

Corso di Immunologia

A.A. 2011-12

Introduzione

Perchè studiare immunologia?

Malattie infettive

Meccanismi di patogenicità
Sviluppo vaccini

Malattie causate da un sistema immune disturbato

ALLERGIA: Risposta immune verso materiale innocuo e.g. **ASMA**

AUTOIMMUNITA': Immunità Anti-self e.g. **MULTIPLE SCLEROSIS**

GRAFT REJECTION: Risposta immune verso **TESSUTO TRAPIANTATO**

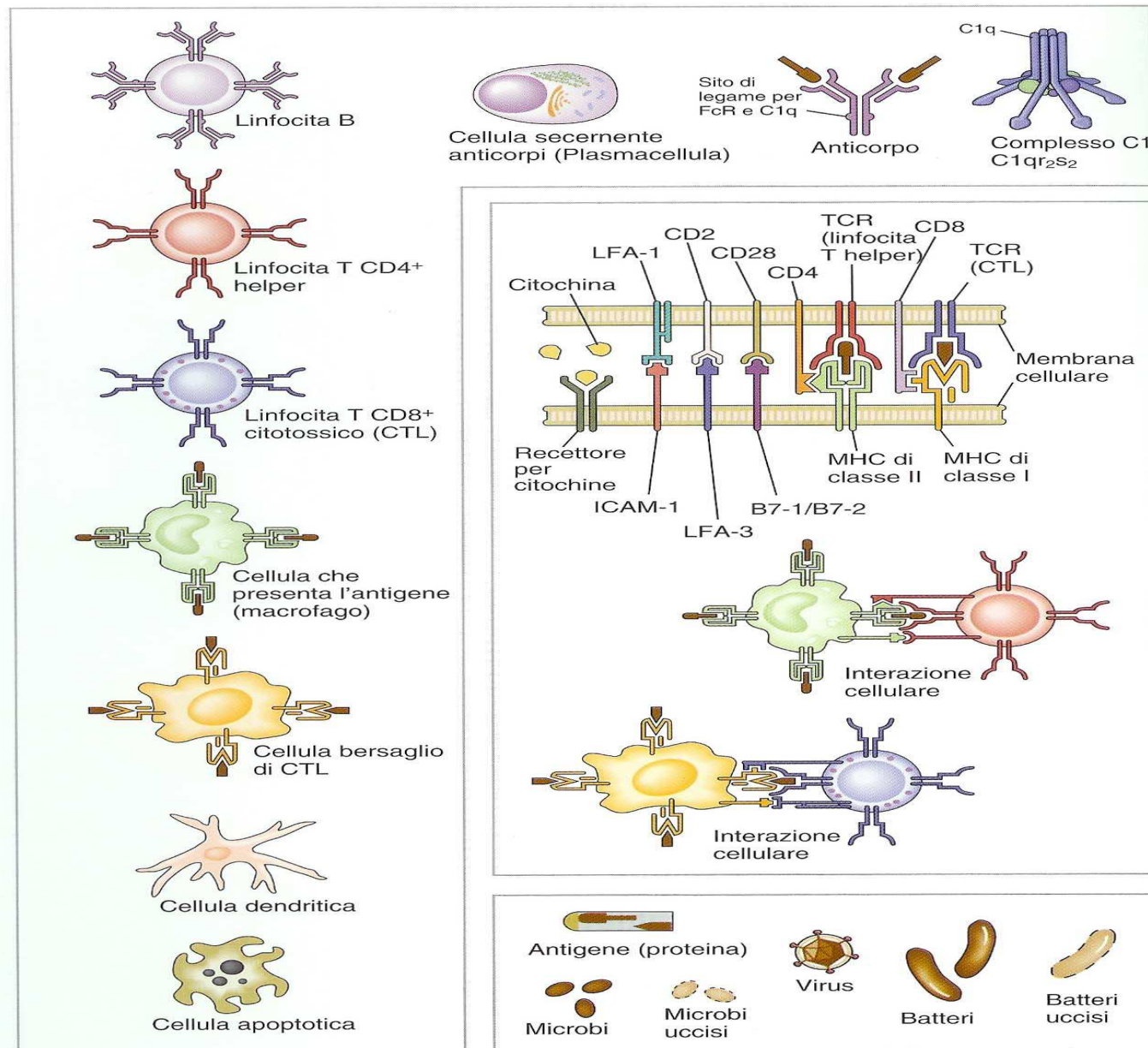
IMMUNODEFICIENZA: Difetti nella risposta immune e.g. **SCID**

Manipolazione dell'immunità per curare malattie

IMMUNOSOPPRESSIONE: Trattamento delle malattie immuni

IMMUNOREGOLAZIONE: Interventi immunoterapeutici

Componenti della risposta immune



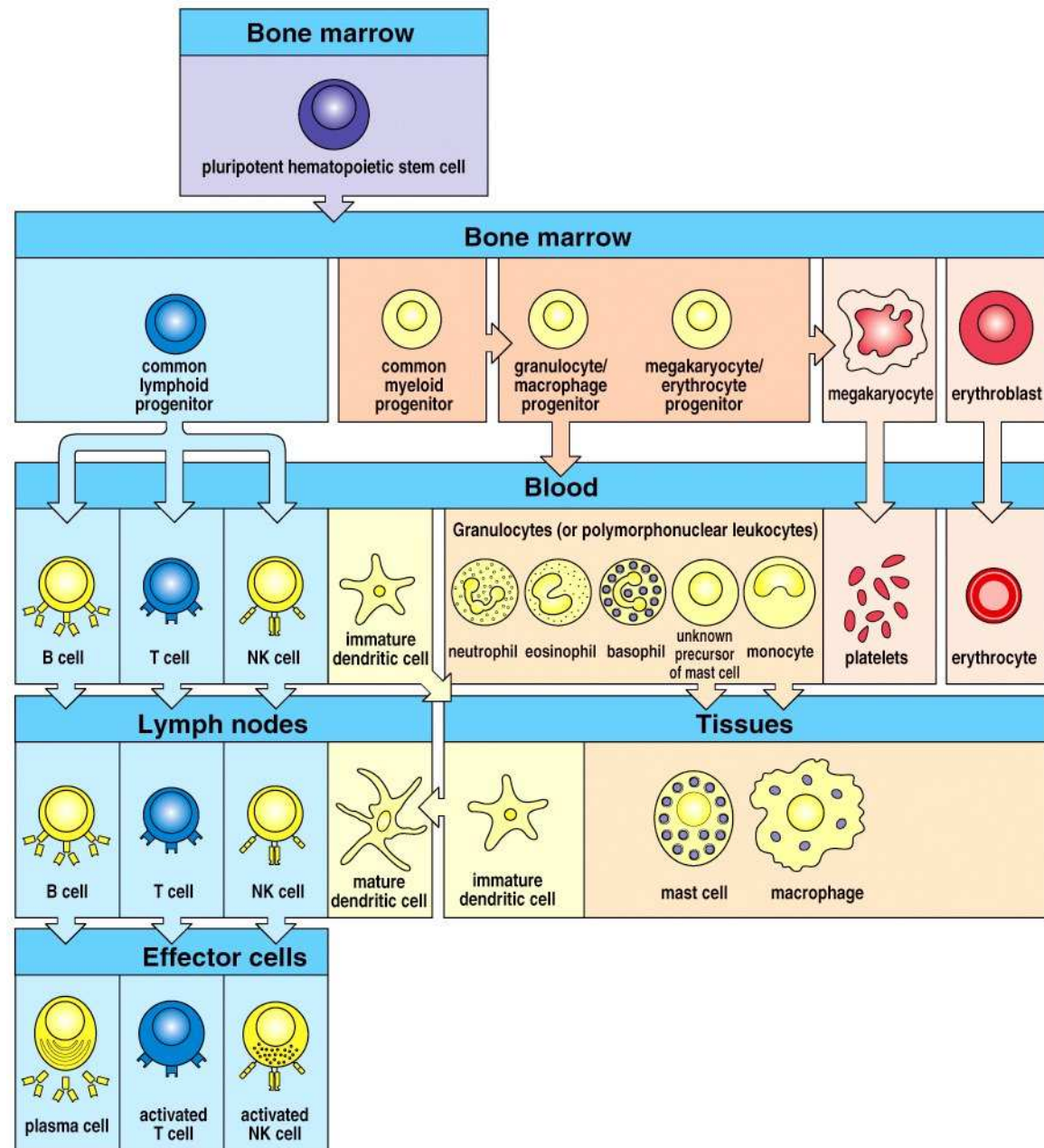


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

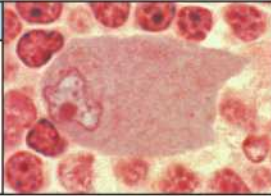
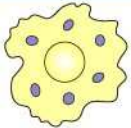
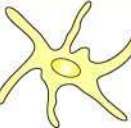
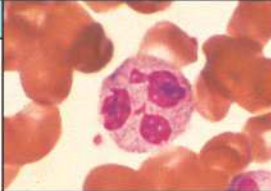
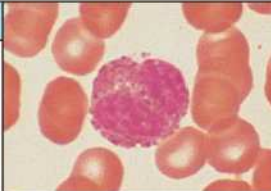
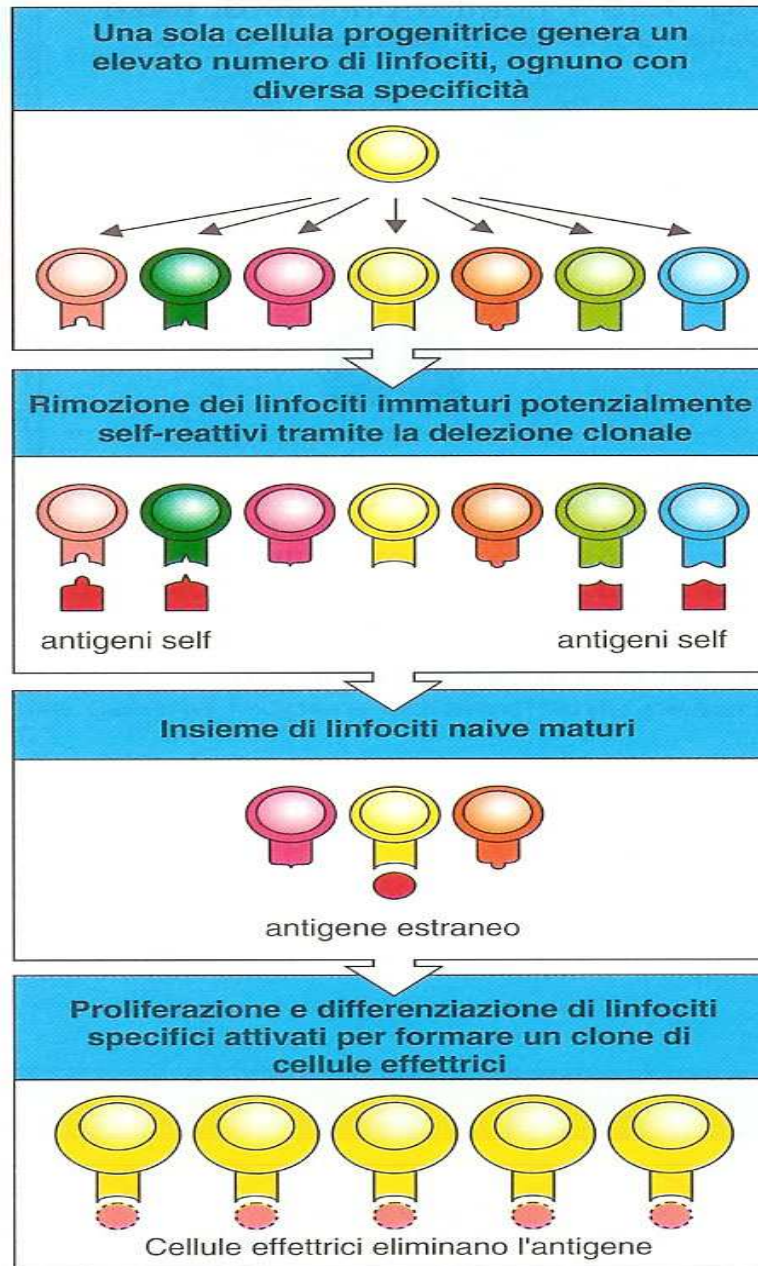
Cell		Activated function
Macrophage		Phagocytosis and activation of bactericidal mechanisms
		Antigen presentation
Dendritic cell		Antigen uptake in peripheral sites
		Antigen presentation in lymph nodes
Neutrophil		Phagocytosis and activation of bactericidal mechanisms
		
Eosinophil		Killing of antibody-coated parasites
		
Basophil		Unknown
		
Mast cell		Release of granules containing histamine and other active agents
		

Figure 1-4 Immunobiology, 6/e. (© Garland Science 2005)

Ipotesi della selezione clonale



Postulates of the clonal selection hypothesis

Each lymphocyte bears a single type of receptor with a unique specificity

Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation

The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived

Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes

Figure 1-15 Immunobiology, 6/e. (© Garland Science 2005)

Numero normale delle cellule circolanti

	Numero Medio per Microlitro	Intervallo Normale
Leucociti (globuli bianchi)	7.400	4.500-11.000
Neutrofili	4.400	1.800-7.700
Eosinofili	200	0-450
Basofili	40	0-200
Linfociti	2.500	1.000-4.800
Monociti	300	0-800

Granulociti neutrofili 55-70 %

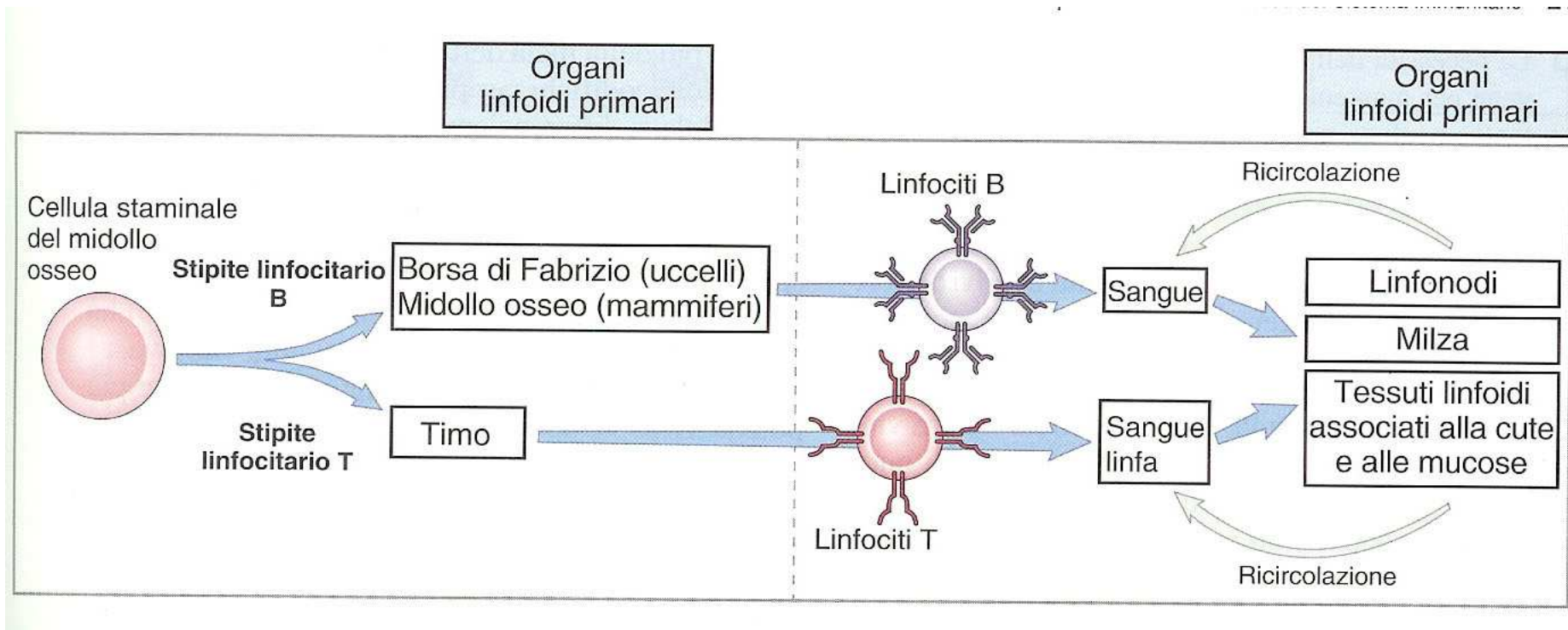
Granulociti eosinofili 1-4 %

Granulociti basofili 0,1-1 %

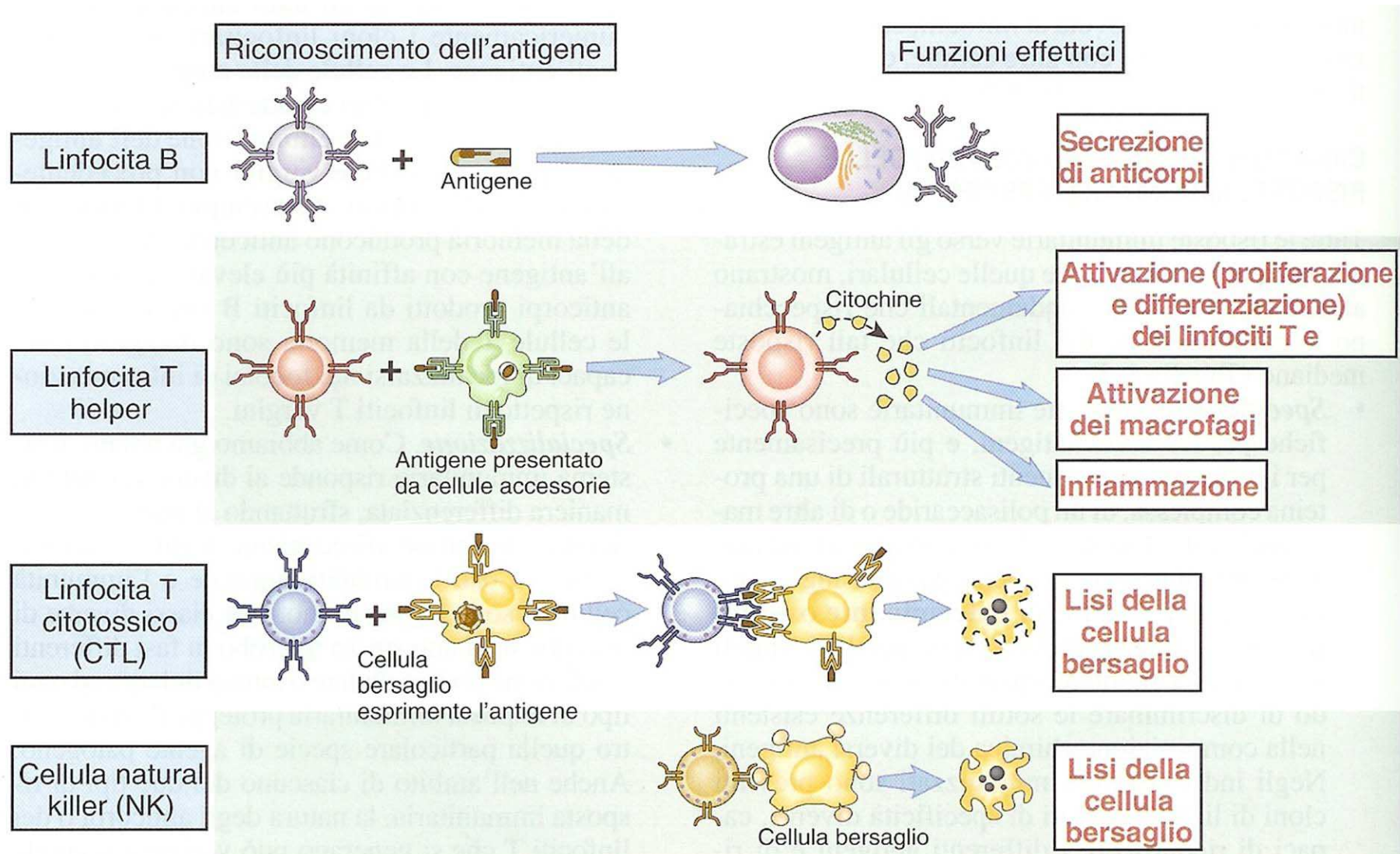
Linfociti 20-30 %

Monociti 2-8 %

Maturazione dei linfociti



Classi di linfociti



Sottopopolazioni linfocitarie

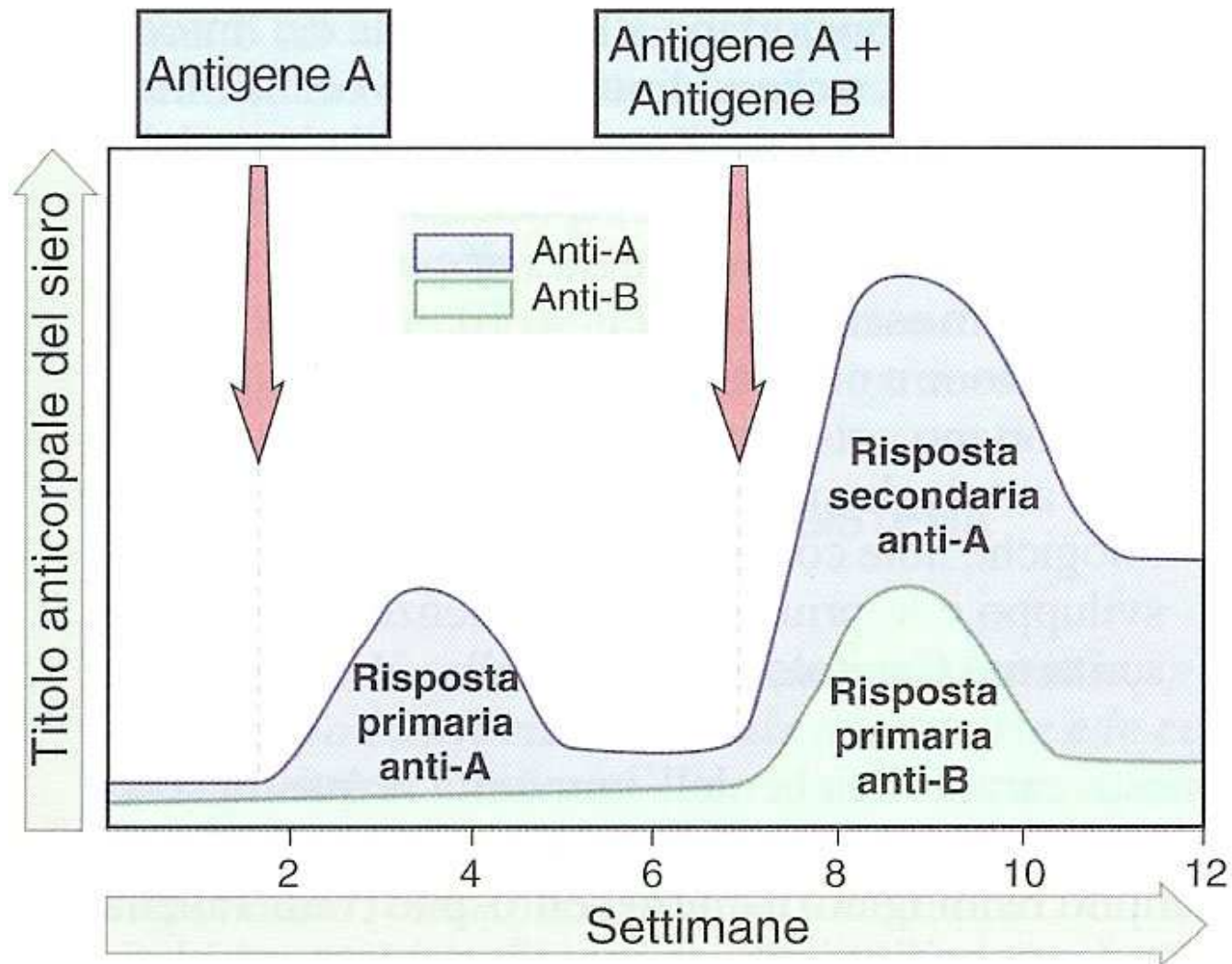
Classe	Funzioni	Recettore per l'Antigene	Principali Marcatori Fenotipici	Percentuale dei Linfociti Totali		
				Sangue	Linfonodi	Milza
Linfociti B	Produzione di anticorpi (immunità umorale)	Anticorpi di membrana (immunoglobuline)	Recettori Fc; MHC di classe II; CD19; CD21	10-15	20-25	40-45
Linfociti T Helper	Stimolazione della crescita e differenziazione dei linfociti B (immunità umorale) Attivazione macrofagica da parte delle citochine prodotte (immunità cellulare)	Eterodimeri $\alpha\beta$	CD3; CD4	50-60*	50-60	50-60
Citotossici	Lisi di cellule infettate da virus, di cellule tumorali, di allotrapianti (immunità cellulare)	Eterodimeri $\alpha\beta$	CD3; CD8	20-25	15-20	10-15
Cellule NK	Lisi di cellule infettate da virus e di cellule tumorali; citotossicità cellulare mediata da anticorpi	?	Recettori per Fc delle IgG (CD16)	~ 10	Rari	~ 10

*Nella maggior parte dei tessuti, il rapporto tra linfociti CD4⁺CD8⁻ e linfociti CD4⁻CD8⁺ è circa di 2 a 1.
Alcuni linfociti T funzionano inibendo le risposte immunitarie; essi prendono il nome di cellule soppressive, ma non è chiaro se rappresentino una popolazione di linfociti T a sé stante.
Abbreviazioni: IgG, immunoglobuline G; MHC, complesso maggiore di istocompatibilità; NK, natural killer.

Caratteristiche basilari delle risposte immunitarie specifiche

Caratteristica	Significato Funzionale nella Immunità Antimicrobica
Specificità	Garantisce che microbi diversi evochino risposte specifiche
Diversificazione	Consente al sistema immunitario di rispondere ad una vastissima gamma di microbi
Memoria	Porta al potenziamento della risposta in caso di ripetute esposizioni ad uno stesso microbo
Specializzazione	Consente la generazione di risposte ottimali per contrastare i diversi tipi di agenti patogeni
Auto-limitazione	Permette al sistema immunitario di rispondere ad antigeni sempre nuovi
Non reattività al <i>self</i>	Previene il danneggiamento dell'ospite nel corso delle risposte contro i microbi

Specificità, memoria ed autolimitazione delle risposte immunitarie



Immunity

Innate & Adaptive

- First line of defense
- Nonspecific
- Rapid onset
- No protective immunity
- No memory
- Phagocyte- mediated

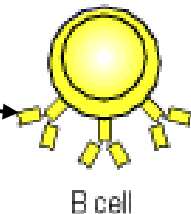
- Activated
- Very specific
- Slower
- Protective immunity possible
- Memory possible
- Lymphocyte- mediated

Lymphocytes

- Unique antigen receptor constructed early
- Selected and activated by non-self proteins
- Clones persist (memory cells)
- Lymphocytes with self-recognizing receptors are culled

B-cells

- Mature in bone marrow
- Lymphoid follicle
- Antigen receptor:
Immunoglobulin
molecule



B cell

T-cells

- Mature in thymus
- Paracortical area
- Antigen receptor:
T-cell receptor

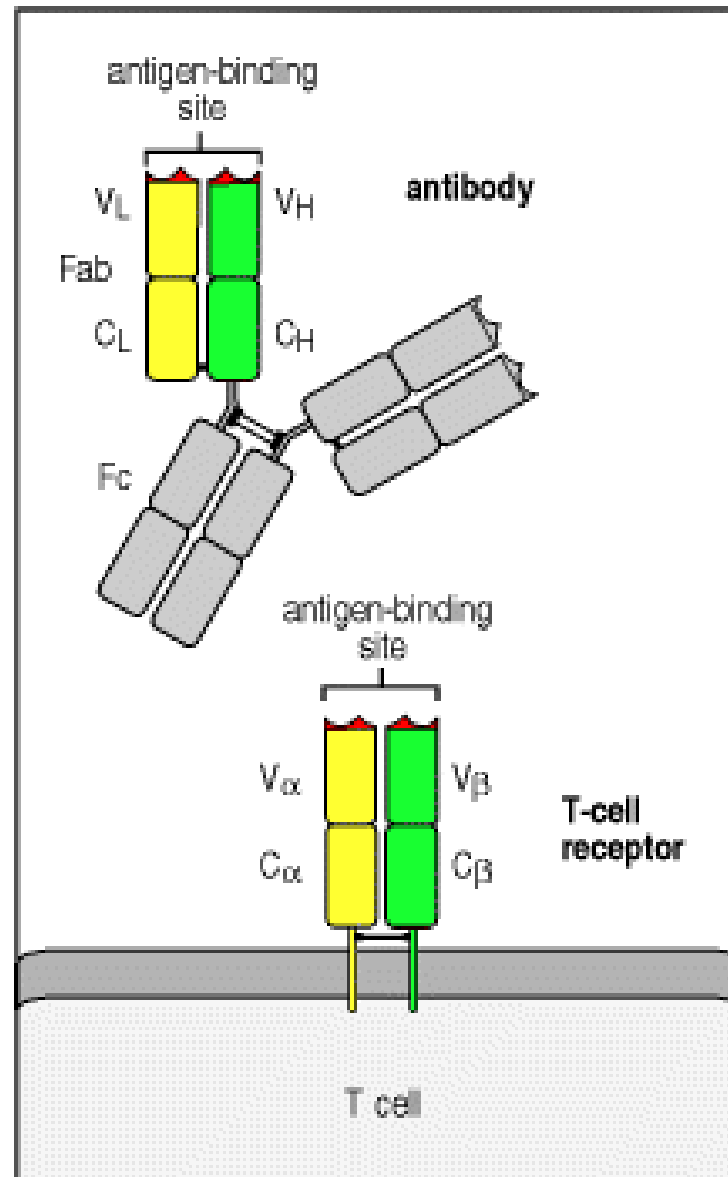


T cell

From, Janeway, CA, *Immunobiology*, 5th ed.

Adaptive Immunity

Antigen Receptors

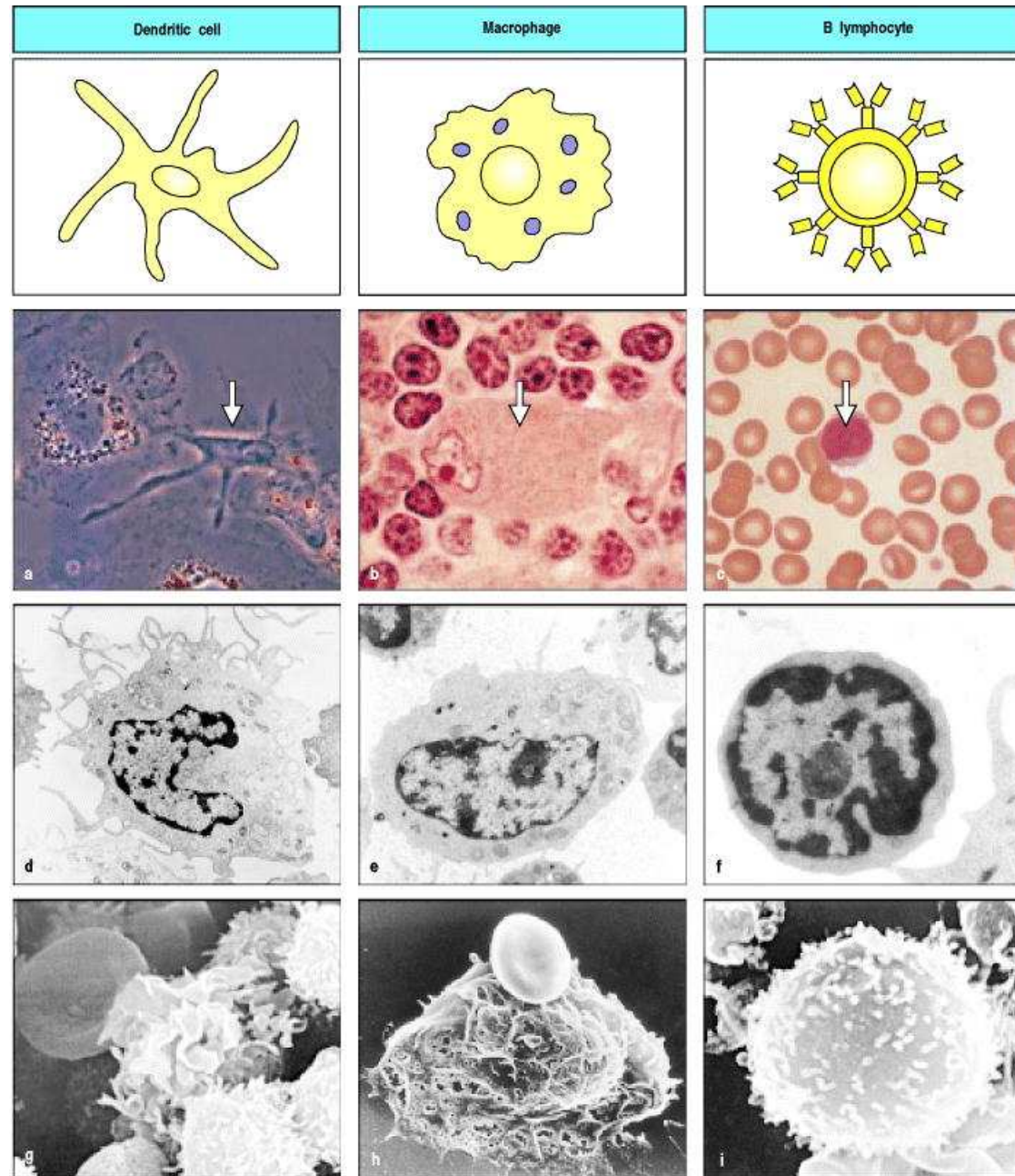


From, Janeway, CA,
Immunobiology, 5th ed.

“Professional” Antigen Presenting Cells

- Dendritic cells, macrophages, B-cells
- Efficiently process antigens
- Cytosolic and vesicular compartments
- Express MHC I and II molecules
- Antigen peptides fit in MHC cleft
- MHC:peptide complex to cell surface
- Provide costimulatory 2nd signal

Antigen Presenting Cells



From, Janeway,
CA, *Immunobiology*,
5th ed.

MHC Molecules

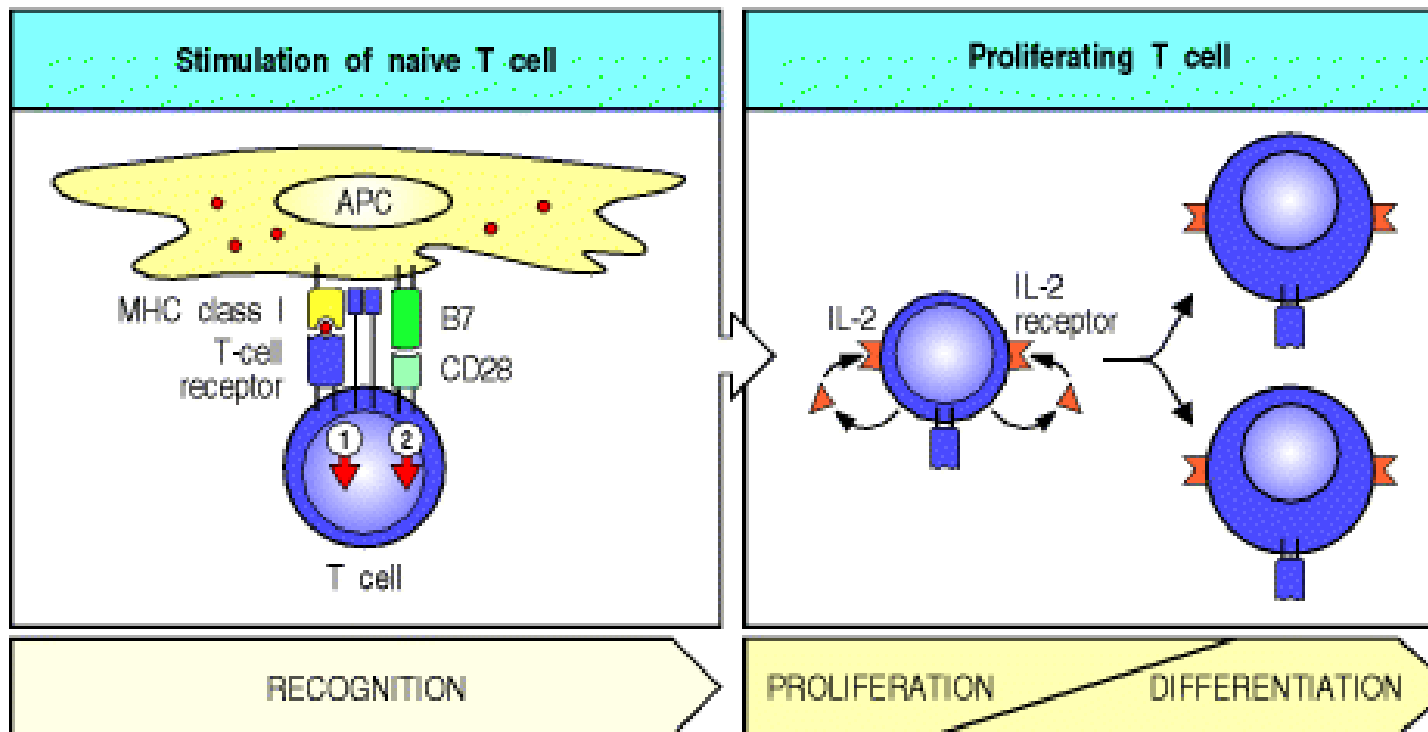
- Function: Bind processed antigen and transport to cell surface
- MHC I:
 - All nucleated cells
 - Process Ag from cytosolic compartment
 - Present to CD8+ cytotoxic T-cells
 - HLA-A, B, C
- MHC II:
 - Dendritic cells, macrophages, B-cells
 - Process Ag from vesicular compartment
 - Present to CD4+ helper T-cells
 - HLA-DR, DP, DQ

Recipe for Successful Antigen Presentation

Place in a lymph node...

- 1 antigen presenting cell (APC) with MHC molecules (I or II)
- 1 antigen processed by APC
- 1 naïve T cell (CD8+ or CD4+) with unique and specific T-cell receptor
- Add costimulatory second signal and a pinch of IL-2
- Stir....Proliferate, differentiate!

To Activate a Lymphocyte...



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Immunobiology, 5th ed.

Cell Adhesion Molecules (CAM): Molecular Velcro

- Cell surface molecules with matching ligands on other cells
- Allow cell-to-cell binding for communication and homing
- Expression of CAMs variable and under complex control
- Example: Intercellular adhesion molecule-1 (ICAM-1) on APC's binding to lymphocyte function-associated antigen-1 (LFA-1) on T-cells

Effector T-Cells

- CD8+ cytotoxic T lymphocyte (CTL)
 - “*The Hitman*”
 - Kills on contact
- CD4+ helper T lymphocyte
 - “*The Bureaucrat*”
 - Directs other cells to do the dirty work

Effector T-cells do not require costimulatory
signal

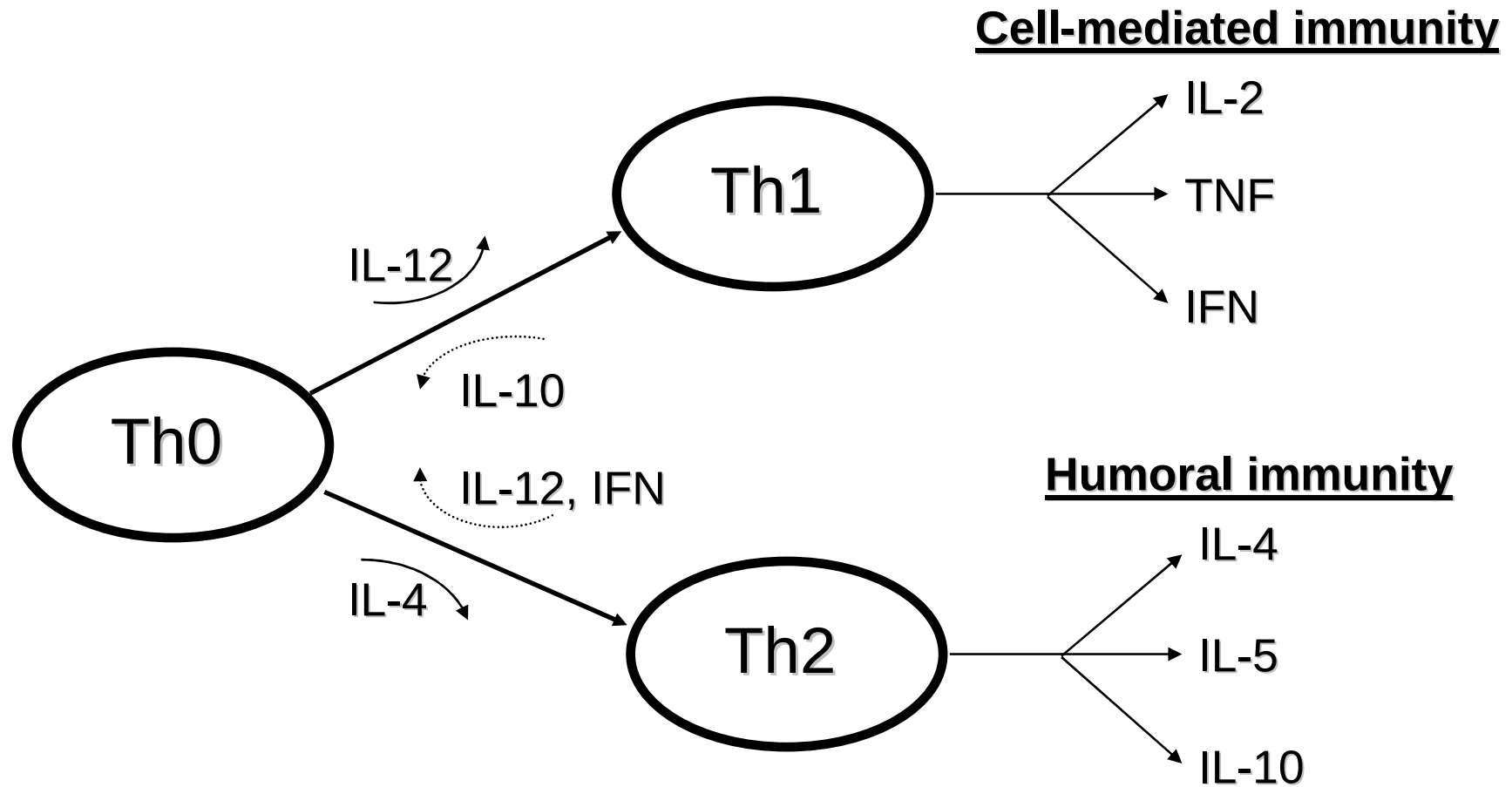
CD8+ Cytotoxic T-cell

- Directly cytotoxic to cells via binding to Ag:MHC I complex
- Cytosolic antigens (e.g., viruses)
- Induces apoptosis
- Cytotoxicity is specific and directional
- Cytotoxins include:
 - Perforin, granzymes
- Also produces cytokines
 - IFN- γ , TNF

CD4+ Helper T-Cells

- Binds to APCs via Ag:MHC II complex
- Then directs other effector cells (macrophages, B cells) to kill pathogens or neutralize toxins
- Uses cytokines as its “memos”

Th1/Th2 Paradigm



CD4+ Helper T-Cells: Th1/Th2 Paradigm

- Th1 (type 1)
 - IL-2, TNF, IFN- γ
 - Activate macrophages and CTL's for intracellular pathogen killing and cytotoxicity
 - Facilitate cell-mediated immunity
 - Inhibit Th2 cell proliferation

CD4+ Helper T-Cells: Th1/Th2 Paradigm

- Th2 (type 2)
 - IL-4, 5, 10
 - Activate B cells and antibody production to neutralize extracellular pathogens & toxins
 - Facilitate humoral immunity
 - Inhibit Th1 cell proliferation

What Determines Th1 vs. Th2 Response?

- Type of pathogen
- Innate immune response to it
 - Macrophages, NK cells release IL-12, IFN- γ
 - Mast cells, basophils release IL-4
- Host's immune constitution
- Density of Ag presented on APC
 - High density $\longrightarrow$ Th1
 - Low density $\longrightarrow$ Th2