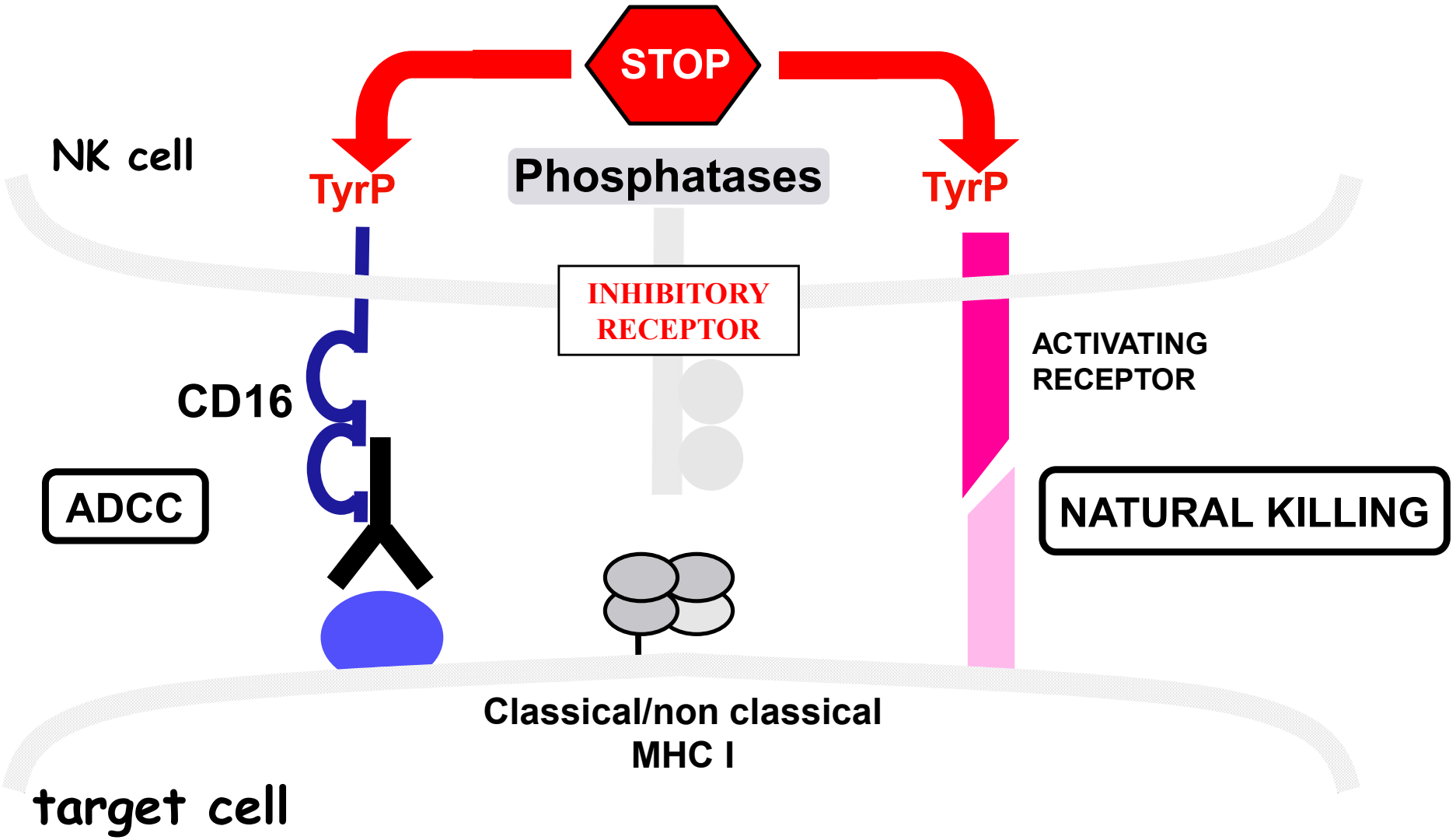
*"The missing-self hypothesis argues that NK cells survey cells of the body for the expression of self MHC class I and destroy those cells in which it is missing".*

**Klas Kärre, PhD thesis,**
**Karolinska Institute, 1981**

**Lack or aberrant expression of class I MHC molecules render a cell the target of NK cells**

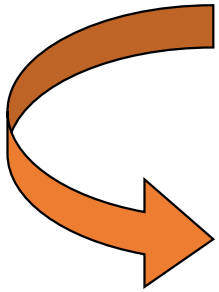

Tolleranza
NK cell
Attivazione
Attivazione
No killing
Inhibitory receptor
Stimulatory receptor
MHC class I molecule
Stimulatory ligand
NK cell activation
NK cell activation
Killing
Killing
Normal cell
Transformation or infection
Transformation or infection
Protection
Target cell
Target cell
NK cell inhibition
Missing-self recognition
Induced-self recognition

# NK CELL ACTIVITY IS INHIBITED BY RECOGNITION OF CLASS I MHC by INHIBITORY RECEPTORS



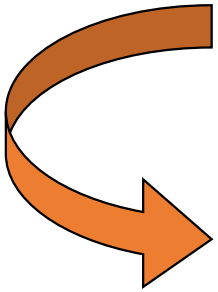
# HOW ARE NK CELLS ACTIVATED?

**Missing self**
**Decreased MHC class I**



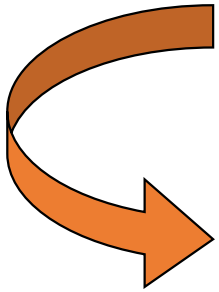
**LOSS of INHIBITION**

**Induced self**
**Induced MIC-A/B, ULBPs**

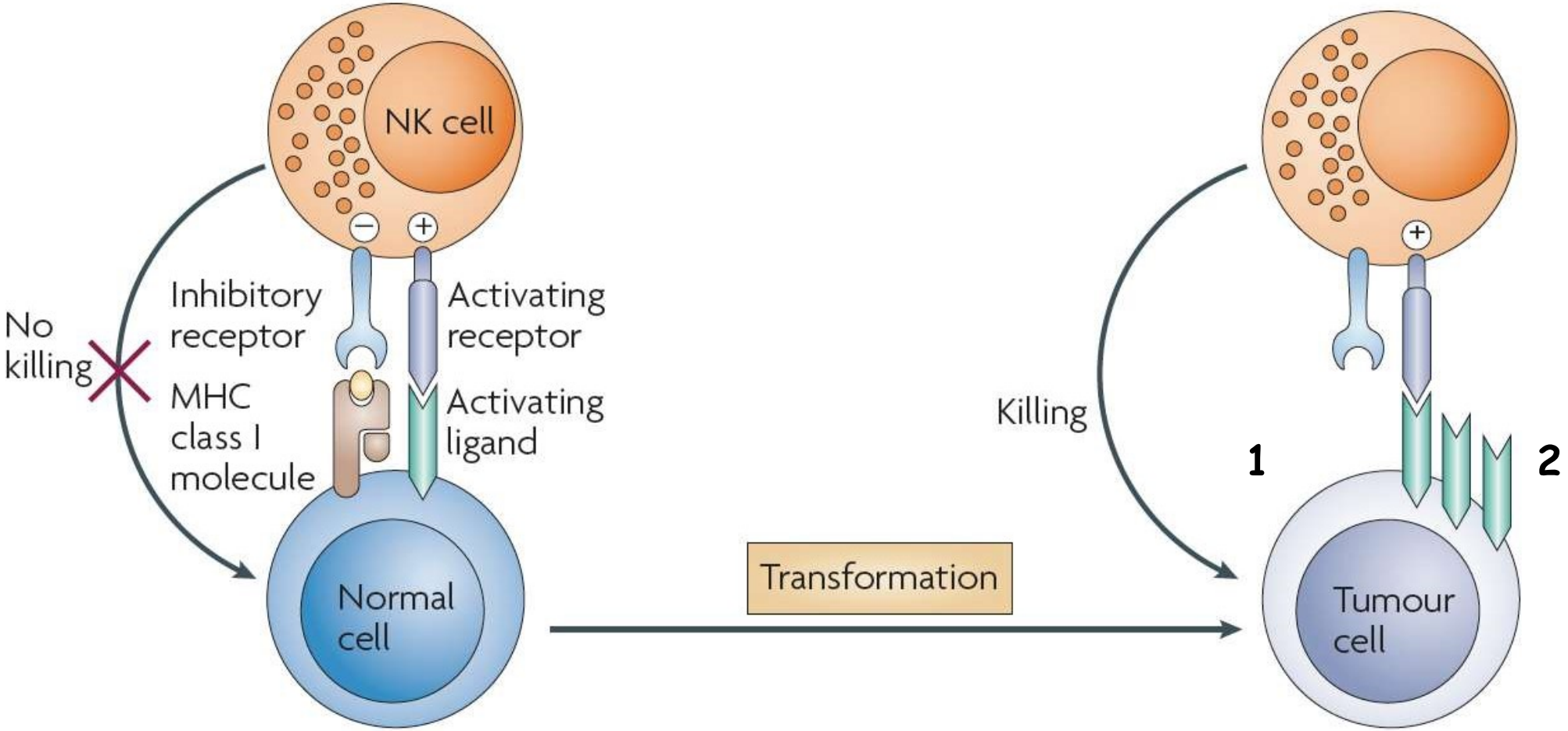


**Super-activation**

**Microbial non self**
**viral proteins, PAMPs**



**ACTIVATION**




**Recognition of tumor cells is mediated by an equilibrium of signals :**

**1-Lack of autologous molecules expression usually espressed by all normal cells (MHC class I);**

**2-increase/induction of other molecules that marks a stressed cell**

# The activation of NK cells is determined by a balance between engagement of activating and inhibitory receptors

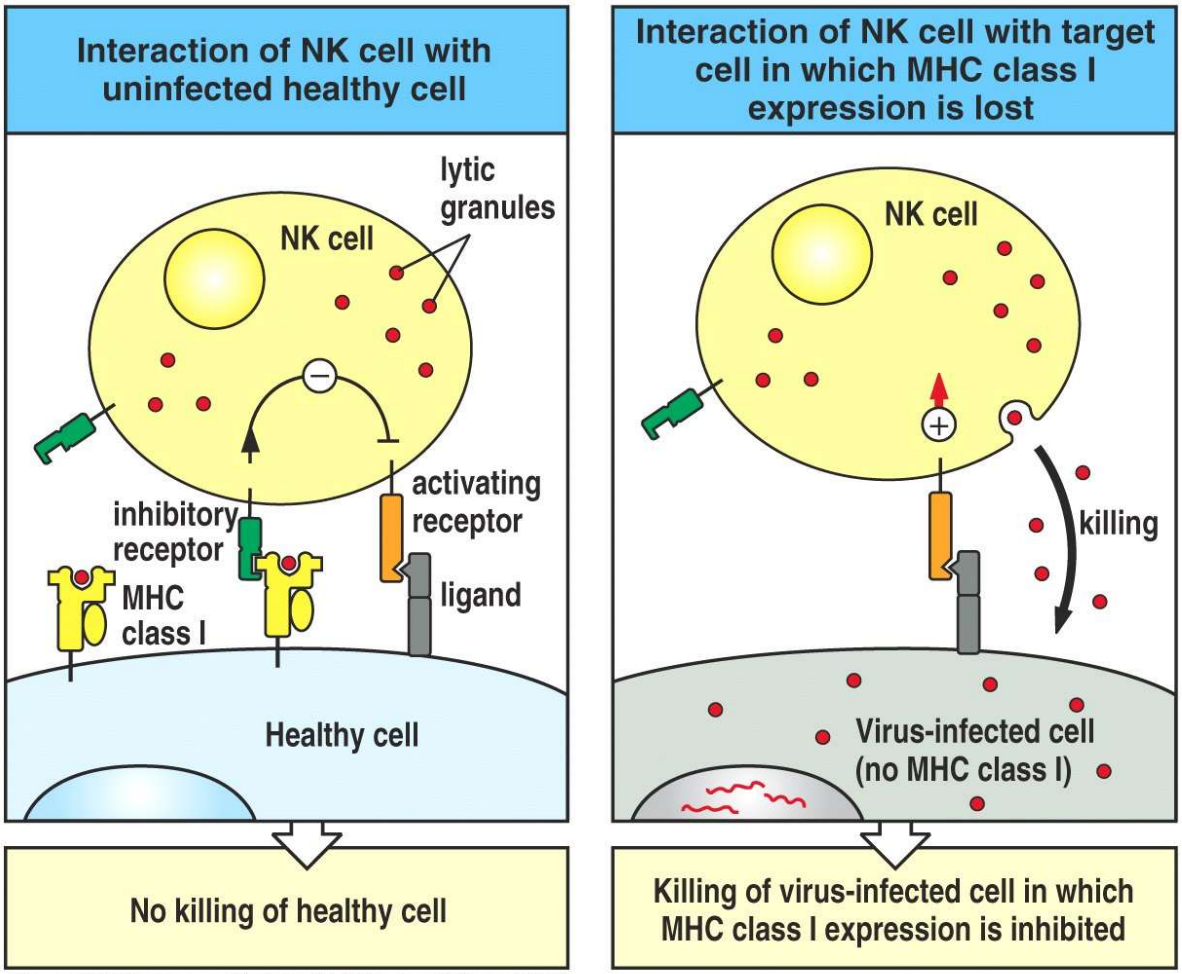



Figure 8-32 The Immune System, 2/e (© Garland Science 2005)

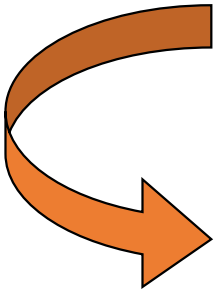
NK cells interpret the presence of class I MHC molecules as markers of normal, healthy self, and their absence is an indication of infection or damage.

**Missing self hypothesis:**

CLASS I MHC EXPRESSION PROTECTS HEALTHY CELLS FROM NK CELL KILLING

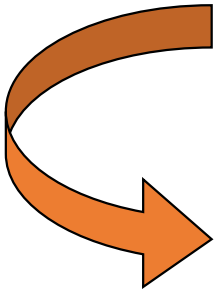
# HOW ARE NK CELLS ACTIVATED?

**Missing self**
**Decreased MHC class I**



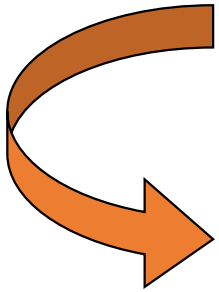
**LOSS of INHIBITION**

**Induced self**
**Induced MIC-A/B, ULBPs**

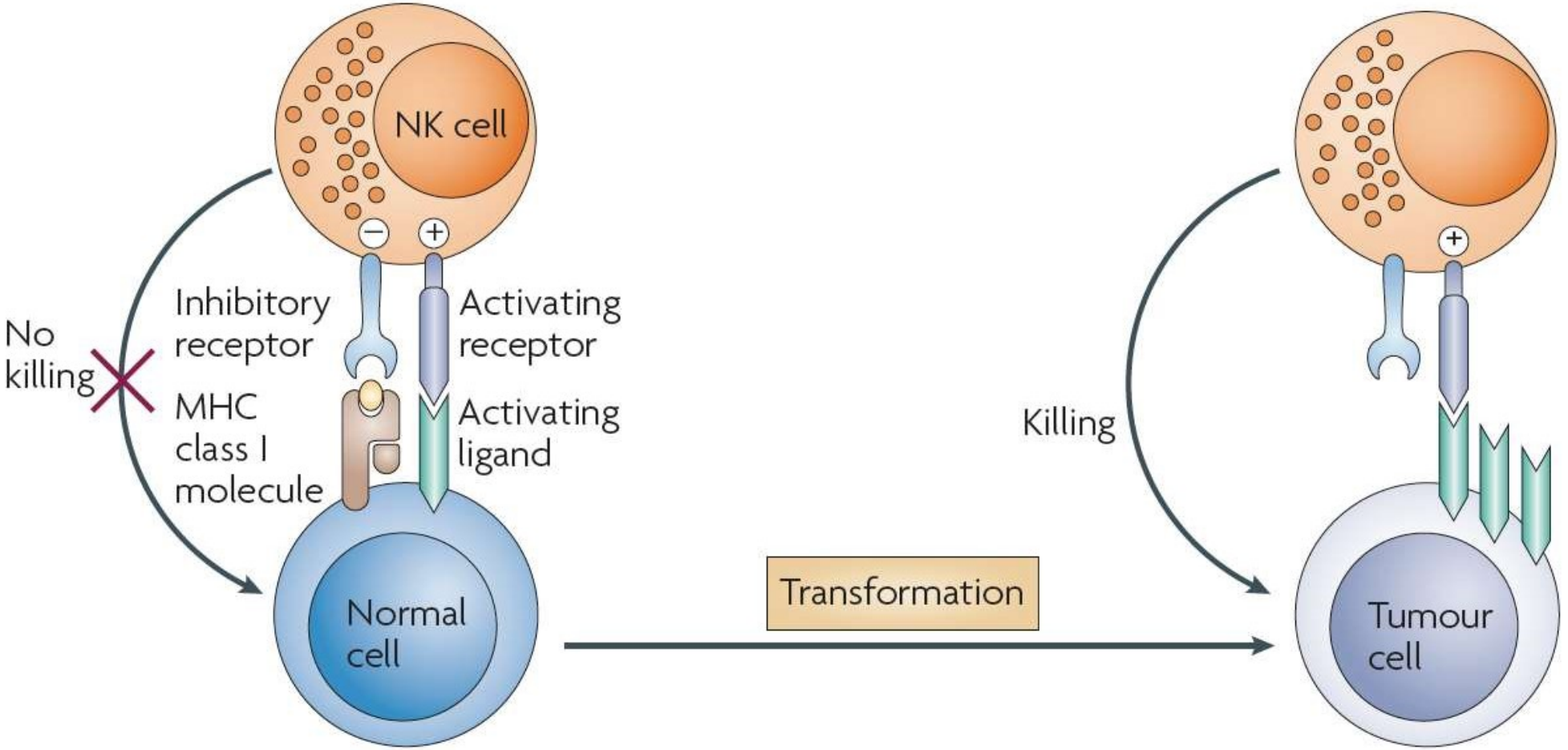


**Super-activation**

**Microbial non self**
**viral proteins, PAMPs**



**ACTIVATION**




**Recognition of tumor cells is mediated by an equilibrium of signals:**

1-Lack of autologous molecules expression usually espressed by all normal cells (MHC class I);

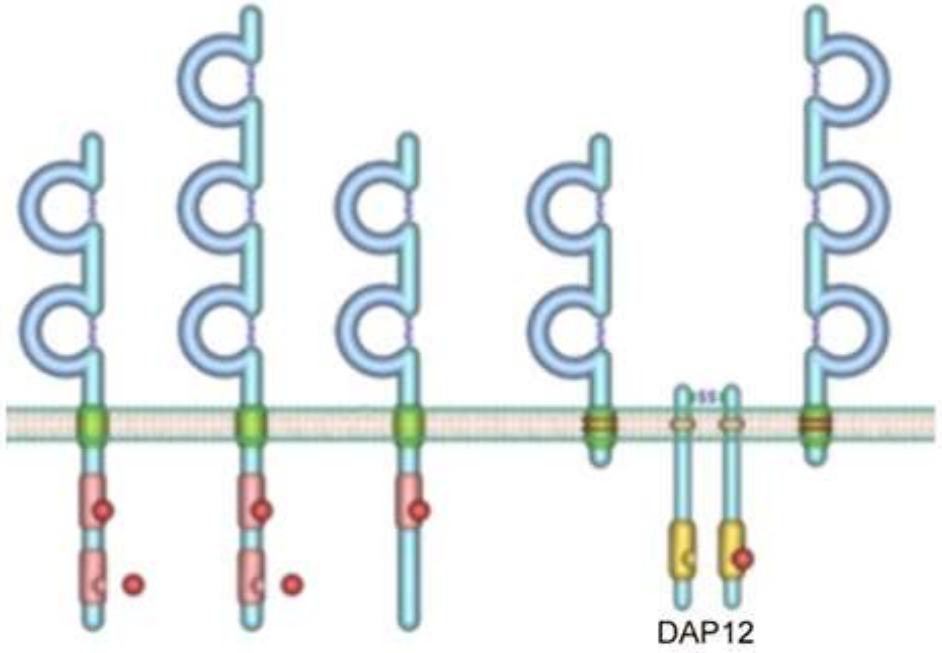
**2-increase/induction of other molecules that marks a stressed cell**

## Which receptors are used by NK cells?

- **Activating receptors**
- **Inhibitory receptors**

# KILLER IMMUNOGLOBULIN-LIKE RECEPTORS

INIBITORI ATTIVATORI




Ig domain

Il numero prima della lettera D rappresenta il numero di domini immunoglobulinici presenti nella porzione extracellulere

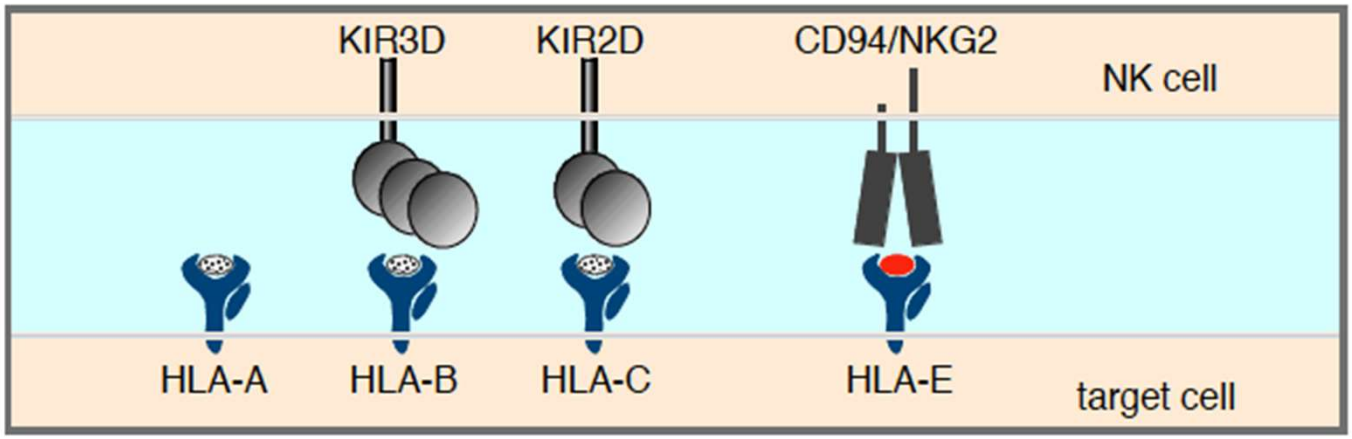
La lettera **L** nel nome significa Long (cytoplasmic tail) ed è associata con la funzione inibitoria)

La lettera **S** nel nome significa short (cytoplasmic tail) ed è associata con la funzione attivatoria

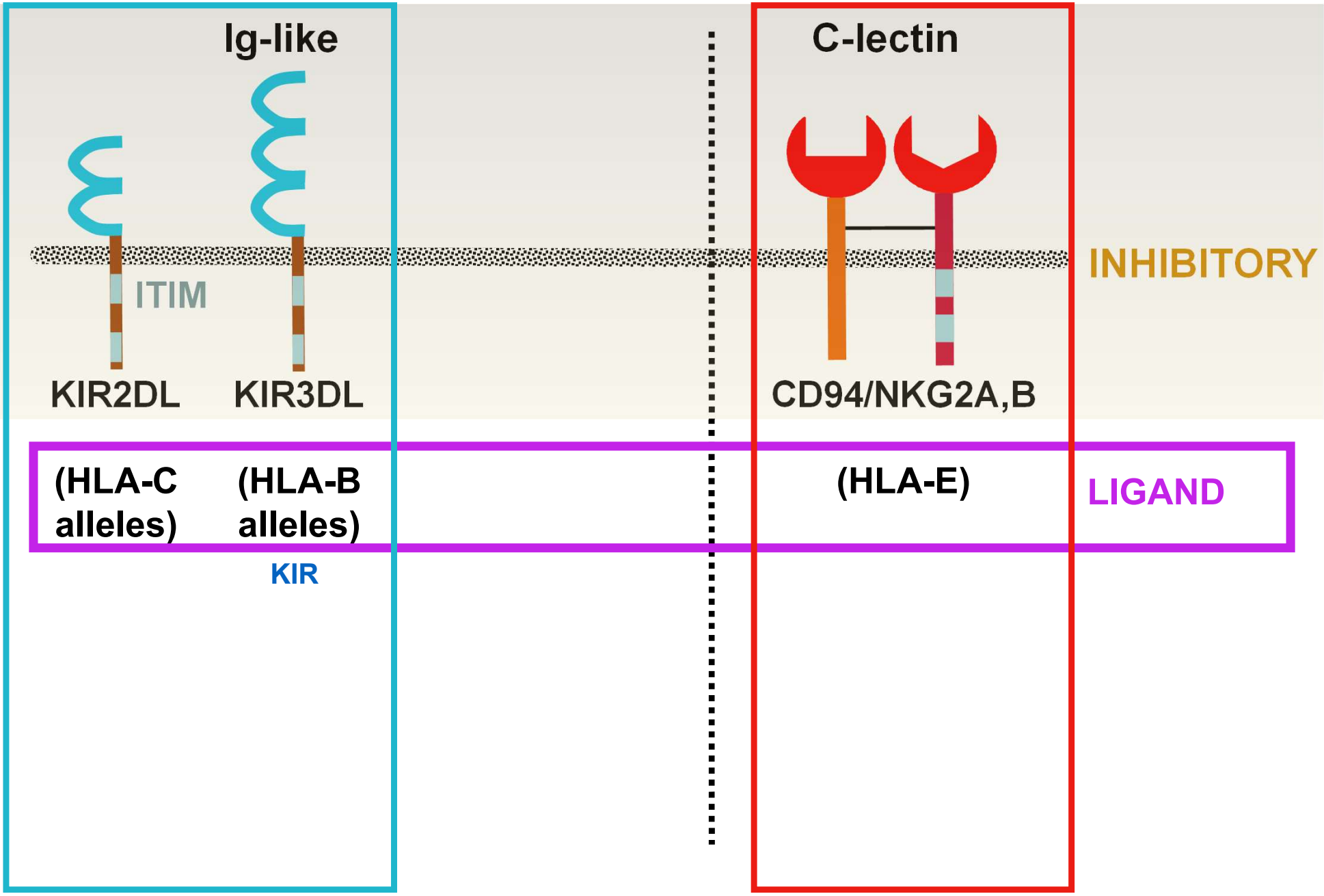
*KIRs with long cytoplasmic tails contain immunoreceptor tyrosin-based inhibiting motifs (ITIMs) reduce the activity of NK cells. In contrast, KIRs with short intracellular tails mediate activating signals via adaptor molecules containing immunoreceptor tyrosin-based activating motifs (ITAMs).*

# I ligandi dei recettori Killer immunoglobulin-like receptors (KIR) e natural killer group2 (NKG2):

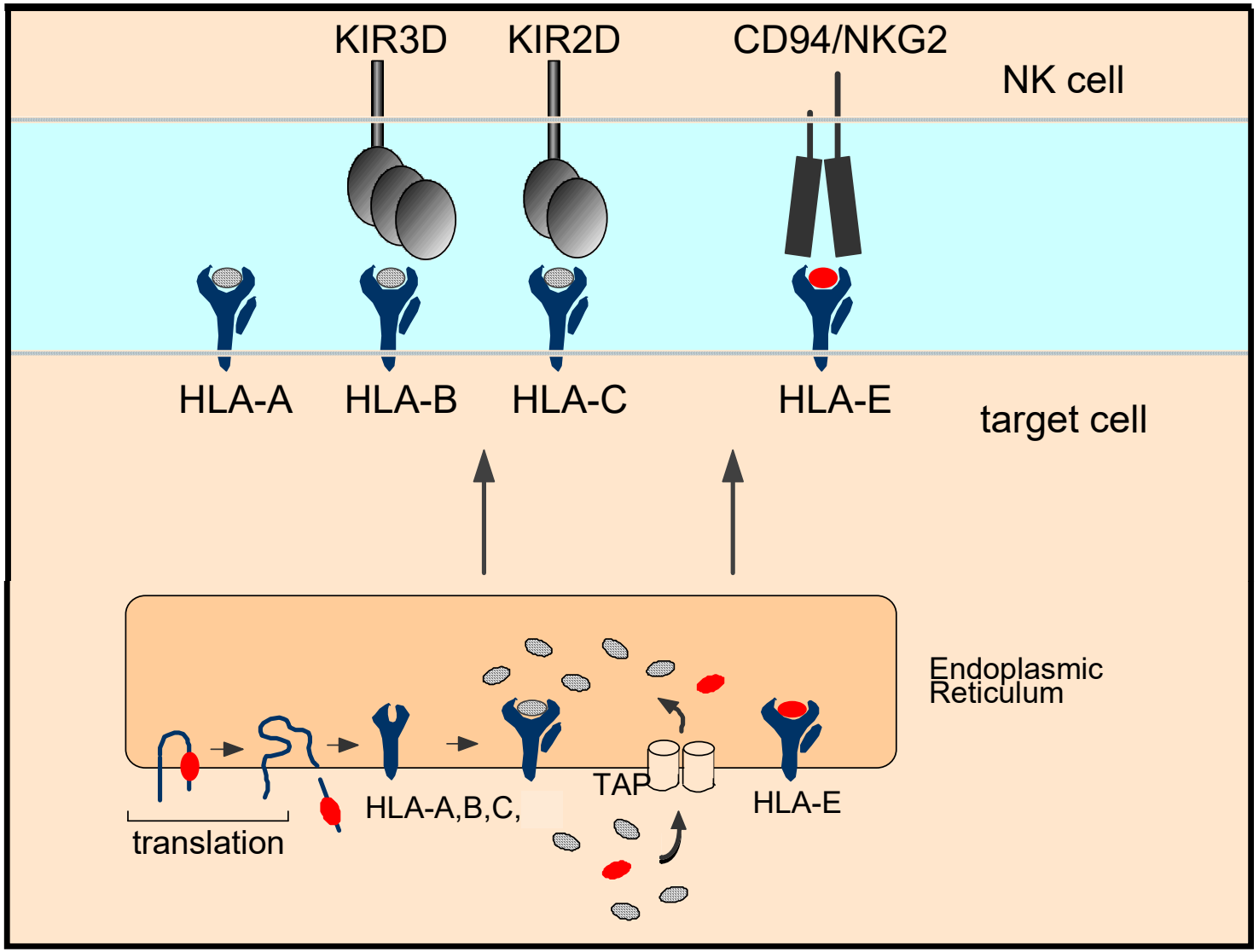
- **Sono molecole MHC di classe I**. Tutte e due le famiglie di recettori riconoscono un complesso MHCI/peptide ma generalmente il peptide è irrilevante in quanto non sembra contribuire l legame
- I recettori KIR3D legano principalmente l'HLA-B
- I recettori KIR2D legano principalmente HLA-C
- Gli eterodimeri CD94/NKG2A legano l'eterodimero HLA-E



# INHIBITORY RECEPTORS FOR MHC I

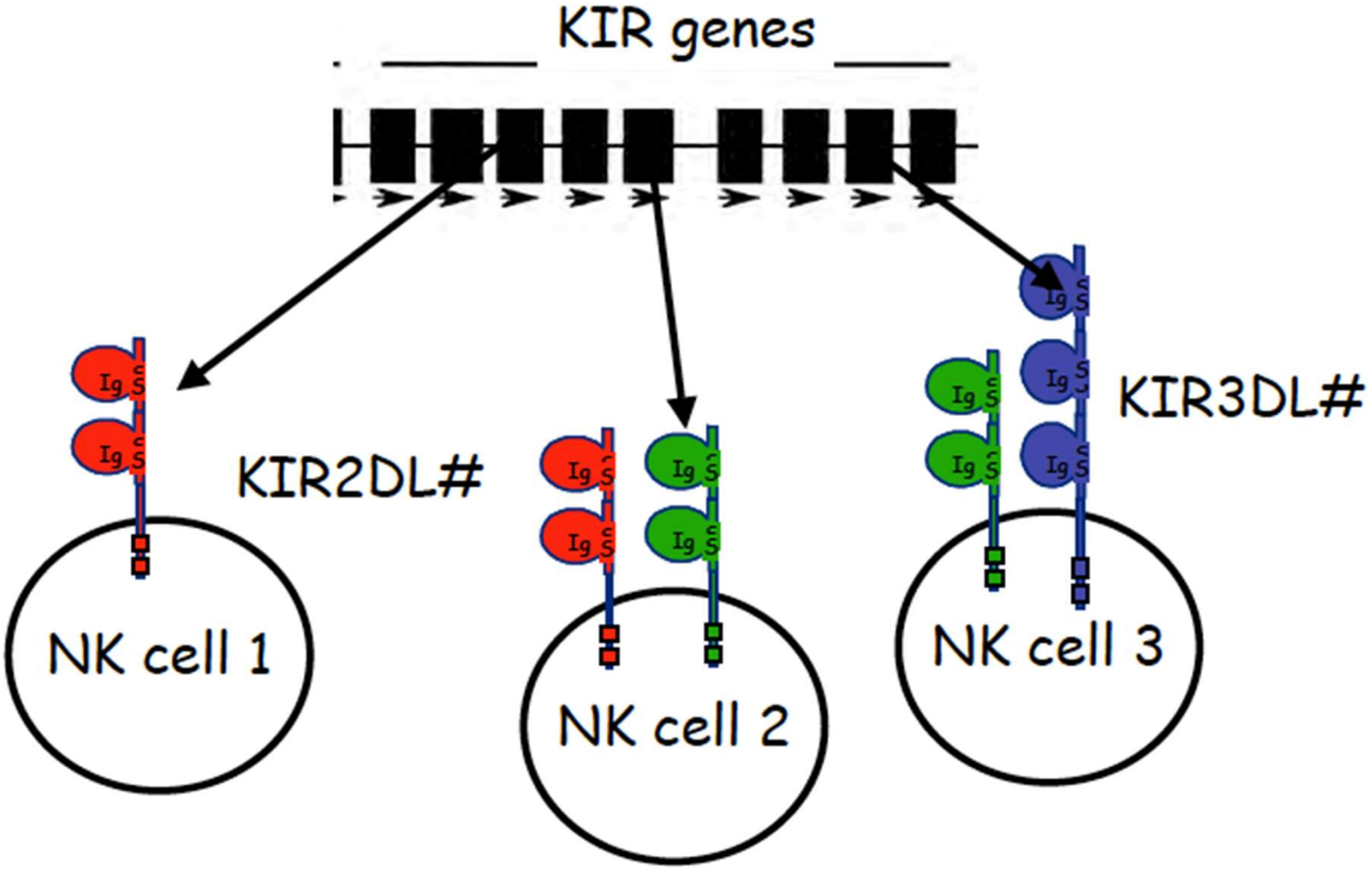


# HLA-E expression levels are proportional to classical MHC I espression on cell membrane




HLA-E binding pocket accomodates a peptide derived from the leader sequence of MHC class I molecules

# Different NK cells of the same individual express different KIR combinations acquired randomly during differentiation




Each NK cell expresses at least one inhibitoy KIR

Thousands of different clones in the same individual

# I geni dei recettori NK

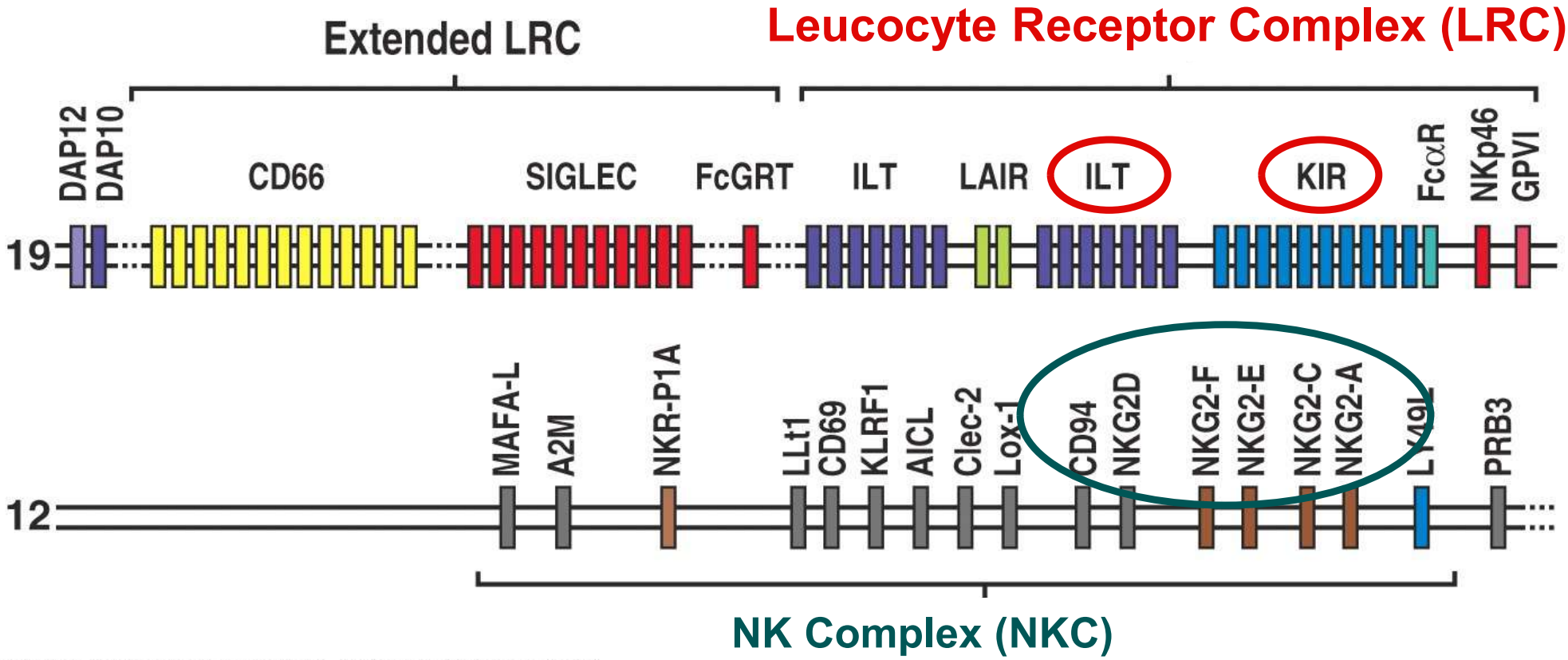


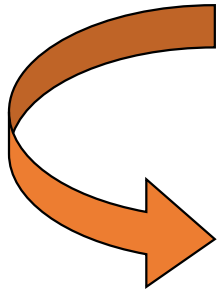

Figure 2-51 Immunobiology, 6/e. (© Garland Science 2005)

I geni che codificano per i KIR e per i KLR (NKG2) sono presenti in loci genici diversi situati in cromosomi differenti

Il grado di polimorfismo è particolarmente elevato per i geni KIR

# INDUCED SELF

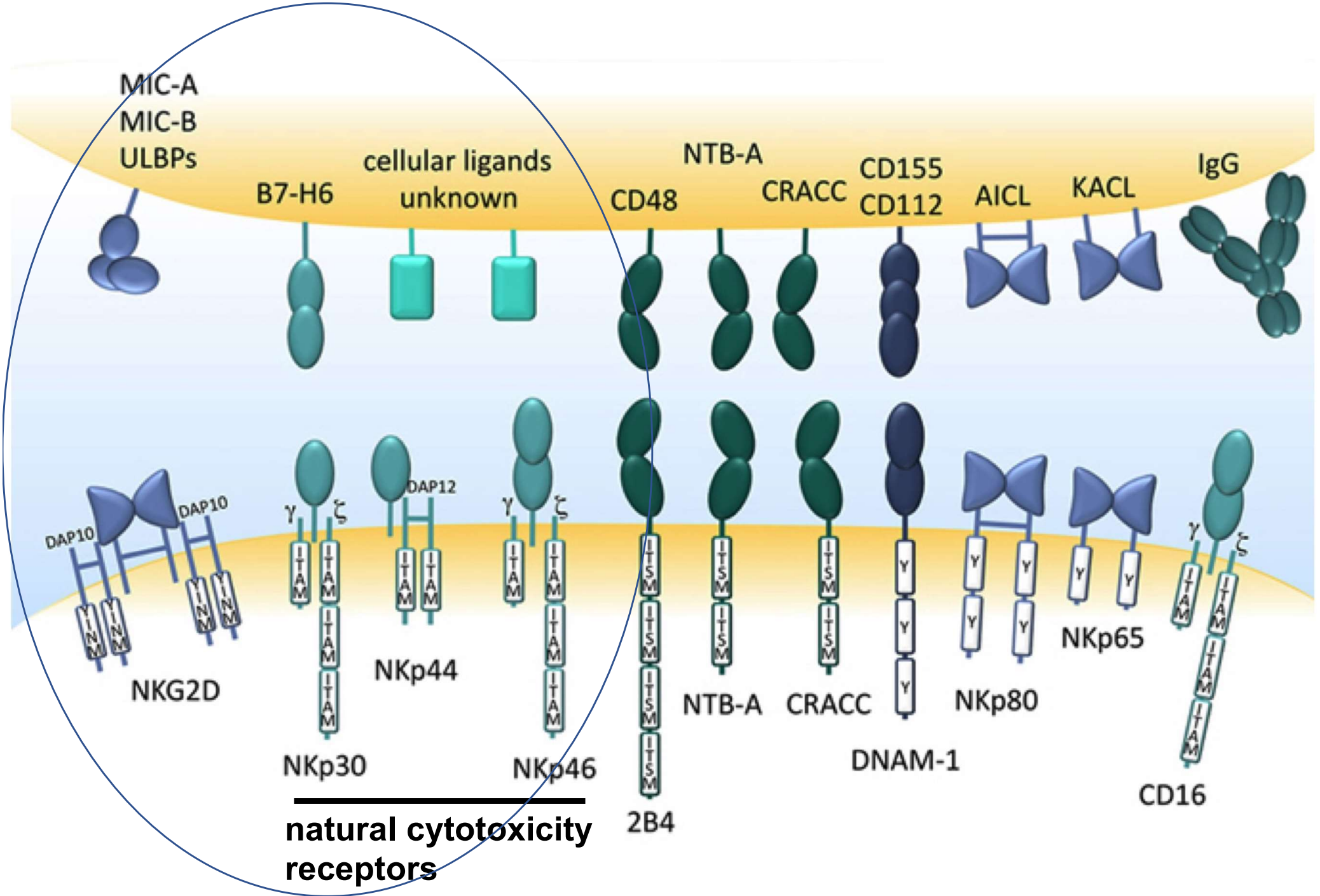
**Induction of expression of ligands for activating receptors (tumors, infections, stress)**



**SuperATTIVATION**

ACTIVATING RECEPTORS

# ACTIVATING NK CELL RECEPTORS AND THEIR LIGANDS



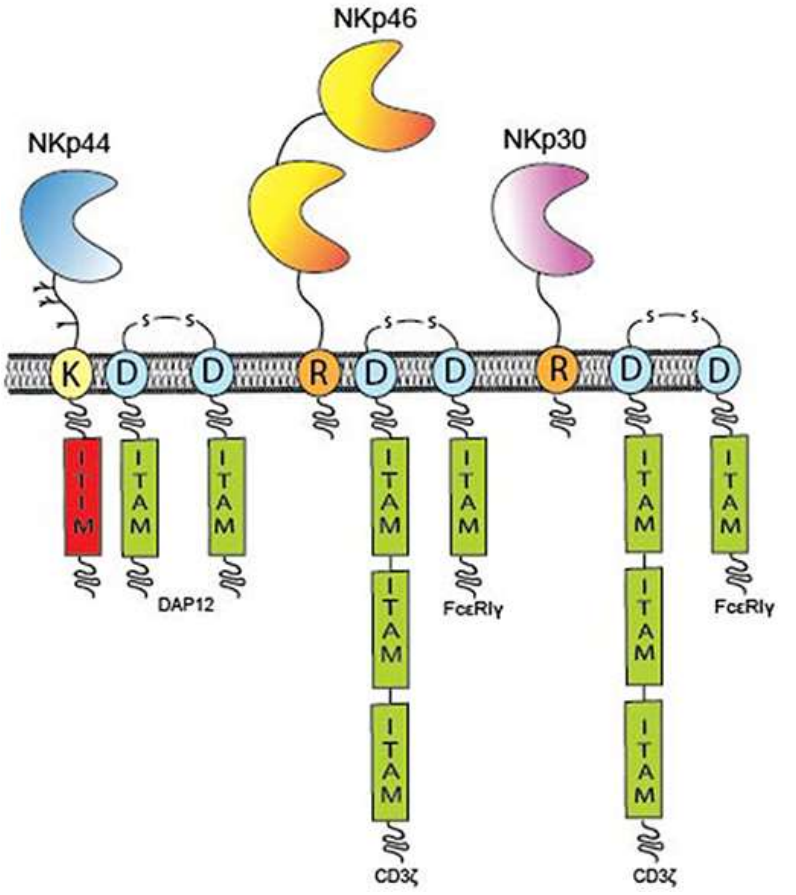
# Activating receptor for NATURAL CYTOTOXICITY

## 1. NCR

### NCR (natural cytotoxicity receptors)

*Immunoglobulin superfamily*

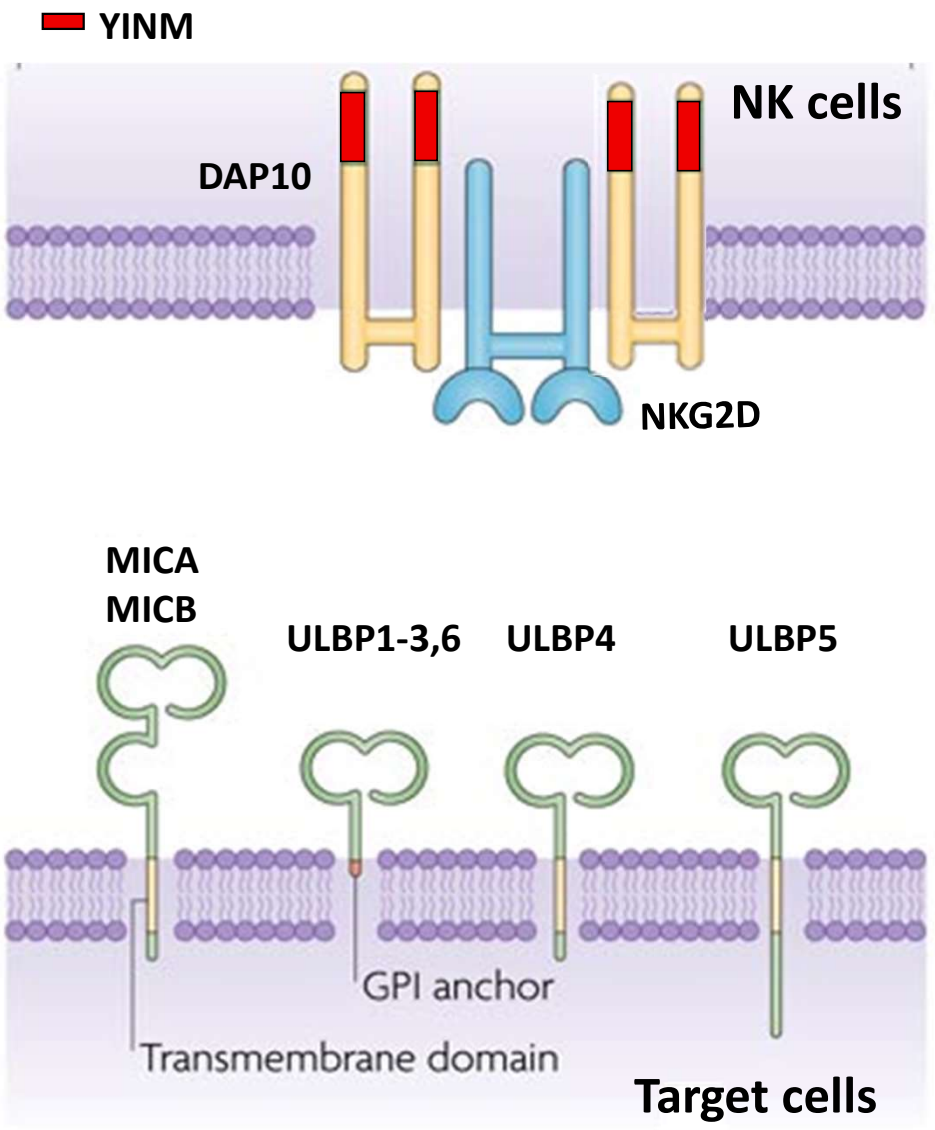
Receptors




**NKp44** **NKp46** **NKp30**

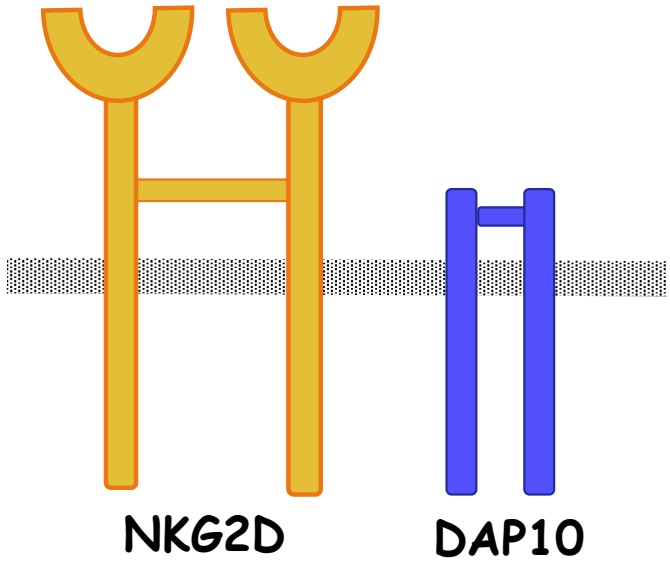
# Activating receptor for NATURAL CYTOTOXICITY

## 2. NKG2D receptor and its ligands



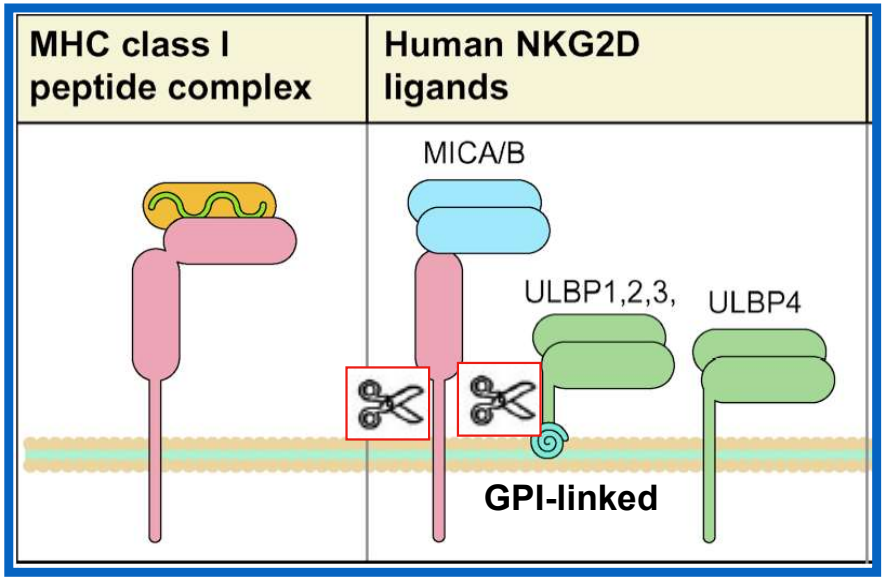
# NKG2D receptor

- C-type Lectin receptor superfamily
- Homodimer associtated to the adaptor DAP-10 (for signal transduction)
- Expressed by NK, TCD8$^+$, T$\gamma\delta$ cells

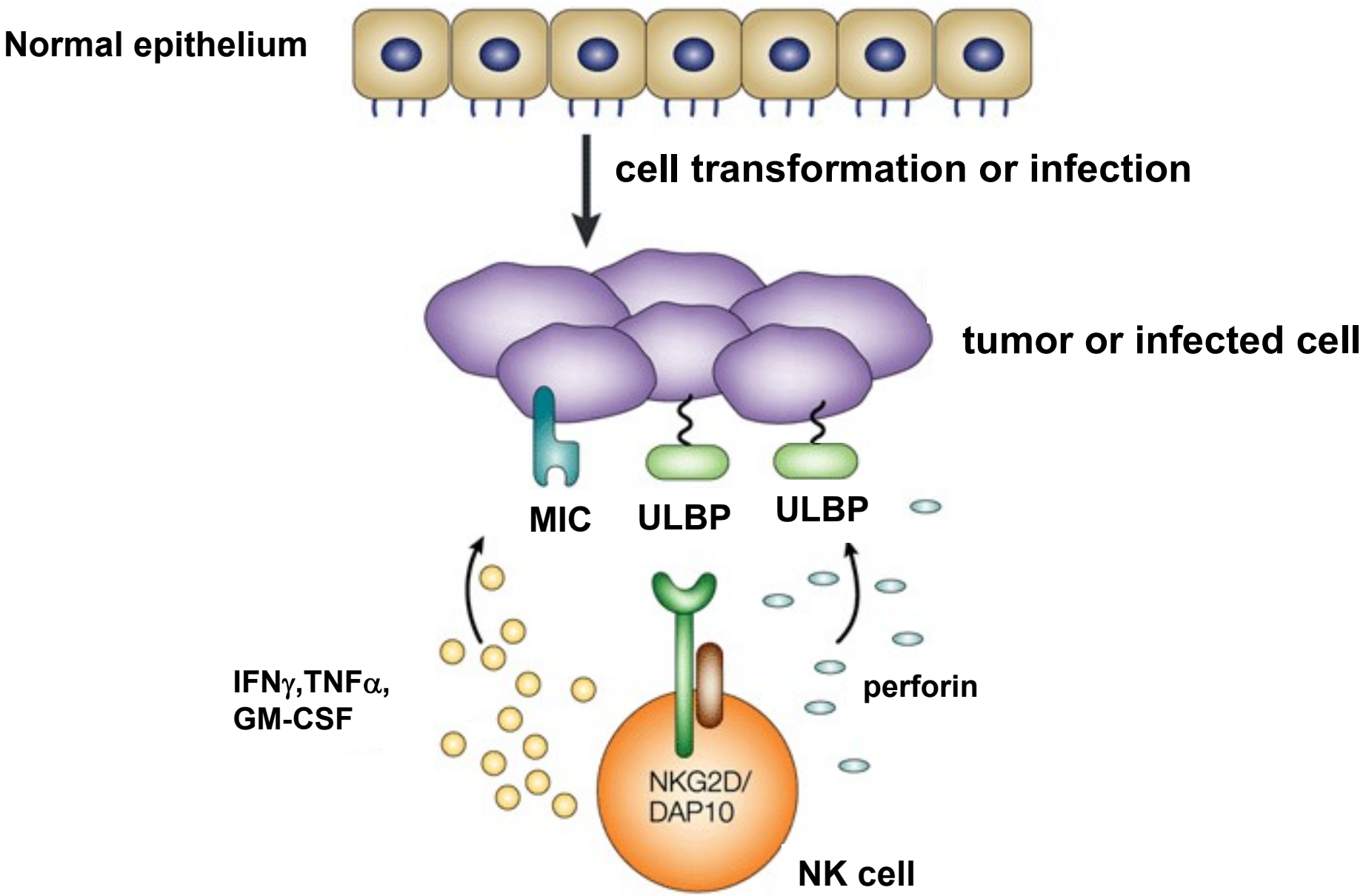



## ……and its ligands

- Encoded by genes present in the HLA locus, omologous to Class I MHC molecules.
- Induced by cell stress (viral infections, transformation, genotoxic damage)
- Increased expression by cytokines (IL-15, TNF, IFN$\alpha$) and bacterial products
- Also released in soluble form (proteolysis)

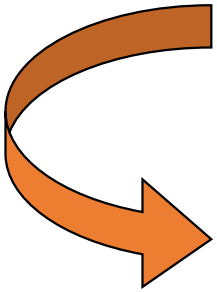


# NKG2D mediates altered self expressing cell recognition



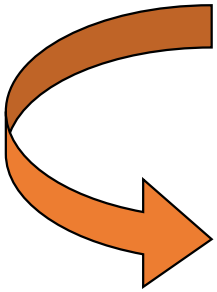
# HOW ARE NK CELLS ACTIVATED BY RECOGNITION OF TARGET CELLS?

**Missing self**
**Decreased MHC class I**



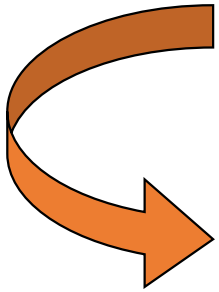
**Loss of inhibition**

**Induced self**
**Induced MIC-A/B, ULBPs**



**Superactivation**

**Microbial non self**
**PAMPs, viral proteins cytokines**



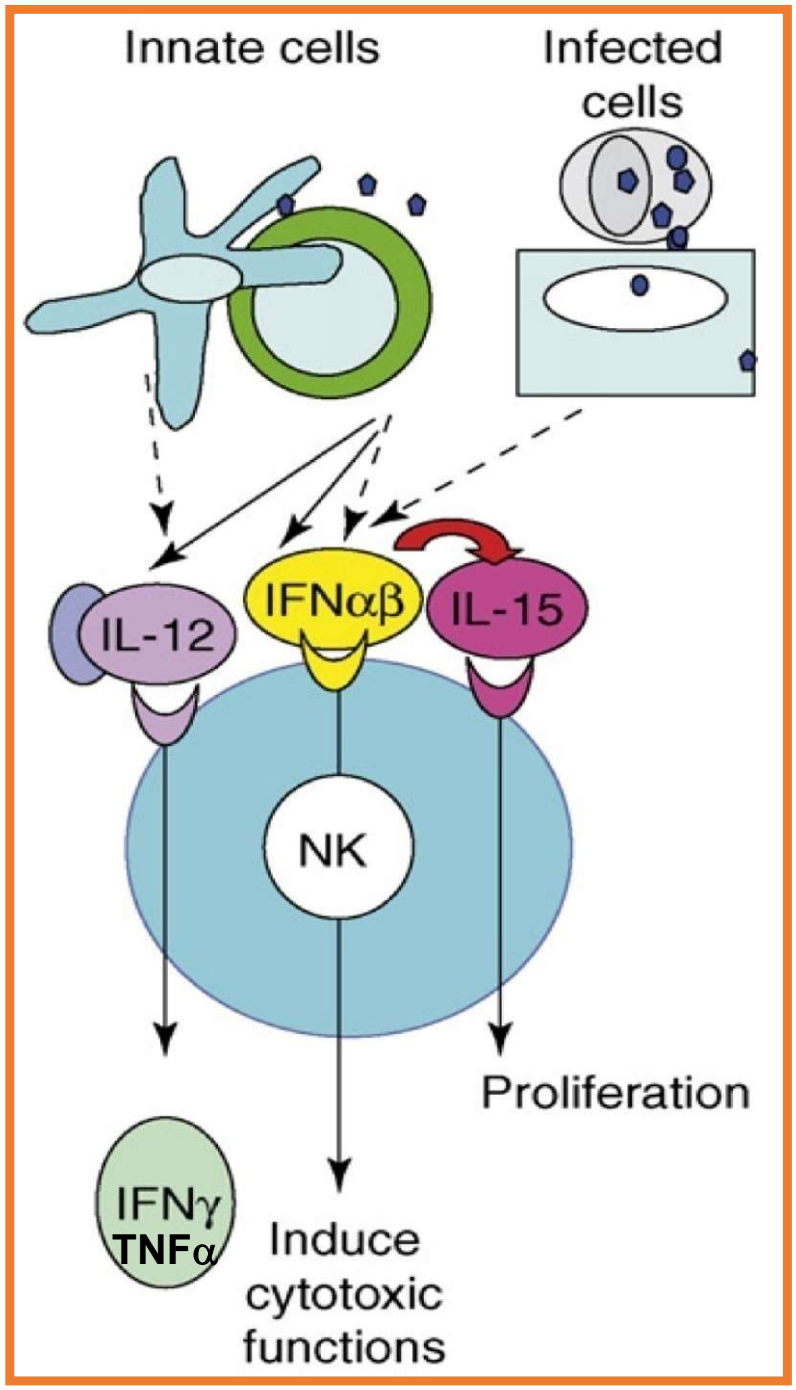
**Activation**

# TLRs espressi dalle cellule NK

| | Ligand(s) type | Expression | Effect |
|---|---|---|---|
| TLR2 | Bacterial lipoprotein (BCG) | Bacteria | cytotoxicity/cytokine release |
| TLR3 | Double-stranded RNA | Viruses | cytotoxicity/cytokine release |
| TLR5 | Flagellin | Bacteria | cytotoxicity/cytokine release |
| TLR7/8 | Single-stranded RNA | Viruses | cytotoxicity/cytokine release |
| TLR9 | CpG DNA motifs | Bacteria/viruses | cytotoxicity/cytokine release |

.

# Cytokine regulation of NK cell function




**NK cells express IL-2/IL-15R β e γc and are responsive to IL-2 produced by T cells**

**IL-2 increases:**

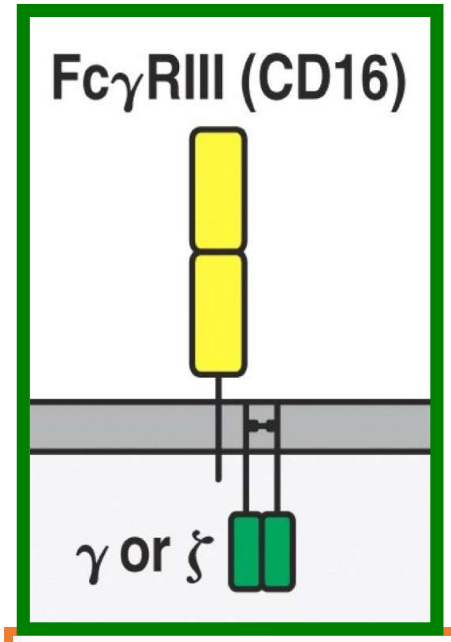
- **Cytotoxic function**
- **Granule content**
- **proliferation**
- **Endothelium adhesiveness**
- **chemotaxis**

**Participates in:**

- **IFNγ e TNFα production**

**IL-12/IL-15**
**IL-15/IL-18**
**Are also potent activators of NK cells in the absence of T cells**

# Antibody dependent cellular cytotoxicity (ADCC)




CD16 is a low affinity receptor for IgG (FcγRIII) and activates antibody-dependent cellular cytotoxicity= ADCC

It is expressed by CD56$^{dim}$ NK cells

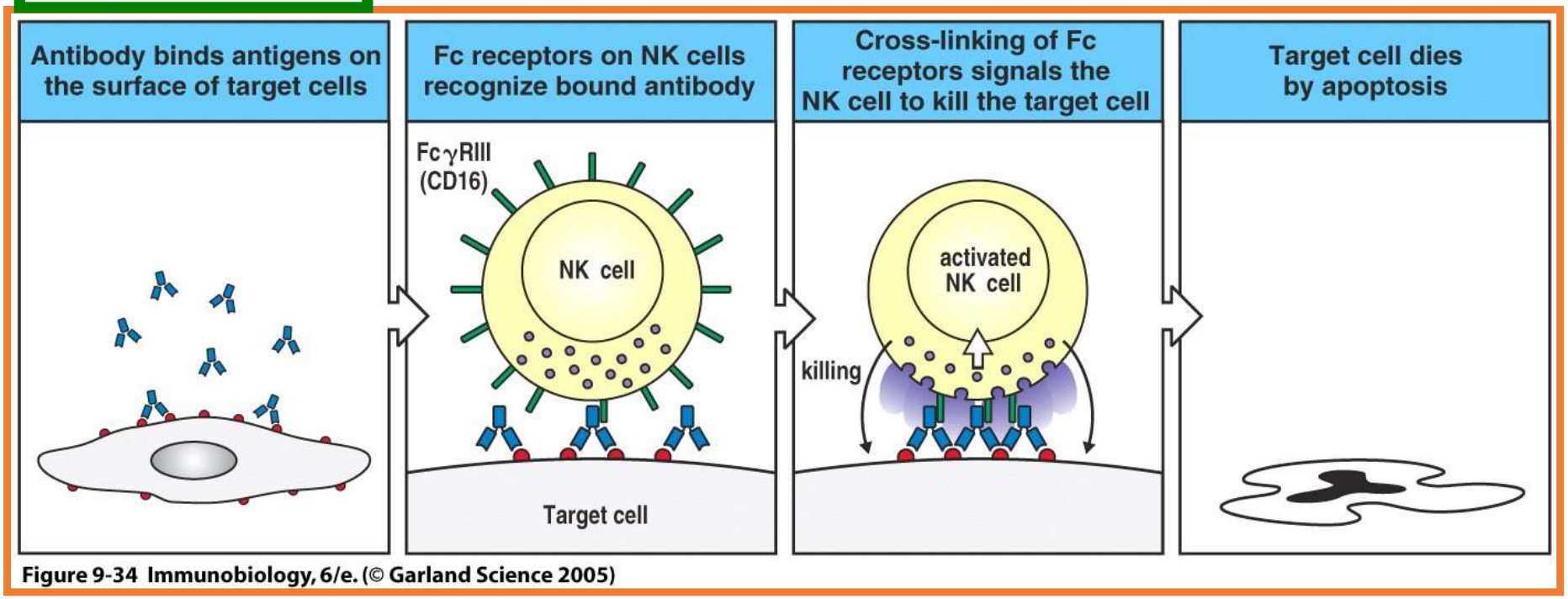



Figure 9-34 Immunobiology, 6/e. (© Garland Science 2005)

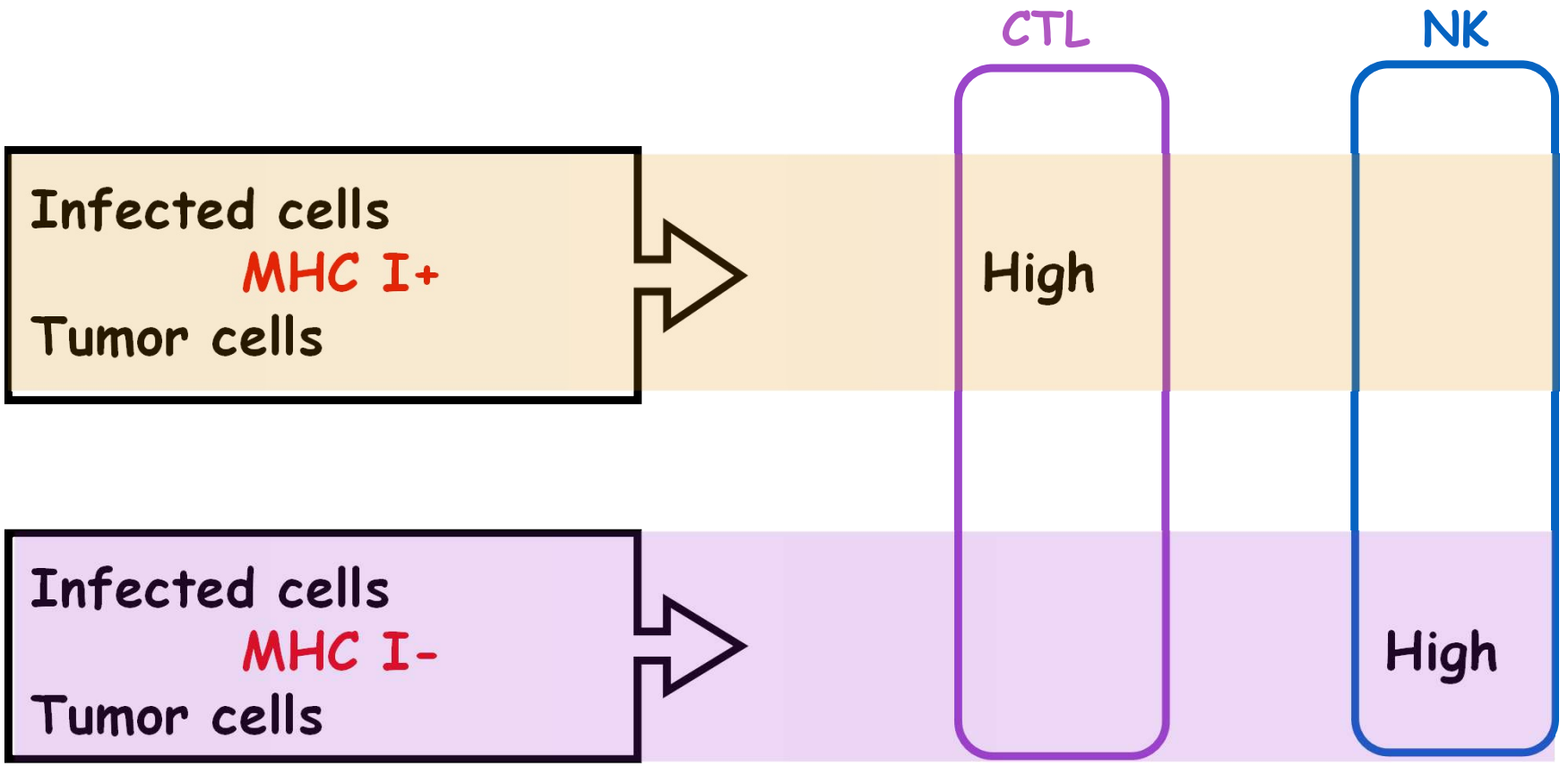
# Two types of cytotoxic lymphocytes

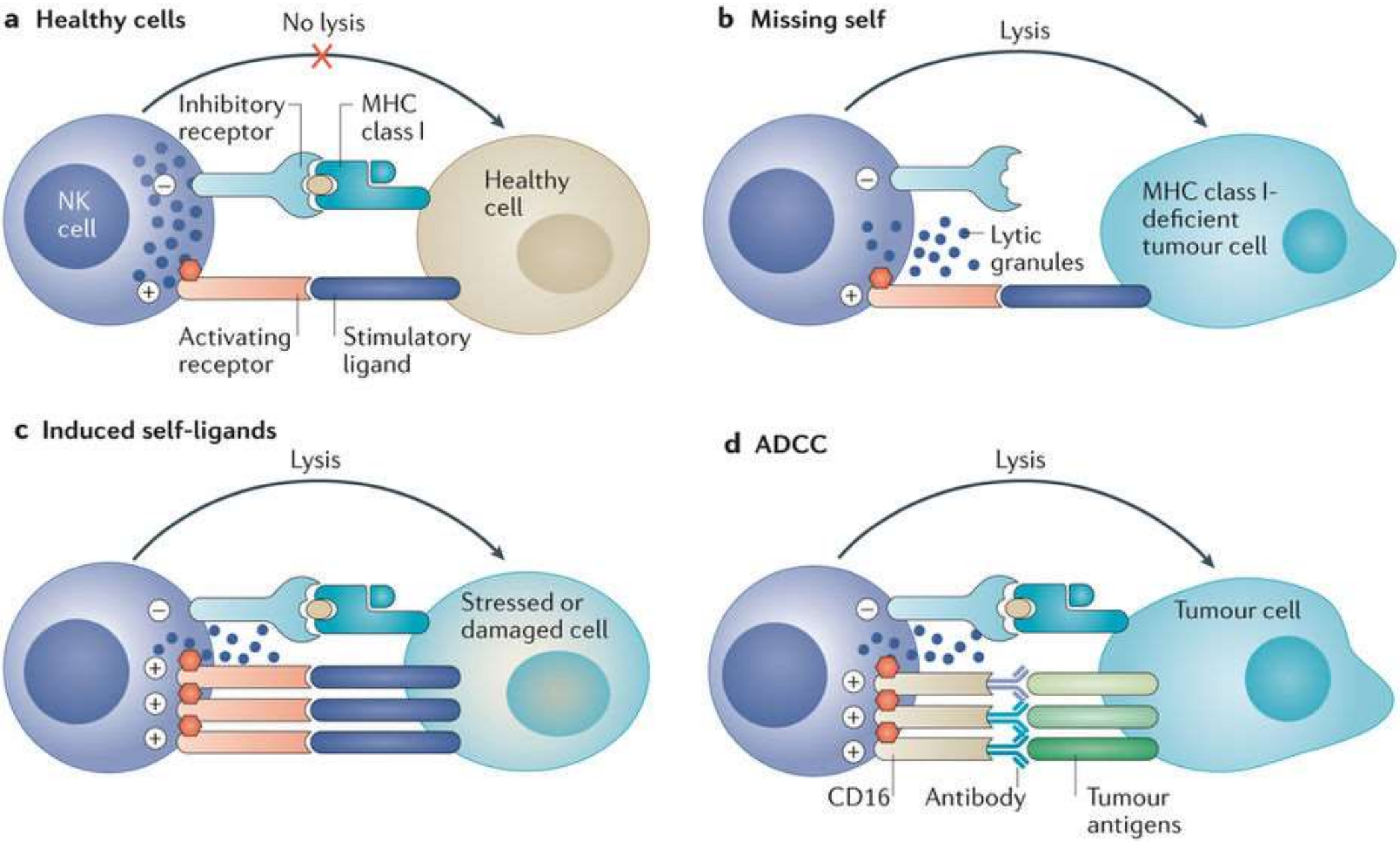

- Different recognition strategies
- Different activation mechanisms
- Common lytic mechanisms

**WHY?** They use complementary defensive strategies against intracellular pathogens and tumor cells

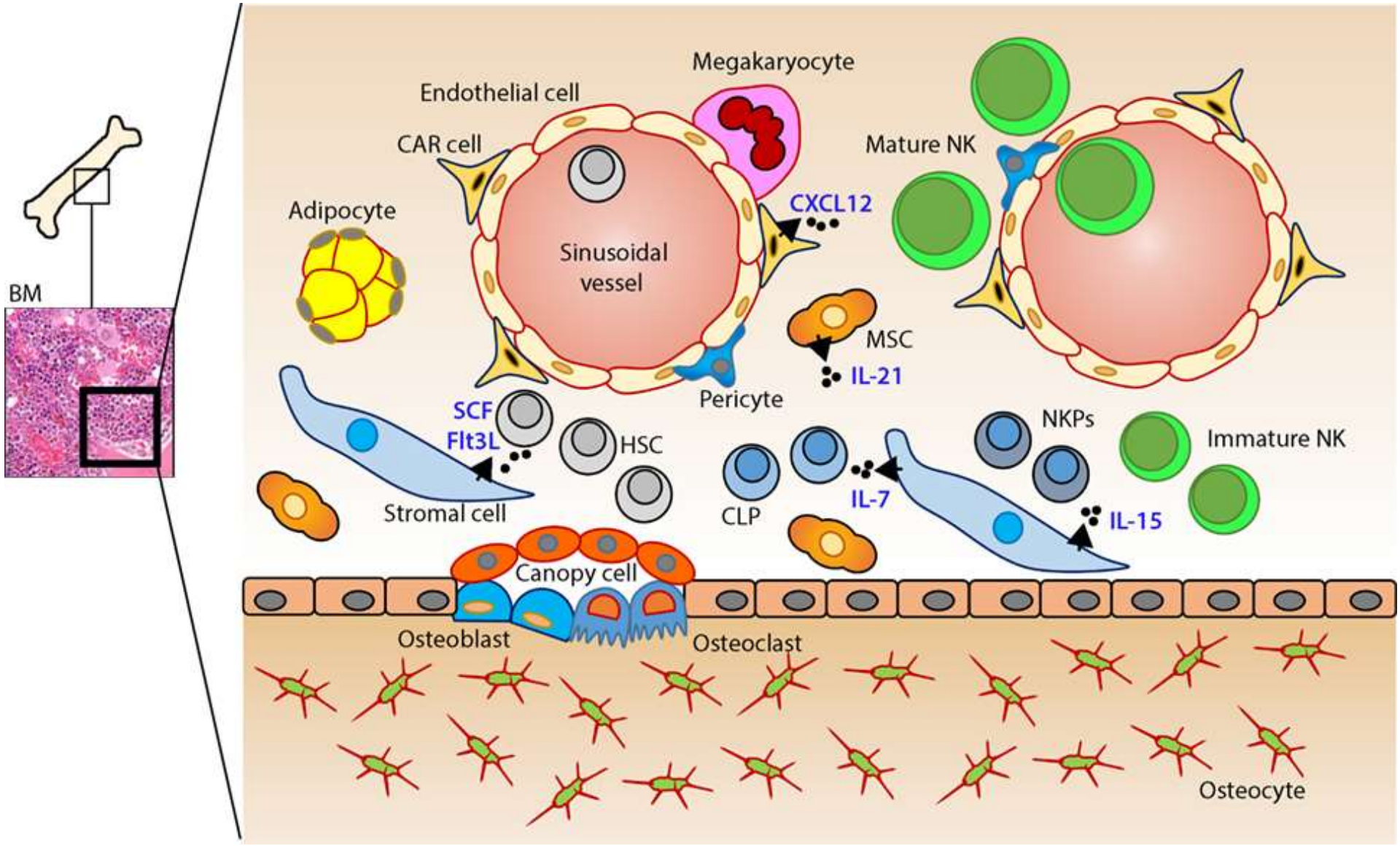
# Expression of class I MHC molecules opposively regulate cytotoxic function of NK and T cells

susceptibility to cell lysis:




a Healthy cells
No lysis
Inhibitory receptor
MHC class I
NK cell
Healthy cell
Activating receptor
Stimulatory ligand
b Missing self
Lysis
Lytic granules
MHC class I-deficient tumour cell
c Induced self-ligands
Lysis
Stressed or damaged cell
d ADCC
Lysis
Tumour cell
CD16
Antibody
Tumour antigens

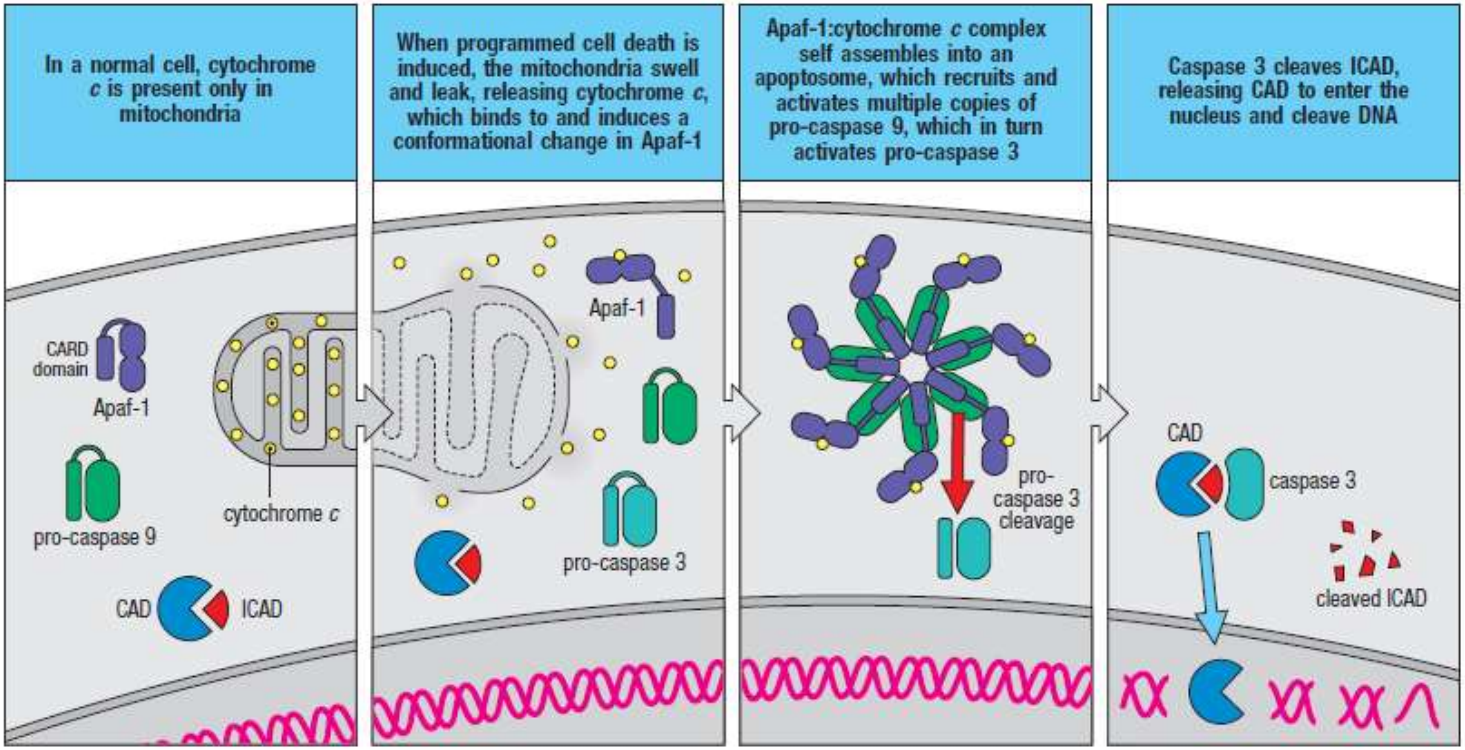
# Lo sviluppo delle cellule NK umane




MIDOLLO OSSEO

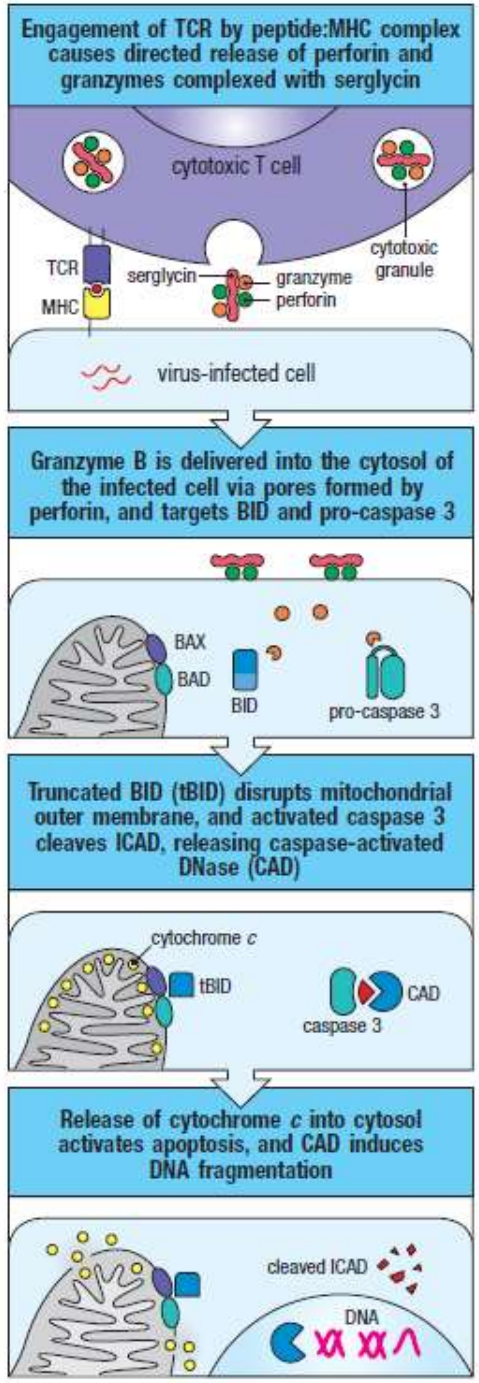
Il contatto diretto e le citochine/fattori di crescita **(principalmente IL-15)** prodotti dalle cellule stromali sono fondamentali per lo sviluppo delle cellule NK nel midollo osseo

# The intrinsic pathway of apoptosis is mediated by the release of cytochrome c from mitochondria




In the intrinsic pathway, cytochrome c release from mitochondria induces formation of the apoptosome, which activates pro-caspase 9 to initiate programmed cell death.

CAD: Caspase-activated Dnase



# Perforin polymerization creates pores on target cell membrane