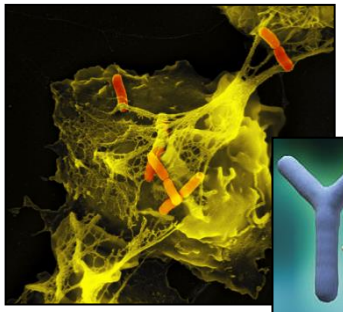
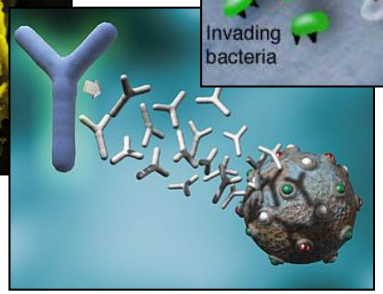
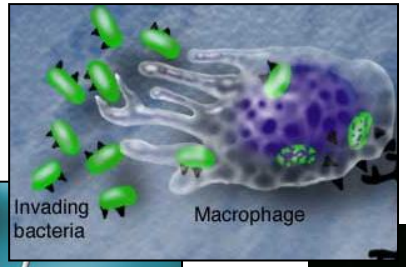
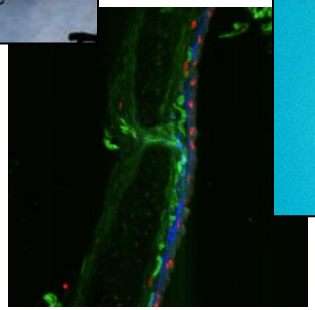
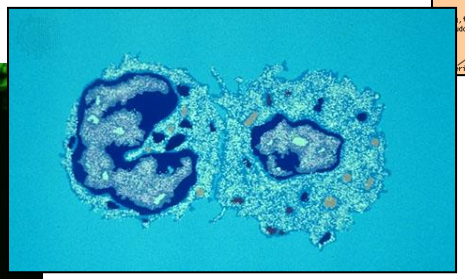
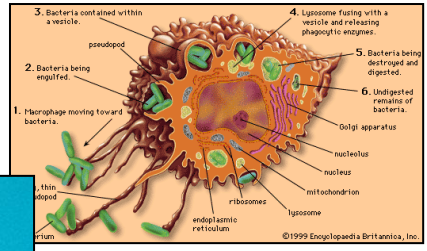
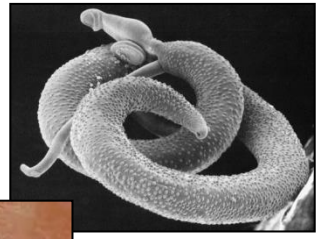
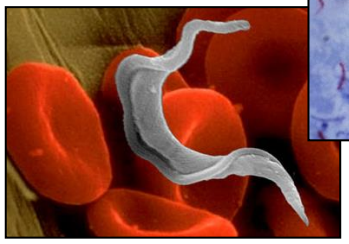
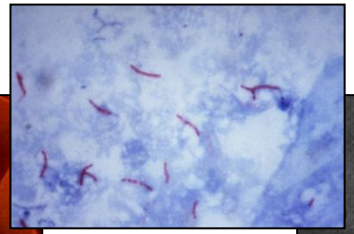
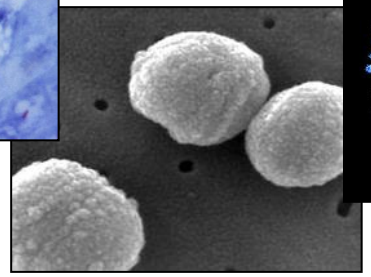
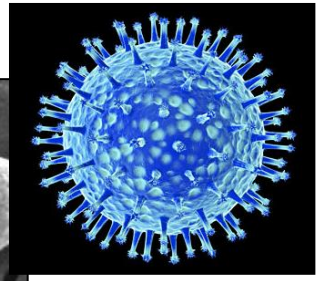




A Resposta Imune Celular e Humoral Contra Parasitas

Profa. Isabel de Miranda Santos
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Aulas anteriores

- Componentes do Sistema Imune
  - Componentes dos "humores" ou líquidos corporais
    - Imunoglobulinas
    - Complemento
    - Proteínas de fase aguda
    - Lisozima
    - .....
  - Componentes celulares
- Geração de respostas
- **Mecanismos efetores**

Roteiro

- Características Gerais da Imunidade Contra os Parasitas
- Tipos de Patógenos
- Tipos de Componentes Celulares
- Tipos de Componentes Humorais
  - Imunidade pré-formada: pentraxinas, MBL, NETs
  - Imunidade adquirida: Anticorpos
    - Tipos de anticorpos
- Mecanismos Efetores Humorais Contra os Diferentes Tipos de Patógenos
- Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

Características Gerais da Imunidade Contra Parasitas

- As defesas contra os parasitas são mediadas por componentes da imunidade pré-formada e pela imunidade adquirida

- A imunidade pré-formada determina a natureza da imunidade adquirida
  - Complemento > anticorpos
  - IL-12 > Imunidade tipo Th1 com produção de IFNγ

- Existem vários tipos de mecanismos efetores especializados em tipos diferentes de parasitas
  - Bactérias intracelulares e extracelulares
  - Vírus, bactérias, fungos, protozoários, helmintos, artrópodes

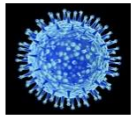
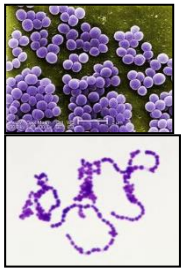
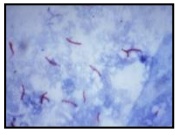
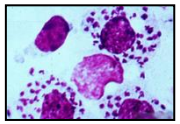
- O desfecho de infecções e a sobrevivência dos parasitas num hospedeiro dependem da capacidade do parasita de sobreviver à imunidade protetora
  - Mecanismos de escape

- A injúria tissular e a doença resultante da infecção podem ser causadas por:
  - Respostas do hospedeiro contra o parasita
  - Toxinas e fatores de virulência do parasita

Tipos de Patógenos

Contextualizados nos mecanismos efetores

"Habitats" preferenciais no hospedeiro seriam determinantes dos mecanism efetores imunes mais eficazes

- **Unicelulares**
  - Vírus  •Intracelulares
  - Bactérias
    - Extracelulares 
      Staphylococcus aureus
      Steptococcus pneumoniae
    - Intracelulares 
      Mycobacterium tuberculosis
  - Protozoários
    - Extracelulares 
      Trypanosoma brucei
    - Intracelulares 
      Leishmania infantum

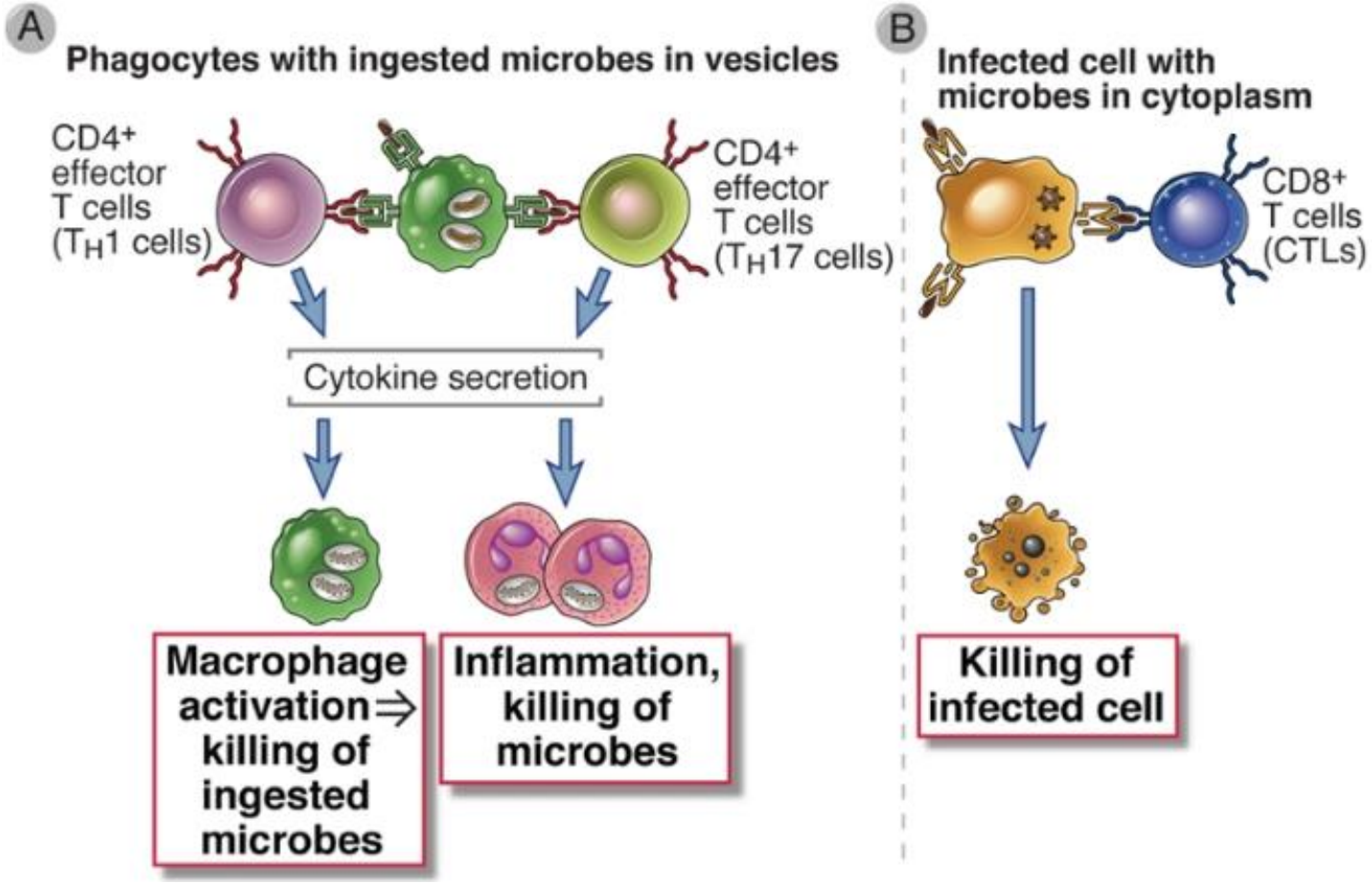
- **Multicelulares**
  - Extracelulares
    - Endoparasitas
      - Helmintos 
    - Ectoparasitas
      - Helmintos
      - Artrópodes
        - Histiófagos
        - Hematófagos 

	Infectious agent	Disease	Humoral immunity				Cell-mediated immunity	
			IgM	IgG	IgE	IgA	CD4 T cells (macro-phages)	CD8 killer T cells
Viruses	Herpes zoster	Chickenpox						
	Epstein–Barr virus	Mononucleosis						
	Influenza virus	Influenza						
	Polio virus	Poliomyelitis						
Intra-cellular bacteria	*Rickettsia prowazekii*	Typhus						
	Mycobacteria	Tuberculosis, leprosy						
Extra-cellular bacteria	*Staphylococcus aureus*	Boils						
	Streptococcus pneumoniae	Pneumonia						
	Neisseria meningitidis	Meningitis						
	Corynebacterium diphtheriae	Diphtheria						
	Vibrio cholerae	Cholera						
Fungi	*Candida albicans*	Candidiasis						
Protozoa	*Plasmodium* spp.	Malaria						
	Trypanosoma spp.	Trypanosomiasis						
Worms	Schistosome	Schistosomiasis						

Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)

Vermelho: defesas da imunidade primária; amarelo: defesas da imunidade protetora

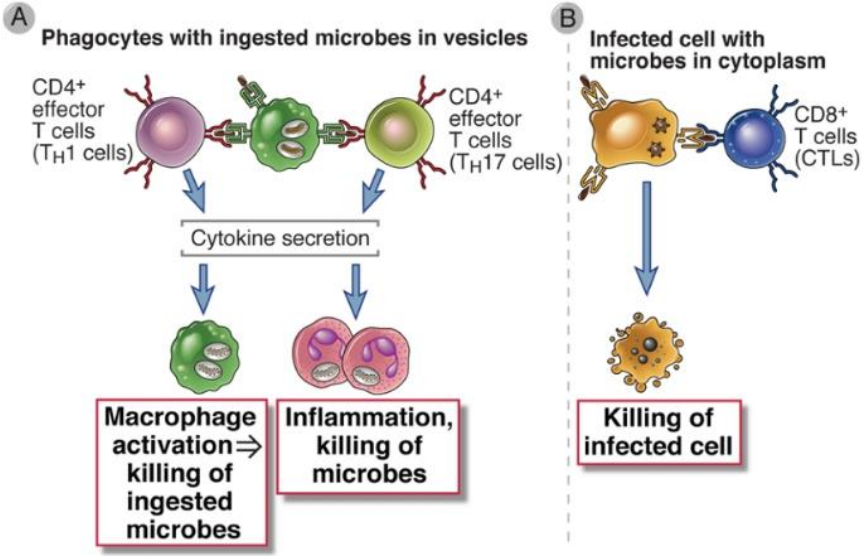
Cell-mediated immune responses



Types of cell-mediated immune responses

Effector T cells of the CD4⁺ lineage link specific recognition of microbes with the recruitment and activation of other leukocytes that destroy the microbes

- The adaptive immune response to microbes that are phagocytosed and live within the phagosomes of macrophages is mediated by **T_H1 cells**, which recognize microbial antigens and activate the phagocytes to destroy the ingested microbes.
- The response to extracellular microbes, including many fungi and bacteria, is mediated by **T_H17** cells, which recruit neutrophils.
- The response to helminthic parasites is mediated by **T_H2 cells**, which induce IgE
- The adaptive immune response to microbes that infect and replicate in the cytoplasm of cells, including nonphagocytic cells, is mediated by **CD8⁺ cytotoxic T lymphocytes** (CTLs), which kill infected cells and eliminate the reservoirs of infection
- Funções de outras subpopulações de linfócitos T (**γδ e NKT**)
- **T cell–dependent inflammation may damage normal tissues.**



Funções Gerais de linfócitos CD4+ efetores

- Recrutamento de outros leucócitos
- Ativação dos leucócitos recrutados
- Amplificação da resposta imune
- Regulação da resposta imune

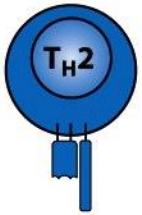
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	CD4 regulatory T cells (various types)
Types of effector T cell					
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	Extracellular bacteria (e.g. *Salmonella enterica*)	

Figure 8-1 Immunobiology, 7ed. (© Garland Science 2008)

	Infectious agent	Disease	Humoral immunity				Cell-mediated immunity	
			IgM	IgG	IgE	IgA	CD4 T cells (macro-phages)	CD8 killer T cells
Viruses	Herpes zoster	Chickenpox						
	Epstein–Barr virus	Mononucleosis						
	Influenza virus	Influenza						
	Polio virus	Poliomyelitis						
Intra-cellular bacteria	*Rickettsia prowazekii*	Typhus						
	Mycobacteria	Tuberculosis, leprosy						
Extra-cellular bacteria	*Staphylococcus aureus*	Boils						
	Streptococcus pneumoniae	Pneumonia						
	Neisseria meningitidis	Meningitis						
	Corynebacterium diphtheriae	Diphtheria						
	Vibrio cholerae	Cholera						
Fungi	*Candida albicans*	Candidiasis						
Protozoa	*Plasmodium* spp.	Malaria						
	Trypanosoma spp.	Trypanosomiasis						
Worms	Schistosome	Schistosomiasis						

Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)

Vermelho: defesas da imunidade primária; amarelo: defesas da imunidade protetora

The induction and the effector phases of cell-mediated immunity

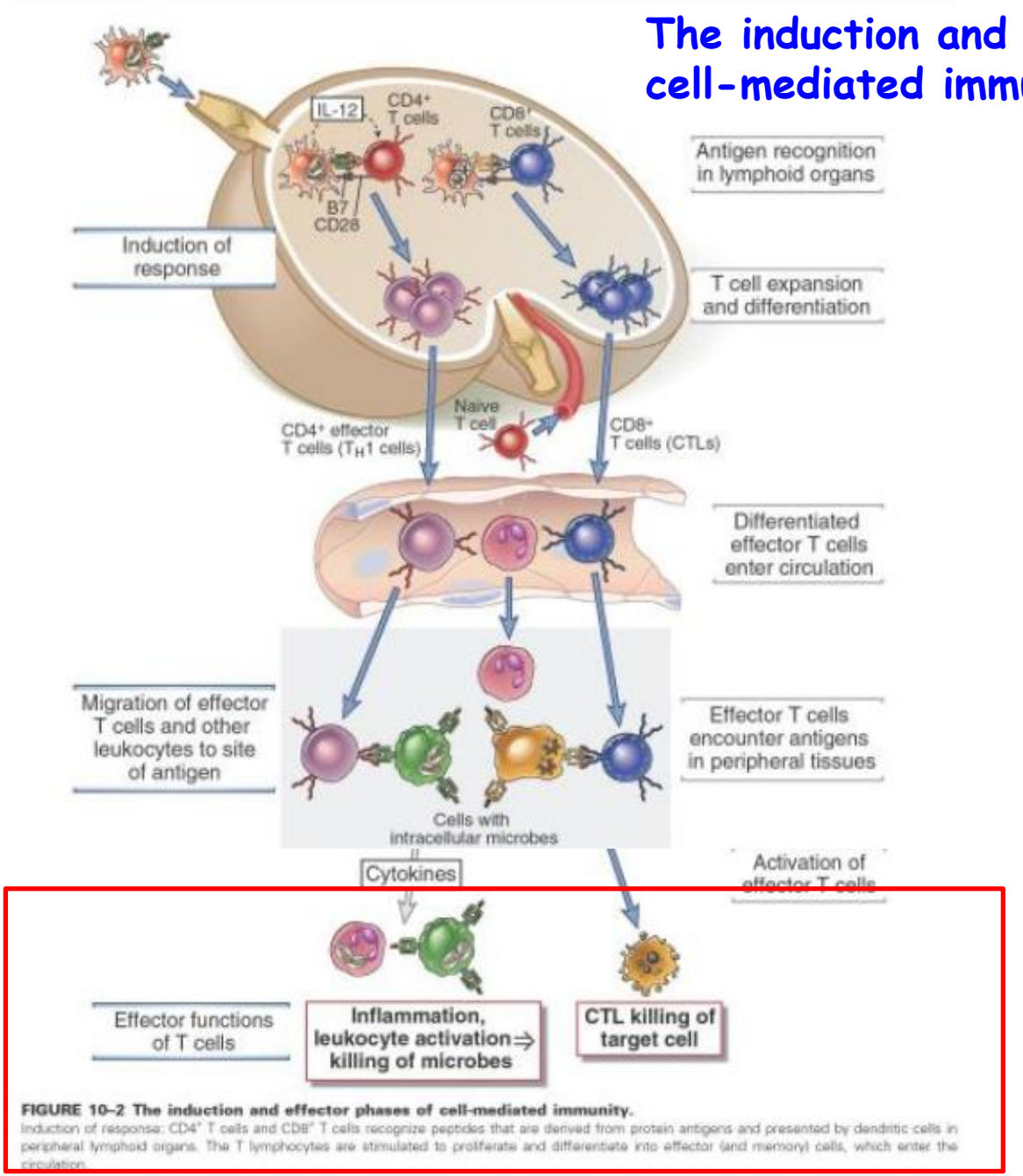


FIGURE 10–2 The induction and effector phases of cell-mediated immunity.
Induction of response: $CD4^+$ T cells and $CD8^+$ T cells recognize peptides that are derived from protein antigens and presented by dendritic cells in peripheral lymphoid organs. The T lymphocytes are stimulated to proliferate and differentiate into effector (and memory) cells, which enter the circulation.

Migração de Linfócitos T Efetores

- A migração de Linfócitos T efetores da circulação para sítios periféricos de infecção independe de antígeno, mas células que reconhecem antígeno em tecidos extravasculares podem ficar prefencialmente retidos lá
- As subpopulações de linfócitos CD4+ TH1, TH2 e TH17 possuem fenótipos distintos quanto ao seu direcionamento diferentes sítios do corpo
  - TH1 dirigem-se preferencialmente para sítios onde bactérias induzem fortes reações da imunidade inata
  - ~~CD8+
  - TH2 migram a tecidos que costumam ser infestados por helmintos ou onde ocorrem processos alérgicos

Funções de linfócitos efetores CD4+ TH1

- Ativar macrófagos para ingerir e destruir parasitas
  - IFN-gama ativa o macrófago para matar parasitas
  - Marco dos macrófagos ativados classicamente
  - IFN-gama
    - age sobre linfócitos B para que produzam certas subclasses de IgG
    - Promove a diferenciação de TH1 e inibe a de TH2 e TH17
- **Linfócito T reconhece, mas macrófago é que mata**

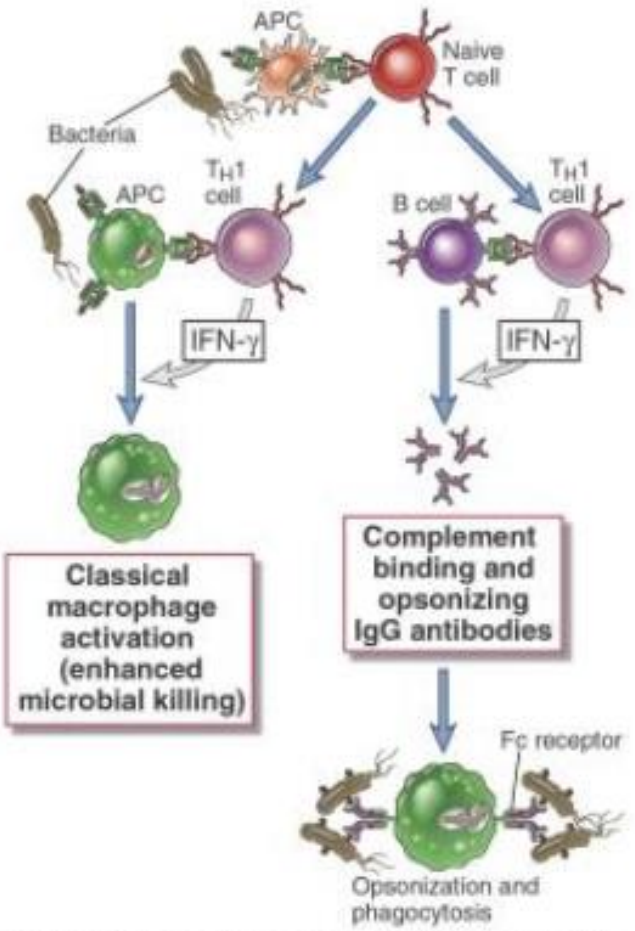
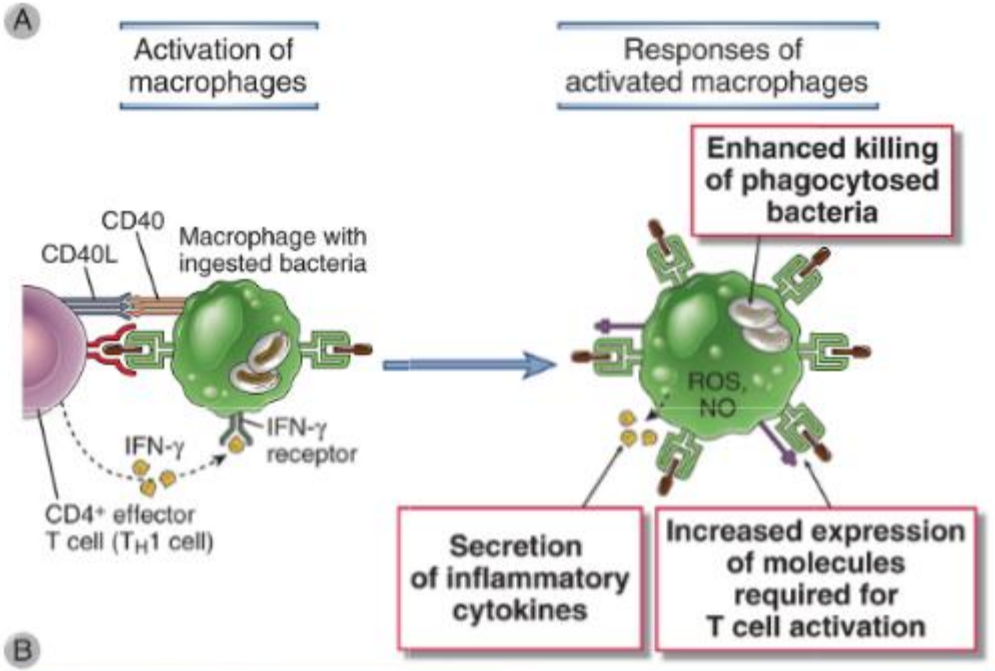


FIGURE 10–5 Functions of T_H1 cells. $CD4^+$ T cells that differentiate into T_H1 cells secrete IFN-γ, which acts on macrophages to increase phagocytosis and killing of microbes in phagolysosomes and on B lymphocytes to stimulate production of IgG antibodies that opsonize microbes for phagocytosis. The cells also produce TNF, which activates neutrophils and promotes inflammation (not shown).

Macrophages are activated by CD40L-CD40 interactions and by IFN-γ expressed by **TH1 cells** and perform several functions that kill microbes, stimulate inflammation, and enhance the antigen-presenting capacity of the cells.

A



B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12) and chemokines	TNF, IL-1, chemokines: leukocyte recruitment (inflammation) IL-12: T_H1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification of T cell response)

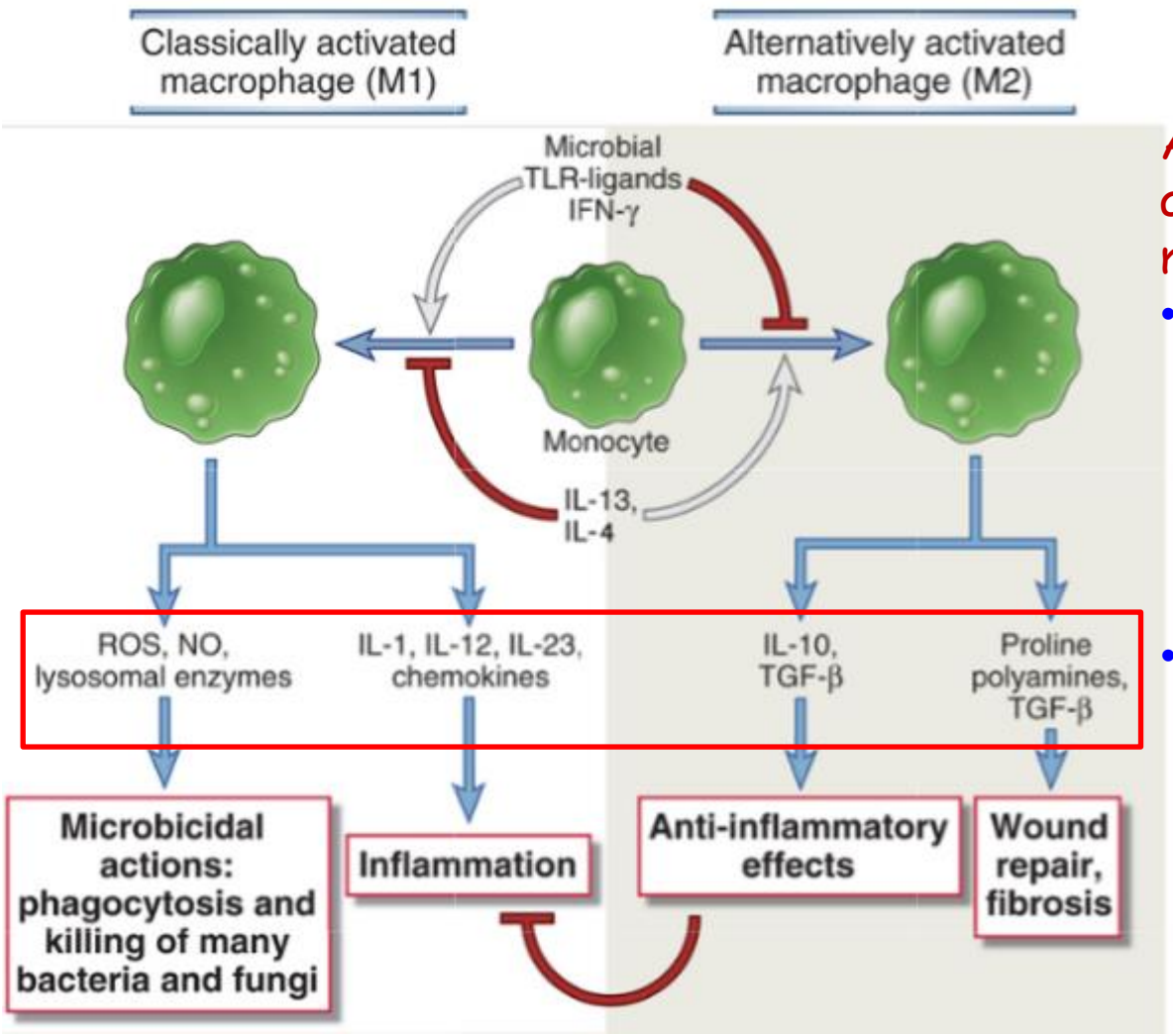
The principal molecules that mediate the functions of macrophages are listed.

Subsets of activated macrophages

Different stimuli activate monocytes-macrophages to develop into functionally distinct populations.

Classically activated macrophages

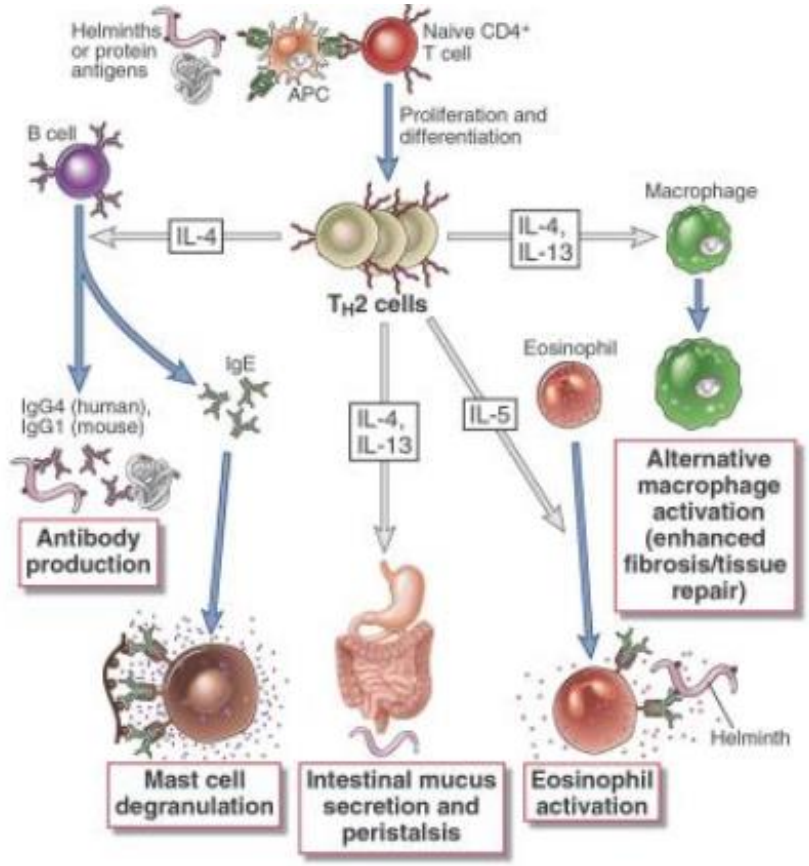
- induced by microbial products + cytokines (IFN-γ)
- microbicidal
- involved in potentially harmful inflammation



Alternatively activated macrophages

- induced by IL-4 and IL-13 produced by TH2 cells and other leukocytes
- important in tissue repair and fibrosis

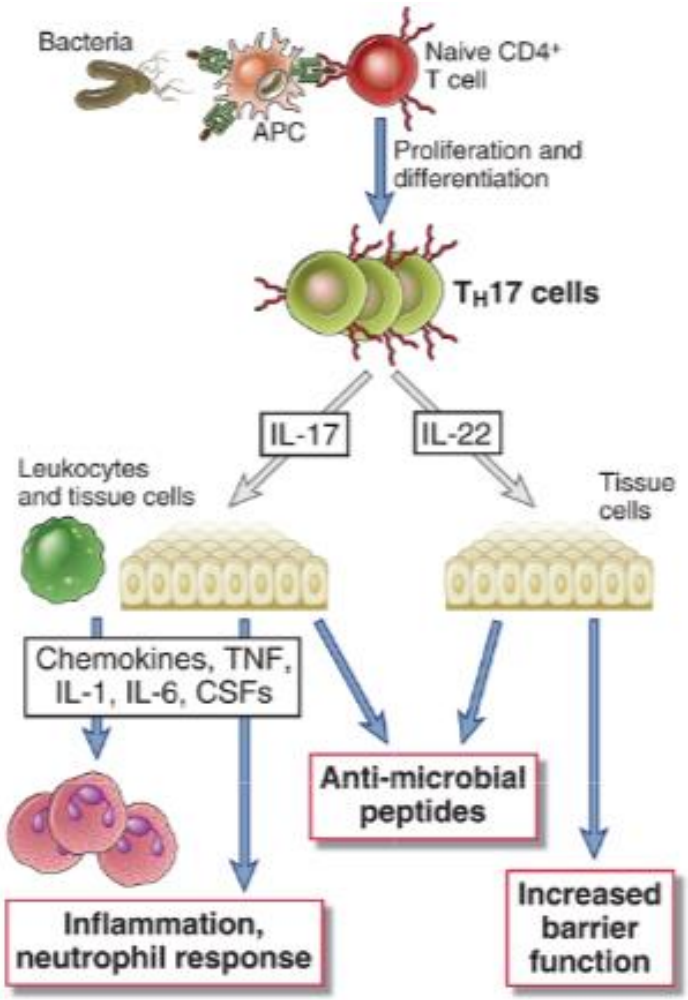
Funções de linfócitos efetores CD4+ TH2



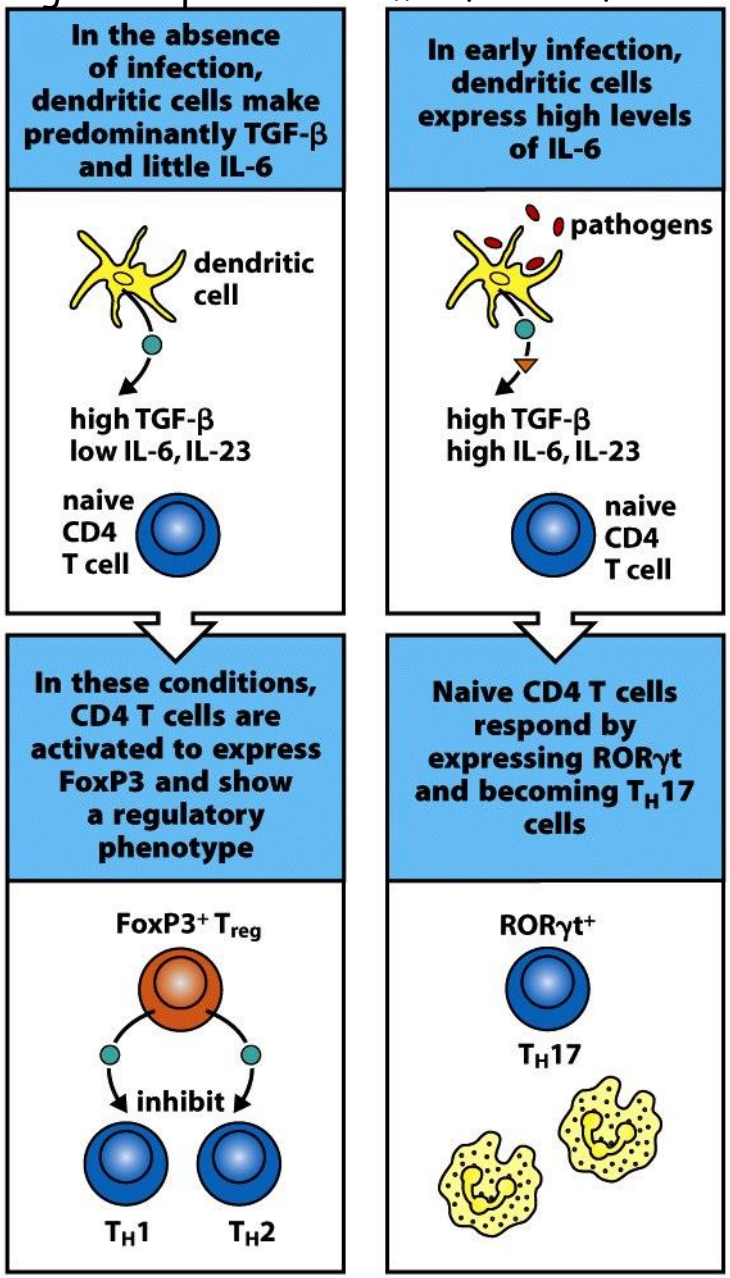
- Linfócitos Th2 estimulam produção de IgE, por meio de IL-4 e reações mediadas por eosinófilos que erradicam infestações por helmintos
- IL-4 estimula o desenvolvimento de mais linfócitos Th2
- IL-4 + IL13 (produzido pelo TH2) contribuem para ativação de macrófagos no padrão alternativo
- IL-4 e IL-13 ajudam a peristalse do intestino e IL-13 aumenta a produção de muco
- IL-4 e IL-13 recrutam eosinófilos que possuem muitas moléculas efetoras em seus grânulos

Funções de linfócitos efetores CD4+ TH17

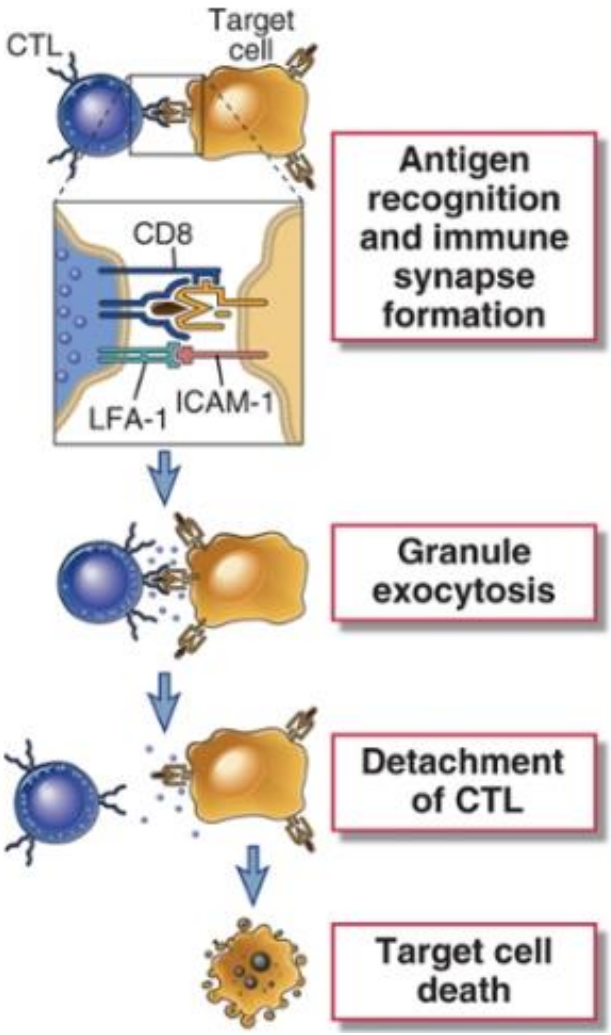
Cytokines produced by TH17 cells stimulate local production of chemokines and inflammation and the production of antimicrobial peptides (defensins) and promote epithelial barrier functions.

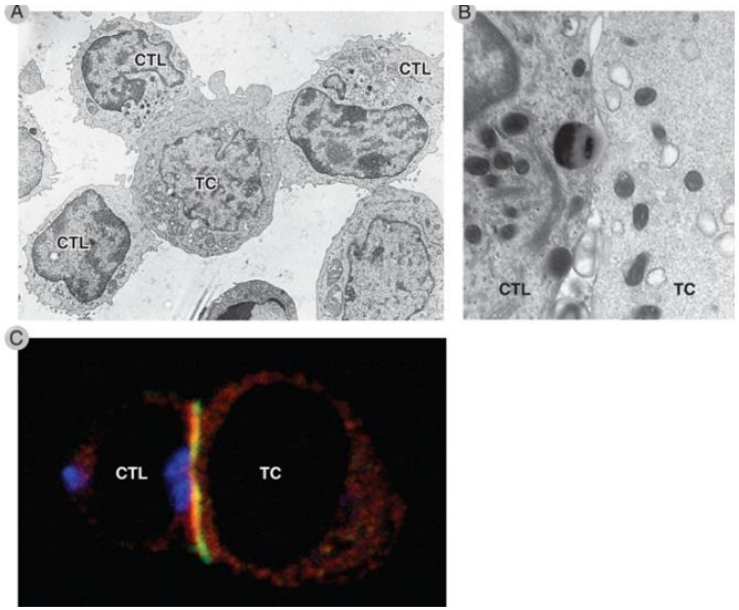


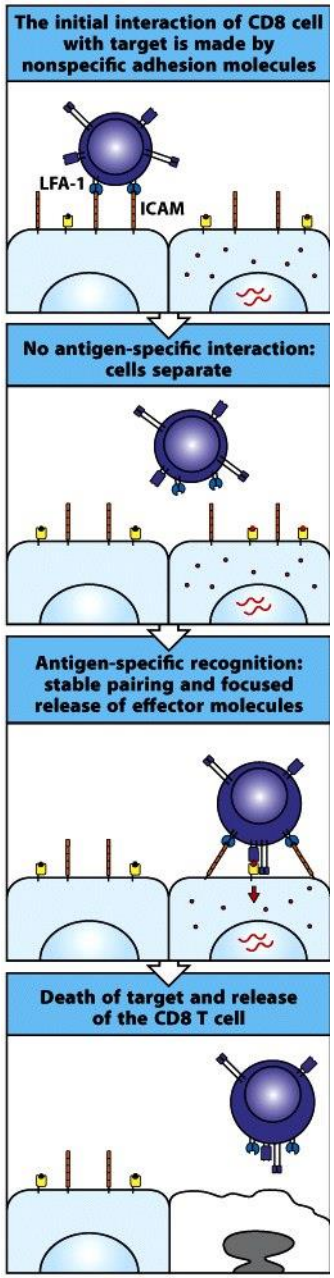
Mudança do programa para ser linfócito regulador para virar um linfócito efetor TH17



Funções de linfócitos efetores CD8+ citotóxicos







Interações de linfócitos T com seus alvos no início são inespecíficas

Protein in granules of cytotoxic T cells	Actions on target cells
Perforin	Aids in delivering contents of granules into the cytoplasm of target cell
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
Granulysin	Has antimicrobial actions and can induce apoptosis

Figure 8-37 Immunobiology, 7ed. (© Garland Science 2008)

Proteínas efetoras dos linfócitos citotóxicos

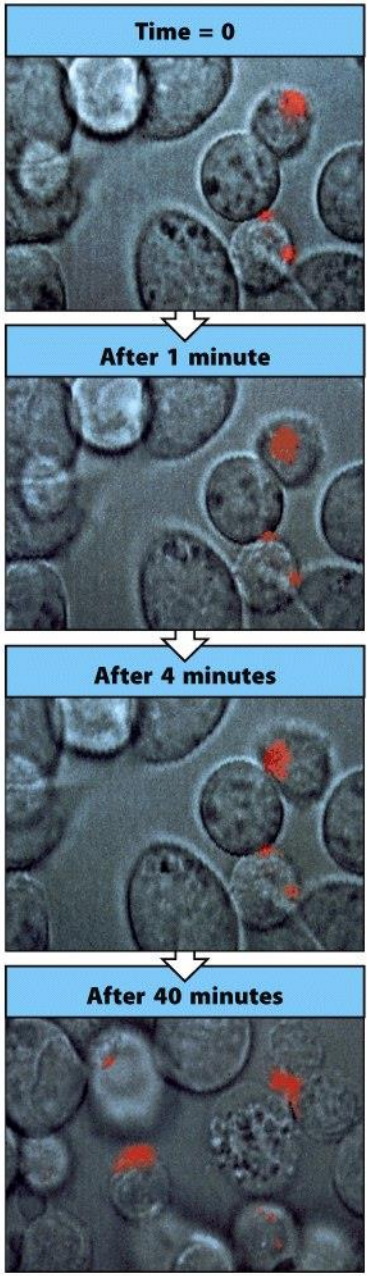


Figure 8-39 Immunobiology, 7ed. (© Garland Science 2008)

Citólise é polar

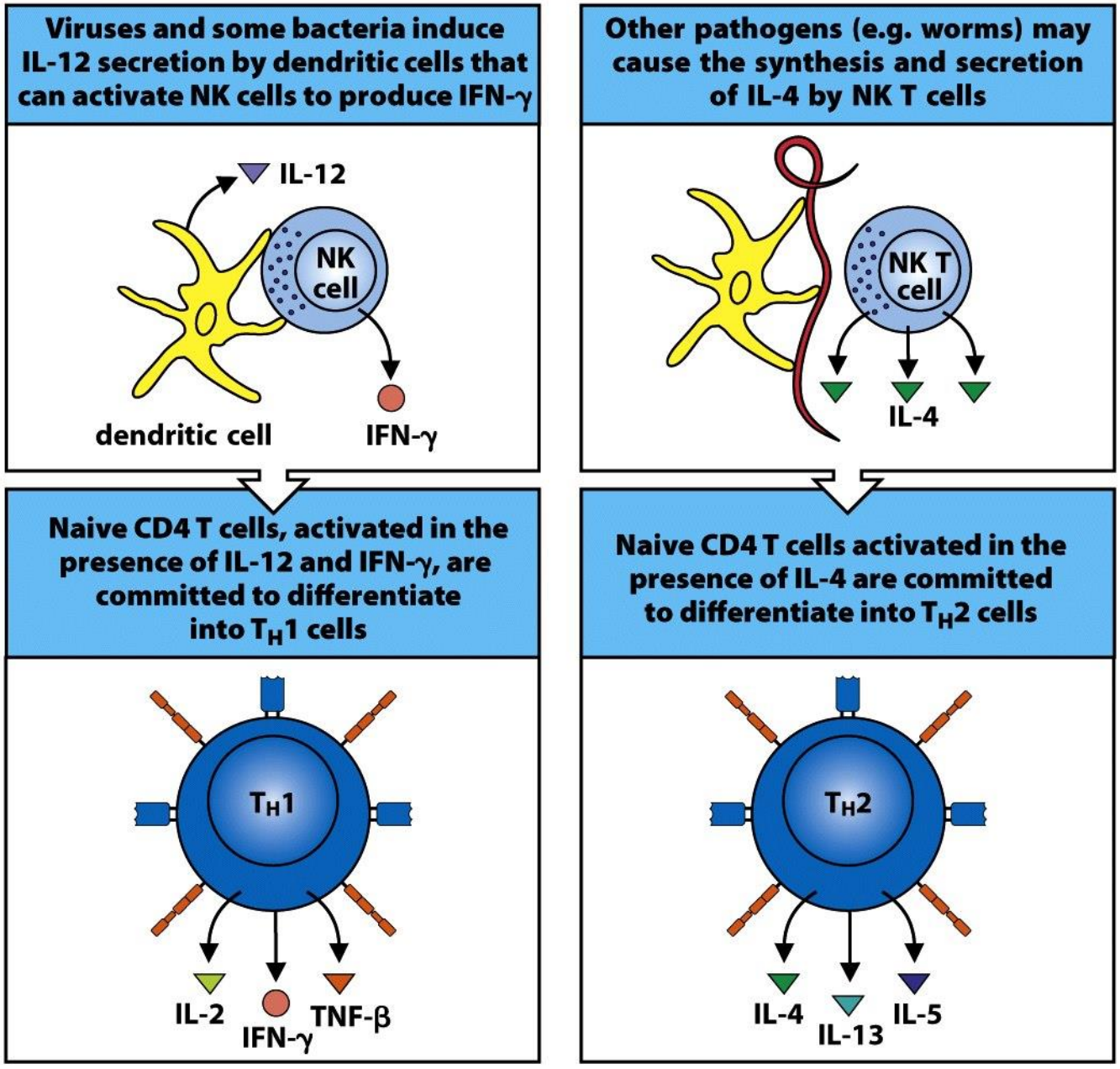


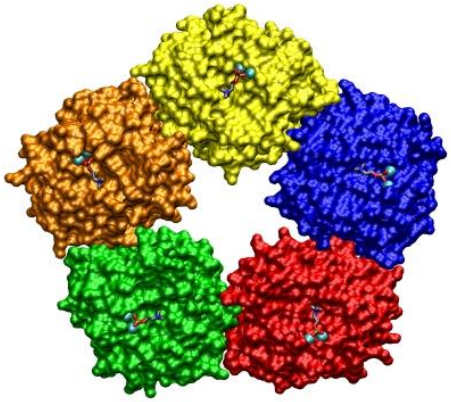
Figure 10-5 Immunobiology, 7ed. (© Garland Science 2008)

γδ T cells and NKT cells recognize a wide variety of antigens, many of which are not peptides, and these are not displayed by class I and class II MHC molecules on APCs.

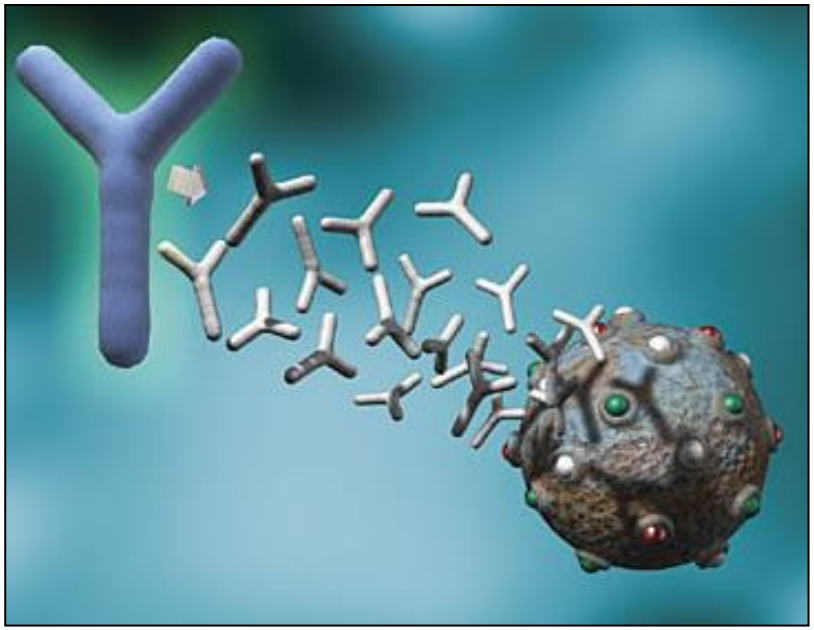
The antigen receptors of many γδ T cells and NKT cells have limited diversity, suggesting that both cell types may have evolved to recognize a small group of microbes. Because of this feature, these T cells are often said to be at the crossroads of innate and adaptive immunity.

Both cell types are abundant in epithelial tissues, such as the gastrointestinal tract.

Innate-like lymphocytes		
	Epithelial γ:δ cells	**NK T cells**
	Produce cytokines rapidly	**Produce cytokines rapidly**
	Ligands are MHC class IB associated	**Ligands are lipids bound to CD1d**
	Cannot be boosted	**Cannot be boosted**



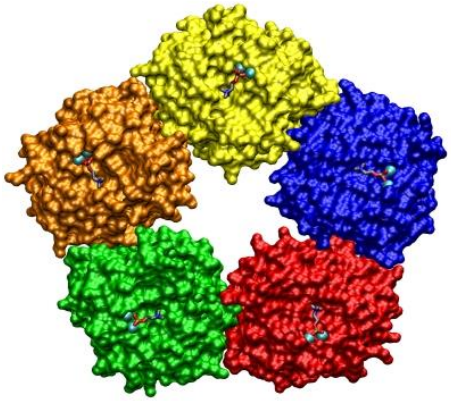
Mecanismos Efetores Humorais

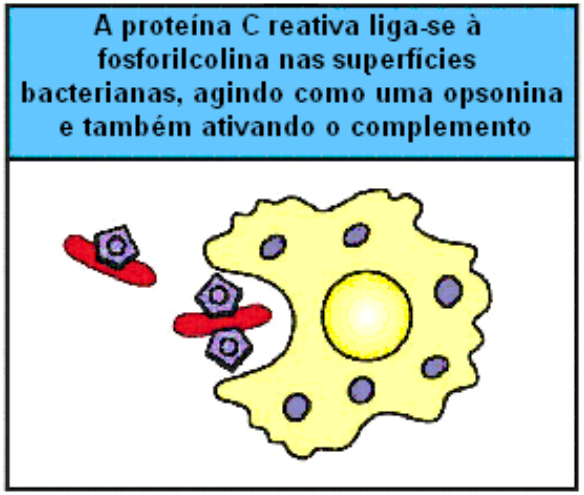


Mecanismos Efetores:

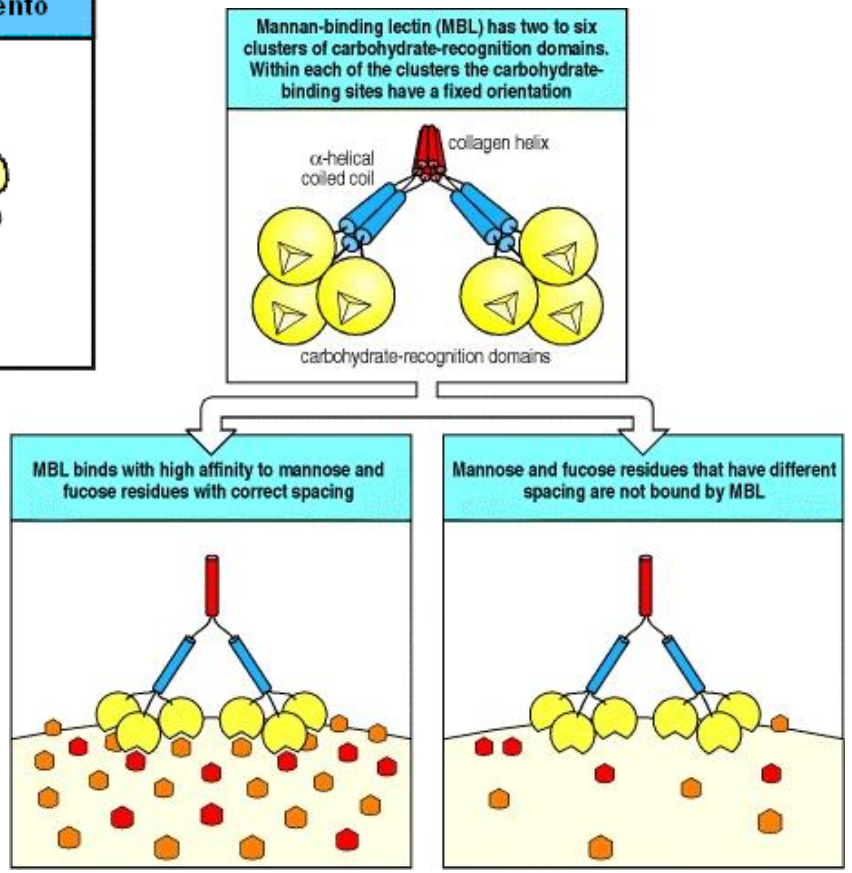
Fatores humorais pré-formados e reação de fase aguda

Proteína C reativa (Pentraxina)

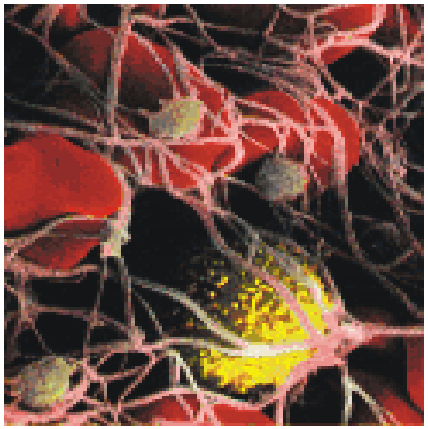




Ficolinas, Surfactantes
Lectina ligante de manana



Proteínas da Coagulação



Evita difusão sanguínea dos microrganismos aos tecidos

Mecanismos Efetores:

Fatores humorais pré-formados

(fronteira entre imunidade pré-formada e imunidade adquirida)

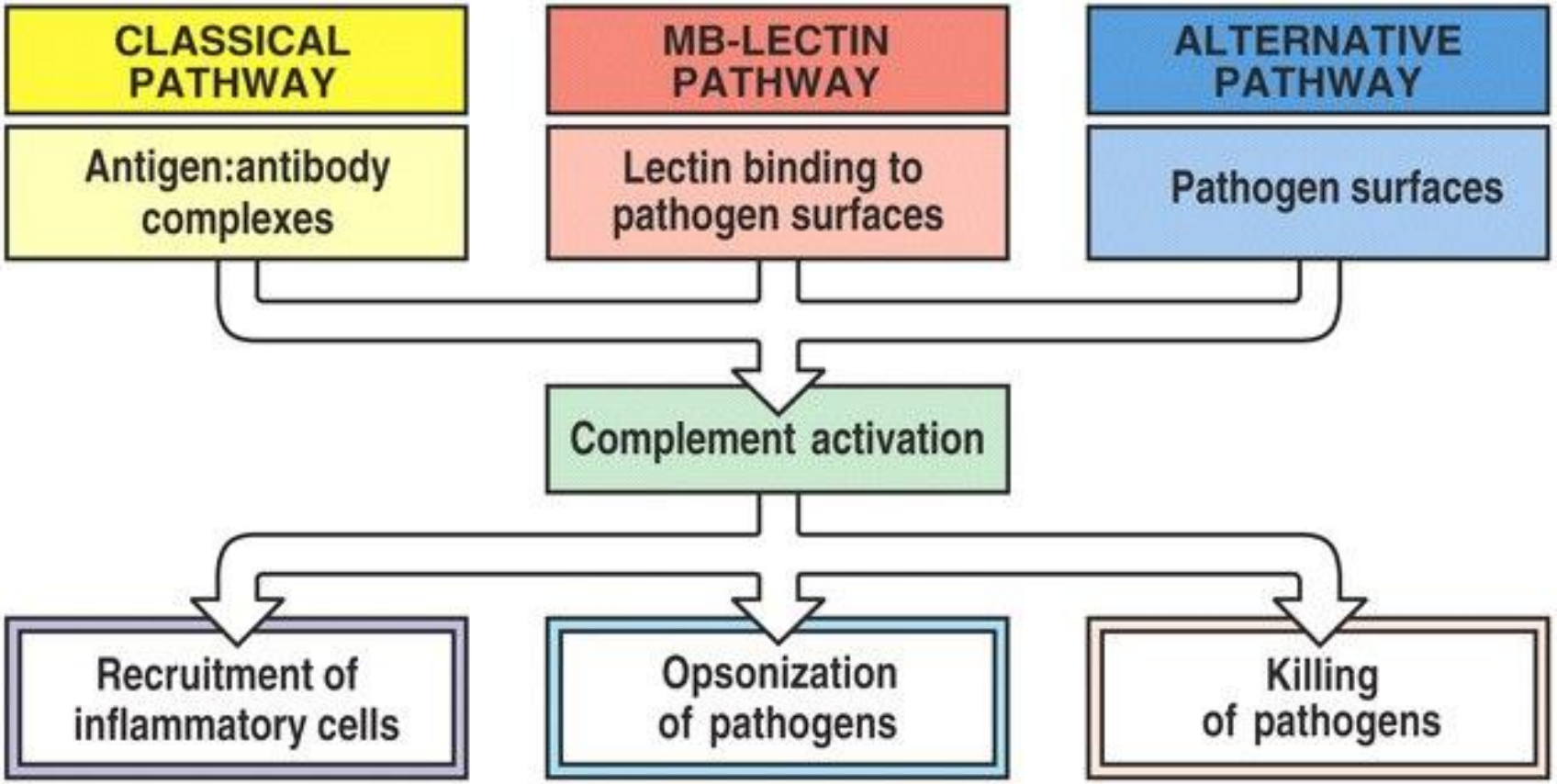


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

Mecanismos Efetores:

Estratégias antimicrobianas dos granulócitos

(fronteira entre imunidade pré-formada e imunidade adquirida)

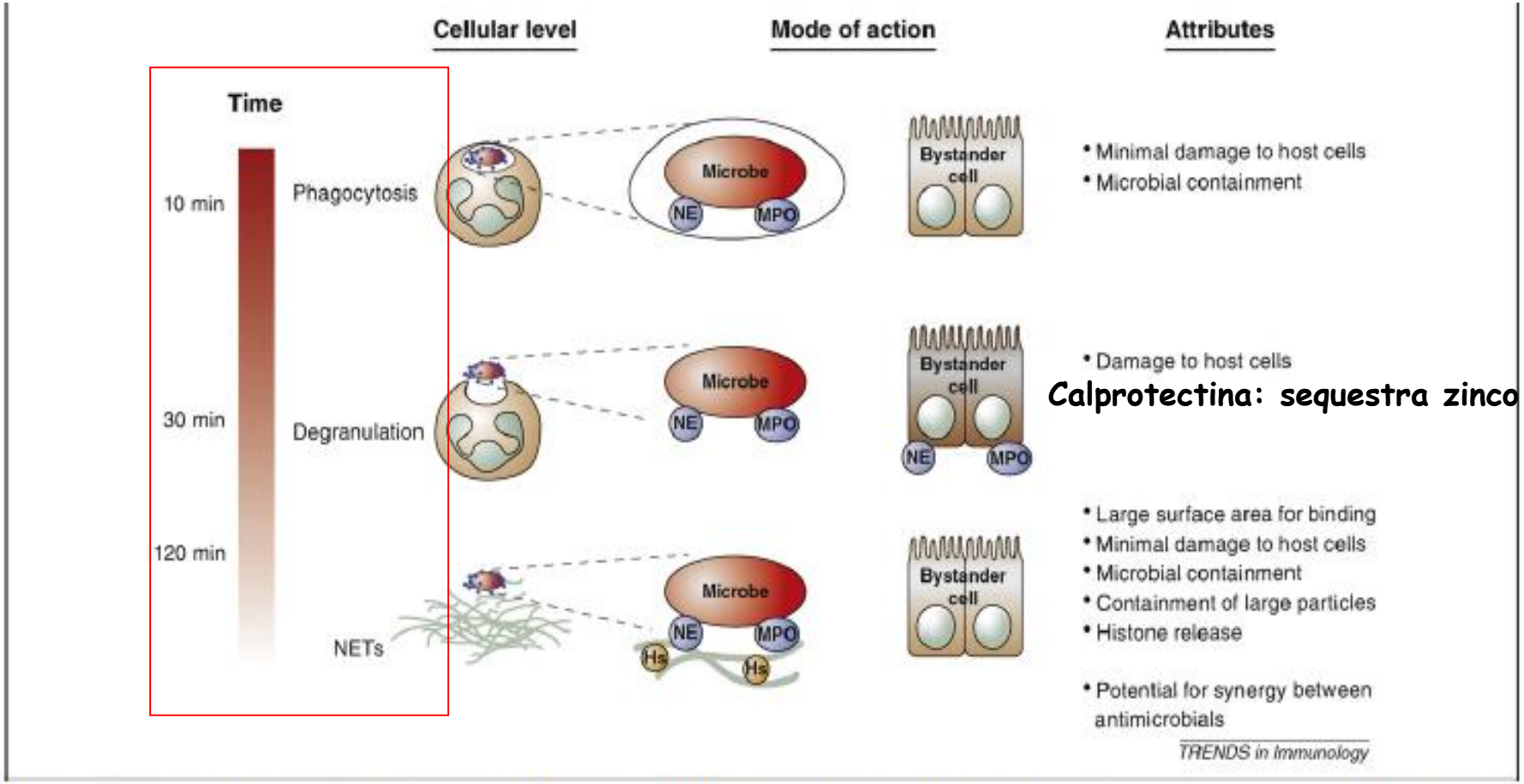
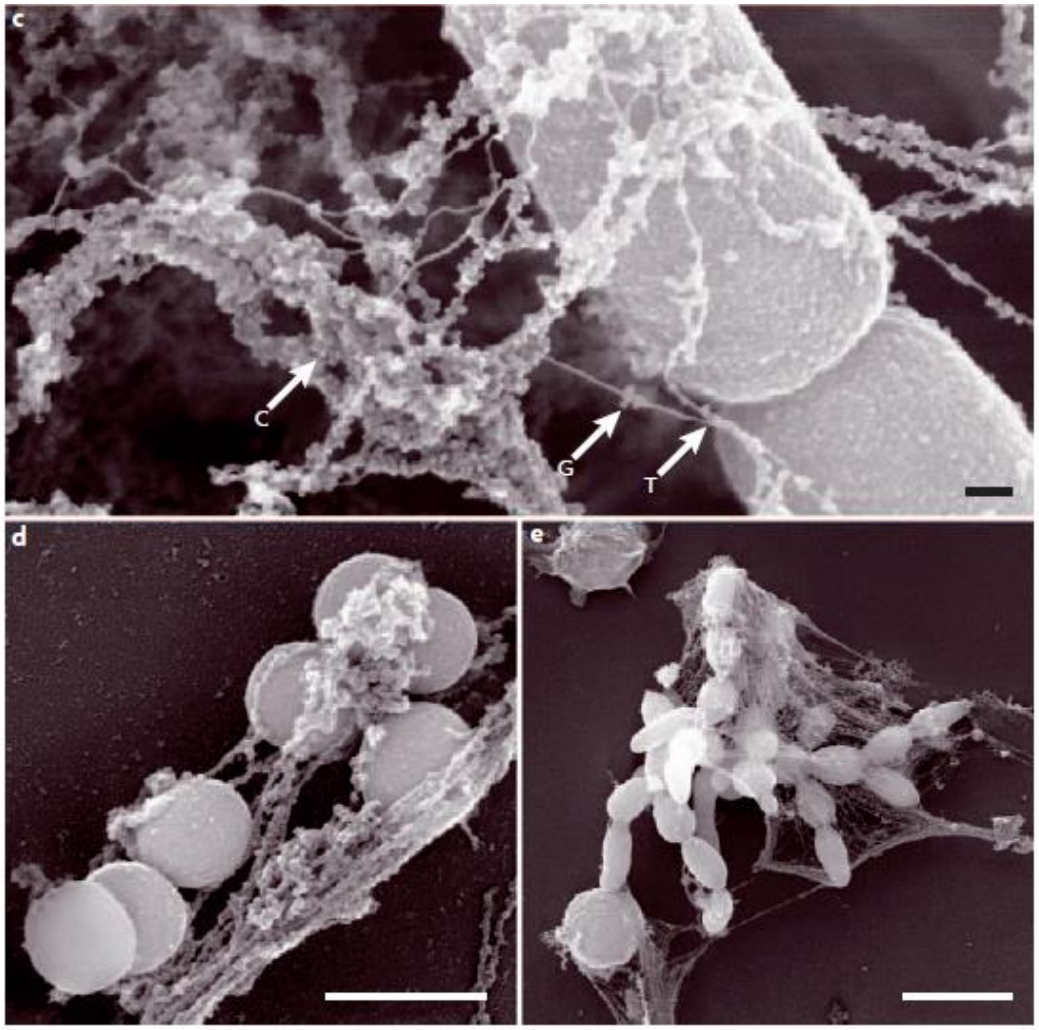


Figure 2. The antimicrobial strategies of neutrophils. Neutrophils use three major strategies to combat and clear microbes: phagocytosis, degranulation, and NET formation. These operate over different timescales (indicated on the left), and have varying effects on bystander cells (i.e. collateral damage), and have different attributes. Ingestion of microbes into a phagolysosome minimises damage to host cells during phagocytosis whereas degranulation disseminates granule proteases and can cause widespread damage. The incorporation of granule proteases into NETs limits their diffusion and hence the potential for host cell damage, increases their effective local concentration, and entraps microbes. Red: Microbe, Blue: granular proteins in the phagolysosome, extracellular space, or tethered within the NET, Gray: decondensed DNA of the NET. Abbreviations: Hs, histones; MPO, myeloperoxidase; NE, neutrophil elastase.

Mecanismos Efetores:

Imunidade pré-formada - armadilhas extracelulares formados pelos granulócitos com DNA e proteínas tóxicas



Induzidas por
bactérias e protozoários

Figure 1 | **Neutrophils and neutrophil extracellular traps (NETs).** NETs can trap Gram-negative bacteria, Gram-positive bacteria and fungi. **a** | A transmission electron micrograph showing an unstimulated human neutrophil. **b** | A scanning electron micrograph (SEM) showing stimulated neutrophils forming NETs (as indicated by the arrow). **c** | A SEM showing a detailed view of NETs trapping *Shigella flexneri*. The 'threads' (T), globular domains (G) and cables (C) are indicated. **d** | A SEM showing NETs trapping *Staphylococcus aureus*. **e** | A SEM showing NETs trapping *Candida albicans*. The scale bars represent 5 μm for **a**, 10 μm for **b** and **e**, 100 nm for **c**, and 1 μm for **d**.

Mecanismos Efetores:
Imunidade pré-formada - armadilhas extracelulares

Table 1. Antimicrobial components of NETs.

Myleoperoxidase (MPO)
Neutrophil elastase (ET)
Proteinase 3
Cathepsin G
Bacterial permeability increasing protein (BPI)
Lactoferrin
Gelatinase
LL-37
Tryptase
Histones (nucleosome histones, H1)

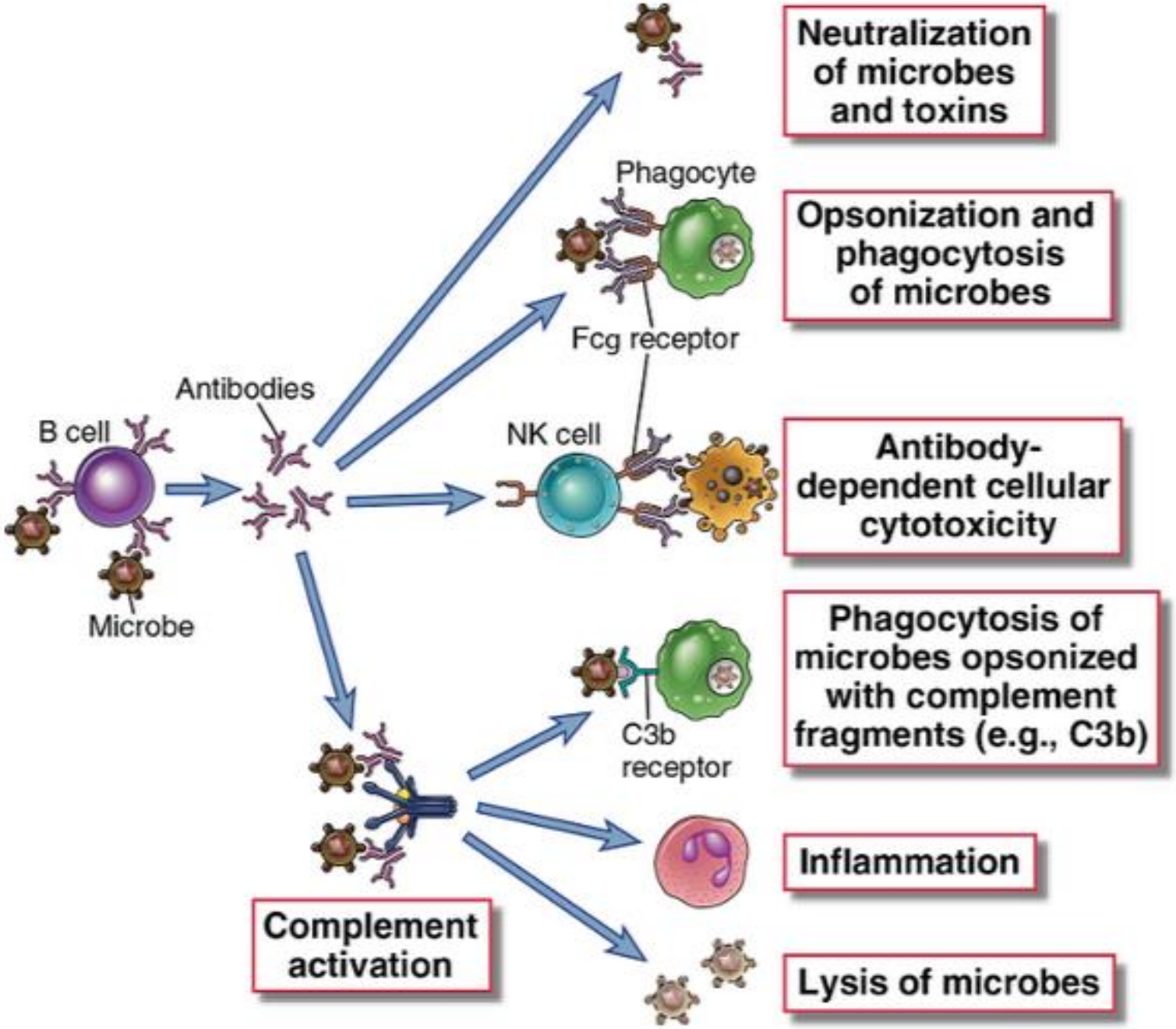
Table 1

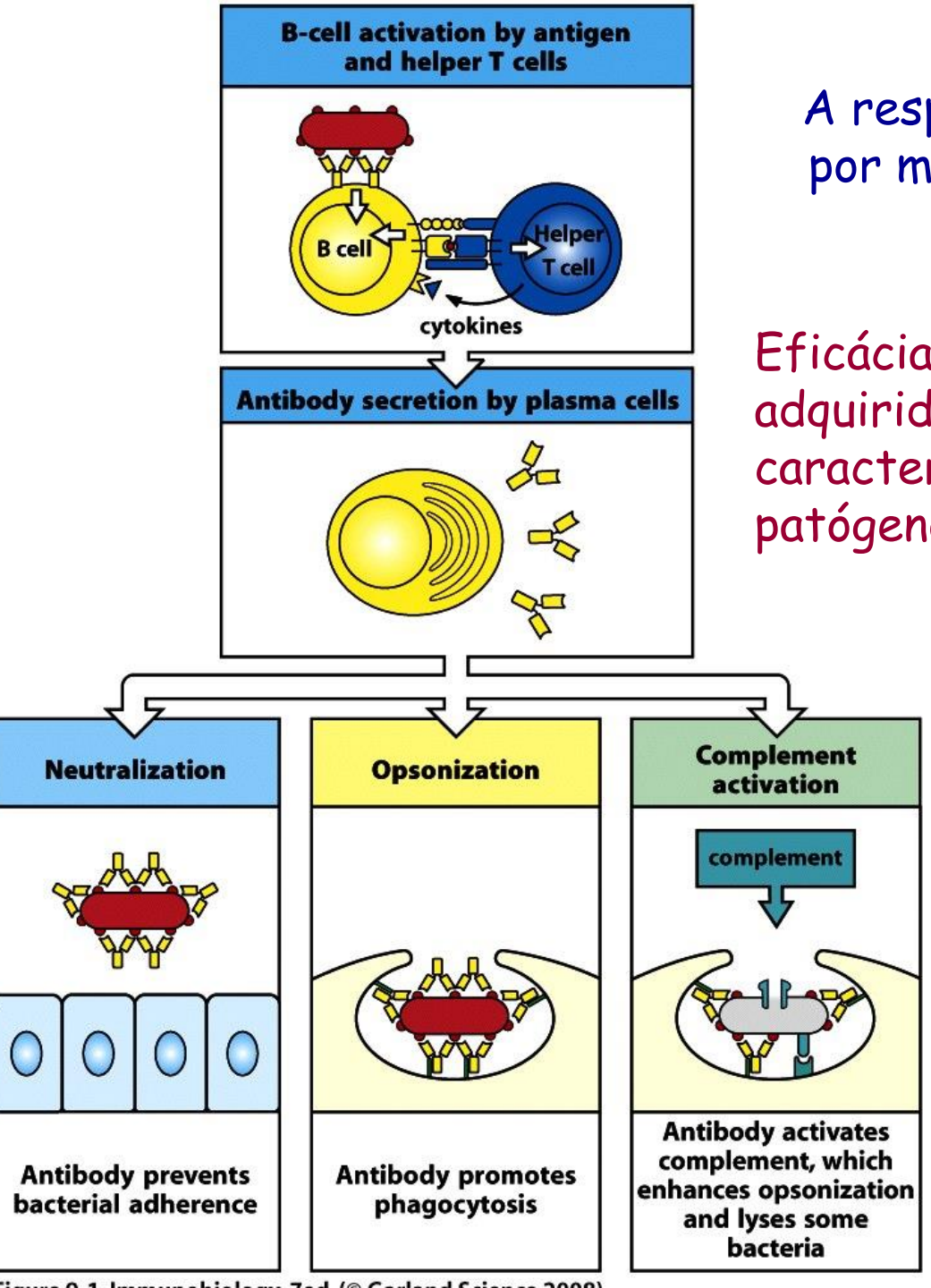
Proteins present in NETs and their cellular origins.

Source of protein	Name
Nucleus	Histones h1, h2a, h2b, h3, and h4
Azurophilic (primary) granules	Neutrophil elastase
	Cathepsin G
	Myeloperoxidase (MPO)
	Bactericidal permeability increasing protein (BPI)
Specific (secondary) granules	Lactoferrin
Tertiary granules	Gelatinase
	Peptidoglycan recognition proteins (PGRPs) [23]

Mecanismos Efetores:
Imunidade Adquirida

ANTICORPOS


Neutralization of microbes and toxins
Phagocyte
Opsonization and phagocytosis of microbes
Fcg receptor
Antibodies
B cell
NK cell
Antibody-dependent cellular cytotoxicity
Microbe
Phagocytosis of microbes opsonized with complement fragments (e.g., C3b)
C3b receptor
Inflammation
Complement activation
Lysis of microbes



A resposta humoral adquirida é mediada por moléculas de anticorpos secretadas por plasmócitos

Eficácia (sucesso) da resposta humoral adquirida depende do conjunto de características do anticorpo e do patógeno ou antígeno

TABLE 12–1 Functions of Antibody Isotypes

Antibody Isotype	Isotype-Specific Effector Functions
IgG	Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells Neonatal immunity: transfer of maternal antibody across the placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement Antigen receptor of naive B lymphocytes*
IgA	Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes*

*These functions are mediated by membrane-bound and not secreted antibodies.

Human Antibody Isotypes

TABLE 5–2 Human Antibody Isotypes

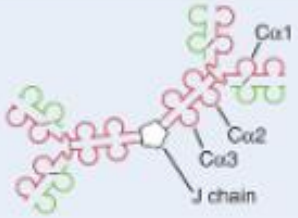
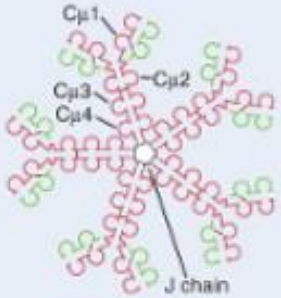
Isotope of Antibody	Subtypes (H Chain)	Serum Concentration (mg/mL)	Serum Half-life (days)	Secreted Form		Functions
IgA	IgA1,2 (α1 or α2)	3.5	6	IgA (dimer) Monomer, dimer, trimer		Mucosal immunity
IgD	None (δ)	Trace	3	None		Naive B cell antigen receptor
IgE	None (ε)	0.05	2	IgE Monomer		Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4 (γ1, γ2, γ3, or γ4)	13.5	23	IgG1 Monomer		Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None (μ)	1.5	5	IgM Pentamer		Naive B cell antigen receptor, complement activation

Table 1 | Properties of human IgG subclasses.

	IgG1		IgG2		IgG3		IgG4	
General								
Molecular mass (kD)	146		146		170		146	
Amino acids in hinge region	15		12		62[a]		12	
Inter-heavy chain disulfide bonds	2		4[b]		11[a]		2	
Mean adult serum level (g/l)	6.98		3.8		0.51		0.56	
Relative abundance (%)	60		32		4		4	
Half-life (days)	21		21		7/~21[a]		21	
Placental transfer	++++		++		++/++++[a]		+++	
Antibody response to:								
Proteins	++		+/–		++		++[e]*	
Polysaccharides	+		+++		+/–		+/–	
Allergens	+		(–)		(–)		++	
Complement activation								
C1q binding	++		+		+++		–	
Fc receptors								
FcγRI	+++[c]	65[d]	–	–	++++	61	++	34
$Fc\gamma RIIa_{H131}$	+++	5.2	++	0.45	++++	0.89	++	0.17
$Fc\gamma RIIa_{R131}$	+++	3.5	+	0.10	++++	0.91	++	0.21
FcγRIIb/c	+	0.12	–	0.02	++	0.17	+	0.20
$Fc\gamma RIIIa_{F158}$	++	1.2	–	0.03	++++	7.7	–	0.20
$Fc\gamma RIIIa_{V158}$	+++	2.0	+	0.07	++++	9.8	++	0.25
FcγRIIIb	+++	0.2	–	–	++++	1.1	–	–
FcRn (at pH < 6.5)	+++		+++		++/+++[a]		+++	

[a]Depends onallotype.
[b]ForA/Aisomer.
[c]Multivalent binding to transfected cells. Adapted from Bruhnsetal.(2).
[d]Association constant (X 10^6 M^{-1}) for monovalent binding (2).
[e]After repeated encounters with protein antigens, often allergens.

Distribuição e função das classes de imunoglobulinas

Anticorpos de diferentes classes operam em locais distintos e possuem funções efetoras diferentes

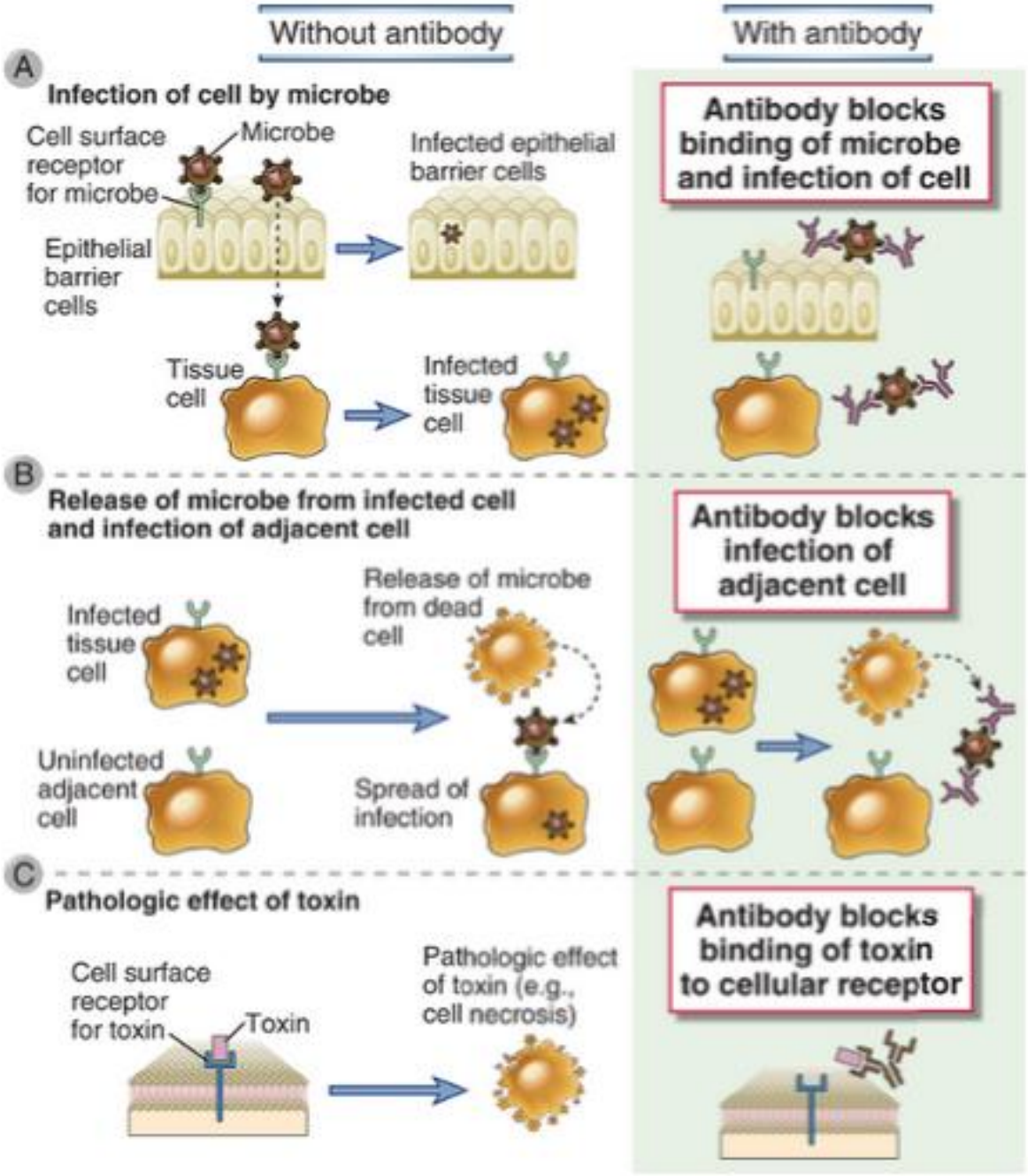
Maioria das vacinas em uso funciona por meio de anticorpos NEUTRALIZANTES

Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

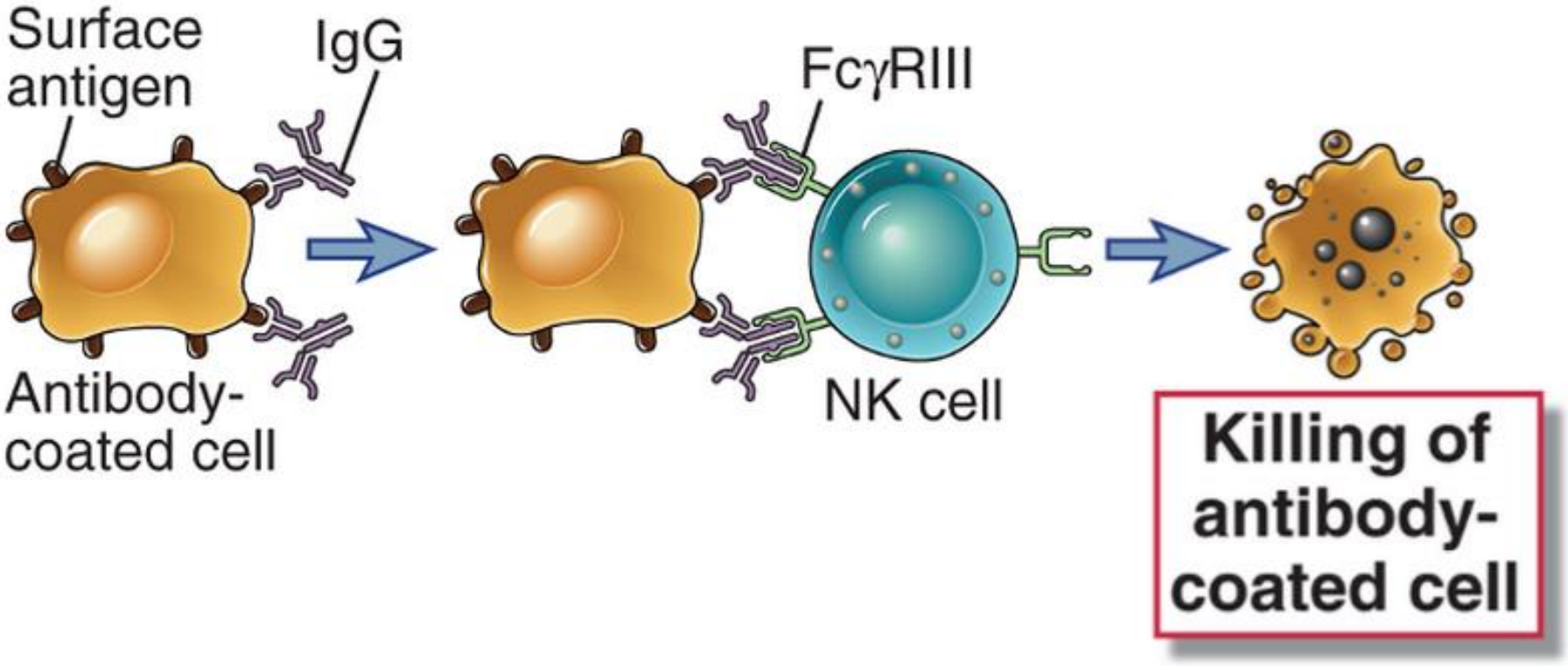
Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (mono-mer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

Figure 9-19 Immunobiology, 7ed. (© Garland Science 2008)

Neutralization



Antibody-dependent cell-mediated cytotoxicity



Distribuição e função das classes de imunoglobulinas

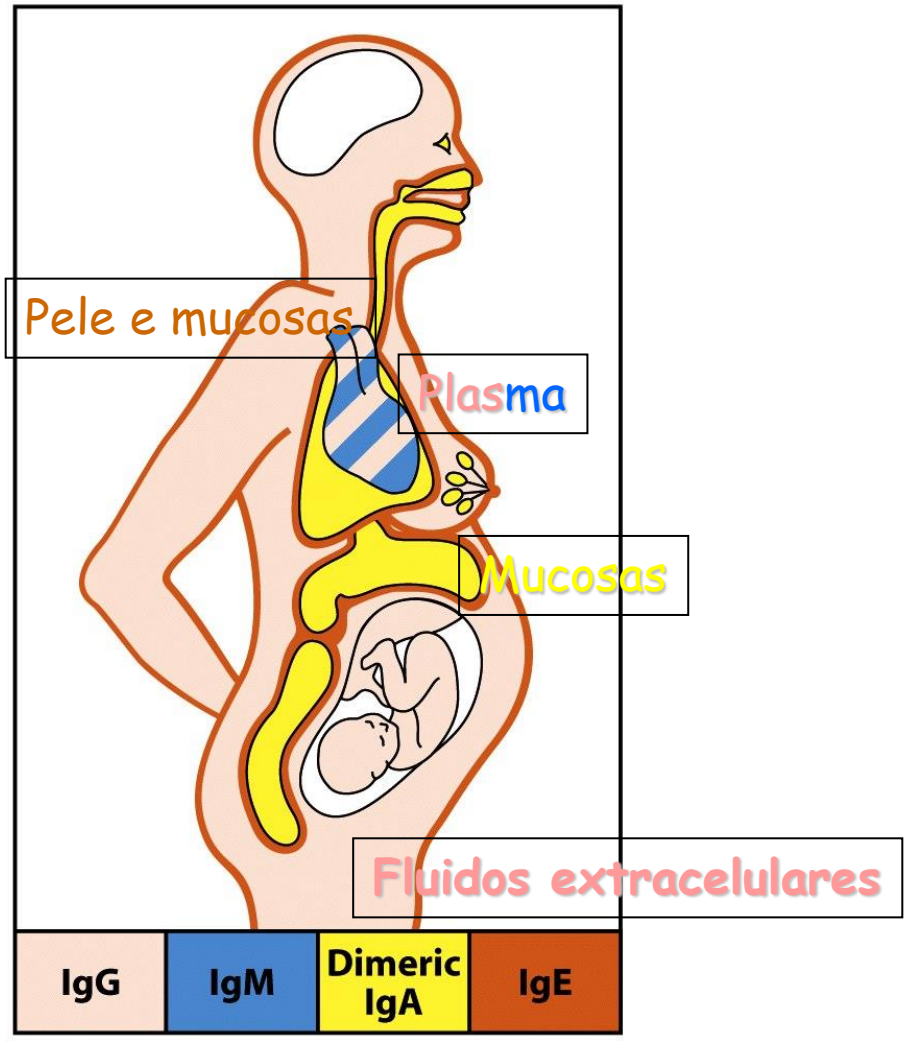


Figure 9-22 Immunobiology, 7ed. (© Garland Science 2008)

Distribuição e função das classes de imunoglobulinas

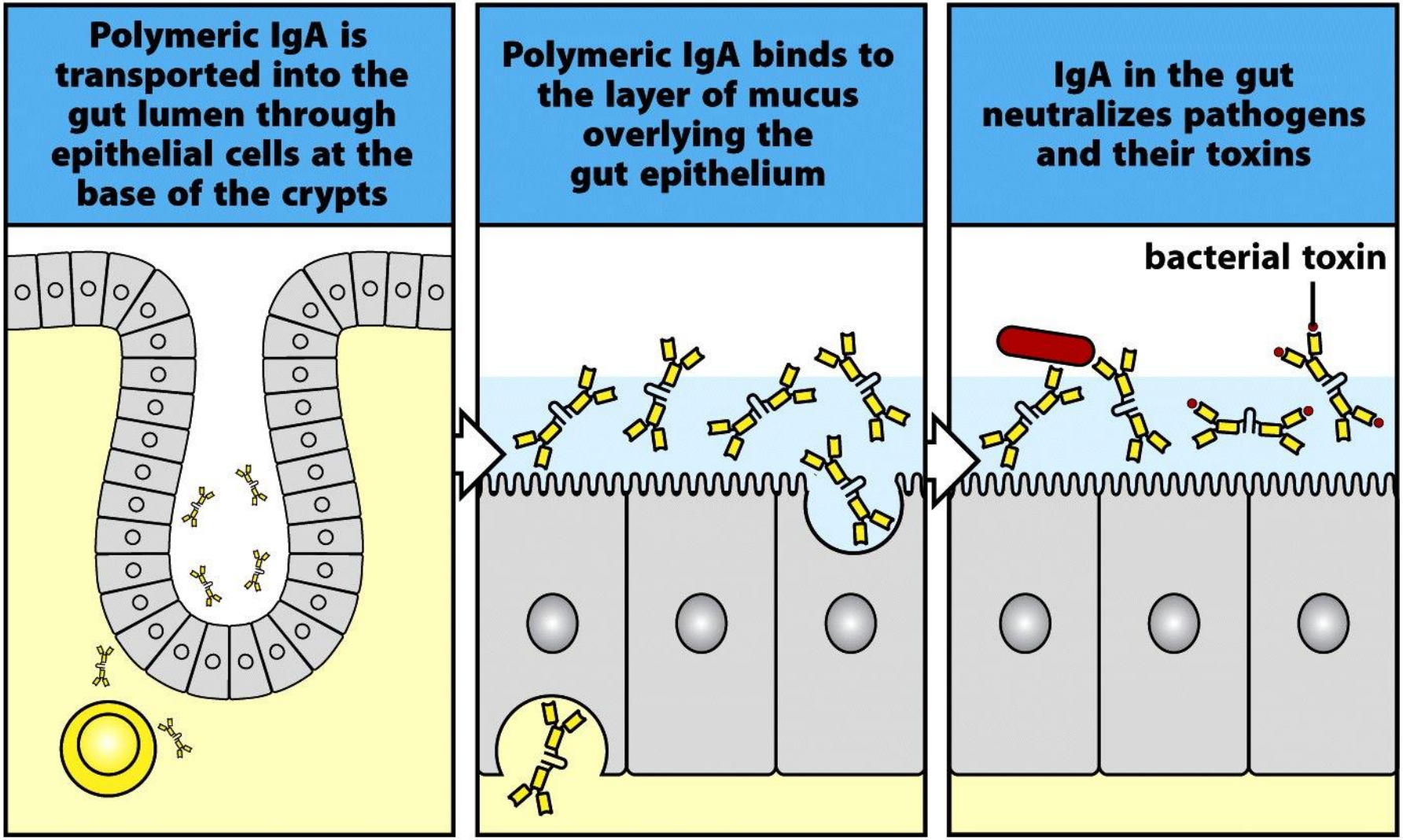


Figure 9-20 Immunobiology, 7ed. (© Garland Science 2008)

Anticorpos IgG e **IgA** de alta afinidade podem neutralizar toxinas

Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action, leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis, leading to epithelial cell damage and myocarditis
Gas gangrene	*Clostridium perfringens*	Clostridial toxin	Phospholipase activation, leading to cell death
Cholera	*Vibrio cholerae*	Cholera toxin	Activates adenylate cyclase, elevates cAMP in cells, leading to changes in intestinal epithelial cells that cause loss of water and electrolytes
Anthrax	*Bacillus anthracis*	Anthrax toxic complex	Increases vascular permeability, leading to edema, hemorrhage, and circulatory collapse
Botulism	*Clostridium botulinum*	Botulinum toxin	Blocks release of acetylcholine, leading to paralysis
Whooping cough	*Bordetella pertussis*	Pertussis toxin	ADP-ribosylation of G proteins, leading to lymphoproliferation
		Tracheal cytotoxin	Inhibits cilia and causes epithelial cell loss
Scarlet fever	*Streptococcus pyogenes*	Erythrogenic toxin	Vasodilation, leading to scarlet fever rash
		Leukocidin Streptolysins	Kill phagocytes, allowing bacterial survival
Food poisoning	*Staphylococcus aureus*	Staphylococcal enterotoxin	Acts on intestinal neurons to induce vomiting. Also a potent T-cell mitogen (SE superantigen)
Toxic-shock syndrome	*Staphylococcus aureus*	Toxic-shock syndrome toxin	Causes hypotension and skin loss. Also a potent T-cell mitogen (TSST-1 superantigen)

Figure 9-23 Immunobiology, 7ed. (© Garland Science 2008)

No soro **IgA** é menos abundante que IgGs, mas no corpo é o mais produzido!!!!

TABLE 12–2 Vaccine-Induced Humoral Immunity

Infectious Disease	Vaccine	Mechanism of Protective Immunity
Polio	Oral attenuated poliovirus	Neutralization of virus by mucosal IgA antibody
Tetanus, diphtheria	Toxoids	Neutralization of toxin by systemic IgG antibody
Hepatitis, A or B	Recombinant viral envelope proteins	Neutralization of virus by systemic IgG antibody
Pneumococcal pneumonia, *Haemophilus*	Conjugate vaccines composed of bacterial capsular polysaccharide attached to a carrier protein	Opsonization and phagocytosis mediated by IgM and IgG antibodies, directly or secondary to complement activation

Selected examples of vaccines that work by stimulating protective humoral immunity are listed.

Anticorpos IgG e IgA de alta afinidade podem neutralizar toxinas

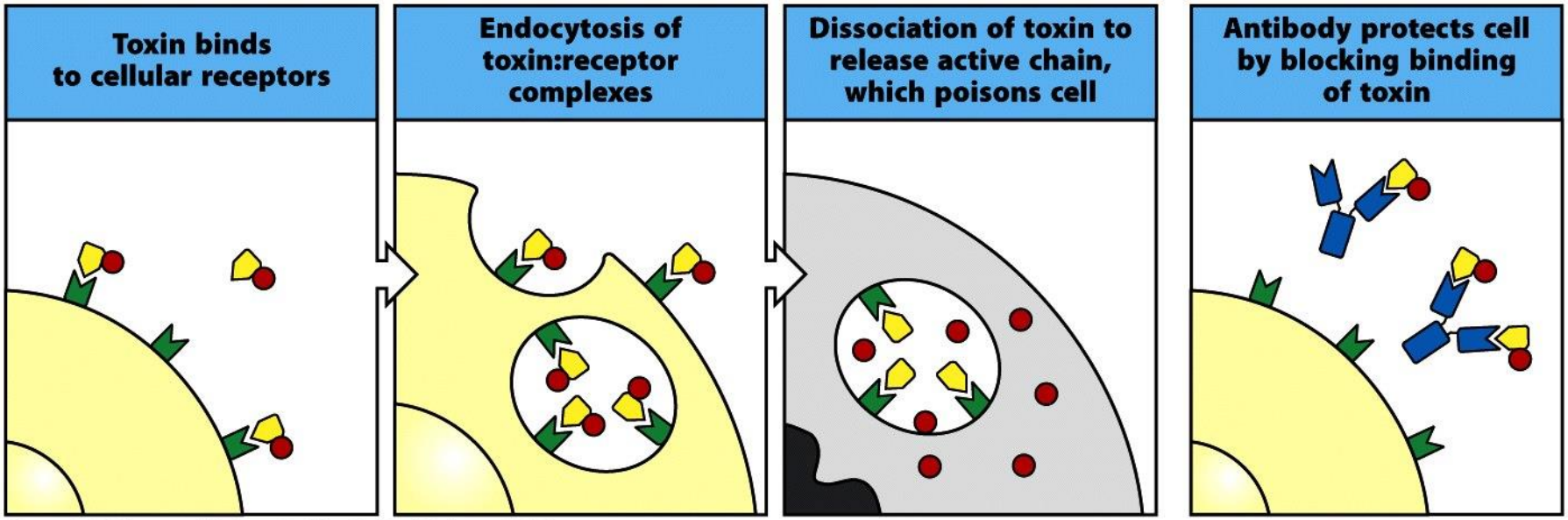


Figure 9-24 Immunobiology, 7ed. (© Garland Science 2008)

Anticorpos IgG e IgA de alta afinidade podem neutralizar patógenos

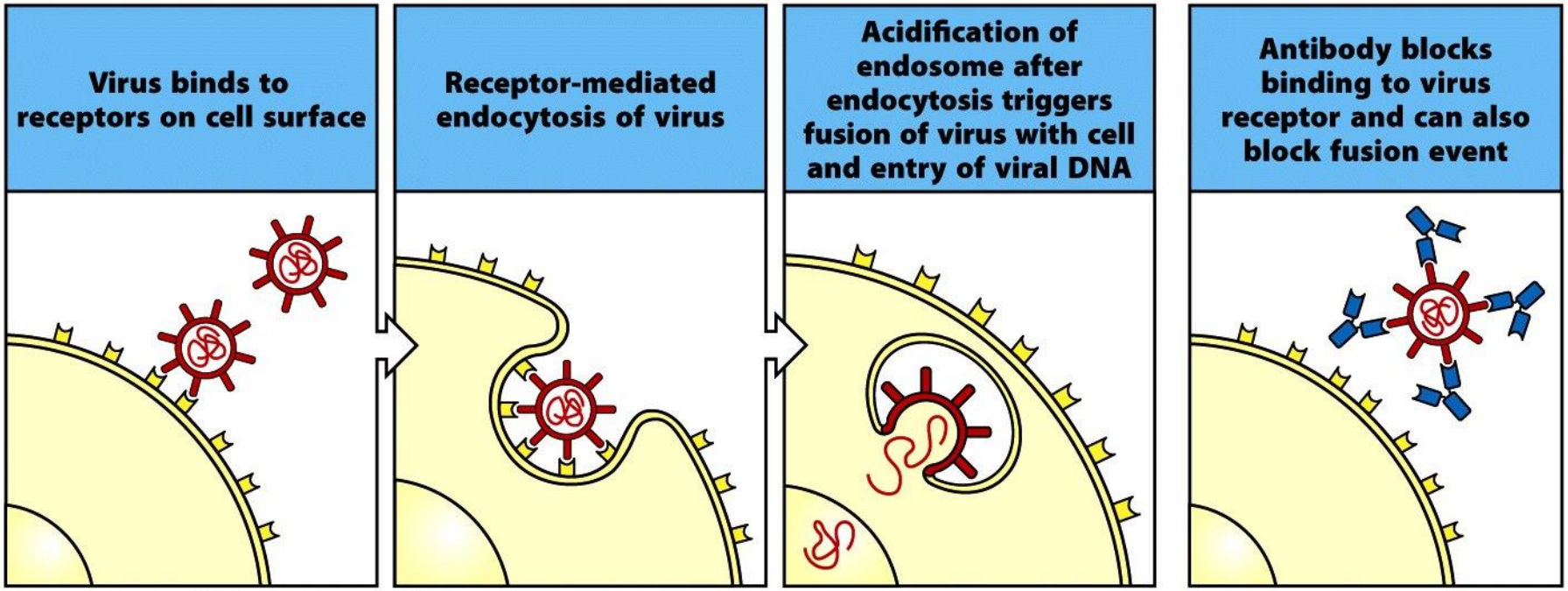
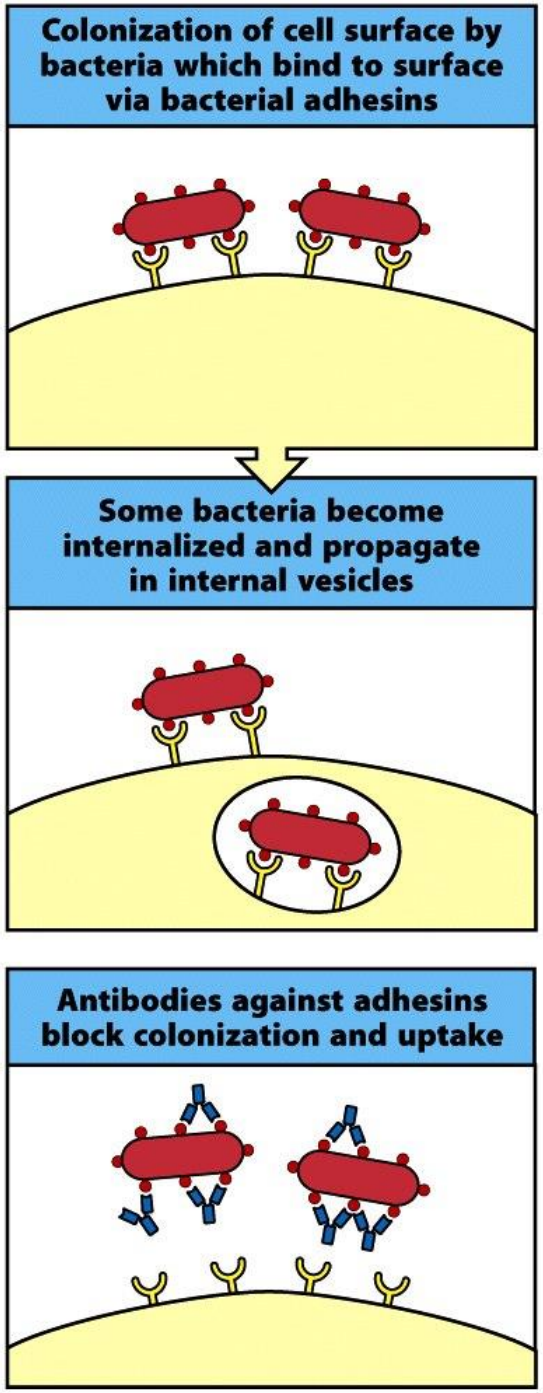
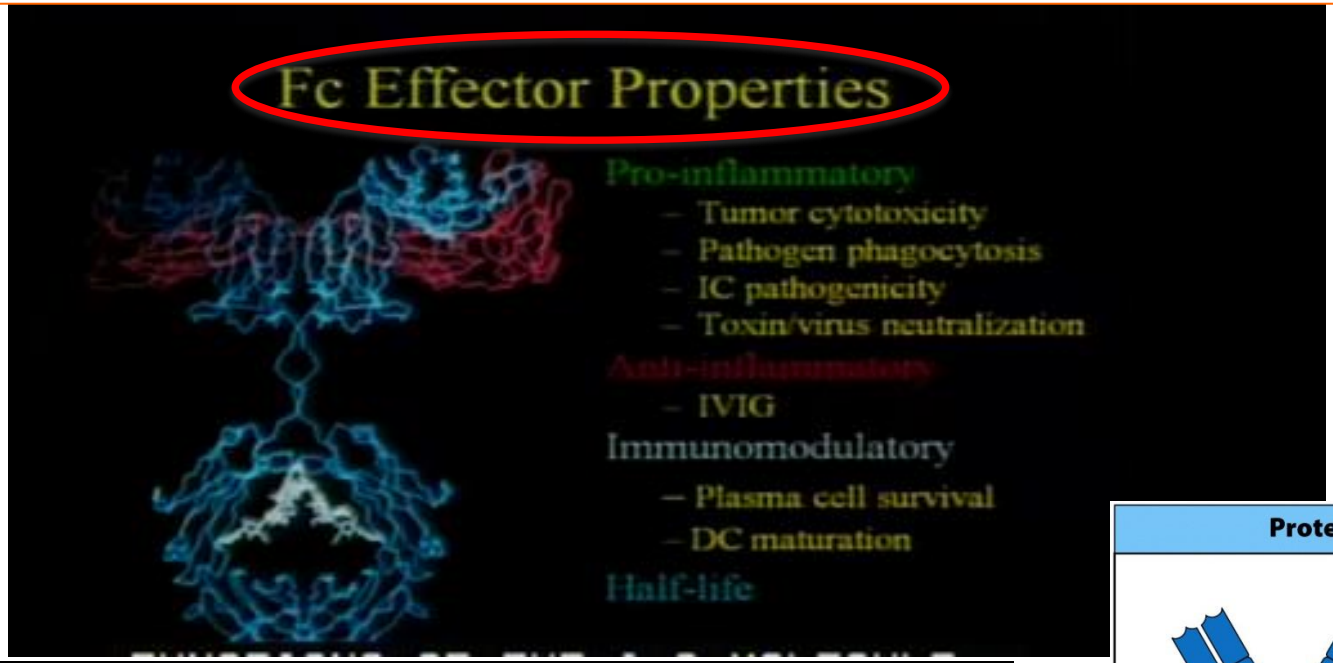


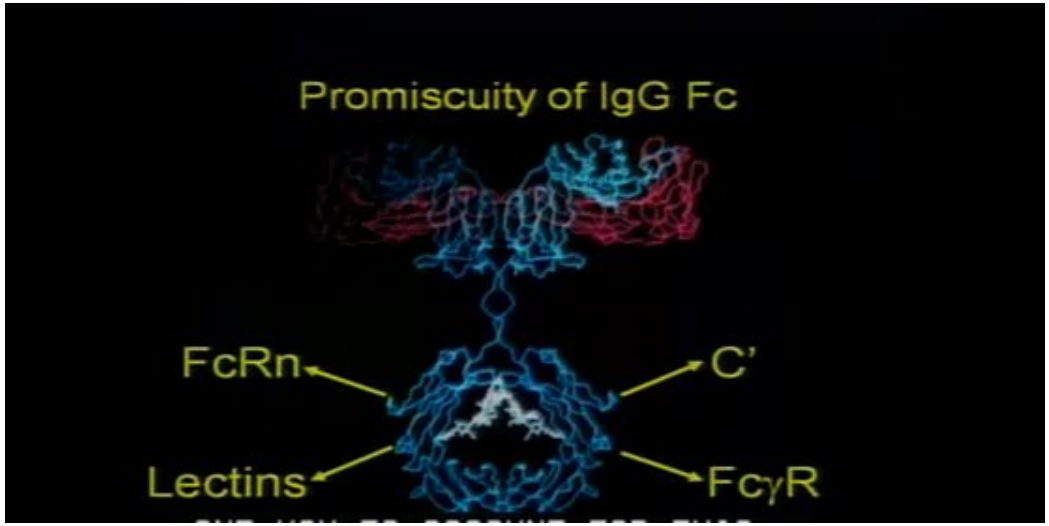
Figure 9-25 Immunobiology, 7ed. (© Garland Science 2008)



Anticorpos IgG e IgA podem bloquear a adesão de patógenos

Depois de reconhecer o antígeno, como o **anticorpo** exerce suas funções?





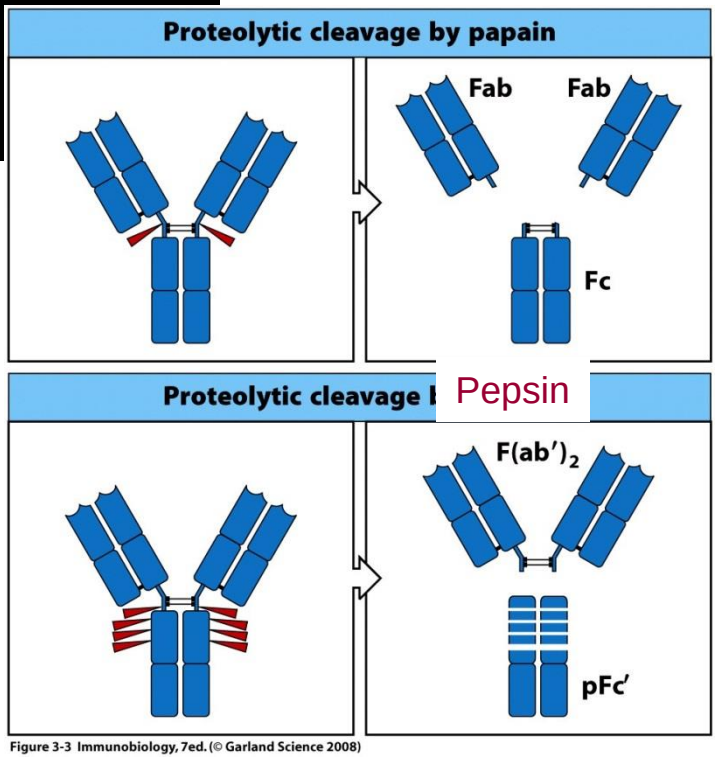
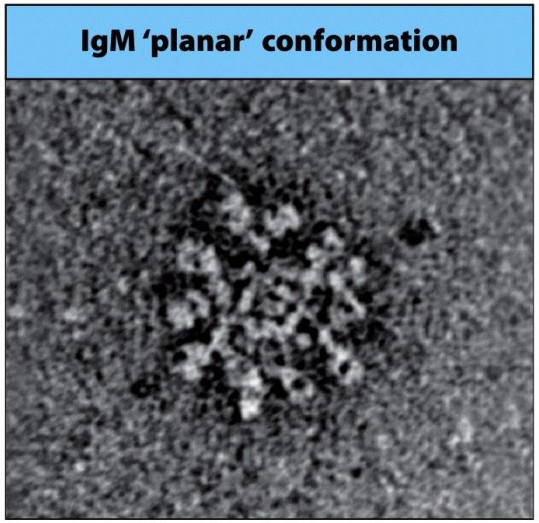


Figure 3-3 Immunobiology, 7ed. (© Garland Science 2008)

Complexos de antígenos e anticorpos ativam a via clássica do sistema complemento



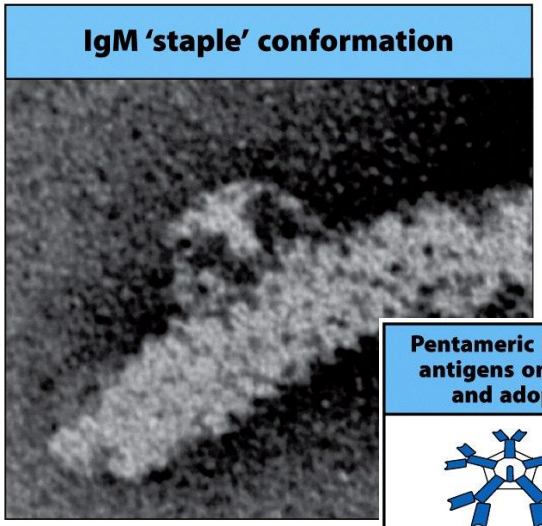
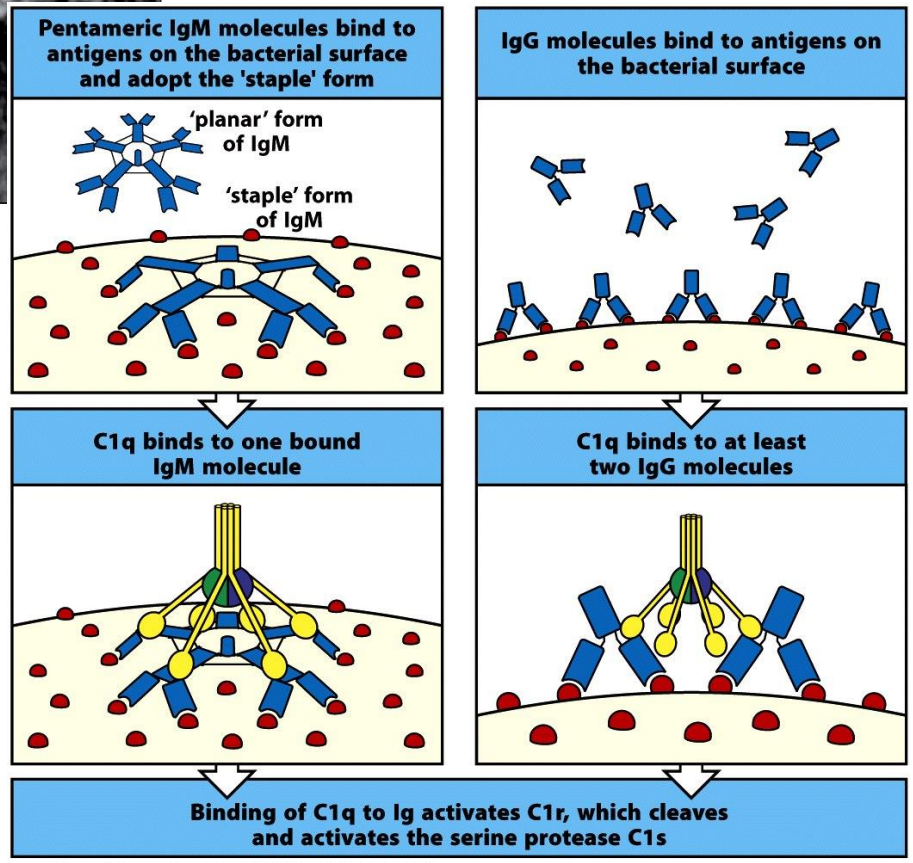
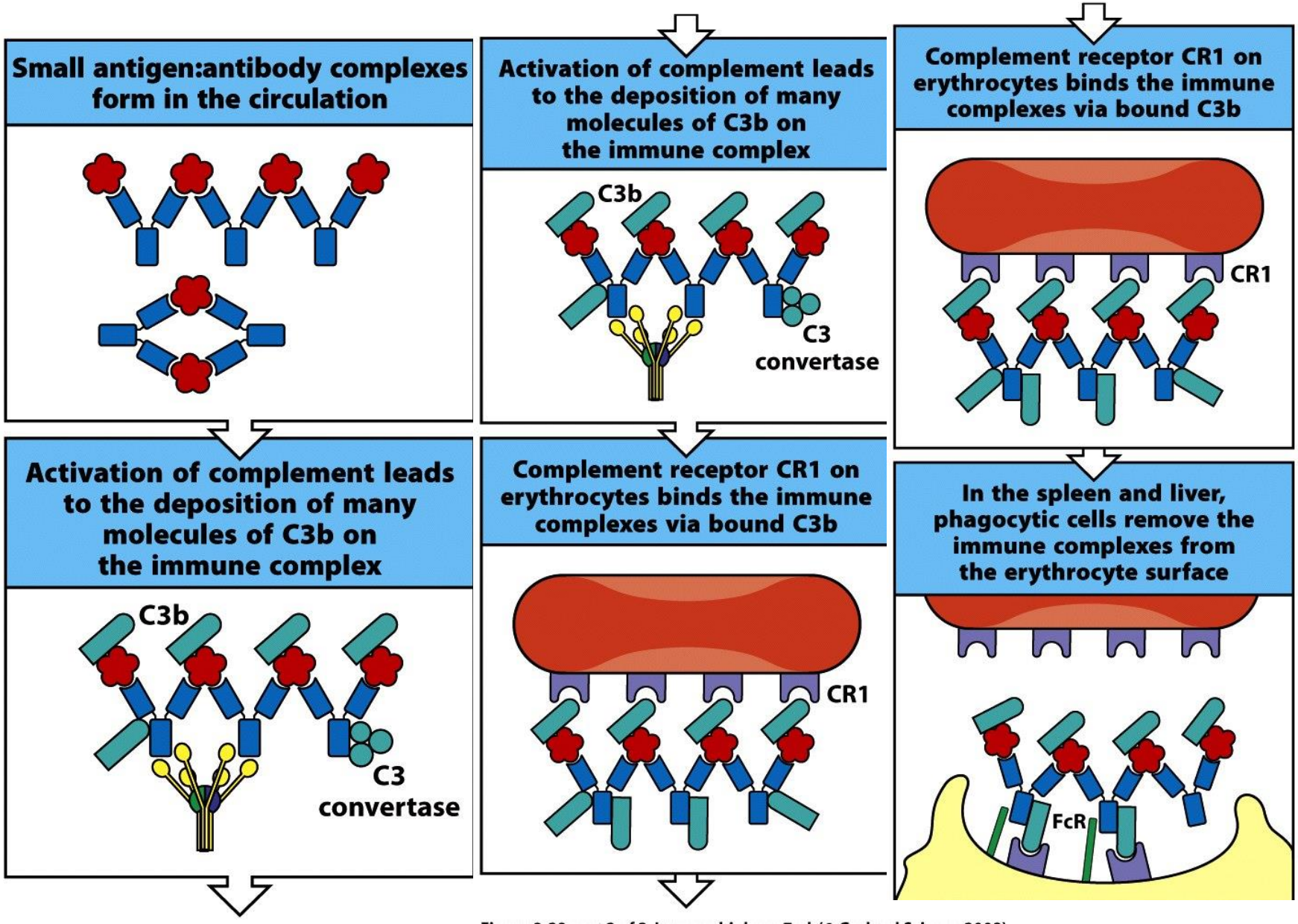


Figure 9-27 Immunobiology, 7ed. (© Garland Science 2008)

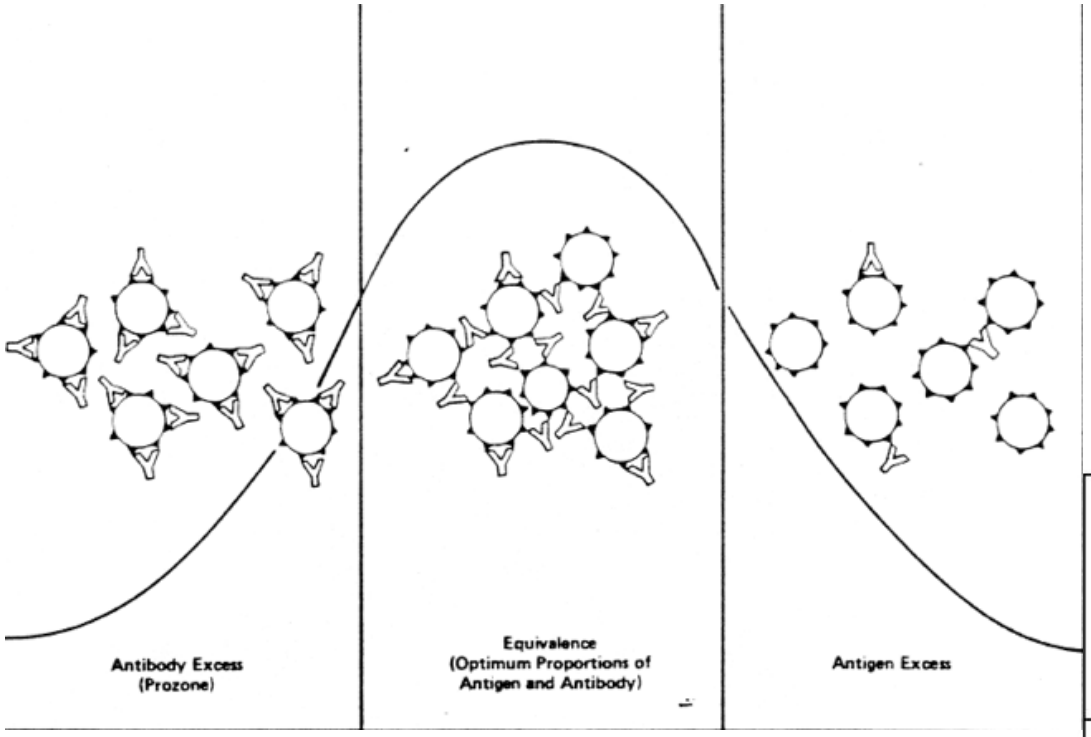
IgM ligado a
flagelo de bactéria

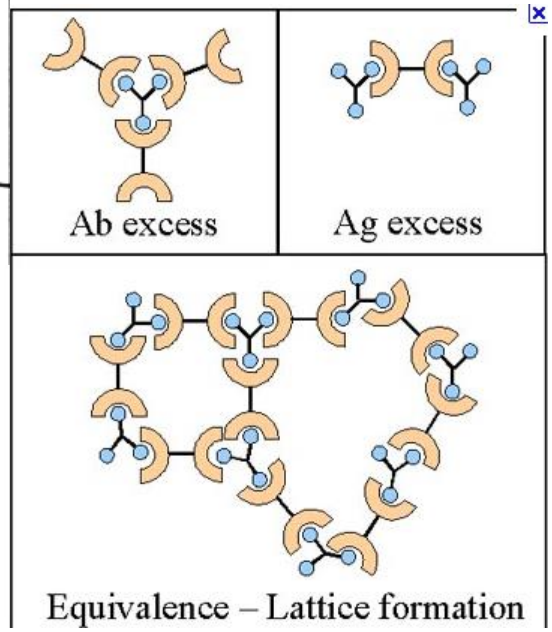


Receptores para complemento são importantes para remover complexos imunes da circulação



Excesso de complexos imunes causa doença





Excesso de anticorpo PROZONA

Equivalência REDE INSOLÚVEL

Excesso de antígeno PÓSZONA

Complexos solúveis

A destruição de patógenos opsonizados por meio de receptores de Fc de Igs

PROPERTIES OF ANTIBODIES CYTOPHILIC FOR MACROPHAGES*

By ARTHUR BERKEN,‡ M.D., AND BARUJ BENACERRAF,§ M.D.

(*From the Department of Pathology, New York University School of Medicine, New York*)

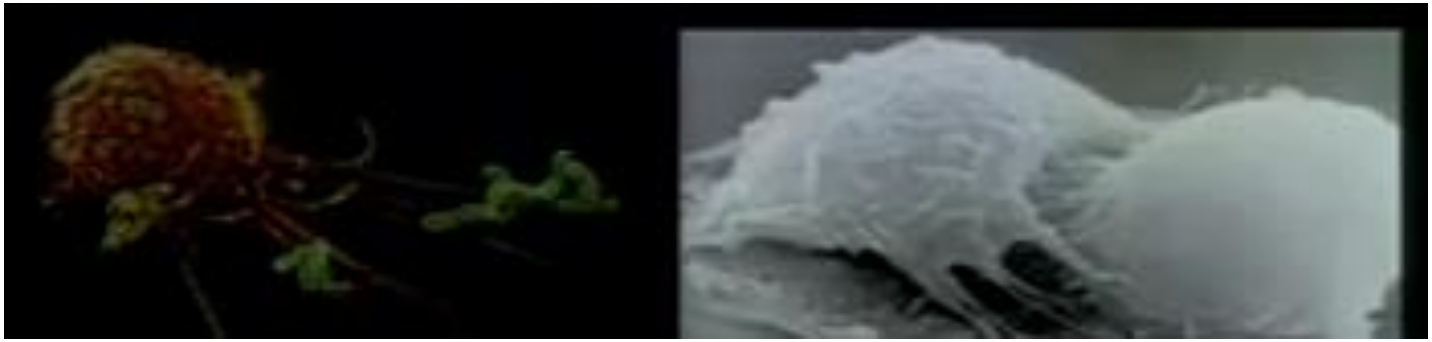
PLATES 21 AND 22

(Received for publication 7 July 1965)

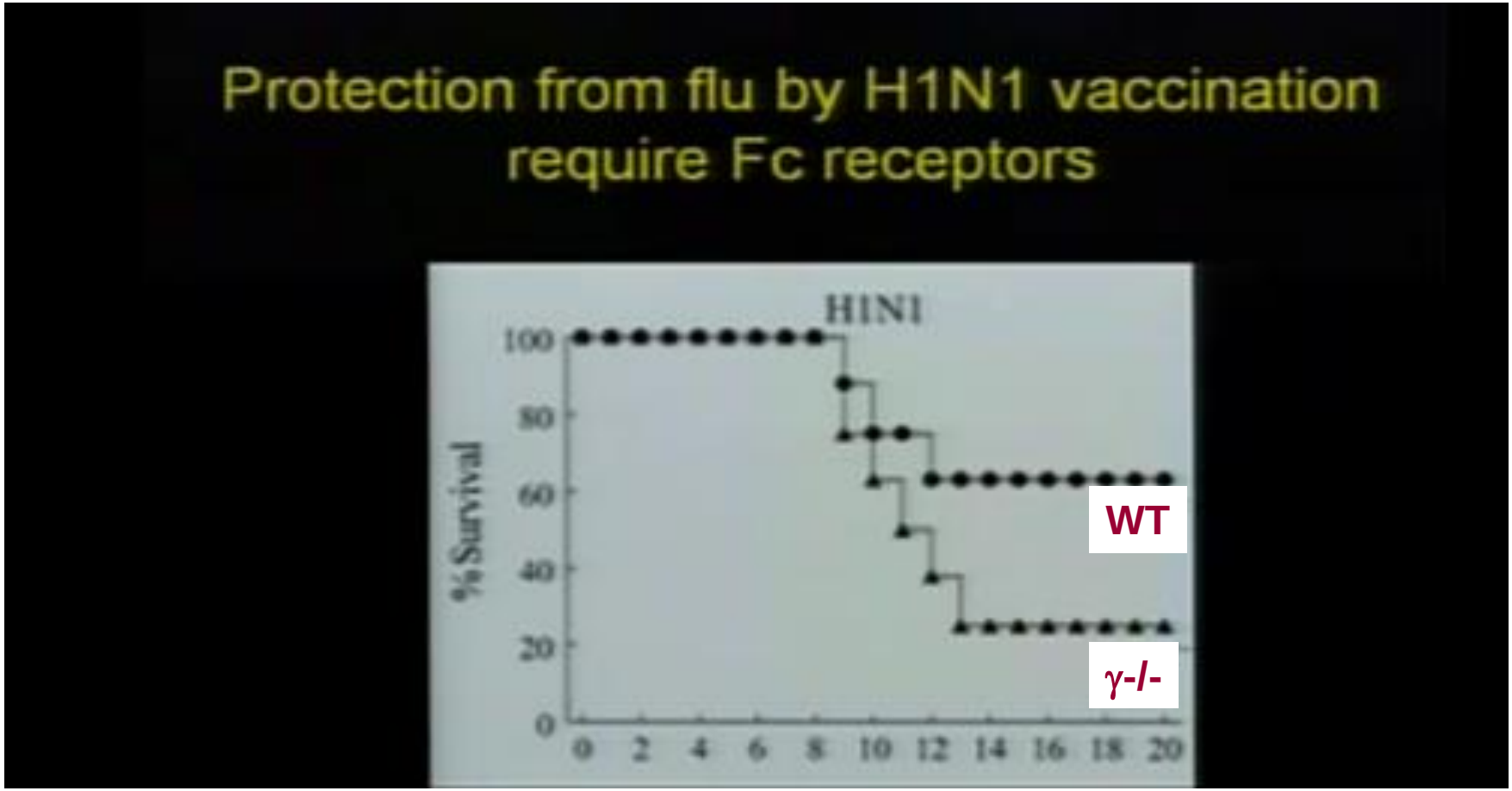
The production of an antibody cytophilic for spleen cells in rabbits immunized with human serum albumin was described by Boyden and Sorkin (1, 2, 3) several years ago. These investigators detected the presence of cytophilic antibody by the capacity of the antisera to confer upon normal cells the capability of specifically adsorbing radio-iodinated antigen. Among the deficiencies in such a system is the failure to distinguish from among the heterogeneous population of cells in the tissue suspensions that cell type which is capable of adsorbing the antigen. This deficiency was recently overcome by Boyden (4) who demonstrated in guinea pig anti-sheep red cell serum the presence of an antibody which could selectively bind to homologous peritoneal macrophages and confer upon them the ability to adsorb sheep red cells.

The present work was designed to identify some of the physical and biological properties of this antibody. In the guinea pig, 7S antibodies with the same im-

Journal of Experimental Medicine, January, 1966



A imunidade mediada por Anticorpos depende de **FcRs**



Nature. 2007 Sep 6;449(7158):101-4.
Fc receptor but not complement binding is important in antibody protection against HIV.
Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR.

FcRs dos fagócitos são ativados por anticorpos ligados à superfície de patógenos e medeiam a ingestão e/ou destruição destes

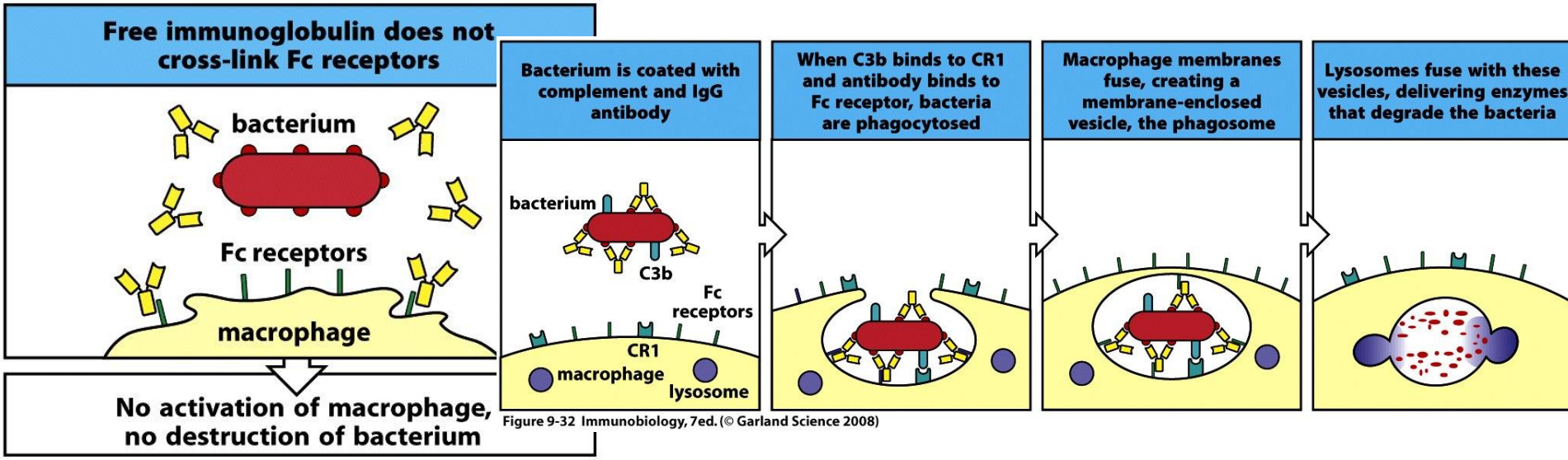


Figure 9-32 Immunobiology, 7ed. (© Garland Science 2008)

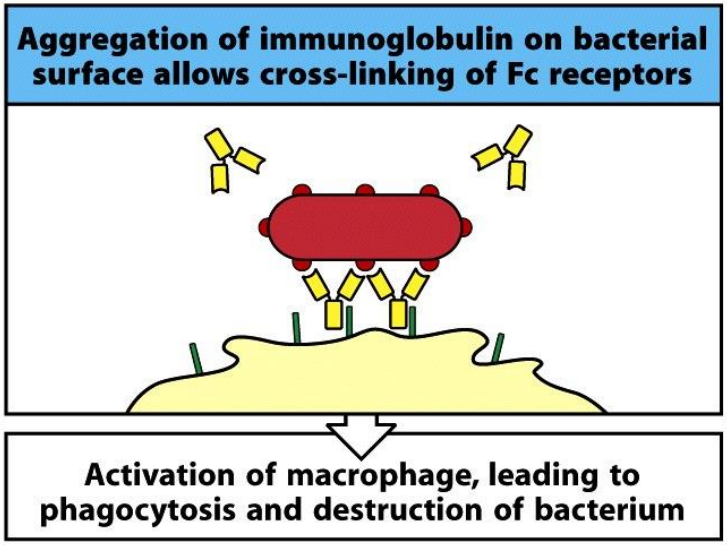
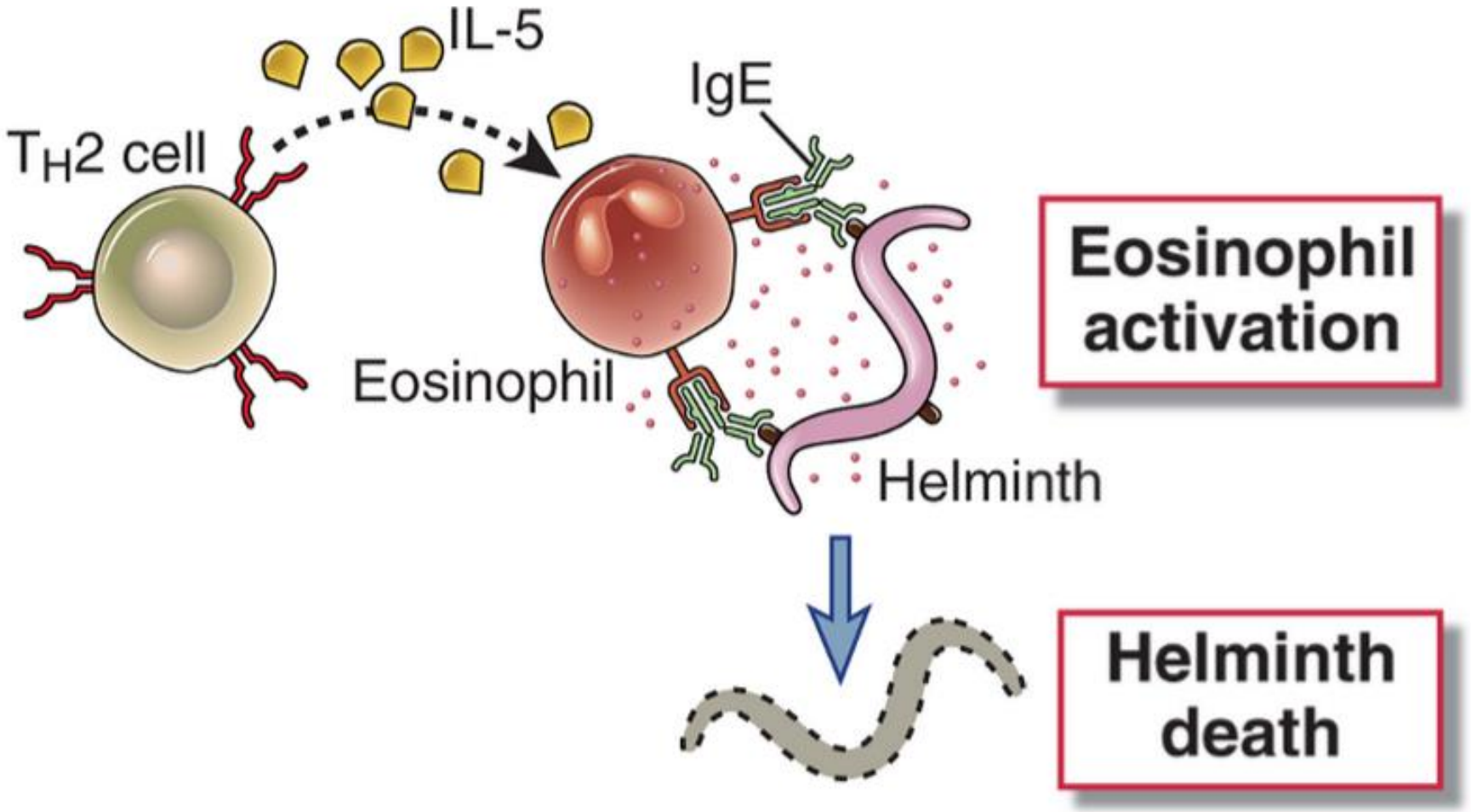


Figure 9-31 Immunobiology, 7ed. (© Garland Science 2008)

FcRs dos basófilos e eosinófilos são ativados por anticorpos ligados à superfície de patógenos e medeiam a destruição destes



FcRs dos basófilos e eosinófilos são ativados por anticorpos ligados à superfície de patógenos e medeiam a destruição destes

Citotoxicidade de uma larva de *Schistosoma mansoni* sendo atacada por IgE específico e eosinófilos.

Reação intermediada pelos FcεR do eosiníofilo

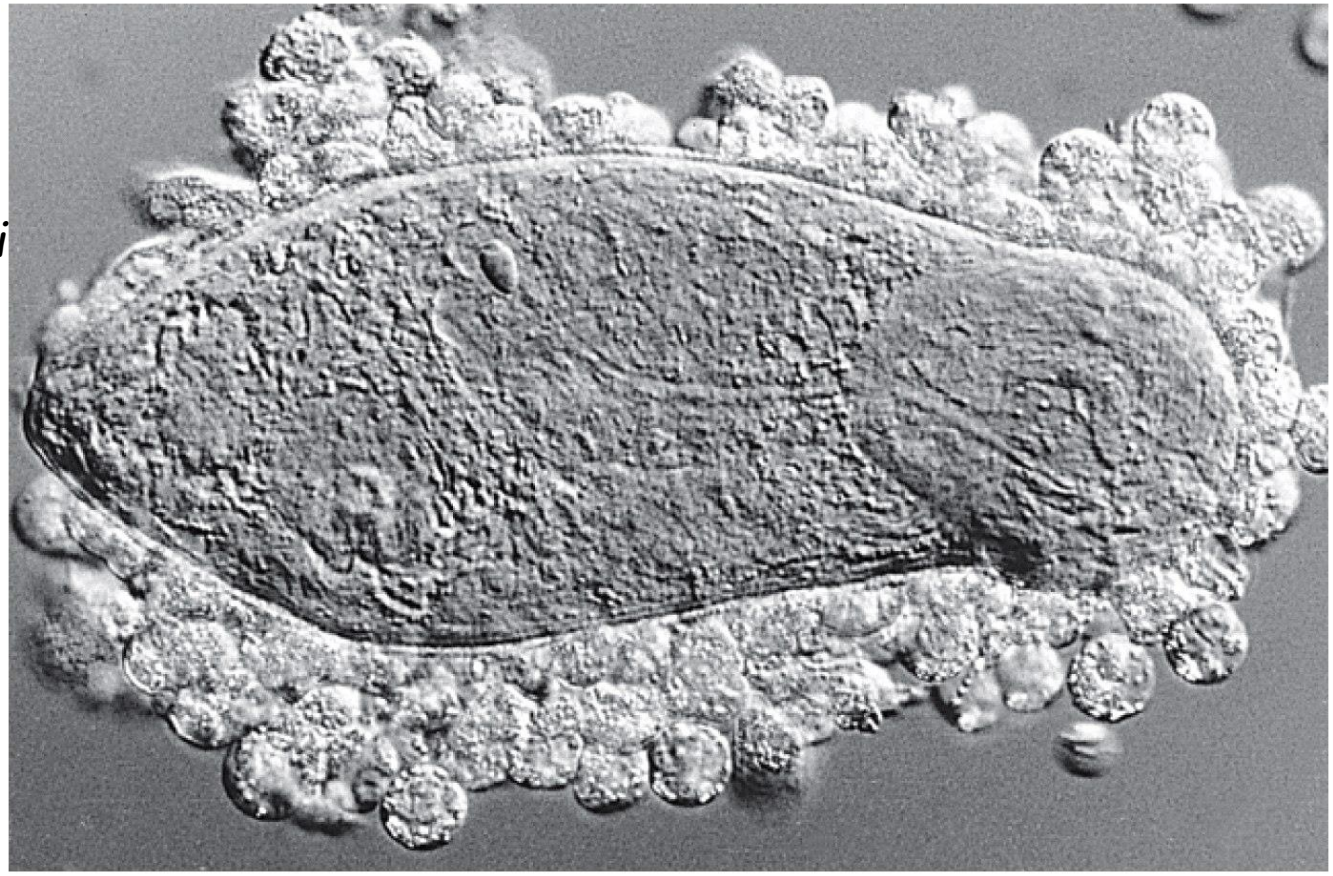


Figure 9-33 Immunobiology, 7ed. (© Garland Science 2008)

A agregação por antígeno de moléculas de IgE aderida a FcεRs na superfície de mastócitos, basófilos e eosinófilos leva a desgranulação celular e liberação de mediadores inflamatórios

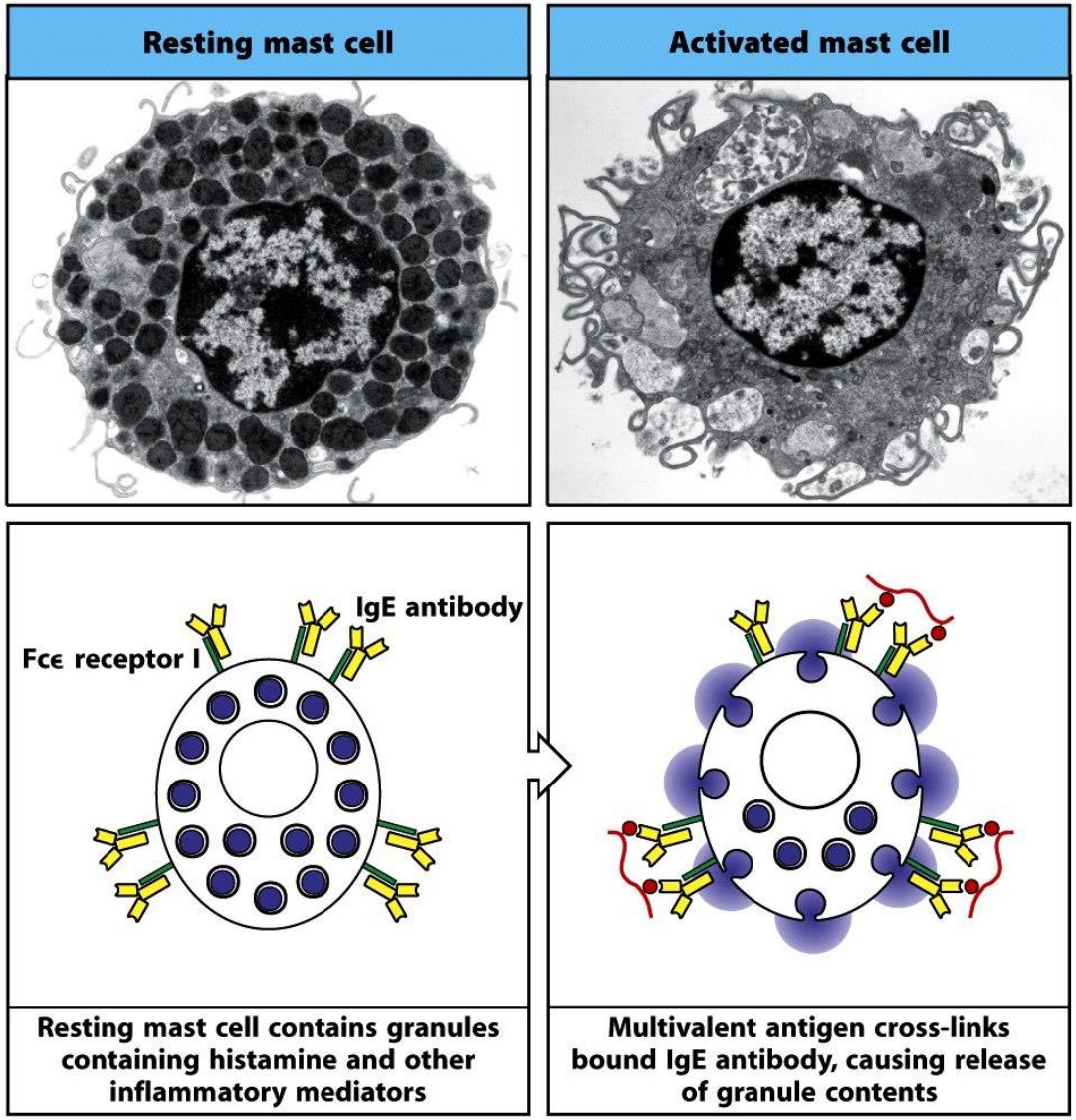


Figure 9-35 Immunobiology, 7ed. (© Garland Science 2008)

Células, e.g., tumorais podem ser mortas por células NK na reação de citotoxicidade mediada por anticorpos (ADCC)

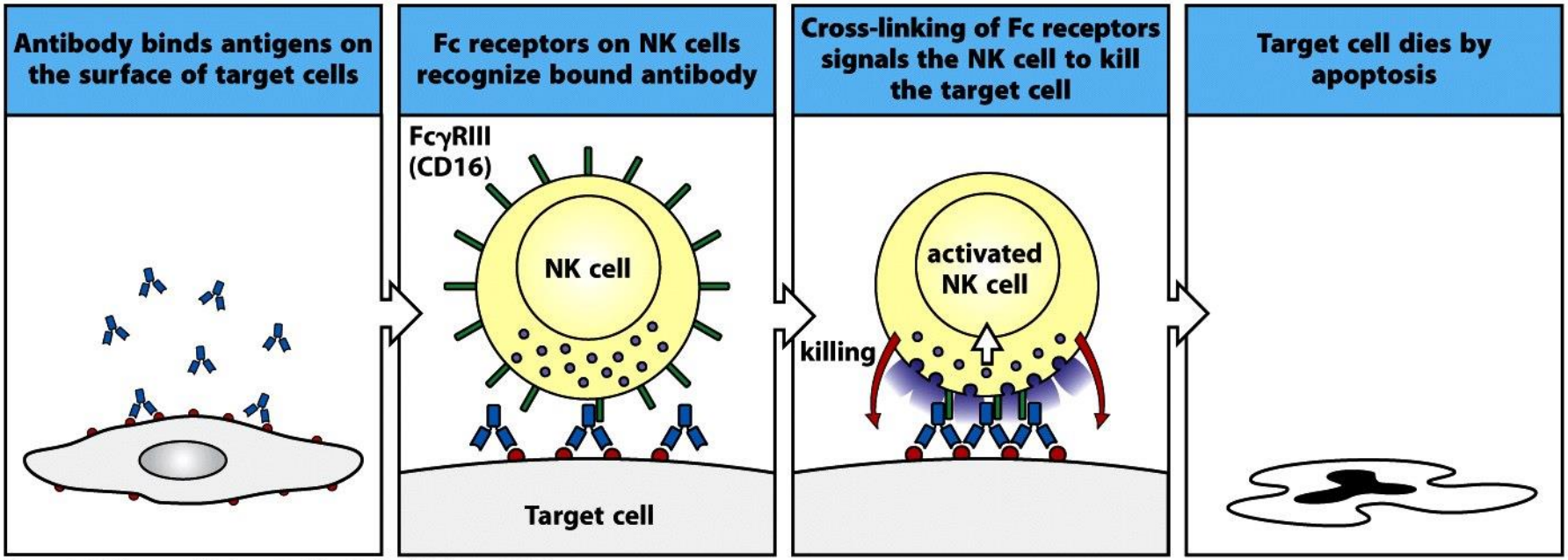
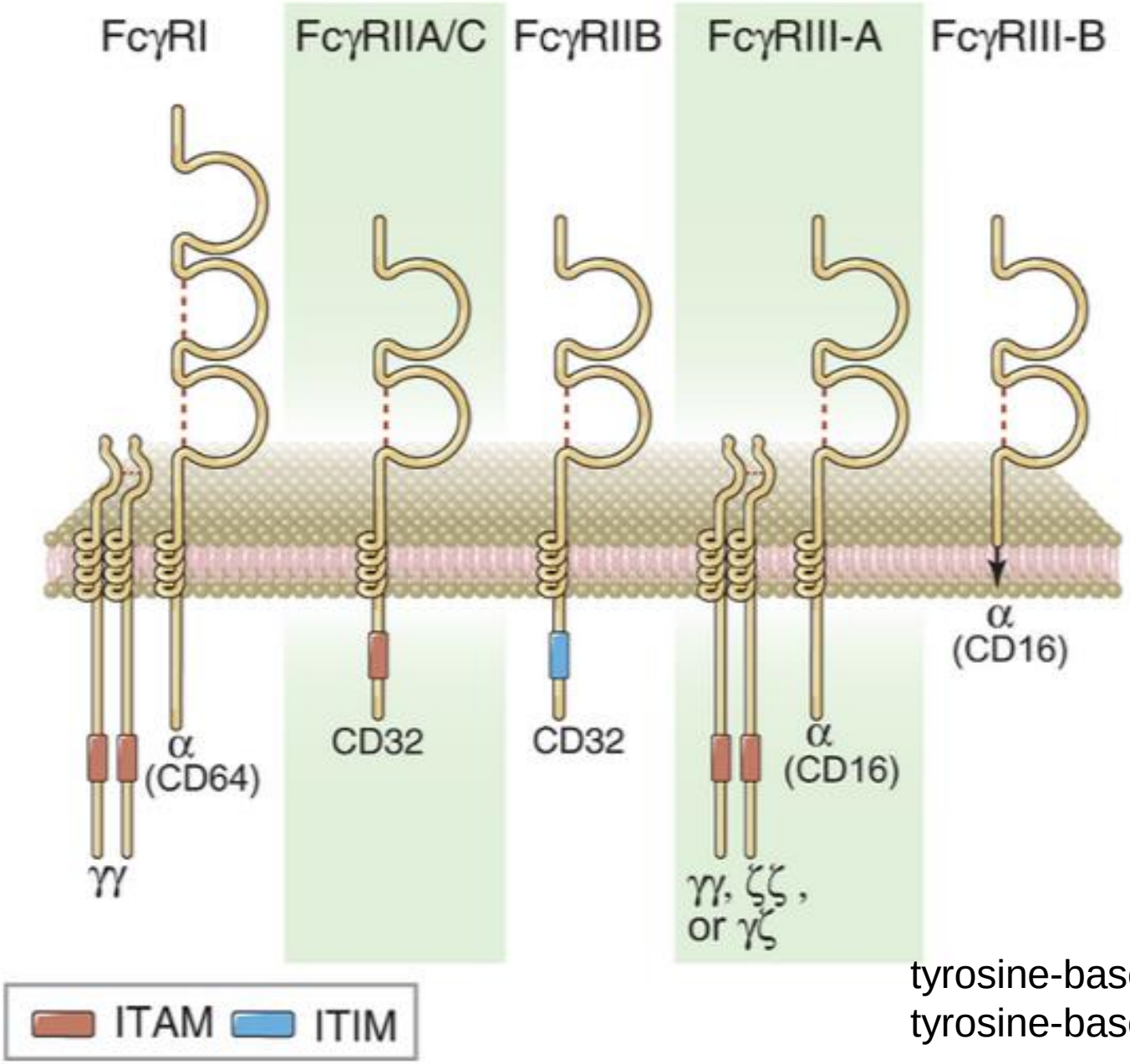


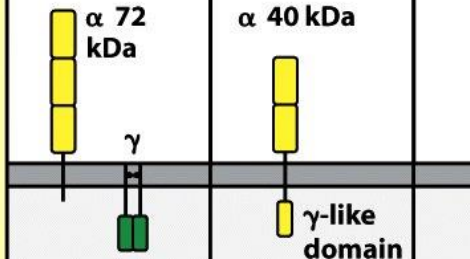
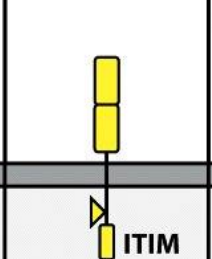
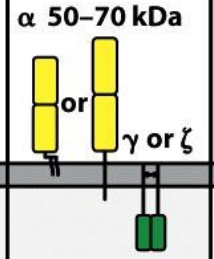
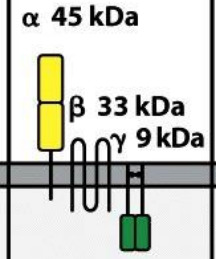
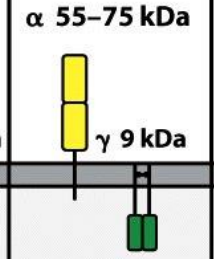
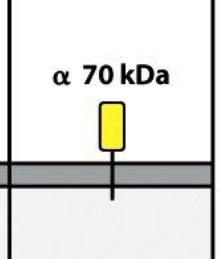
Figure 9-34 Immunobiology, 7ed. (© Garland Science 2008)

Subunit composition of Fcγ receptors.



tyrosine-based activation motif
tyrosine-based inhibition motif

Diferentes tipos de receptores para a região Fc de classes distintas de Igs (FcRs) são expressos em diferentes tipos de células acessórias

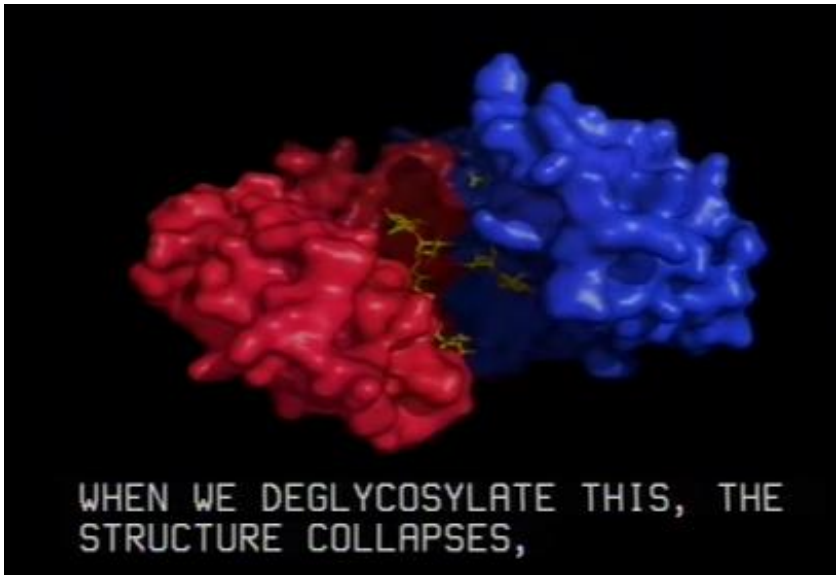
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)	Fcα/μR
Structure								
Binding Order of affinity	IgG1 $10^8\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $2 \times 10^6\ M^{-1}$ 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 $5 \times 10^5\ M^{-1}$ IgG1=IgG3	IgE $10^{10}\ M^{-1}$	IgA1, IgA2 $10^7\ M^{-1}$ IgA1=IgA2	IgA, IgM $3 \times 10^9\ M^{-1}$ 1) IgM 2) IgA
Cell type	Macrophages Neutrophils† Eosinophils† Dendritic cells	Macrophages Neutrophils Eosinophils Platelets Langerhans cells	Macrophages Neutrophils Eosinophils	B cells Mast cells	NK cells Eosinophils Macrophages Neutrophils Mast cells	Mast cells Eosinophils† Basophils	Macrophages Eosinophils‡ Neutrophils	Macrophages B cells
Effect of ligation	Uptake Stimulation Activation of respiratory burst Induction of killing	Uptake Granule release (eosinophils)	Uptake Inhibition of stimulation	No uptake Inhibition of stimulation	Induction of killing (NK cells)	Secretion of granules	Uptake Induction of killing	Uptake

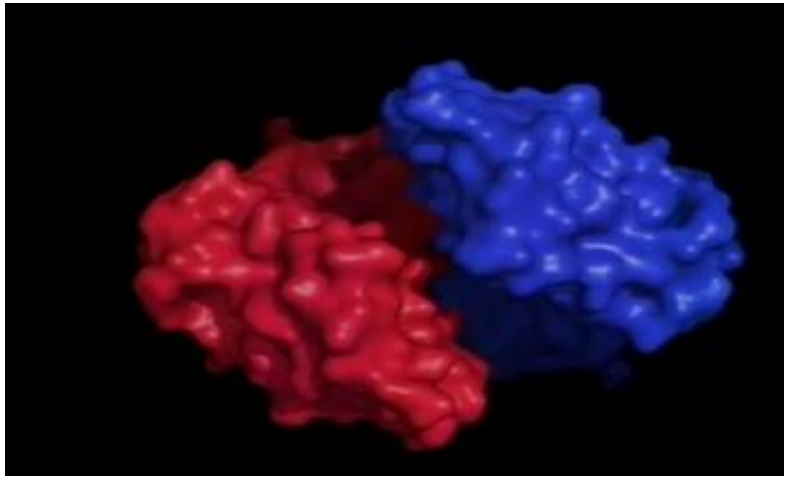
Maioria das vacinas em uso funciona por meio de anticorpos NEUTRALIZANTES

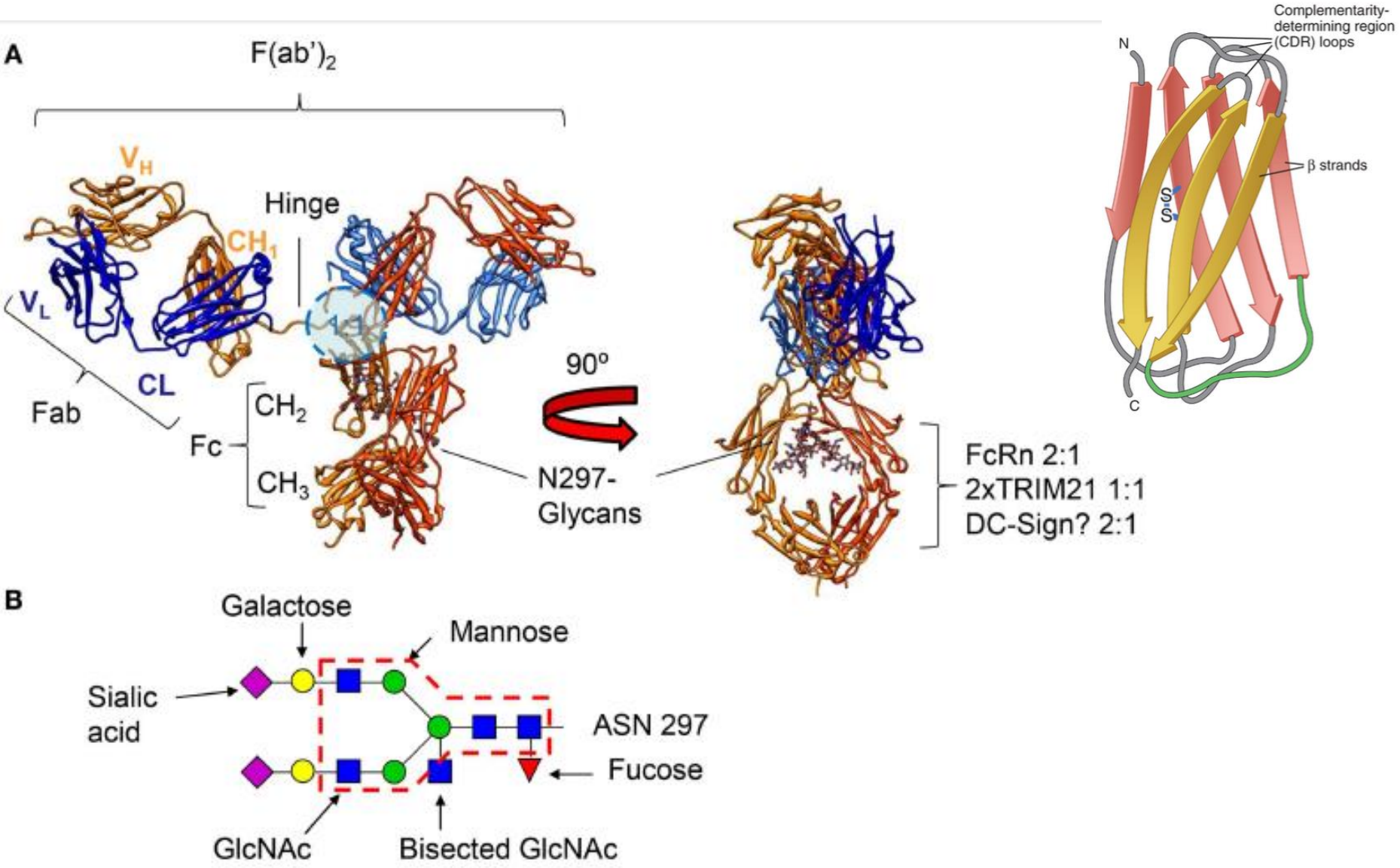
Figure 9-30 Immunobiology, 7ed. (© Garland Science 2008)

IgG2a anti-antígeno tumoral de melanoma tem alta afinidade para receptores de Fc pró-inflamatórios

Propriedades das Igs dependem do tipo e nível de glicosilação

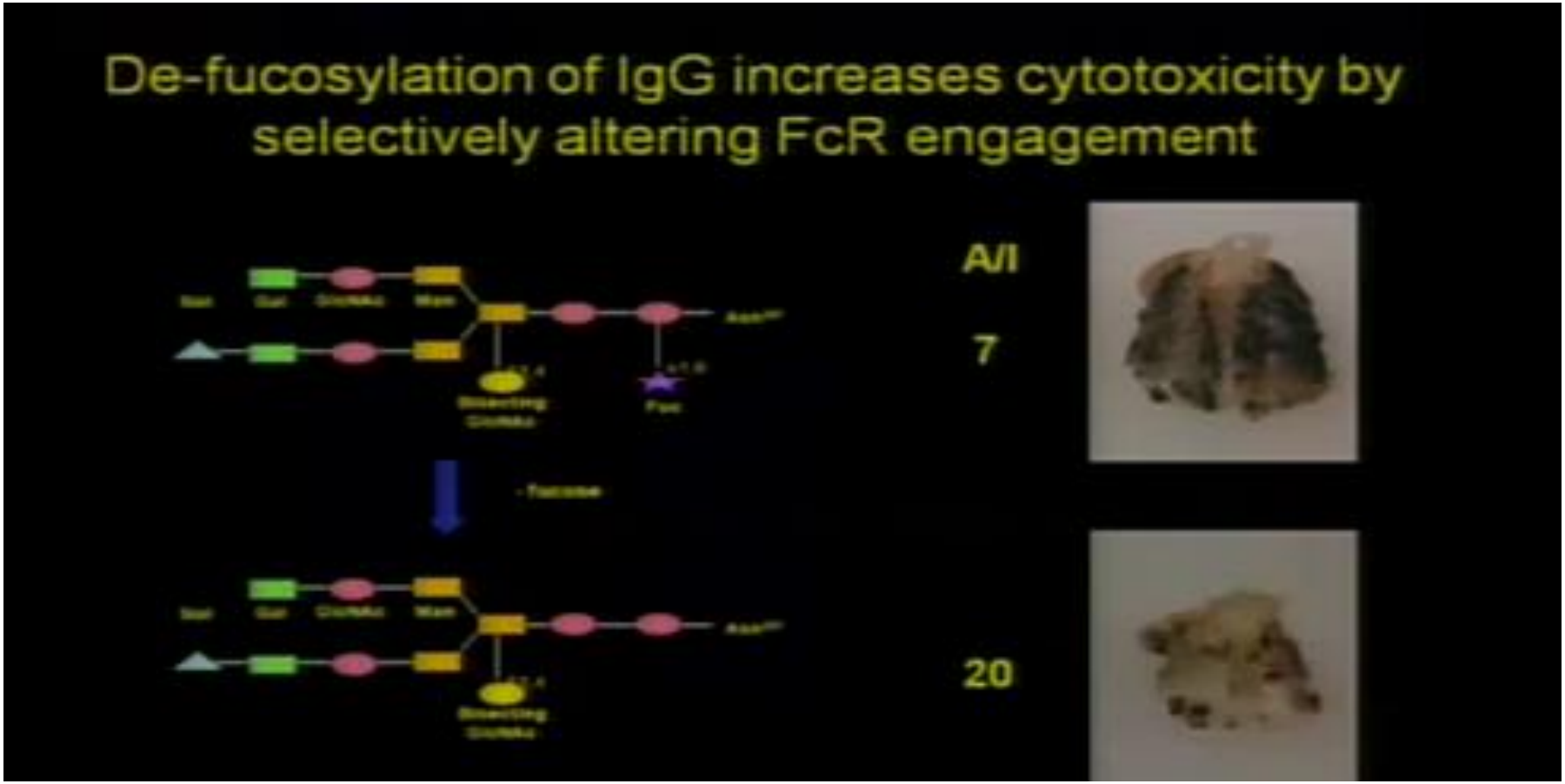




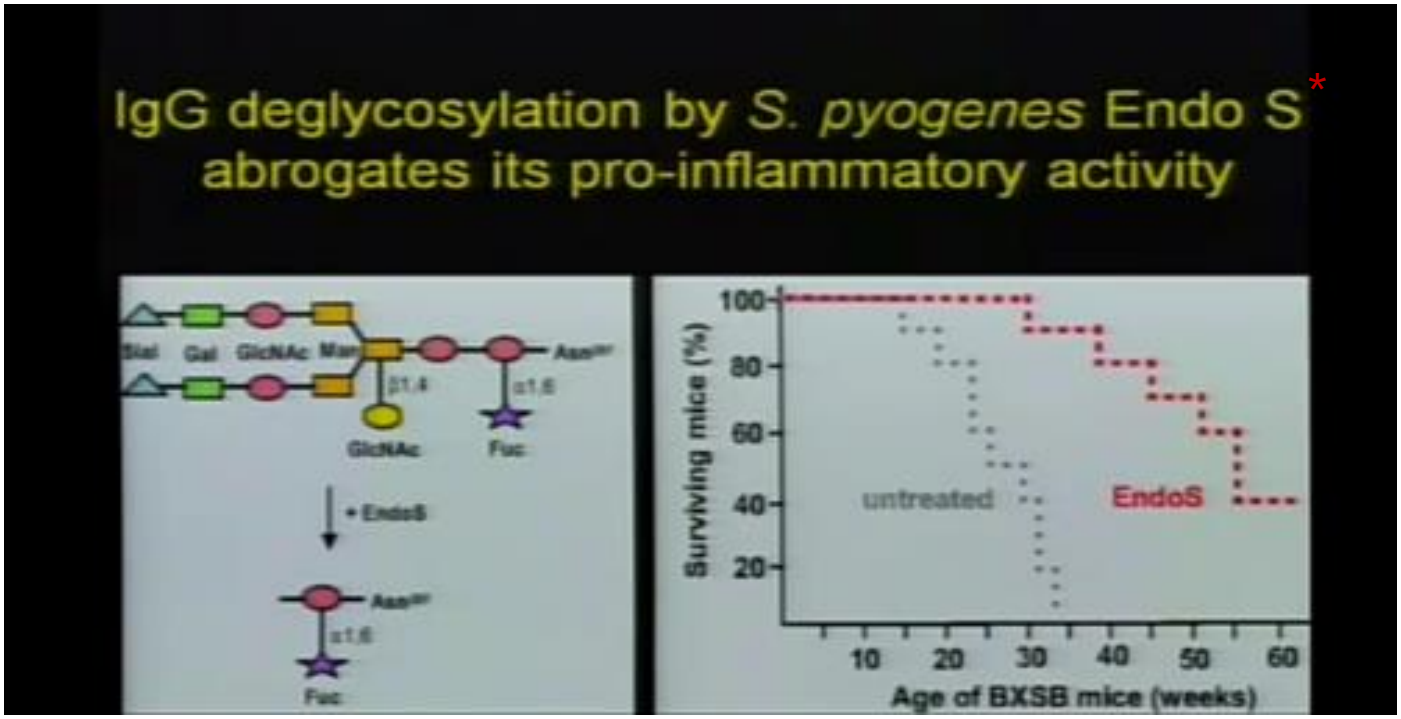


Crystal structure of na human IgG1 molecule viewed from two different angles, demonstrating theflexibility of the two Fab fragments with respect to each other and the Fc tail.
The N-linked glycan found at position 297 can be found as a core structure, common to all IgG found in human beings and rodents (core structure indicated with a red dashed line)

Propriedades das Igs dependem do tipo e nível de glicosilação



Propriedades **anti-inflamatórias** das Igs dependem do tipo e nível de glicosilação



Animal geneticamente propenso a doença autoimune

* Por que *S. pyogenes* tem glicosidase????

Estratégias de Defesa e a Relação Custo Benefício da Resposta Imune Efetora

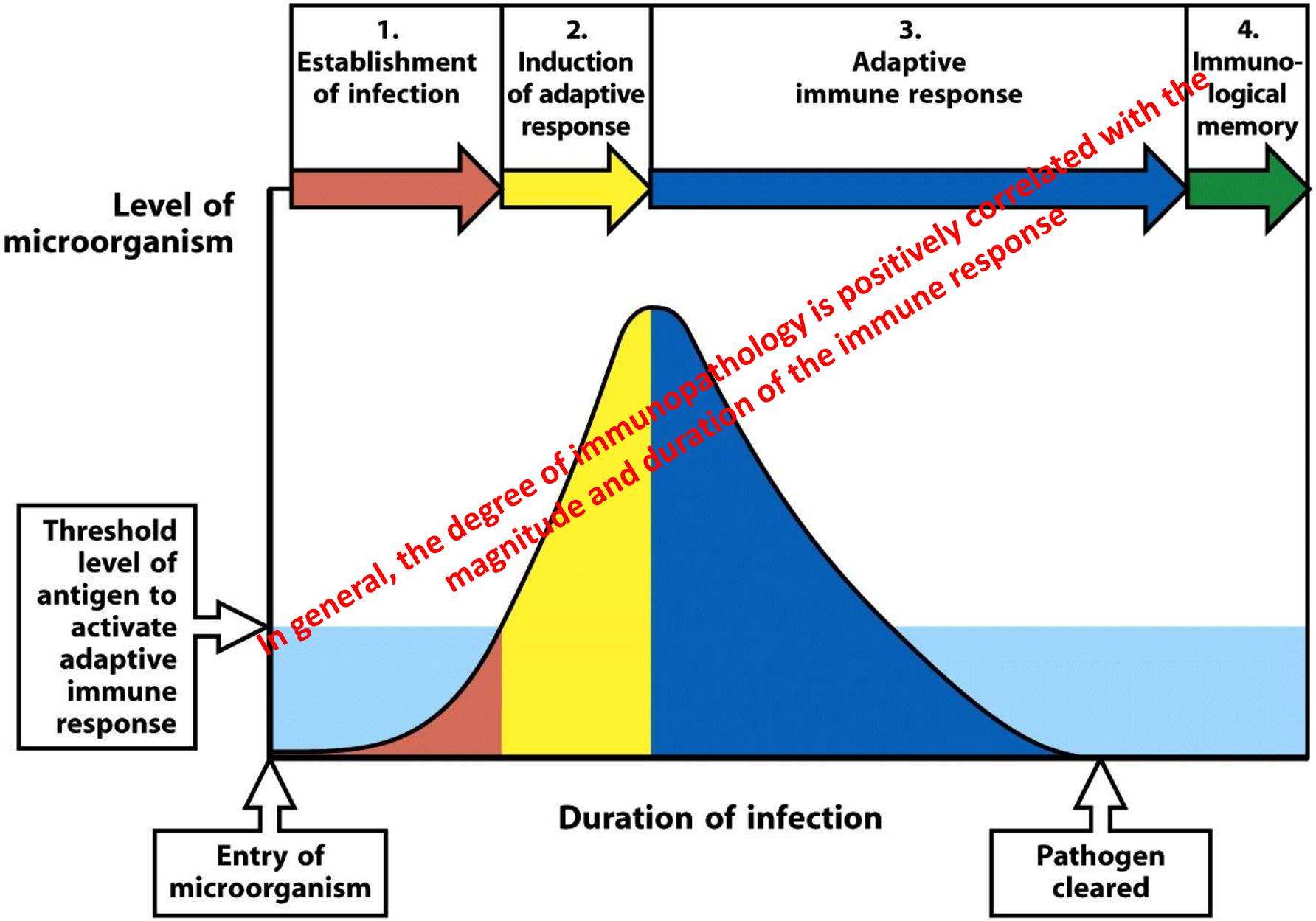


Figure 10-1 Immunobiology, 7ed. (© Garland Science 2008)

Mecanismos Efetores Contra os Diferentes Tipos de Patógenos

	Infectious agent	Disease	Humoral immunity			
			IgM	IgG	IgE	IgA
Viruses	Herpes zoster	Chickenpox				
	Epstein–Barr virus	Mononucleosis				
	Influenza virus	Influenza				
	Polio virus	Poliomyelitis				
Intra-cellular bacteria	*Rickettsia prowazekii*	Typhus				
	Mycobacteria	Tuberculosis, leprosy				
Extra-cellular bacteria	*Staphylococcus aureus*	Boils				
	Streptococcus pneumoniae	Pneumonia				
	Neisseria meningitidis	Meningitis				
	Corynebacterium diphtheriae	Diphtheria				
	Vibrio cholerae	Cholera				
Fungi	*Candida albicans*	Candidiasis				
Protozoa	*Plasmodium* spp.	Malaria				
	Trypanosoma spp.	Trypanosomiasis				
Worms	Schistosome	Schistosomiasis				

Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)

Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

Se temos mecanismos efetores de imunidade por que ficamos doentes quando infectados com patógenos?

- Patogenicidade e o resultado da invasão: depende da capacidade do invasor de lidar com as defesas locais do seu hospedeiro
  - i.e., complementariedade entre as defesas existentes no nicho anatômico que o patógeno ocupa e repertório dos seus fatores de virulência
    - ectoparasita, endoparasita, "intraparasita" extracelular ou intracelular
    - pele, mucosa respiratória, trato digestivo, sangue, etc.
- Composição química, física e imunológica das defesas depende do sítio anatômico onde ocorre a invasão

"A doença geralmente representa as negociações inconclusivas para alcançar a simbiose entre patógeno e hospedeiro ....

...É a má interpretação sobre o que sejam as fronteiras"

Lewis Thomas, 1972

Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

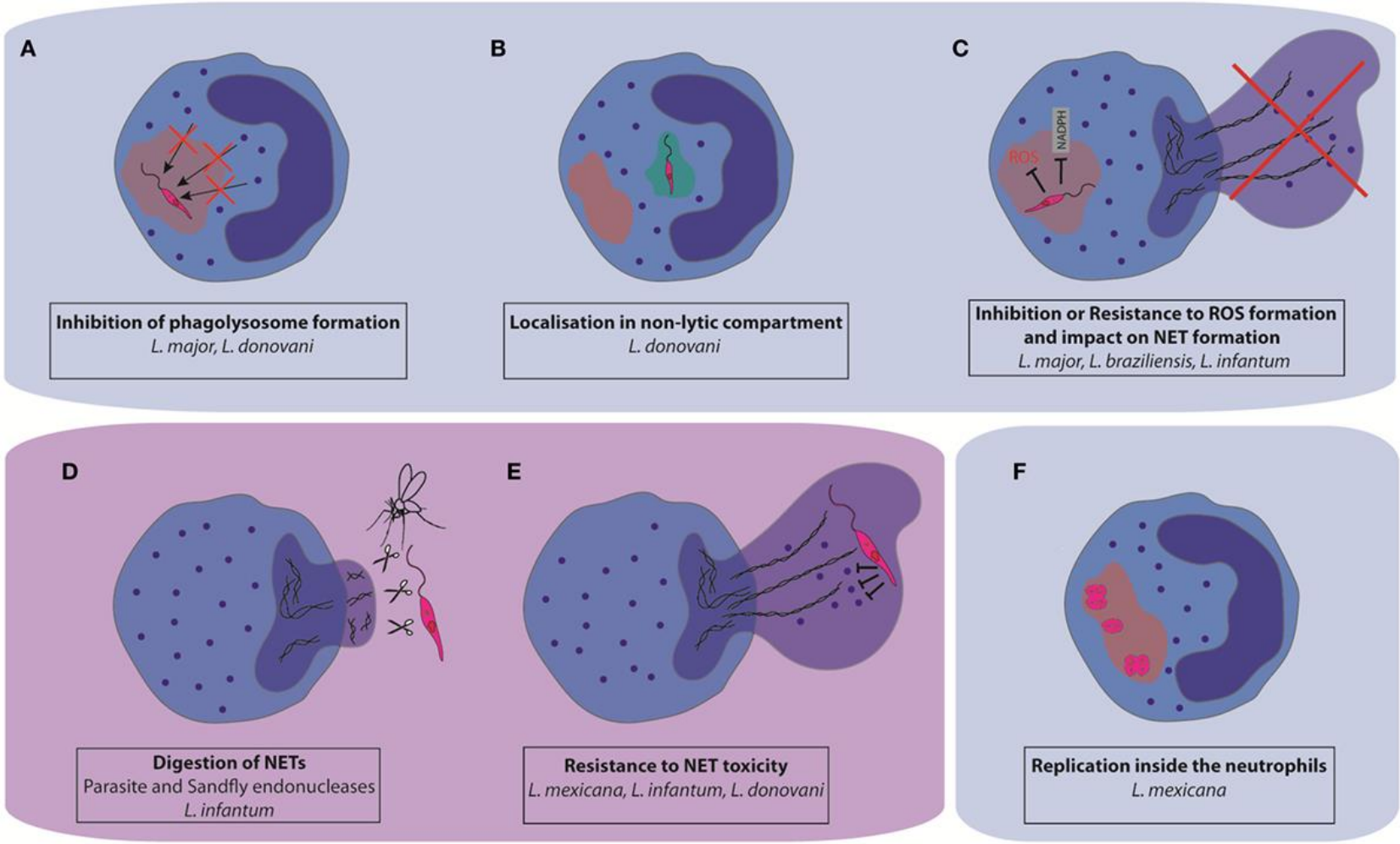
- Sequestro anatômico
  - Cistos, intestino
- Disfarce molecular
  - Moléculas de MHC, grupos sanguíneos
- Barreiras físicas
  - Tegumento resistente a enzimas citolíticas
- Variação antigênica
- Ecdise antigênica
- Inibição de componentes do sistema imune

Mechanisms used by bacteria to subvert the host immune system

Bacterial strategy	Mechanism	Result	Examples
Extracellular bacteria			
Shielding or inhibition of MAMPs	Capsular polysaccharide	Block detection of lipopolysaccharide (LPS)	*S. pneumoniae*
	Hypoacylation of lipid A	Antagonism of TLR-4	*P. gingivalis*
	Coating of bacterium by self proteins (e.g., fibrin)	Block detection of peptidoglycan	*S. aureus*
Antigenic variation	Modulation of expressed pili, fimbriae	Antibodies that block bacterial attachment become ineffective	*N. gonorrhoeae, E. coli*
Inhibition of opsonization	Secretion of complement-degrading factors	Cleavage of complement components	*N. meningitidis, P. aeruginosa, S. aureus*
	Capsular polysaccharide	Block fixation of complement	*S. pneumoniae, H. influenzae, K. pneumoniae*
	Expression of Fc-binding surface moleclues (e.g., Protein A)	Prevents binding of antibody to Fc receptors of phagocytes	*S. aureus*
Inhibition/scavenging of reactive oxygen species (ROS)	Secretion of catalase and superoxide dismutase	Neutralize ROS produced by NADPH and myeloperoxidase (MPO)	*S. aureus, B. abortus*
Resistance to antimicrobial peptides (AMPs)	Secretion of AMP-degrading peptidases	Cleavage of AMPS	*E. coli*
	Modulation of cell membrane phospholipids	Prevents binding, functional insertion of AMPs in cell membrane	*S. aureus*

Intracellular bacteria			
Antigenic variation	Modulation of expressed pili, fimbriae	Antibodies that block bacterial attachment become ineffective	*Salmonella* spp.
Inhibition of MAMP recognition/ signaling	Production of peptidoglycan hydrolase	Block detection of peptidoglycan by NODs	*L. monocytogenes*
	Secretion of intracellular toxins	Block NFκB and MAP kinase signaling pathways	*Y. pestis*
Resistance to anti-microbial peptides	Secretion of AMP-degrading peptidases	Cleavage of AMPS	*Y. pestis*
	Modulation of cell membrane phospholipids	Prevents binding, functional insertion of AMPs in cell membrane	*Salmonella* spp.
Inhibition of fusion of phagosome with lysosome	Release of bacterial cell wall components	Inhibits phago-lysosomal fusion	*M. tuberculosis, M. leprae, L. pneumophila*
Survival within phagolysosome	Waxy, hydrophobic cell wall containing mycolic acids and other lipids	Resistance against lysosomal enzymes	*M. tuberculosis, M. leprae*
Escape from phagosome	Production of hemolysins (e.g., listeriolysin O)	Lysis of phagosome; escape into cytosol	*L. monocytogenes, Shigella* spp.

Different mechanisms used by some *Leishmania* spp. to escape neutrophil killing



Variação Antigênica

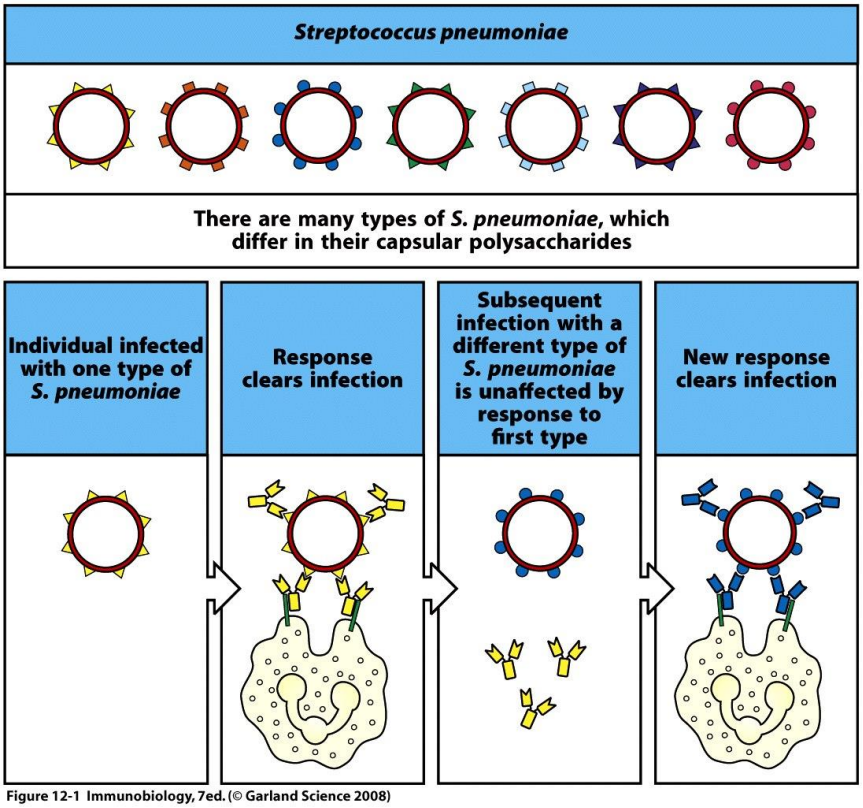
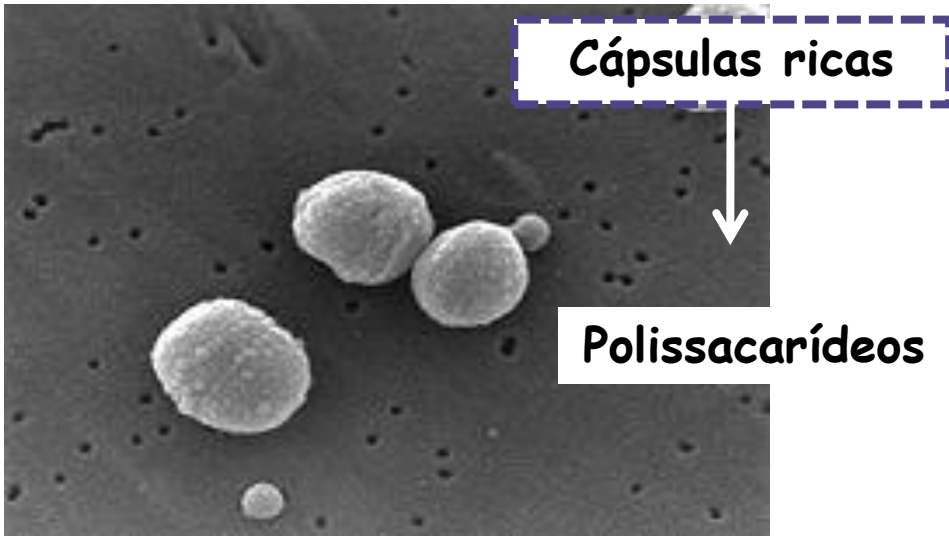


Figure 12-1 Immunobiology, 7ed. (© Garland Science 2008)

Resistência à fagocitose

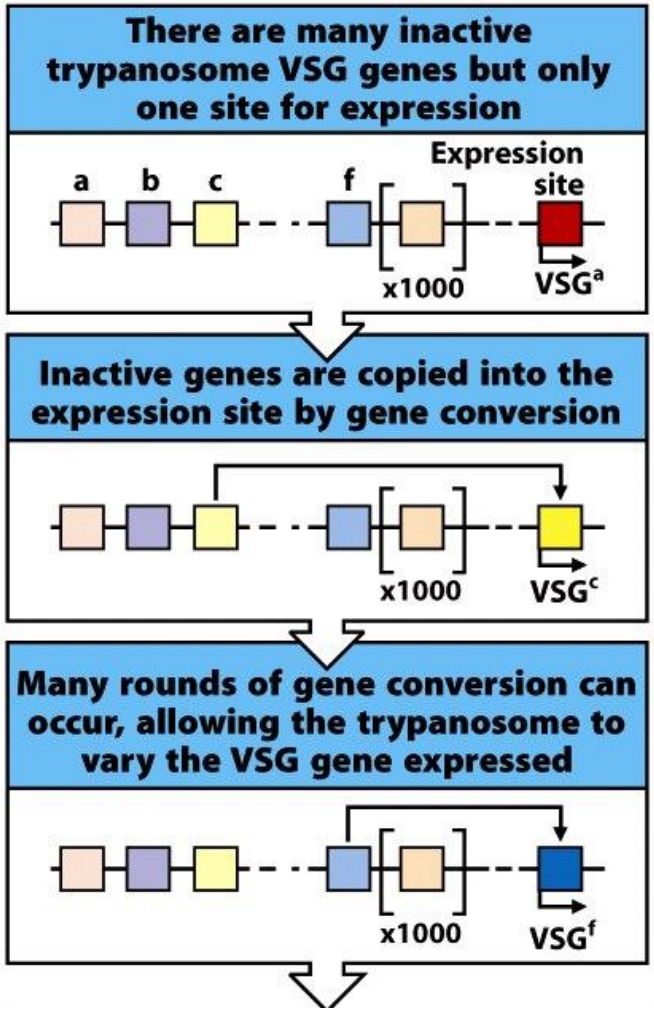


Streptococcus pneumoniae

Patógeno Extracelular

Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro.

Patógeno Extracelular



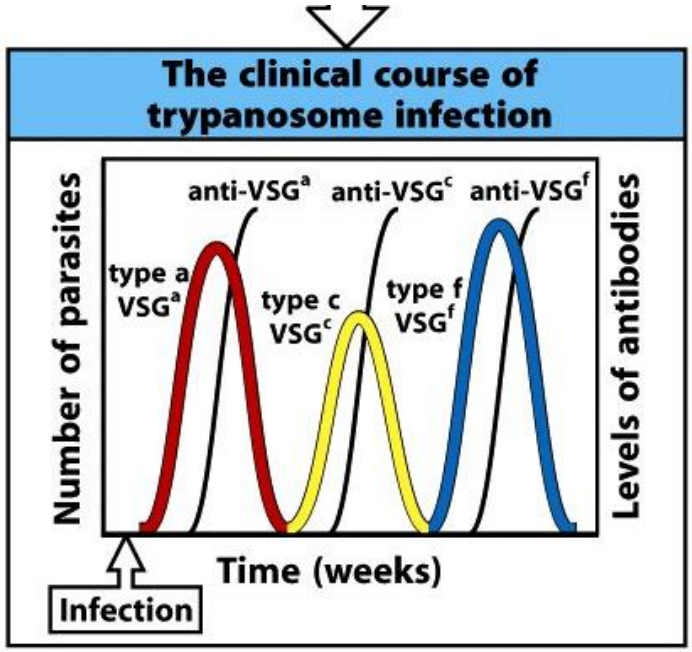
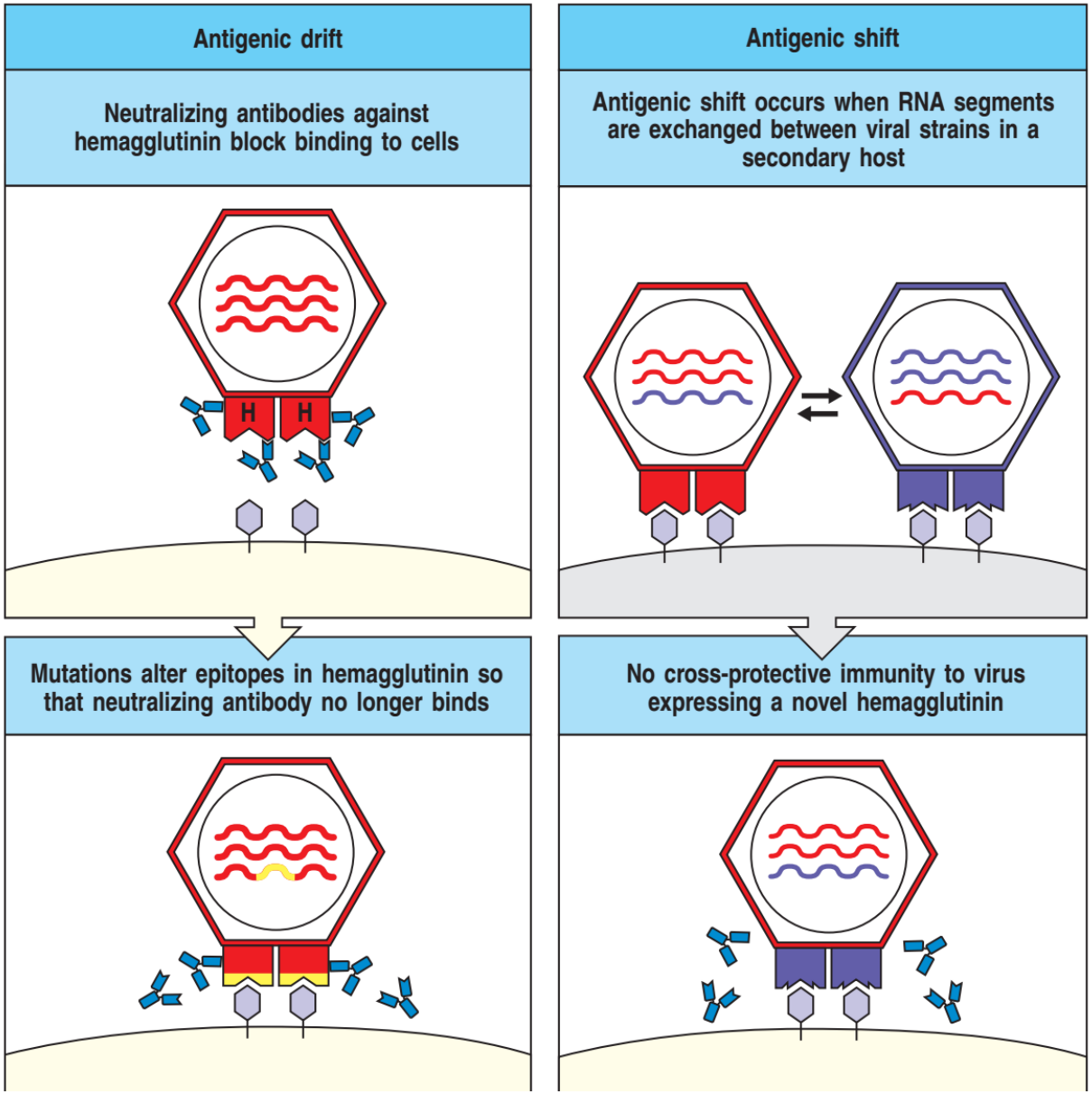


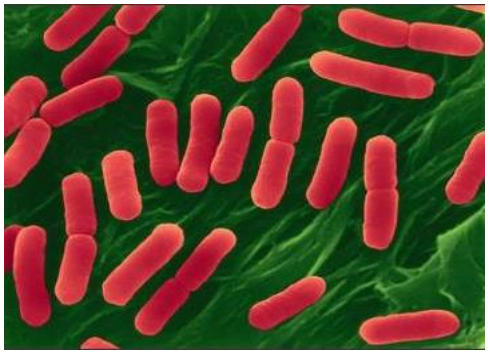
Figure 12-3 Immunobiology, 7ed. (© Garland Science 2008)

Two types of variation allow repeated infection with type A influenza virus.

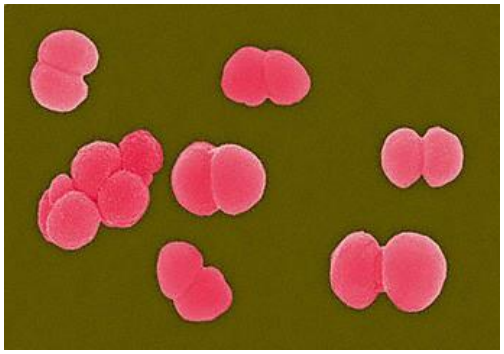


Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

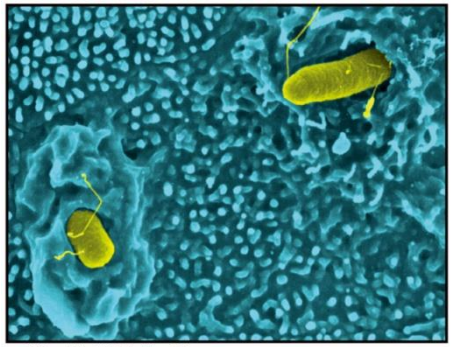
Variação antigênica



Escherichia coli



Neisseria meningitidis



Salmonella typhimurium

Pilosidades - estruturas responsáveis pela adesão bacteriana

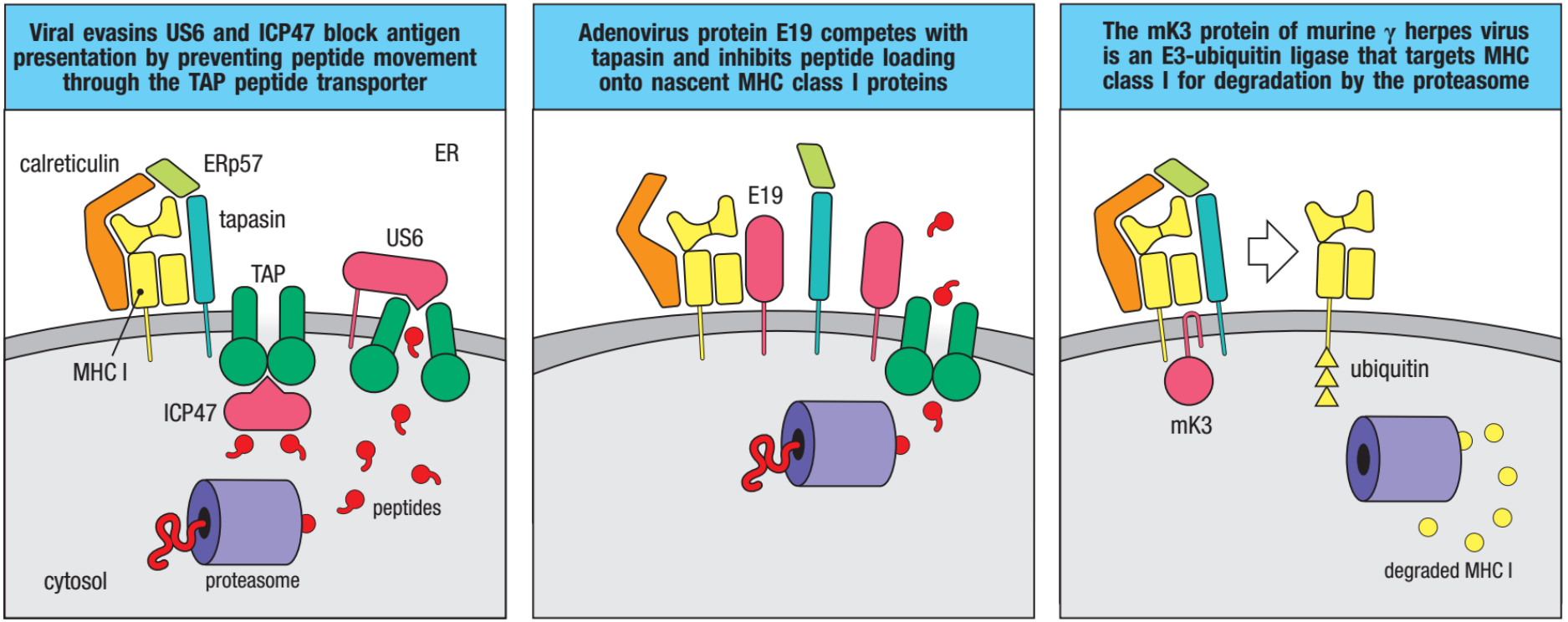
→ **Antígenos de superfície - Pilina**

Patógeno Extracelular que depende de adesão a mucosas

Mechanisms used by viruses of the herpes and pox families to subvert the host immune system

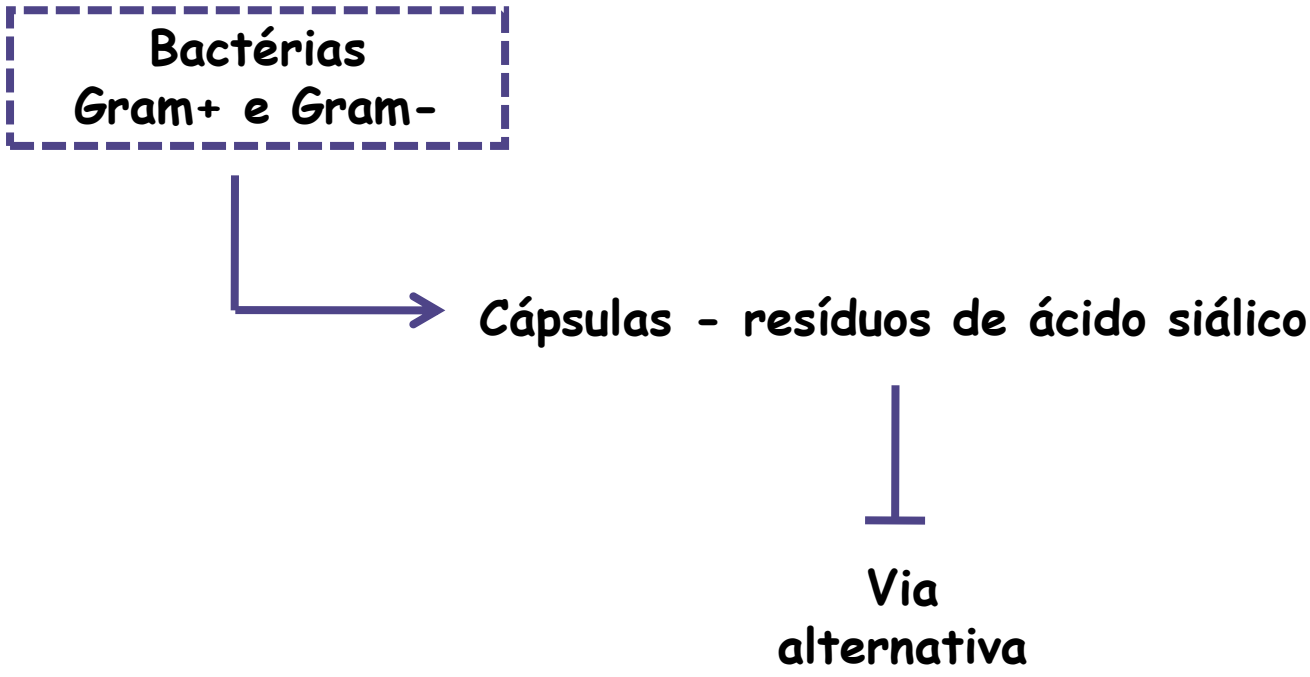
Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of humoral immunity	Virally encoded Fc receptor	Blocks effector functions of antibodies bound to infected cells	Herpes simplex Cytomegalovirus
	Virally encoded complement receptor	Blocks complement-mediated effector pathways	Herpes simplex
	Virally encoded complement control protein	Inhibits complement activation by infected cell	Vaccinia
Inhibition of inflammatory response	Virally encoded chemokine receptor homolog, e.g., β-chemokine receptor	Sensitizes infected cells to effects of β-chemokine; advantage to virus unknown	Cytomegalovirus
	Virally encoded soluble cytokine receptor, e.g., IL-1 receptor homolog, TNF receptor homolog, interferon-γ receptor homolog	Blocks effects of cytokines by inhibiting their interaction with host receptors	Vaccinia Rabbit myxoma virus
	Viral inhibition of adhesion molecule expression, e.g., LFA-3 ICAM-1	Blocks adhesion of lymphocytes to infected cells	Epstein–Barr virus
	Protection from NFκB activation by short sequences that mimic TLRs	Blocks inflammatory responses elicited by IL-1 or bacterial pathogens	Vaccinia
Blocking of antigen processing and presentation	Inhibition of MHC class I expression	Impairs recognition of infected cells by cytotoxic T cells	Herpes simplex Cytomegalovirus
	Inhibition of peptide transport by TAP	Blocks peptide association with MHC class I	Herpes simplex
Immunosuppression of host	Virally encoded cytokine homolog of IL-10	Inhibits T_H1 lymphocytes Reduces interferon-γ production	Epstein–Barr virus

The peptide-loading complex in the endoplasmic reticulum is targeted by viral immunoevasins



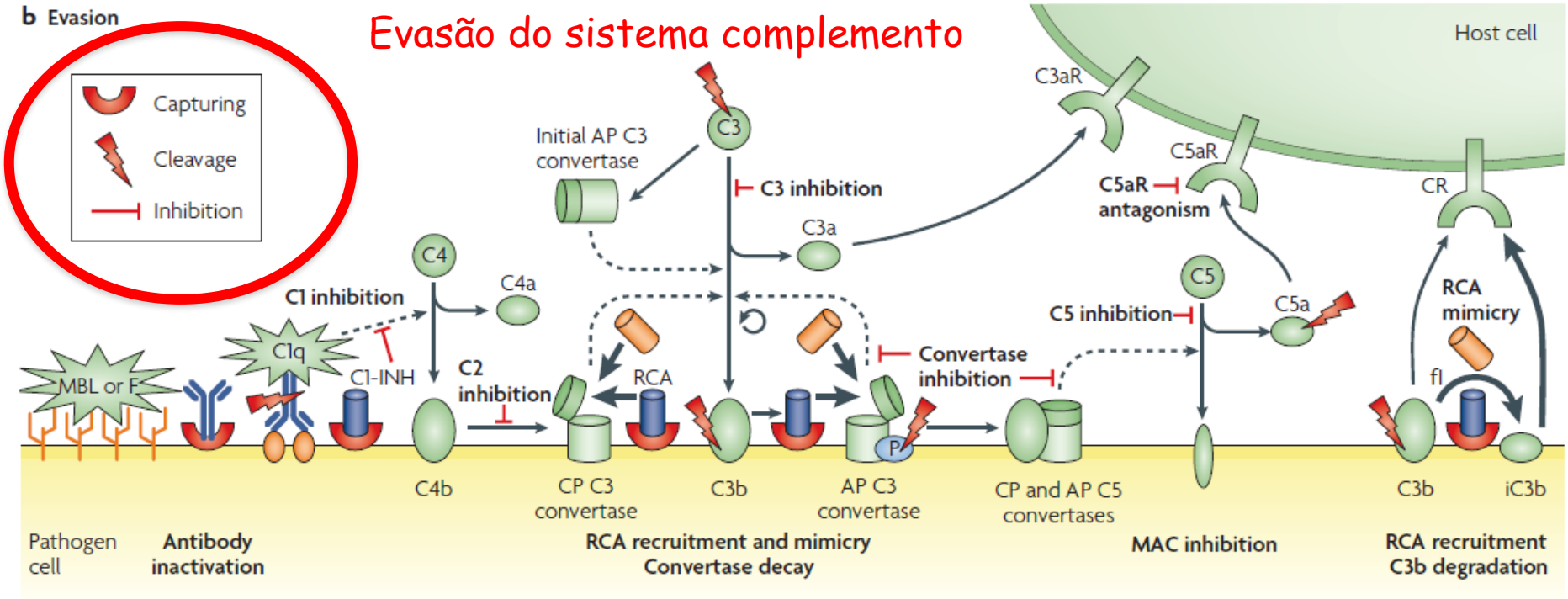
Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

Inibição da ativação do sistema complemento



Praticamente todos os patógenos, até ectoparasitas!

Evasão do sistema complemento

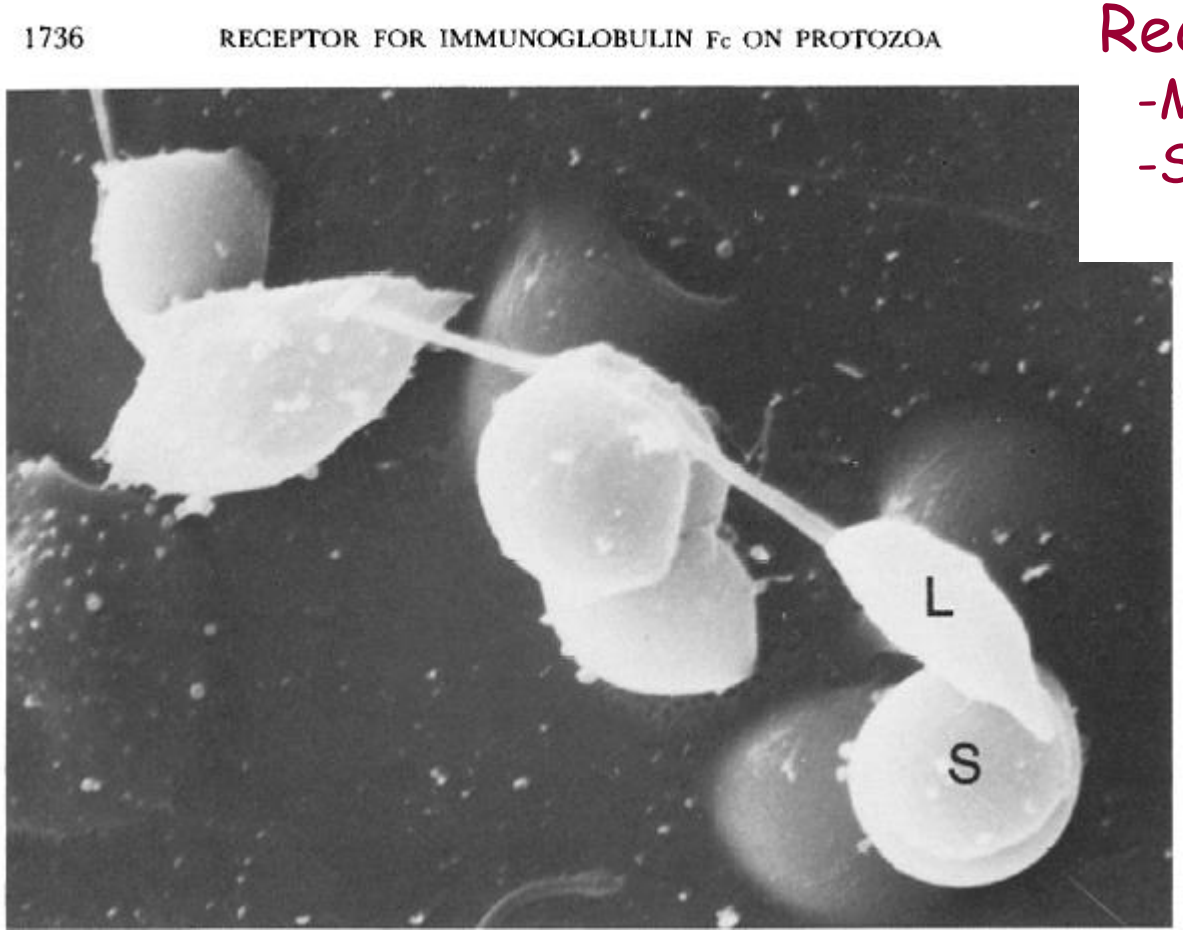


- Trapping endogenous C1 inhibitor (C1-INH) to the surface
- Inactivating antibodies through the capture of their Fc regions
- Certain viruses produce structural mimics of C1 inhibitor
- Some microbial proteins have similar activities to CD59 in preventing MAC formation
  - CD59 binds to C5b678 and prevents C9 from binding and polymerizing
- Viruses such as HIV, human cytomegalovirus and vaccinia incorporate host cell CD59 into their own viral envelope to prevent lysis by complement
- Direct inhibition of C3, the C3 and C5 convertases, C5 or the C5a receptor (C5aR) is a prominent strategy of *Staphylococcus aureus*.
- Microbial proteases can degrade many of the crucial components of the complement system. These proteases act directly or by capturing and activating a human protease.
- F, ficolin; fB, factor B; fD, factor D; fI, factor I, MASP, MBL-associated serine protease; MBL, mannose-binding lectin; RCA, regulators of complement activation.

Table 1 | **Examples of complement evasion proteins and their targets on host cells***

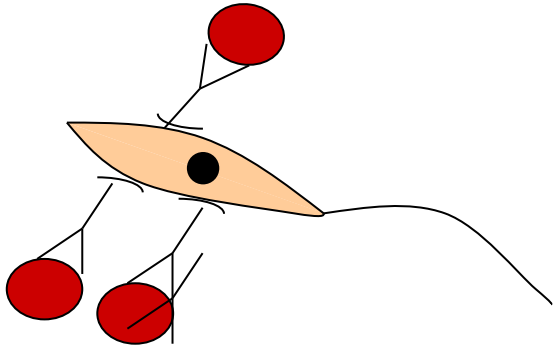
Complement evasion protein	Host target
Antibody depletion	
Staphylococcal protein A (SpA)	IgG
Complement inhibition	
Extracellular fibrinogen-binding protein (Efb)	C3 and C3b-containing convertases
Staphylococcal superantigen-like protein-7 (SSL-7)	C5
Staphylococcus complement inhibitor (SCIN)	C3 convertases
Complement C2 receptor trispanning protein (CRIT)	C2
Chemotaxis inhibitory protein of *Staphylococcus aureus* (CHIPS)	C5a receptor (C5aR)
Regulators of complement activation (RCA) recruitment	
Complement-regulator-acquiring protein (CRASP)	Factor H, factor H-like protein-1 (FHL-1) and C4-binding protein (C4BP)
M protein family	Factor H, FHL-1 and C4BP
RCA mimicry	
Variola virus complement-control protein (VCP)	C3b and C3 convertases
Smallpox protein of complement enzymes (SPICE)	C3b and C3 convertases
Proteolytic degradation	
Staphylokinase	C3b and IgG (by activation of plasmin)
Pseudomonas elastase (PaE)	C3
56 kDa protease	C5a

Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro



Receptores de Fc de Igs

- -Mimetismo molecular
- -Subversão de anticorpos

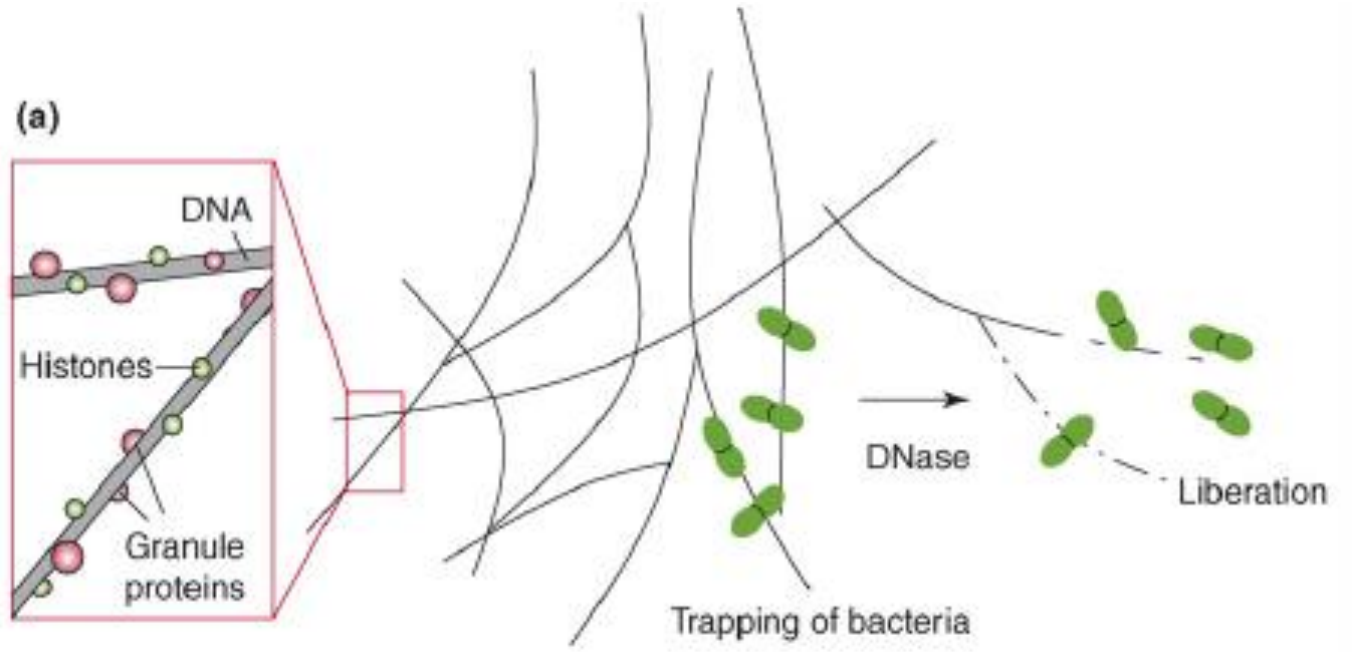


Todos têm FcRs, de vírus a vermes

Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro

Destruição de NETs por DNAses microbianos

Um fator de virulência do *Staphylococcus aureus*



Mecanismos de Escape dos Patógenos à Imunidade Humoral do Hospedeiro.

Viral strategy	Specific mechanism	Result	Virus examples
Inhibition of humoral immunity	Virally encoded Fc receptor	Blocks effector functions of antibodies bound to infected cells	Herpes simplex Cytomegalovirus
	Virally encoded complement receptor	Blocks complement-mediated effector pathways	Herpes simplex
	Virally encoded complement control protein	Inhibits complement activation by infected cell	Vaccinia

Pontos importantes da aula

- Imunidade à infecção depende de uma combinação de mecanismos inatos (i.e. fagocitose, complemento) e da resposta imune adquirida (anticorpos e células T)

- O sistema imune regula qual das respostas específicas irá predominar (humoral vs. celular) baseado no compartimento celular infectado (intra ou extracelular) e nos sinais derivados das citocinas presentes no contato inicial com o antígeno (resposta Th17 vs. Th1 vs. Th2)

Pontos importantes da aula (cont.)

- Microrganismos causadores de doenças têm mecanismos de virulência que auxiliam na sua evasão da resposta imune inata e/ou específica

- Recuperação de infecções naturais promove uma imunidade específica prolongada a re-infecções, caracterizada pela memória imunológica