DES de Biologie Médicale

Enseignement d'Immunologie

CM6.1

Mise en jeu du système immunitaire au cours des infections

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Mise en jeu du système immunitaire au cours des infections

1. Infection et réponse immune - rappels
2. Immunité antivirale
3. Immunité antibactérienne
4. Immunité antiparasitaire
5. Immunité antifongique
6. Pathologies infectieuses
7. Conclusion

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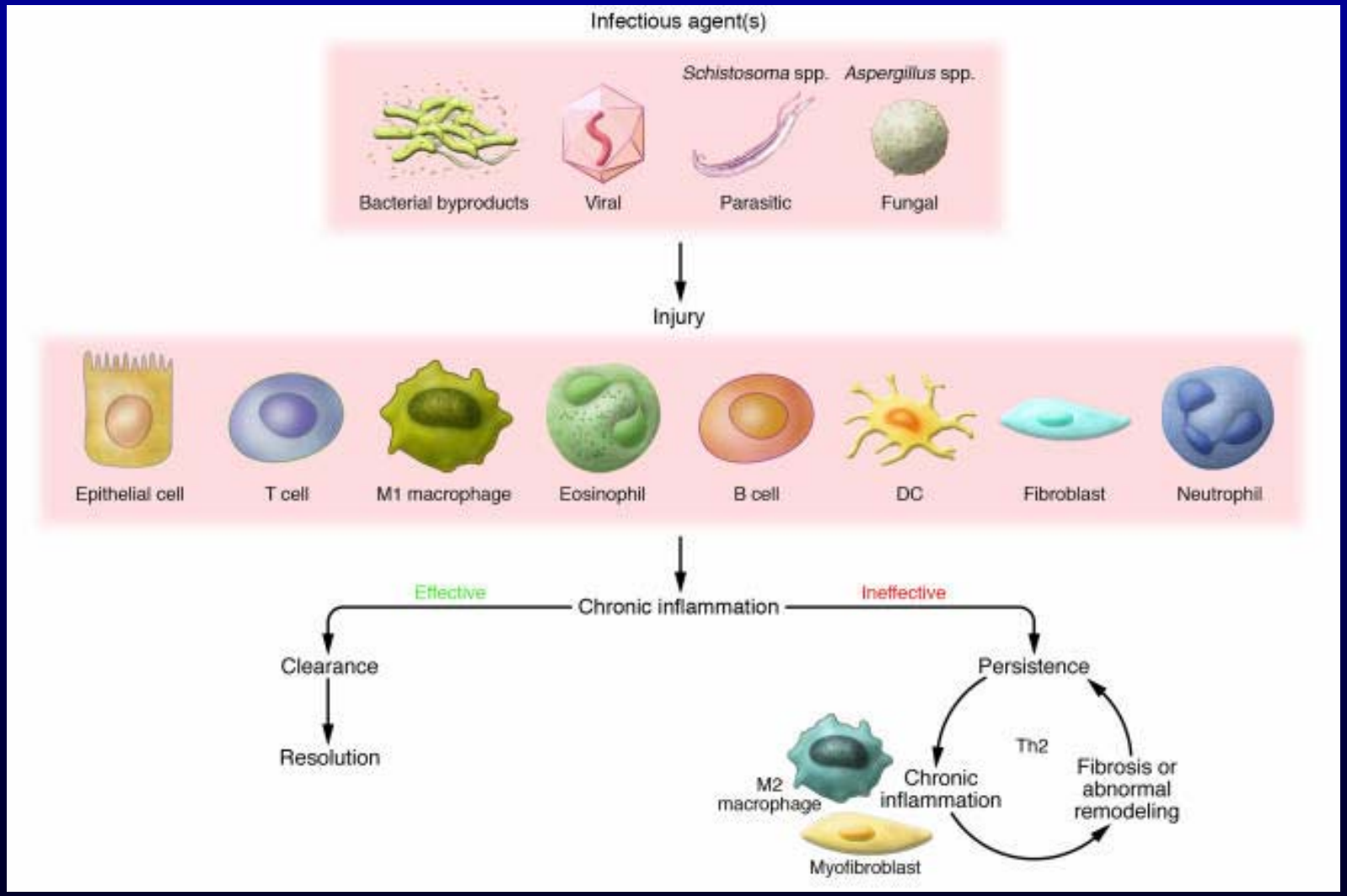
Agents infectieux vs. Acteurs immunitaires



Quatre classes d'agents infectieux

The immune system protects against four classes of pathogen		
Type of pathogen	**Examples**	**Diseases**
Extracellular bacteria, parasites, fungi	*Streptococcus pneumoniae* *Clostridium tetani* *Trypanosoma brucei* *Pneumocystis carinii*	Pneumonia Tetanus Sleeping sickness *Pneumocystis* pneumonia
Intracellular bacteria, parasites	*Mycobacterium leprae* *Leishmania donovani* *Plasmodium falciparum*	Leprosy Leishmaniasis Malaria
Viruses (intracellular)	Variola Influenza Varicella	Smallpox Flu Chickenpox
Parasitic worms (extracellular)	*Ascaris* *Schistosoma*	Ascariasis Schistosomiasis

Figure 1-23 Immunobiology, 6/e. (© Garland Science 2005)

Étapes clés de la réponse immune

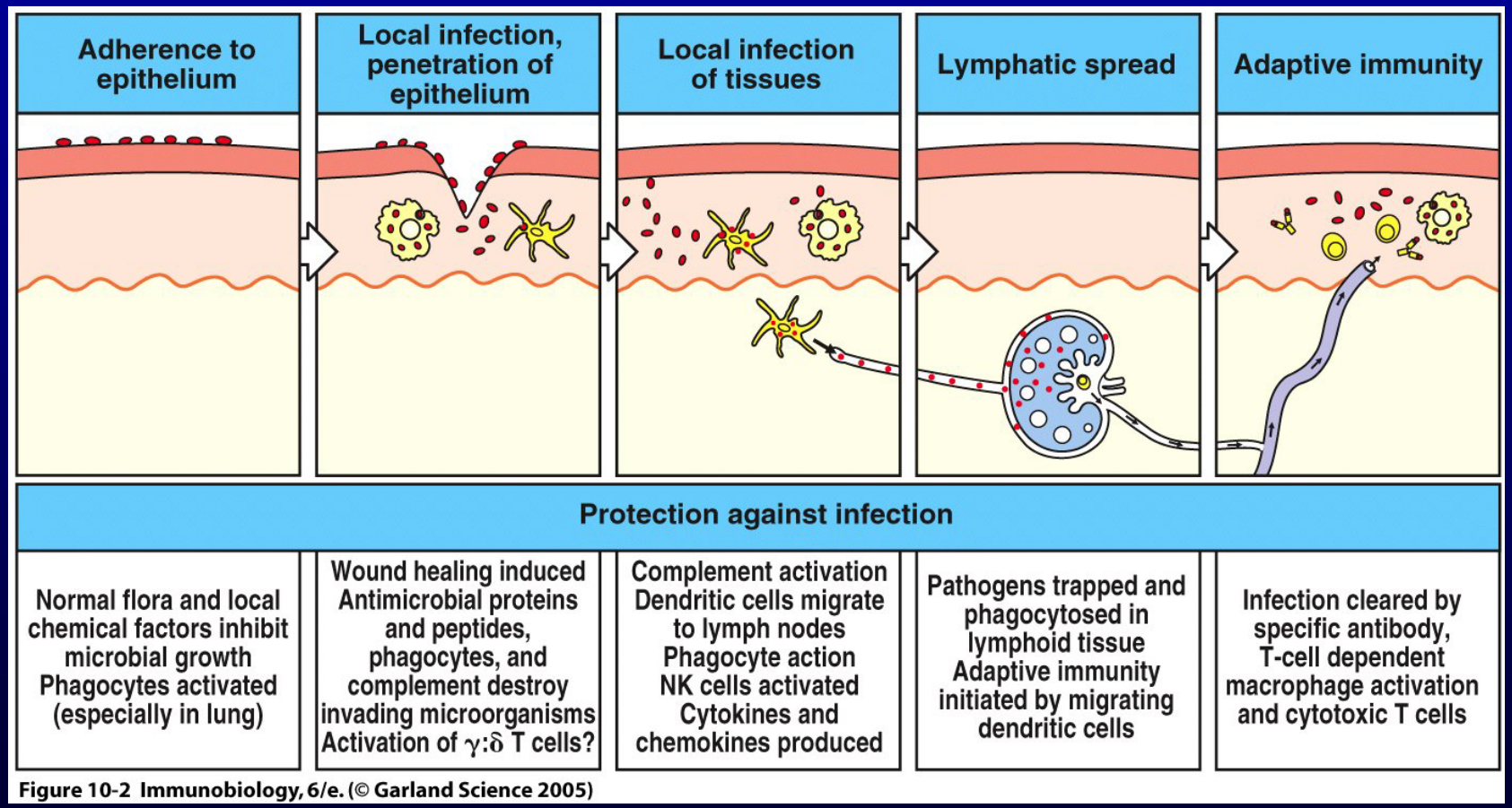


Figure 10-2 Immunobiology, 6/e. (© Garland Science 2005)

Premières barrières anti-infectieuses

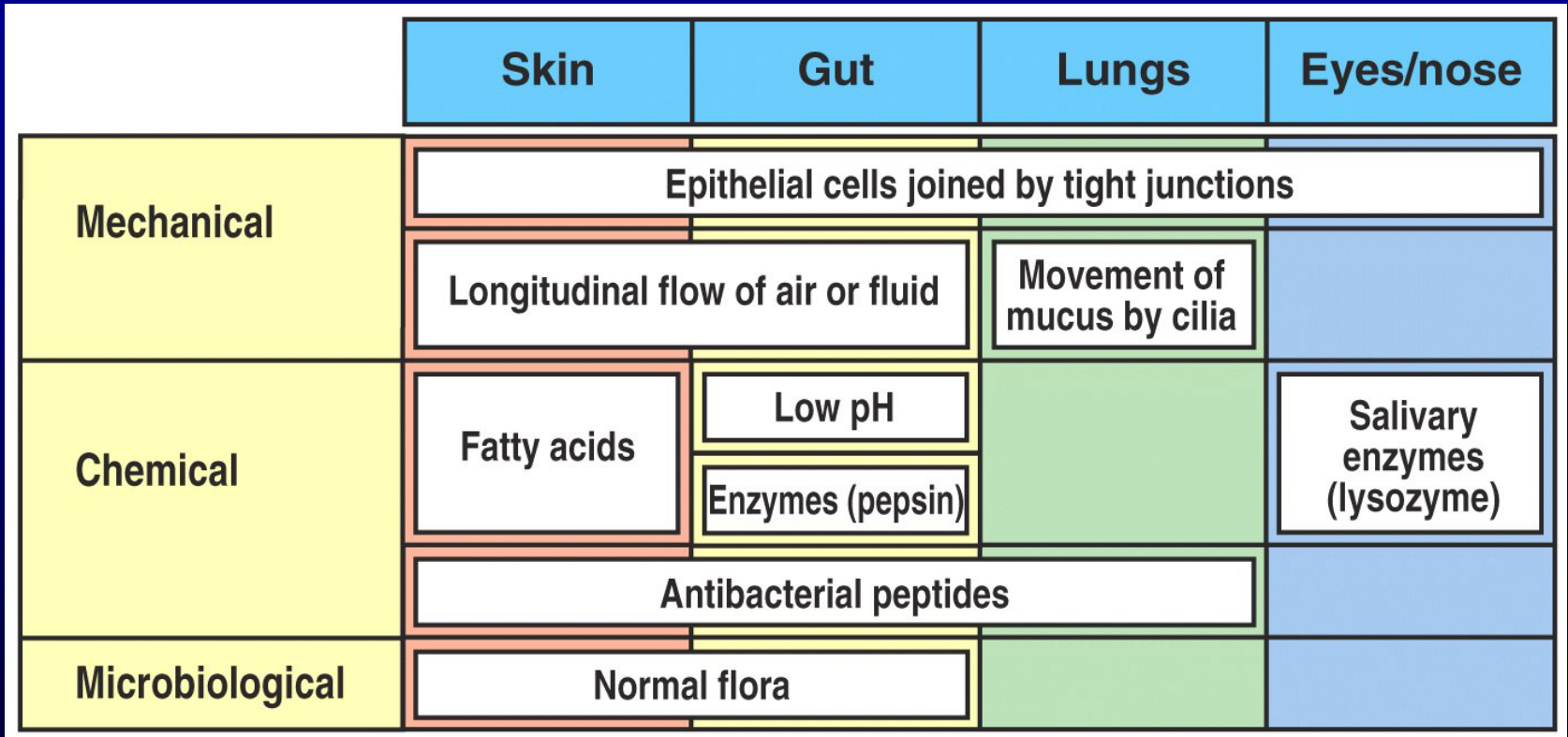


Figure 2-4 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Système du complément

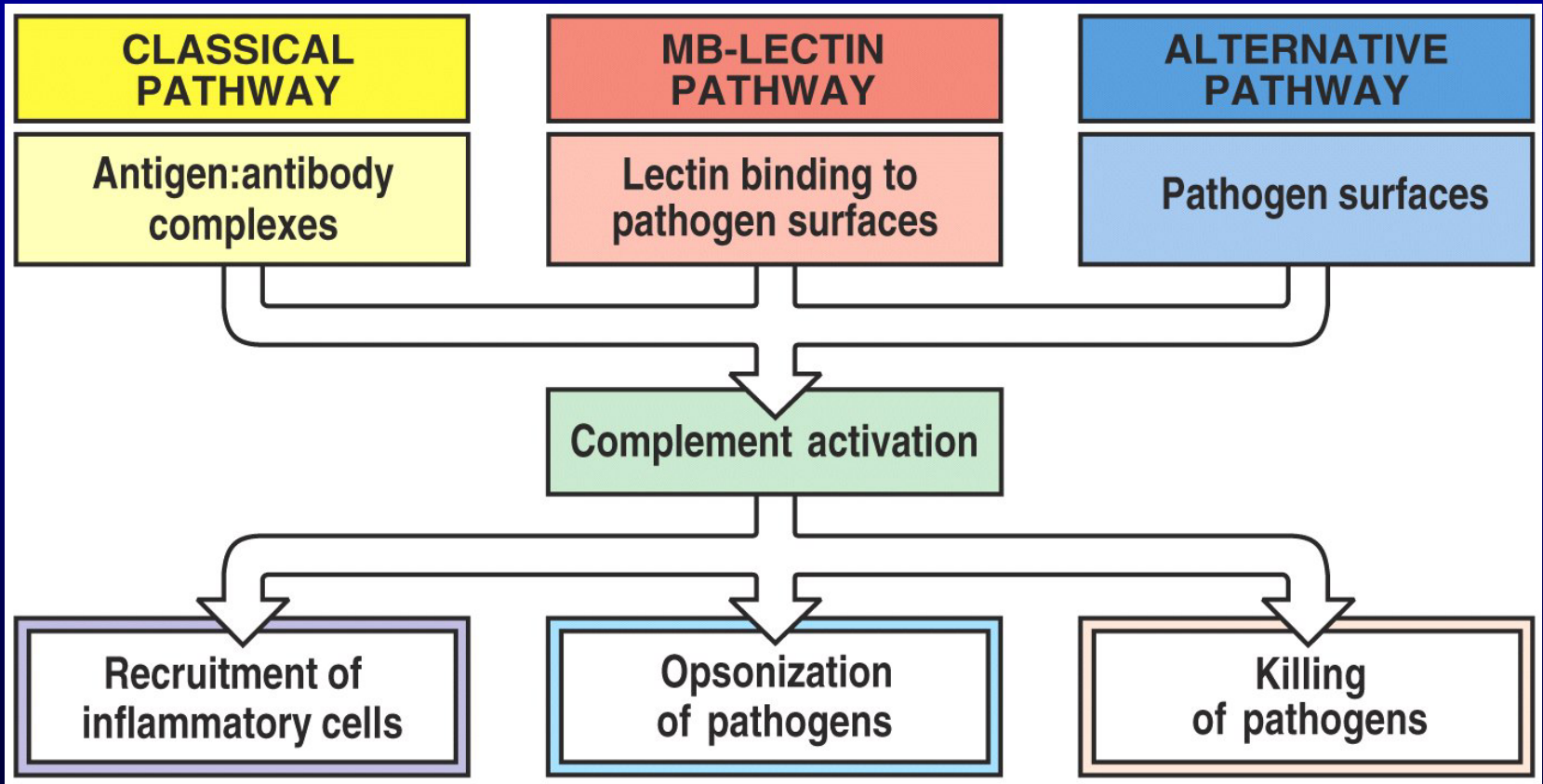


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

Cinétique de la réponse immune

Élimination des germes entrant dans l'organisme:

99% **99,9%** **99,99%**

Immunité innée

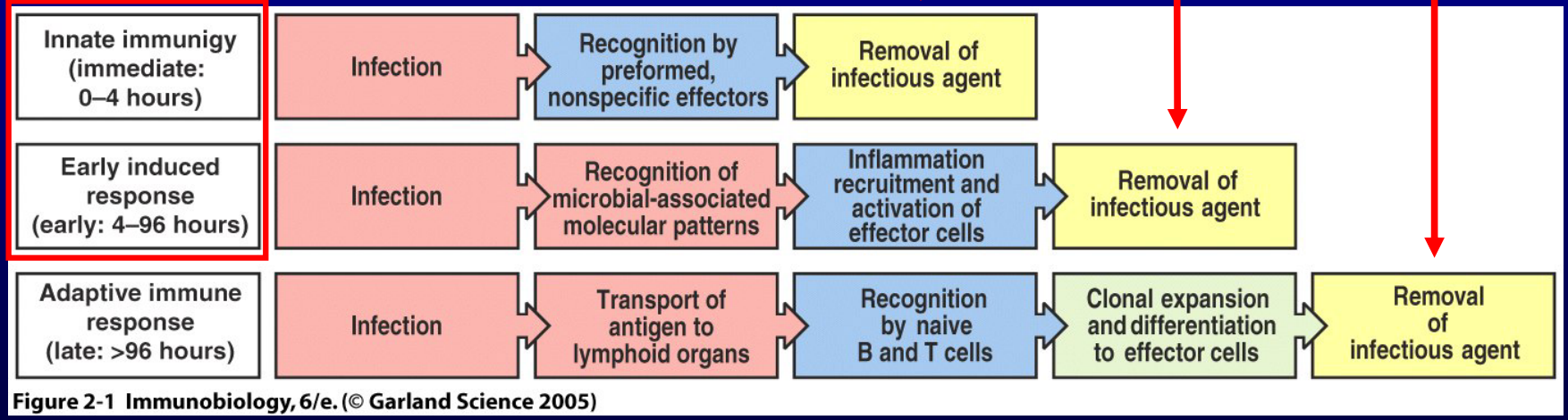


Figure 2-1 Immunobiology, 6/e. (© Garland Science 2005)

→ L'immunité innée contrôle la quasi totalité des infections

Immunité innée vs. immunité adaptative

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Expressed by all cells of a particular type (eg, macrophages)	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogen	Yes	No
Interacts with a range of molecular structures of a given type	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal distribution	No	Yes
Able to discriminate between even closely related molecular structures	No	Yes

Figure 2-10 Immunobiology, 6/e. (© Garland Science 2005)

Différentes voies d'infection

Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
Mucosal surfaces			
Airway	Inhaled droplet	Influenza virus	Influenza
	Spores	*Neisseria meningitidis*	Meningococcal meningitis
		Bacillus anthracis	Inhalation anthrax
Gastrointestinal tract	Contaminated water or food	*Salmonella typhi*	Typhoid fever
		Rotavirus	Diarrhea
Reproductive tract	Physical contact	*Treponema pallidum*	Syphilis
		HIV	AIDS

Figure 2-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Routes of infection for pathogens			
Route of entry	**Mode of transmission**	**Pathogen**	**Disease**
External epithelia			
External surface	Physical contact	*Trichophyton*	Athlete's foot
Wounds and abrasions	Minor skin abrasions	*Bacillus anthracis*	Cutaneous anthrax
	Puncture wounds	*Clostridium tetani*	Tetanus
	Handling infected animals	*Francisella tularensis*	Tularemia
Insect bites	Mosquito bites (*Aedes aegypti*)	Flavivirus	Yellow fever
	Deer tick bites	*Borrelia burgdorferi*	Lyme disease
	Mosquito bites (*Anopheles*)	*Plasmodium* spp.	Malaria

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

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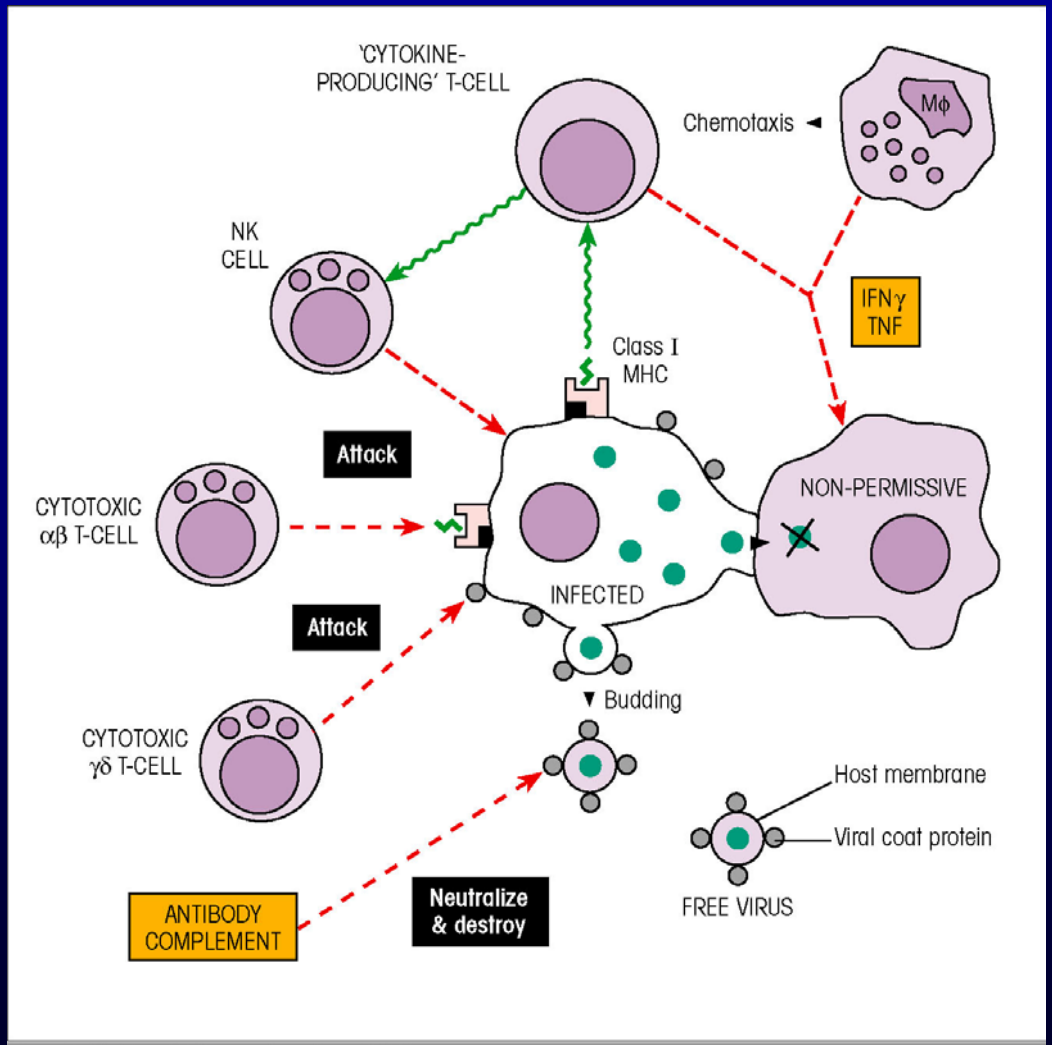
Mécanismes de l'immunité antivirale

Type de réponse	*Molécule ou cellules effectrices*	*Activité*
Humorale	Anticorps (IgA)	Blocage liaison virus à la cellules hôte
	Anticorps IgG, IgM, IgA	Blocage fusion enveloppe virale et membrane plasmique cellules hôte
	Anticorps IgG et IgM	Augmentation de la phagocytose des particules virales (opsonisation)
	Anticorps IgM	Agglutination des particules virales
	Complément activé par un anticorps IgM ou IgG	Opsonisation par le C3b et lyse des particules virales (MAC)
Cellulaire	IFN-γ sécrété par les cellules T_H ou les T_C	Activité antivirale directe
	Lymphocytes T cytotoxiques	Lyse des cellules infectées
	Cellules NK et macrophages	Lyse des cellules infectées par cytotoxicité cellulaire dépendante des anticorps (ADCC)

Mécanismes de l'immunité antivirale



From: *Roitt's Essential Immunology* Eleventh Edition

Mécanismes d'échappement viral

- Variation antigénique
  - → Dérive antigénique
  - → Substitution antigénique
- Interférence avec le système du complément
  - → Récepteurs Fc viraux
  - → Clairance des C3 convertases (alterne & classique)
  - → Récepteurs du complément (entrée du virus)
- Interférence de l'immunité cellulaire
  - → Inhibition de la présentation antigénique
  - → Modulation de l'expression du CMH
  - → Inhibiteur de cytokines, récepteurs…

Variation antigénique

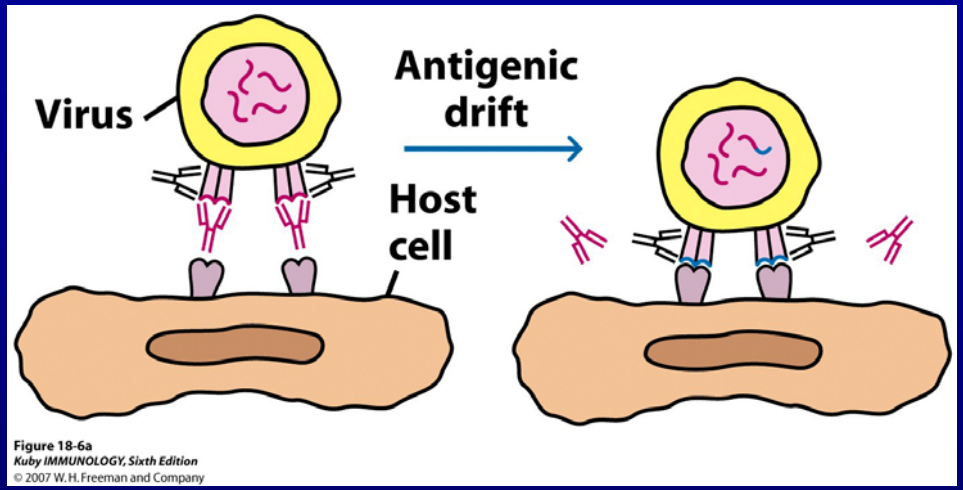


Figure 18-6a
Kuby IMMUNOLOGY, Sixth Edition

Dérive antigénique

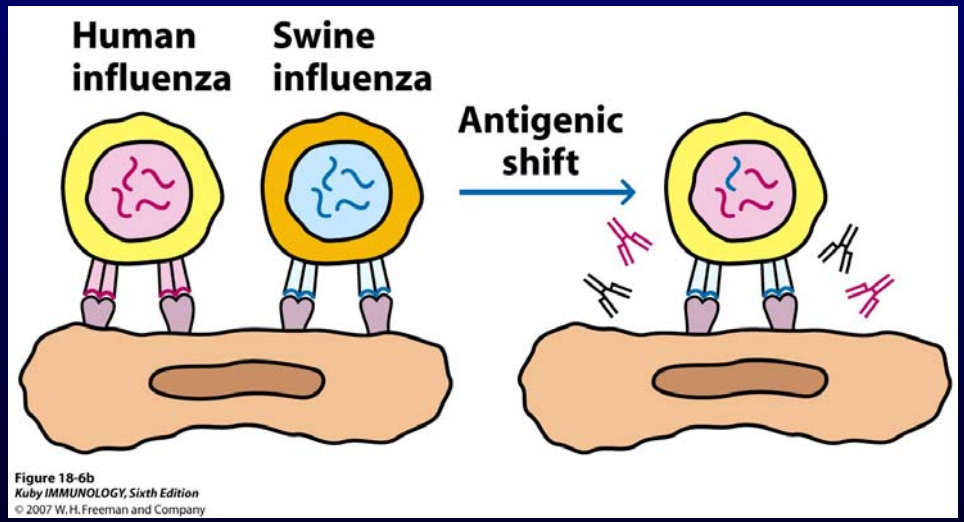


Figure 18-6b
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Substitution antigénique

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Mécanismes de l'immunité antibactérienne

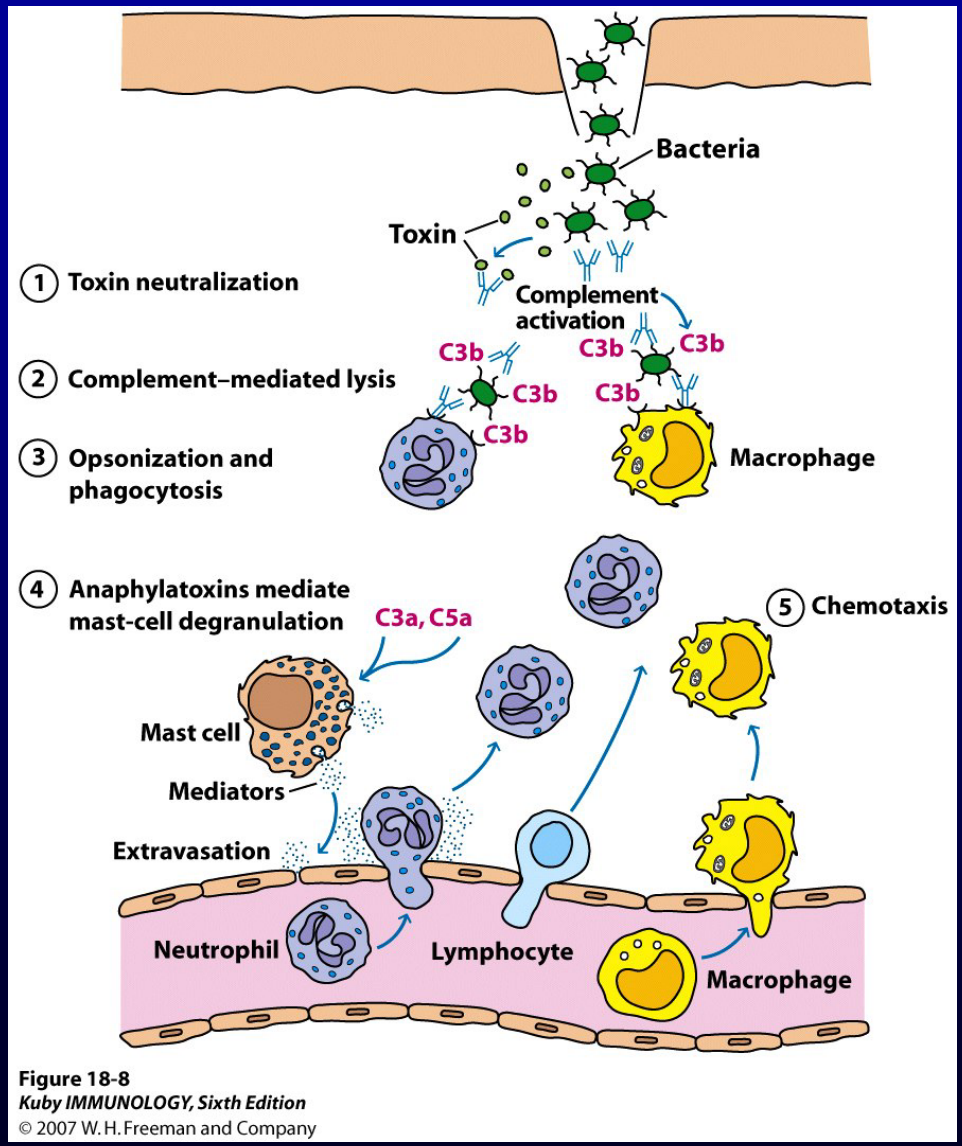

Figure 18-8
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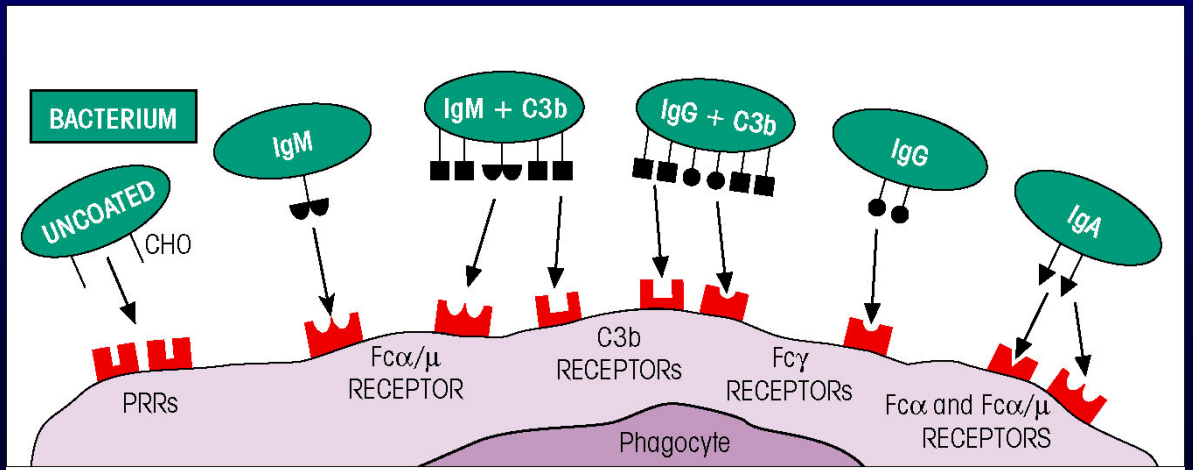
Mécanismes de l'immunité antibactérienne

Processus d'infection	***Défense de l'hôte***
Attachement aux cellules	Blocage de l'attachement par les IgA sécrétoires
Prolifération	Phagocytose (opsonisation médiée par les Ac et le C3b)
	Lyse due au complément et réponse inflammatoire localisée
Invasion des tissus de l'hôte	Agglutination due à des anticorps
Lésion des cellules de l'hôte induite par une toxine	Neutralisation de la toxine par des anticorps



From: *Roitt's Essential Immunology* Eleventh Edition

Mécanismes de l'immunité antibactérienne

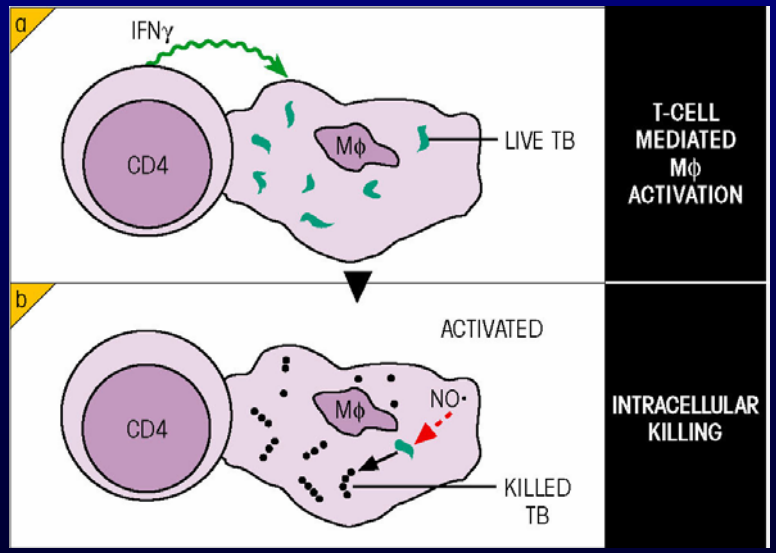
Bactéries intracellulaires:

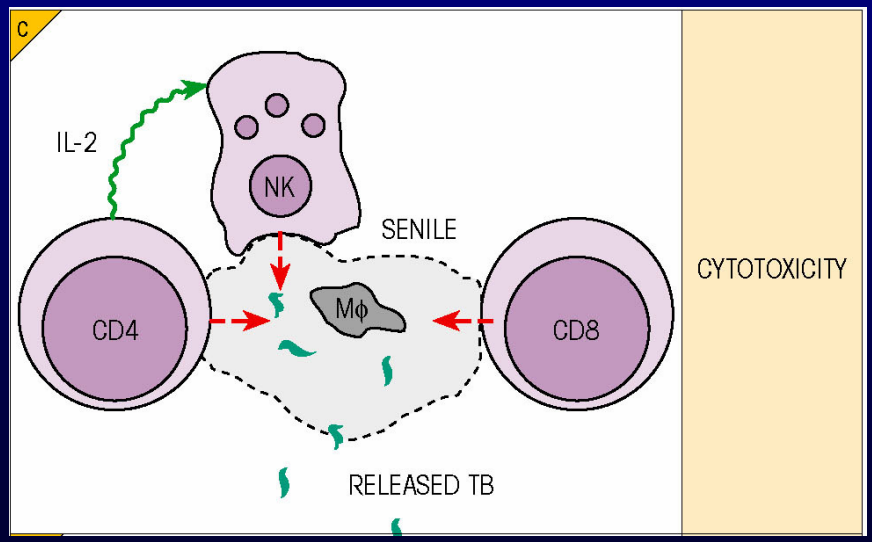
- Développement dans les macrophages
- Échappement aux mécanismes de défense
  - → Entrée facilitée par l'opsonisation
  - → Inhibition de la fusion lysosomes/vacuole phagocytique
  - → Inhibition de la présentation antigénique

Mécanismes de l'immunité antibactérienne

Bactéries intracellulaires:

- Importance de l'immunité cellulaire T
  - → Activation du macrophage
  - → Cytotoxicité (CD4, CD8 & NK)





Mécanismes d'échappement

TABLE 18-3 Host immune responses to bacterial infection and bacterial evasion mechanisms

Infection process	Host defense	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers (*Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae*) Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells Mechanisms for surviving within phagocytic cells Induction of apoptosis in macrophages (*Shigella flexneri*)
	Complement-mediated lysis and localized inflammatory response	Generalized resistance of gram-positive bacteria to complement-mediated lysis Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
Invasion of host tissues	Ab-mediated agglutination	Secretion of elastase that inactivates C3a and C5a (*Pseudomonas*)
Toxin-induced damage to host cells	Neutralization of toxin by antibody	Secretion of hyaluronidase, which enhances bacterial invasiveness

Table 18-3
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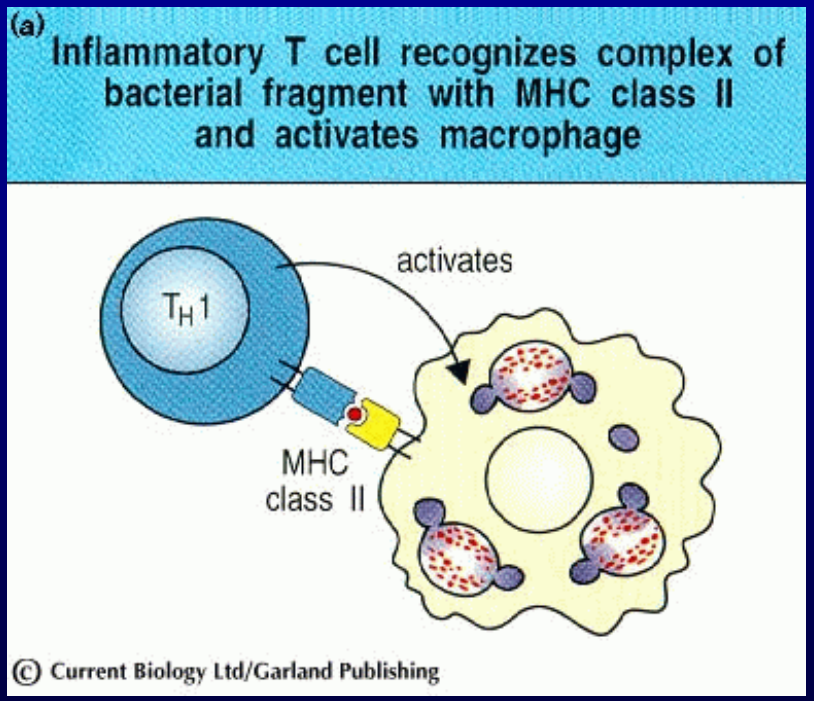
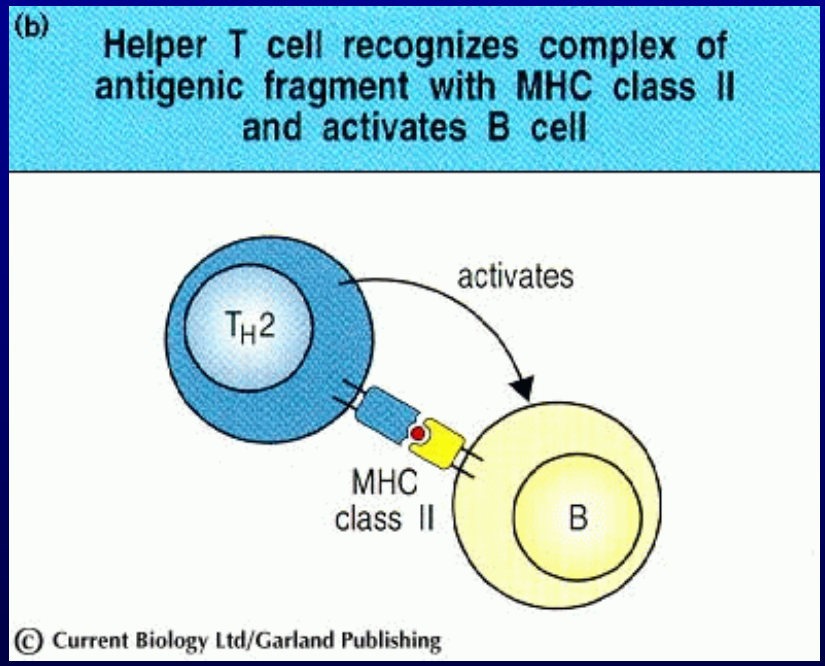
Le paradigme Th1/Th2

Th1: fonction inflammatoire



IFNγ, IL-2

Th2: fonction auxiliaire



IL-4, IL-5, IL-6, IL-10, IL-13

Rôle dans la pathogenèse

Infection *Leishmania* chez la souris:

Souris BALB/c sensibles à l'infection

→ Les macrophages ne produisent pas d'IL-12
→ Défaut de production de cellules Th1 pro-inflammatoires
→ Les cellules auxiliaires Th2 incapables d'activer les macrophages pour combattre l'infection

Souris C57BL/6 résistantes à l'infection

→ Les macrophages produisent de l'IL-12 après infection
→ Différenciation de cellules Th1 pro-inflammatoires
→ Activation des macrophages infectés pour éliminer le parasite *Leishmania*

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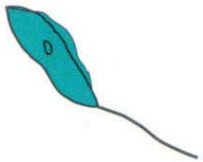
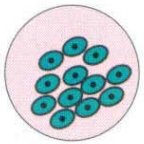
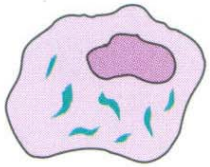
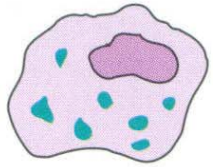
Mécanismes de l'immunité antiparasitaire

PARASITE	TRYPANOSOMA BRUCEI	PLASMODIUM	TRYPANOSOMA CRUZI	LEISHMANIA
HABITAT	Free in blood 	Inside red cell 	Inside macrophage 	Inside macrophage 
ANTIBODY				
Importance	++++	+++	++	+
Mechanism	Lysis with complement Opsonizes for phagocytosis	Blocks invasion Opsonizes for phagocytosis	Limits spread in acute infection	Limits spread
Means of evasion	Antigenic variation	Intracellular habitat Antigenic variation	Intracellular habitat	Intracellular habitat
CELL-MEDIATED				
Importance	–	+	+++ (Chronic phase)	++++
Mechanism	–	Cytokine-mediated activation of macrophages and NK cells	Macrophage activation by cytokines and killing by TNF, metabolites of O_2 and NO· Role for cytotoxic T-cells	

Roitt's Essential Immunology @ Blackwell Science 2001

Mécanismes de l'immunité antiparasitaire

Mécanismes de défense:

- Anticorps: IgE/IgG → éosinophiles
- Lymphocytes CD4 Th1: parasites intracellulaires
- Lymphocytes CD4 Th2: parasites extracellulaires
- Lymphocytes cytotoxiques CD8

Stratégies d'échappement:

- Mimétisme moléculaire; expression de protéine de l'hôte
- Antigène dominant et variation antigénique
- Suppression ou brouillage de la réponse de l'hôte
- Dormance

Variation antigénique

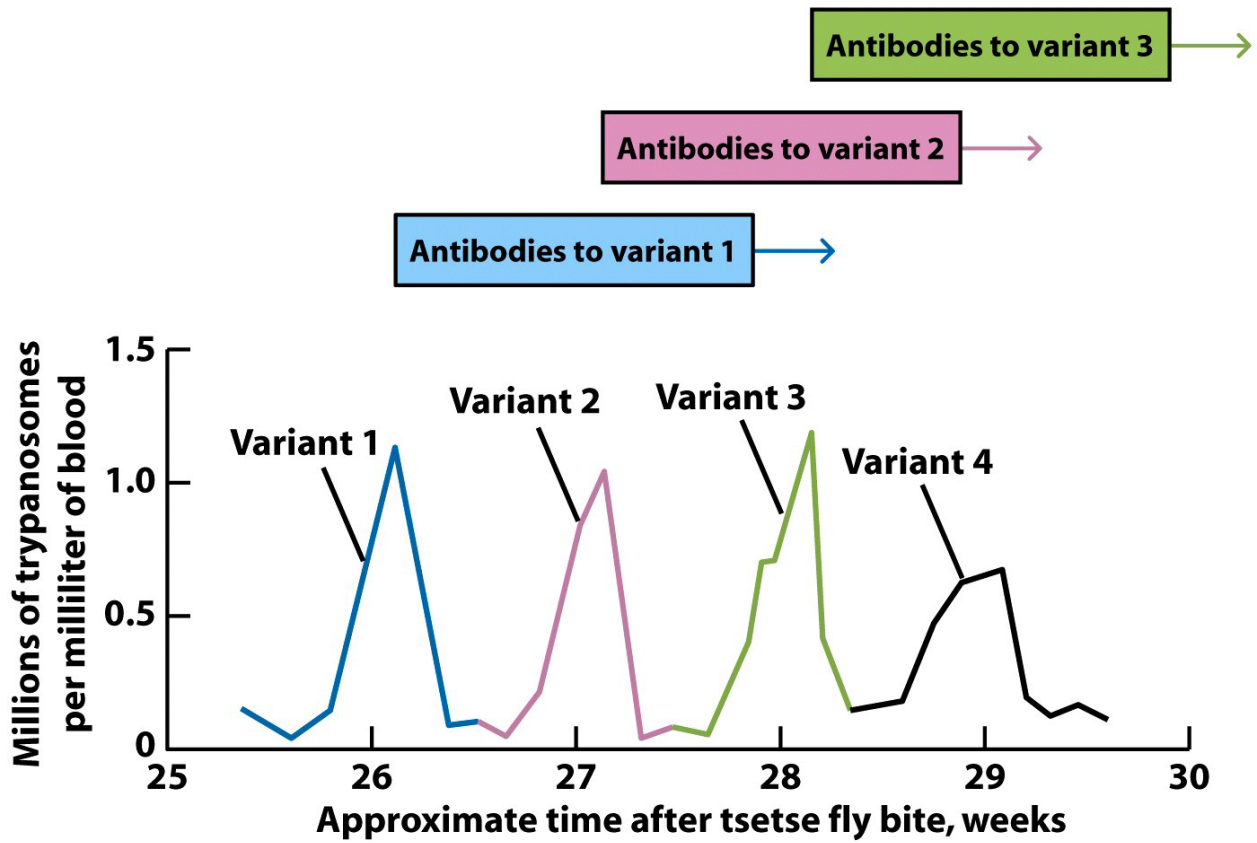


Figure 18-12a
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Mécanismes de l'immunité antifongique

TABLE 18-4 Classification of fungal diseases

Site of infection	Superficial	Epidermis, no inflammation
	Cutaneous	Skin, hair, nails
	Subcutaneous	Wounds, usually inflammatory
	Deep or systemic	Lungs, abdominal viscera, bones, CNS
Route of acquistion neous	Exogenous	Environmental, airborne, cutaneous or percuta-
	Endogenous	Latent reactivation, commensal organism
Virulence	Primary	Inherently virulent, infects healthy host
	Opportunistic	Low virulence, infects immunocompromised host

Table 18-4
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Mécanismes de défense:

- Immunité innée → barrières physiques & chimiques
  → phagocytose (neutrophiles)
  → complément (voies alterne & mannose)
  → protéines du surfactant (poumons)
  → récepteurs (CR1, CR3, CR4, TLR2, TLR4)
- Immunité acquise → anticorps (vaccin polysaccharidique)
  → lymphocytes T (SIDA)

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Pathologies infectieuses

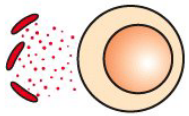
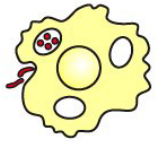
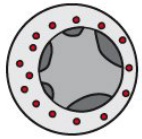
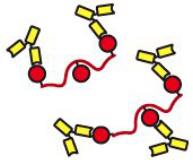
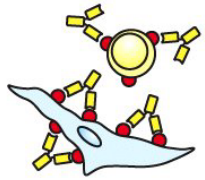
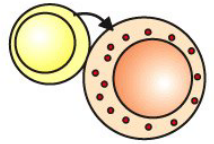
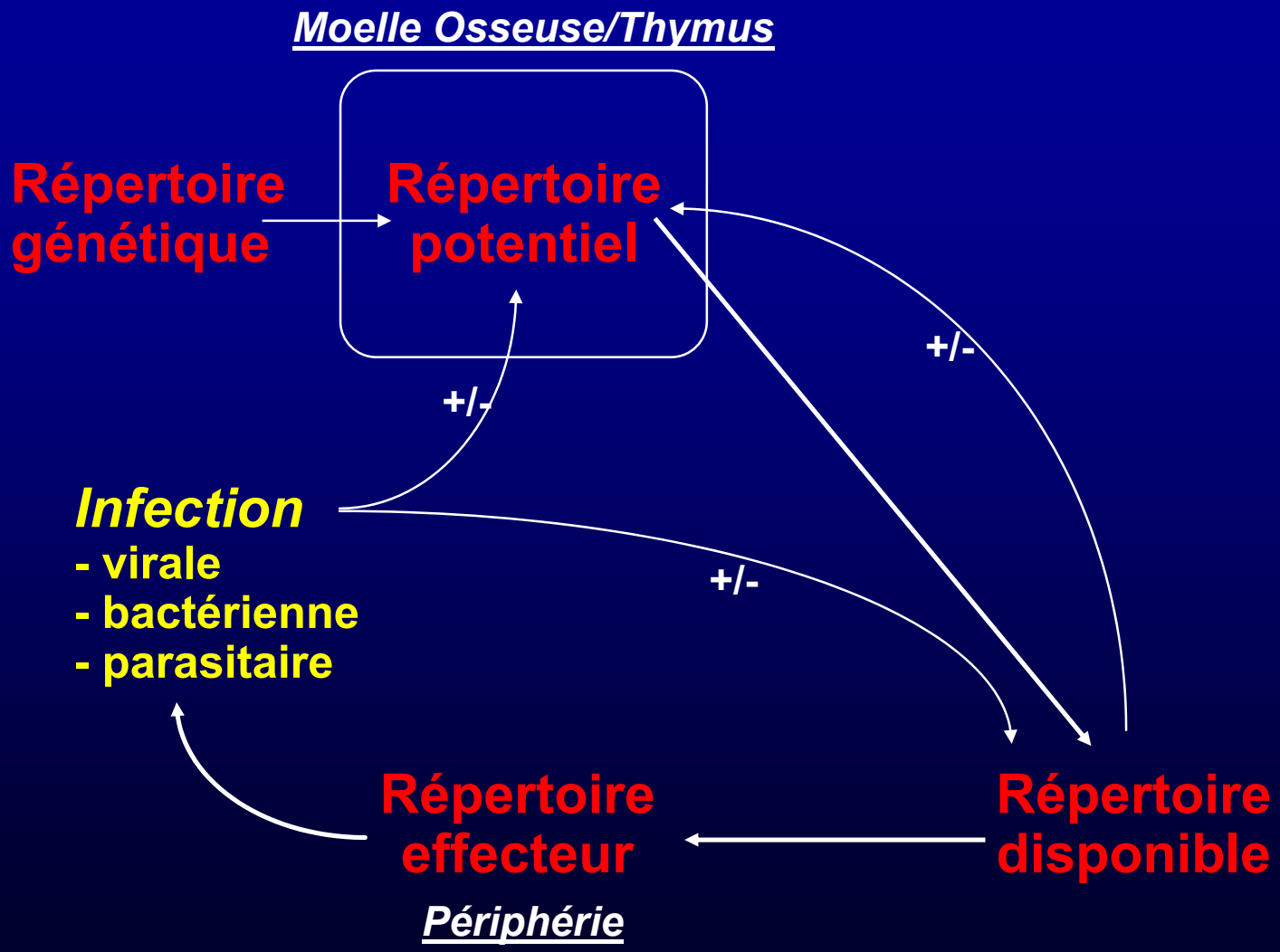
	Direct mechanisms of tissue damage by pathogens			Indirect mechanisms of tissue damage by pathogens		
	Exotoxin production	Endotoxin	Direct cytopathic effect	Immune complexes	Anti-host antibody	Cell-mediated immunity
Pathogenic mechanism						
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridiumtetani* *Vibrio cholerae*	*Escherichia coli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)	Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*	*Mycobacterium tuberculosis* *Mycobacterium leprae* Lymphocytic choriomeningitis virus *Borrelia burgdorferi* *Schistosoma mansoni* Herpes simplex virus
Disease	Tonsilitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid Bacillary dysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles, subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma	Kidney disease Vascular deposits Glomerulonephritis Kidney damage in secondary syphilis Transient renal deposits	Rheumatic fever Hemolytic anemia	Tuberculosis Tuberculoid leprosy Aseptic meningitis Lyme arthritis Schistosomiasis Herpes stromal keratitis

Figure 10-5 Immunobiology, 6/e. (© Garland Science 2005)

Répertoires immunitaires



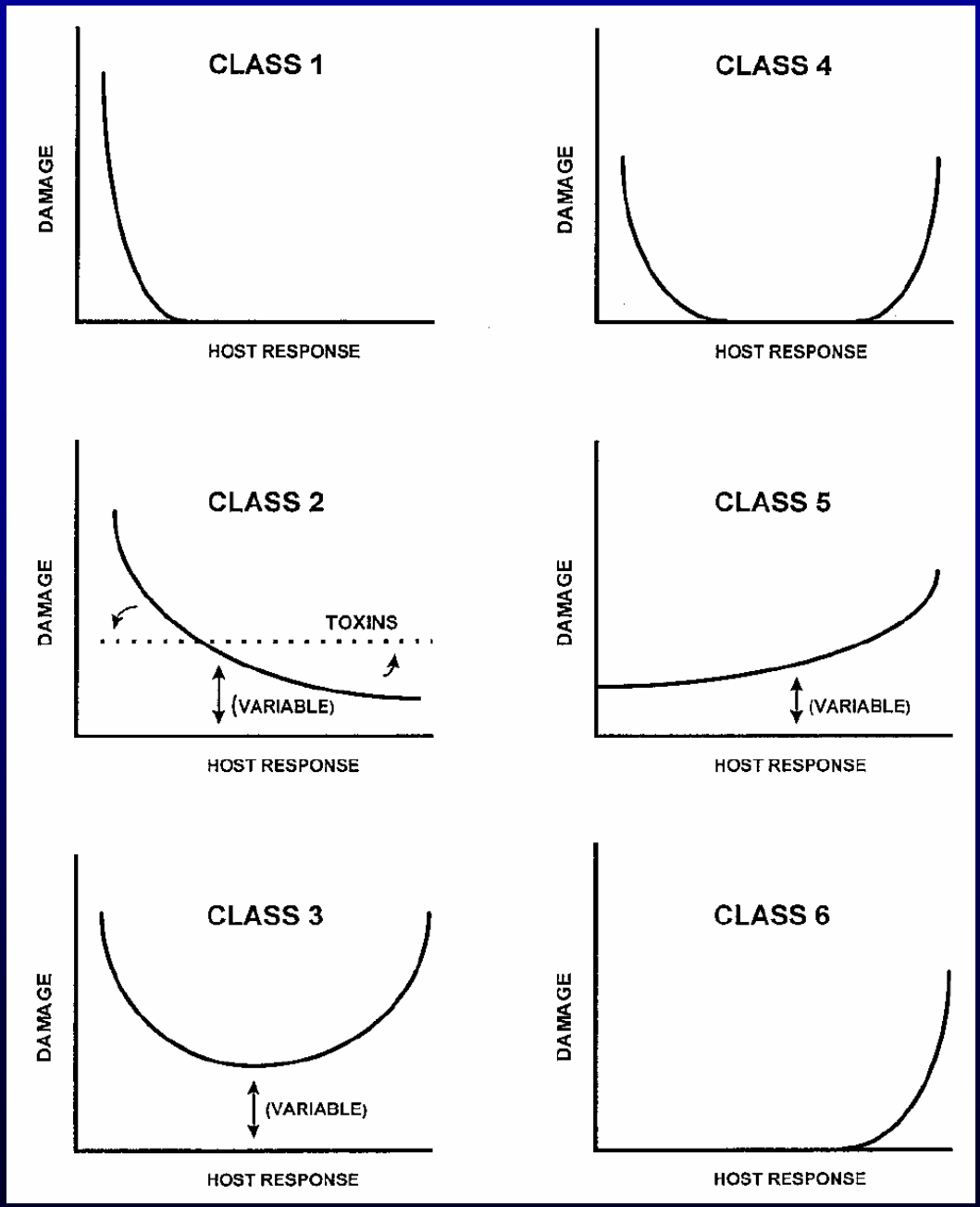
Réponse adéquate vs. inadéquate

Lors d'une infection par un micro-organisme, le système immunitaire peut rencontrer, en même temps, diverses molécules :

- *Antigènes*
- *Mitogènes*
- *Superantigènes* ou *activités superantigènes*

En réponse à ces molécules, il peut apparaître des *réponses adéquates* ou *réponses inadéquates*.

→ Les réponses inadéquates (« non-spécifiques ») peuvent brouiller ou masquer les réponses adéquates (« spécifiques »).



Casadevall & Pirofski (1999) Infection & Immunity 67: 3703-3713.

Exemples de réponses inadéquates

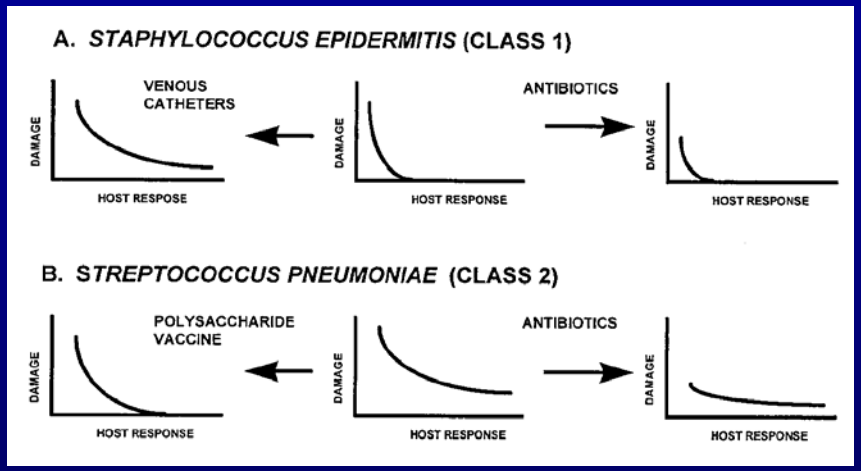
TABLE 2. Examples of weak and strong responses that can be associated with host damage[a]

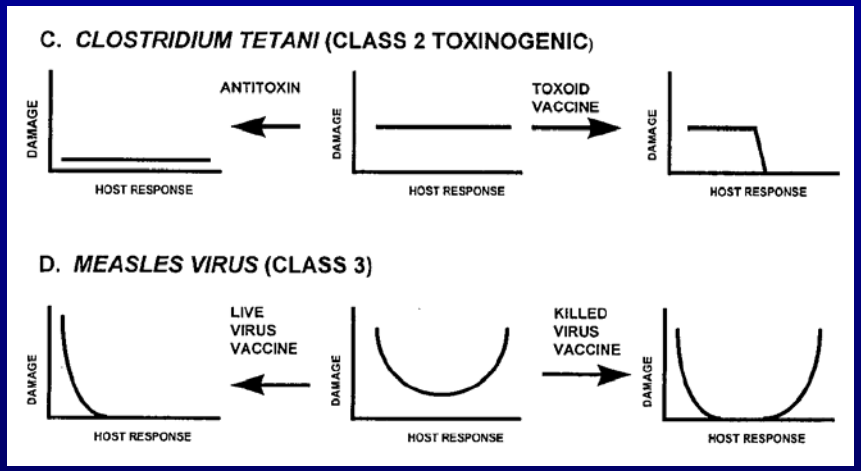
Evaluation	Description of response	
	Weak	Strong
Quantitative	Insufficient number of immune effector cells and/or molecules to prevent host damage	Overproduction of inflammatory mediators that result in tissue fibrosis or promote malignant transformation
Qualitative	(i) Antibodies of specificities or isotype that do not mediate protection	(i) Antigenic mimicry
	(ii) Th2 responses instead of Th1 responses for pathogens that require Th1 responses for containment[b]	(ii) Eosinophilic inflammation in response to certain antigens[c]
		(iii) Antibody-mediated enhancement of disease

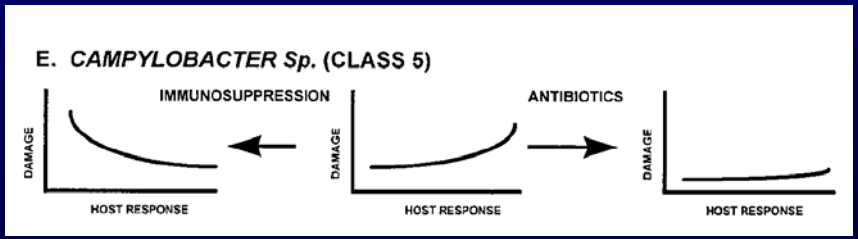
[a] The appropriateness of weak and strong responses must be considered in the context of specific pathogens.
[b] Eosinophilic inflammatory responses may be useful for helminths but not certain fungi.
[c] Th2 responses are associated with strong antibody responses whereas Th1 responses are proinflammatory (15, 25). Th2 responses to pathogens that require strong cellular inflammatory responses for containment and eradication may result in chronic and progressive infections. However, it is noteworthy that this view may be an oversimplification of a very complex process (1).

Casadevall & Pirofski (1999) Infection & Immunity 67: 3703-3713.

Influence des intervention médicales







Casadevall & Pirofski (1999) Infection & Immunity 67: 3703-3713.

Mise en jeu du système immunitaire au cours des infections

1. Infection et réponse immune - rappels
2. Immunité antivirale
3. Immunité antibactérienne
4. Immunité antiparasitaire
5. Immunité antifongique
6. Pathologies infectieuses
7. **Conclusion**

Immunité anti-infectieuse - Synthèse

	Phases of the immune response		
	Immediate (0–4 hours)	**Early (4–96 hours)**	**Late (96–100 hours)**
	Nonspecific Innate No memory No specific T cells	Nonspecific + specific Inducible No memory No specific T cells	Specific Inducible Memory Specific T cells
Barrier functions	Skin, epithelia	Local inflammation (C5a) Local TNF-α	IgA antibody in luminal spaces IgE antibody on mast cells Local inflammation
Response to extracellular pathogens	Phagocytes Alternative and MBL complement pathway	Mannan-binding lectin C-reactive protein Thymus independent B-cell antibody Complement	IgG antibody and Fc receptor-bearing cells IgG, IgM antibody + classical complement pathway
Response to intracellular bacteria	Macrophages	Activated NK-dependent macrophage activation IL-1, IL-6, TNF-α, IL-12	T-cell activation of macrophages by IFN-γ
Response to virus-infected cells	Natural killer (NK) cells	Interferon-α and -β IL-12-activated NK cells	Cytotoxic T cells IFN-γ

Figure 10-38 Immunobiology, 6/e. (© Garland Science 2005)

Immunité anti-infectieuse - Synthèse

	Cell-mediated immunity		Humoral immunity
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii* *Trichinella spiralis*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Effector T cell	Cytotoxic CD8 T cell	T_H1 cell	T_H1 and T_H2 cells
Antigen recognition	Peptide:MHC class I complex on infected cell	Peptide:MHC class II complex on infected macrophage	Peptide:MHC class II complex on antigen-specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

Figure 8-1 Immunobiology, 6/e. (© Garland Science 2005)