Infection and Immunity

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- **The ability for immune surveillance and protection against viral, bacterial, fungal and parasitic pathogens is a basic property of the immune system.**
- **In a healthy individual, the immune system recognizes the different invading pathogens depending upon the composition of human skin, mucous, antibacterial substances, phagocytes, etc., which acts as an innate**

- **defense system able to sense pathogenic invaders and to mediate surveillance and elimination of invading pathogens. This effectiveness is markedly enhanced by the subsequent adaptive immunity.**

IMMUNITY IN VIRAL INFECTIONS

- The immune system would recognize the invading viral pathogens and eliminate them during virus-host interaction and keep the characteristic feature of homeostasis. In response to virus entry there may not be, always, an overt reaction leading to clinical manifestation. There may be simply, subclinical infection, which would protect the individual from later viral exposure. (How to understand the no sign 2019-nCoV infection?)

- A number of specific immune effector mechanisms, for example, circulating antibodies can access most tissues to mediate surveillance and elimination of invading viruses, together with non-specific defense mechanism play roles in eliminating an infective viruses (Table 16.1). However, through evolution, the viruses have developed a number of strategies to avoid such an outcome and successfully establish chronic infections.

Table 16.1 Mechanisms of humoral and cell-mediated immune responses to viruses		
Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially, secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM and IgA antibody	Blocks fusion of viral envelope with host-cell plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex and direct antiviral activity
Cell mediated	IFN secreted by T_h or T_c cells	Kill virus-infected self-cells
	Cytotoxic T lymphocytes (CTLs), NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

Innate Immune Response

- The interferon-alpha and beta (IFN-α and -β), and natural killer(NK)cells play vital roles in imparting innate immune response to viral infection. IFN-α and -β are produced in response to the presence of viruses and certain intracellular bacteria. Double-stranded ribonucleic acid(dsRNA) may be the important inducer.
- Macrophages (Mϕs), monocytes and fibroblasts are also capable of synthesizing these cytokines. IFNs can induce an antiviral response or resistance to viral replication by binding to IFN receptors.

Innate Immune Response

- Following binding of these IFNs with IFN-receptor, there is induction of the synthesis of both 2-5 oligoadenylate synthetase and protein kinase-RNA (PKR) that is considered part of the cytoplasmic pattern-recognition receptors (PRRs). The action
- of 2-5 oligoadenylate synthetase results in the activation of ribonuclease L (RNase L), which can degrade messenger-RNA (mRNA) protein kinase, inactivates the translation initiation factor by phosphorylating it. Both pathways thus, result in the inhibition of protein synthesis and thereby, effectively block viral replication (Figure 16.1).

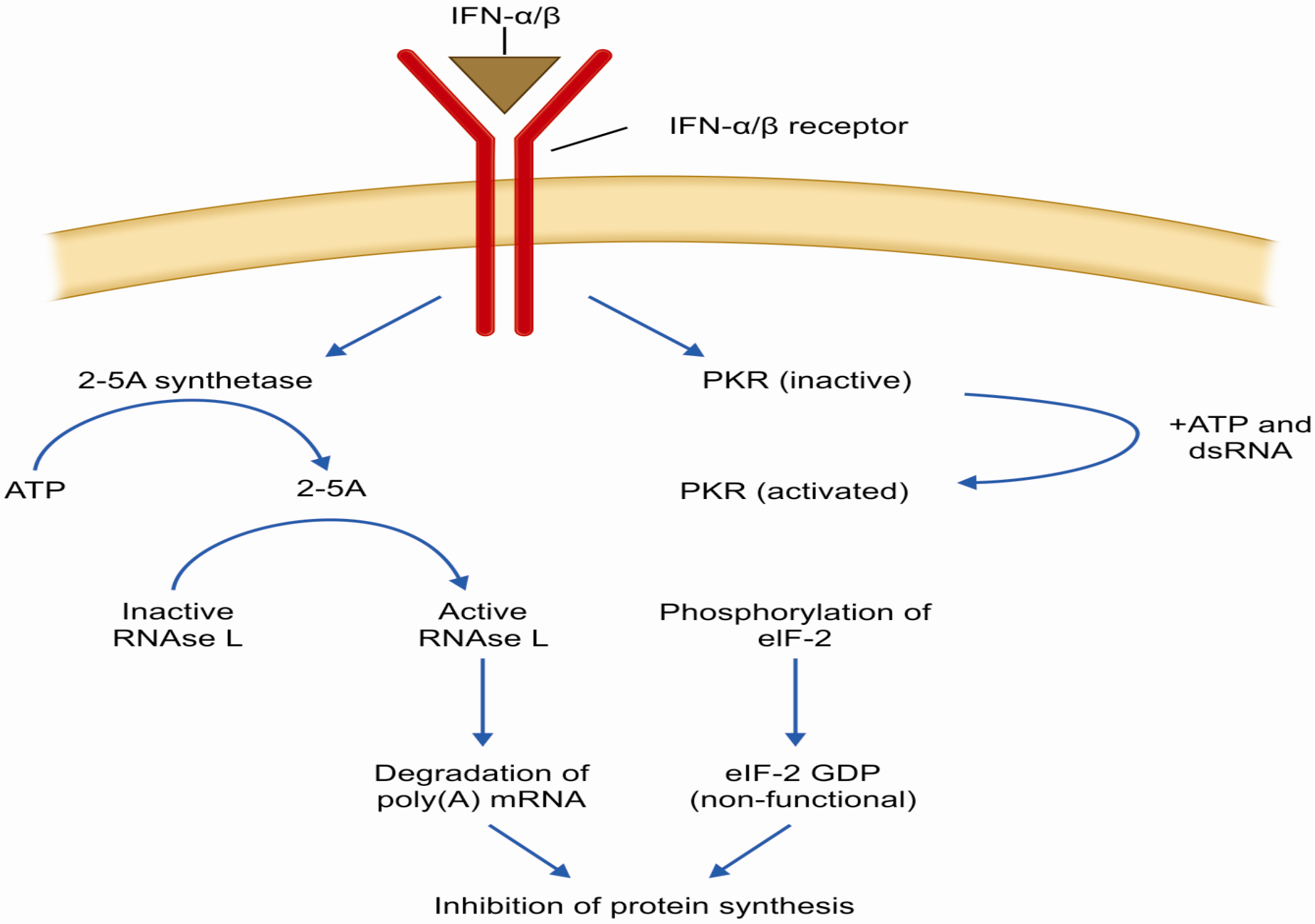


Fig. 16.1 Induction of antiviral activity by IFN-α and -β

Humoral Immunity

Humoral immunity are various ways, how the antibodies(Abs) against the viral components protect the host. Abs have no action against the latent viruses, as well as the viruses those spread from cell to cell. Small amount of Abs in the blood, can neutralize the virus before it reaches its target cells in the nervous system. Most viruses express surface receptor molecules that enable them to initiate infection by binding to these molecules on the complementary part on the tissues [sialic acid

residues] in cell membrane glycoprotein and glycolipid for influenza virus, intercellular adhesion molecules for rhinovirus, type 2 complement receptors on B cell for Epstein-Barr virus (EBV)].

And, what for 2019-nCoV/SARS-Cov-2 infection?

The Abs block the receptor molecules on the viruses, thus, preventing their attachment to the complementary tissues.

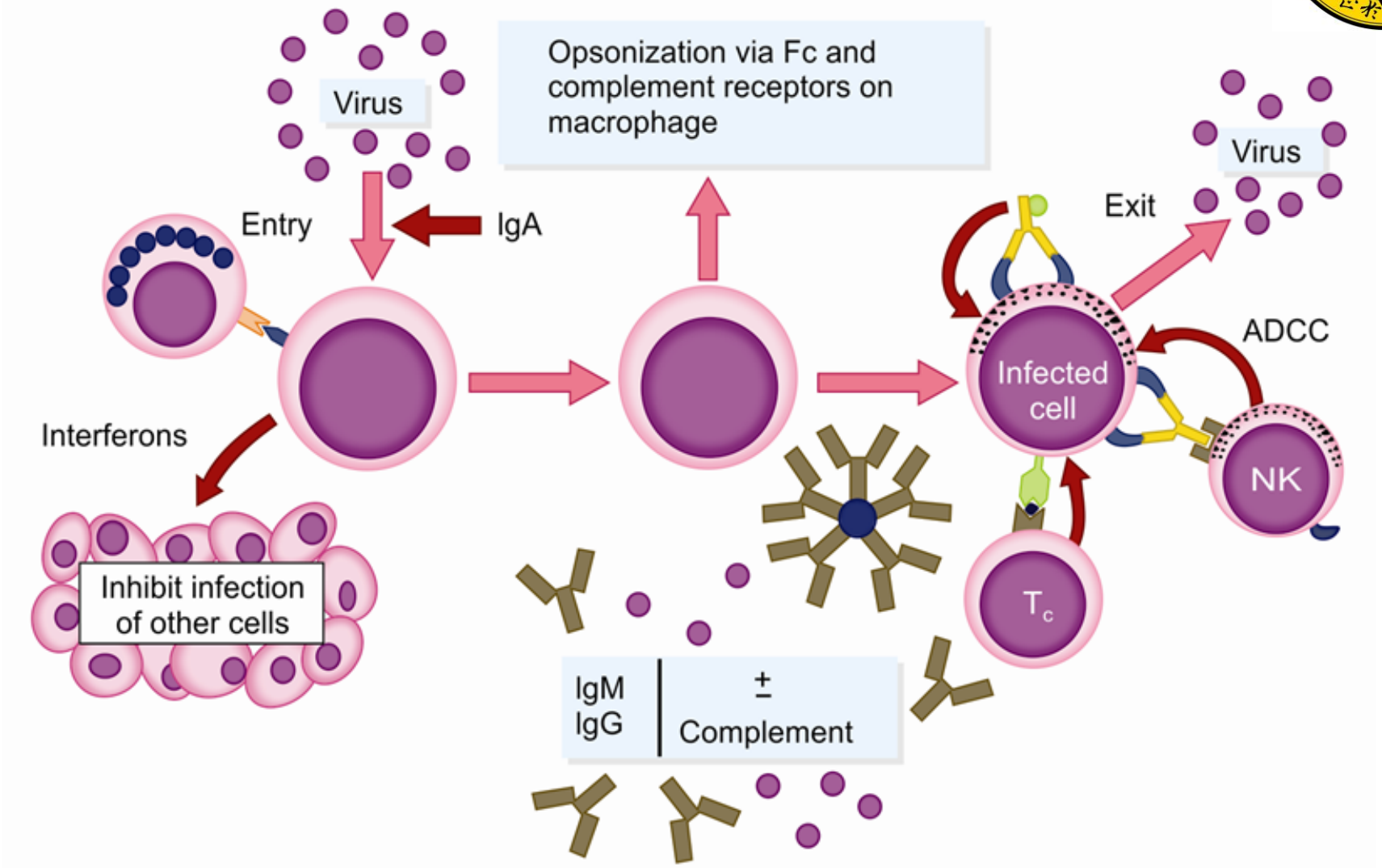
sIgA, which is an Ab class produced by plasma cells residing in the lamina propria, can neutralize viruses by similar mechanism on mucosal surfaces.

Cell-mediated Immunity (CMI)

- **As long as the virus is extracellular and the infection is not established, the Ab plays major role either eliminating the virus by different mechanisms or preventing the entry by blocking the receptor site. Once the virus is intracellular and the DNA of virus is integrated into the host DNA, Ab plays no role.**
- **CMI is imperative to deal with the virus when the infection is established. In general,**

- **$CD8^+$CTLs and $CD4^+T_h1$ cells are the main cell types, which take part in the defense mechanisms. Activated $CD4^+$ T_h1 cells produce a number of cytokines such as IFN-α, IL-2 and TNF-β, which defend against virus infection directly or indirectly. IFN-α acts directly on the viral infected cell and produce antiviral state. IL-2 activates CTLs and potentates the lytic action on viral infected cells.**

- **Both IFN-γ and IL-2 activate NK cells, which play important role in causing lysis of the viral infected cells by ADCC mechanism in the beginning of the infection, when specific CTLs have not developed.**
- **The role of CTLs in defense against viruses is demonstrated by the ability of virus specific CTLs to confer protection for the specific virus on non-immune recipient by adoptive transfer.**


Virus
Opsonization via Fc and complement receptors on macrophage
Entry
IgA
Virus
Exit
ADCC
Infected cell
NK
Interferons
Inhibit infection of other cells
T_c
IgM
IgG
±
Complement

- **Fig. 16.2 Entry of virus at mucosal surfaces inhibited by sIgA.**
- **Following the initial infection, the virus may spread to other tissues via bloodstream, IFNs produced by the innate (IFN-α and IFN-β) and adaptive (IFN-γ) immune responses make neighboring cells resistant to infection by spreading virus. Abs are important in controlling free virus. Whereas T cells and NK cells are effective at killing infected cells (ADCC, antibody-dependent cellular cytotoxicity).**

Viral Evasion of Host Defense Mechanism

- **Despite adequate immune response produced against the viral components, the virus also finds out ways to subvert the defense mechanism and establish the infection.**

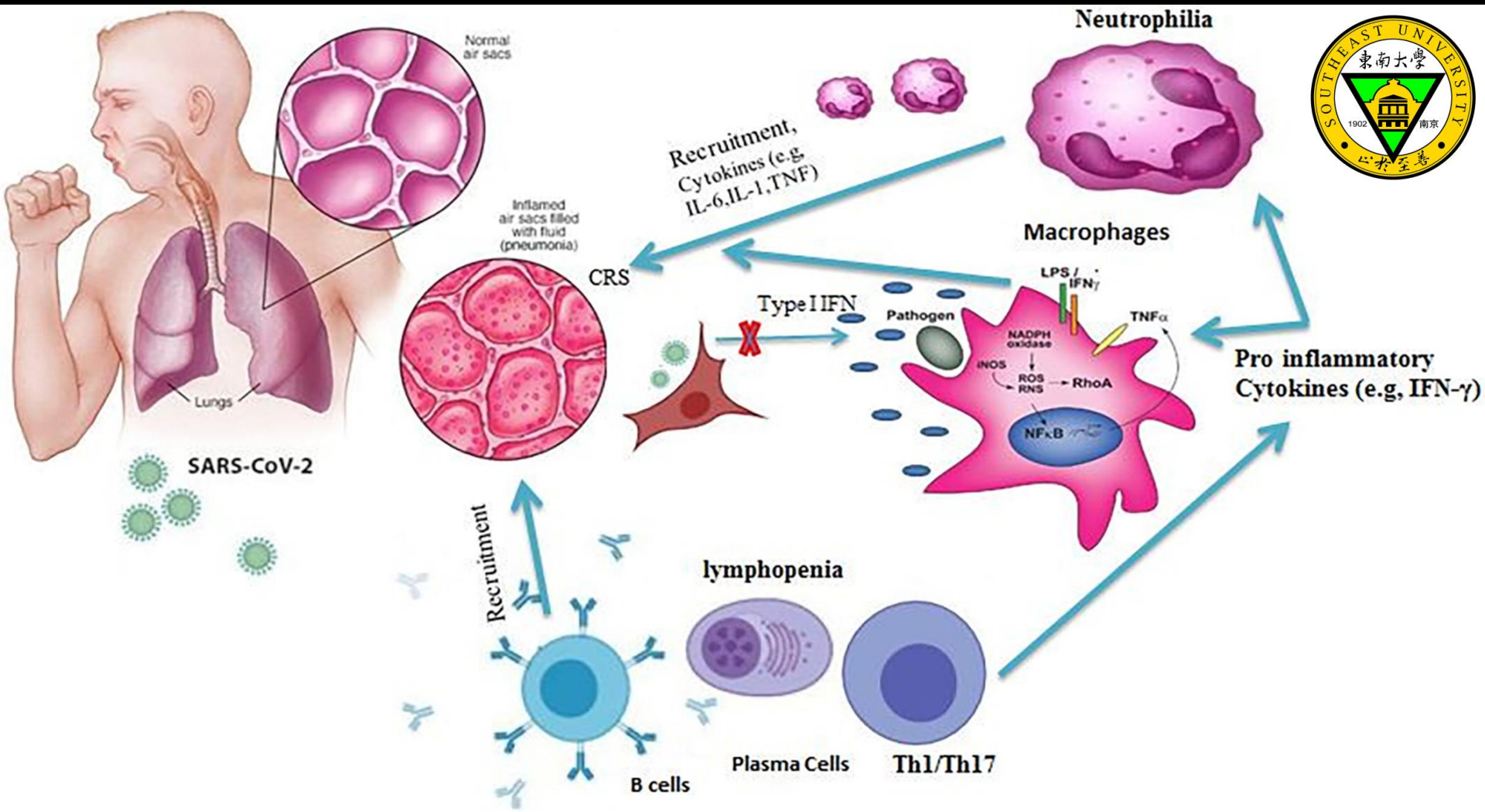
- **In many viruses, additional proteins are produced, which interfere at various levels with specific and non-specific defenses. The advantage of such proteins is that they enable viruses to replicate more effectively amidst host antiviral.**

- **There are certain viruses, which have evolved a myriad of mechanism to evade the action of IFN-α and IFN-β.**
- **1. Evade action of IFN-α and IFN-β.**

  e.g. Hepatitis C blocks PKR.
- **2. Ab + C, Vaccinia secretes protein that binds to C4b, Herpes binds to C3b.**
- **3. Changing antigens. For example too many Rhinoviruses, Influenza shifts and drifts, HIV is one champion at variability.**
- **4. Generalized immunosuppression: mumps,**

EBV (IL-10, BCRF1), CMV, HIV, may directly destroy the lymphocyes and Mϕ.

5. Kill CD4 lymphocytes (HIV).
6. Cytokine imbalance EBV. TH2.
7. Suppress MHC expression, CMV make a protein that retains class I inside cell.
8. Inhibition of antigen presentation.
   HSV: ICP47 inhibits TAP.
9. Retrovirus make inhibitors of protein kinase C during T cell activation.
10. 2019-nCoV make inhibitors of type I IFN?



Host immune responses during SARS-CoV-2 infection

Currently, only a few studies are available on the host innate immune response of 2019-nCoV infected patients.

Mohsen Rokni, et al. Rev Med Virol. 2020 Apr 8. https://doi.org/10.1002/rmv.2107

The important point is, for SARS-CoV-2, the response to viral infection by type I IFN is suppressed (Fig.3). Airborne SARS-CoV-2 leads to infection of angiotensin-converting enzyme 2 (ACE2) expressing target cells such as alveolar type 2 cells or other unknown target cells. Cells infected by the virus may escape IFN I resulting in uncontrolled viral replication. The recruitment of neutrophils and monocytes/Mϕs is by chemotaxis of pro-inflammatory cytokines. The called "cytokine storm" or cytokine release syndrome (CRS) production-specific Th1/ Th17 may cause immunopathologic injury in the lung that leads to

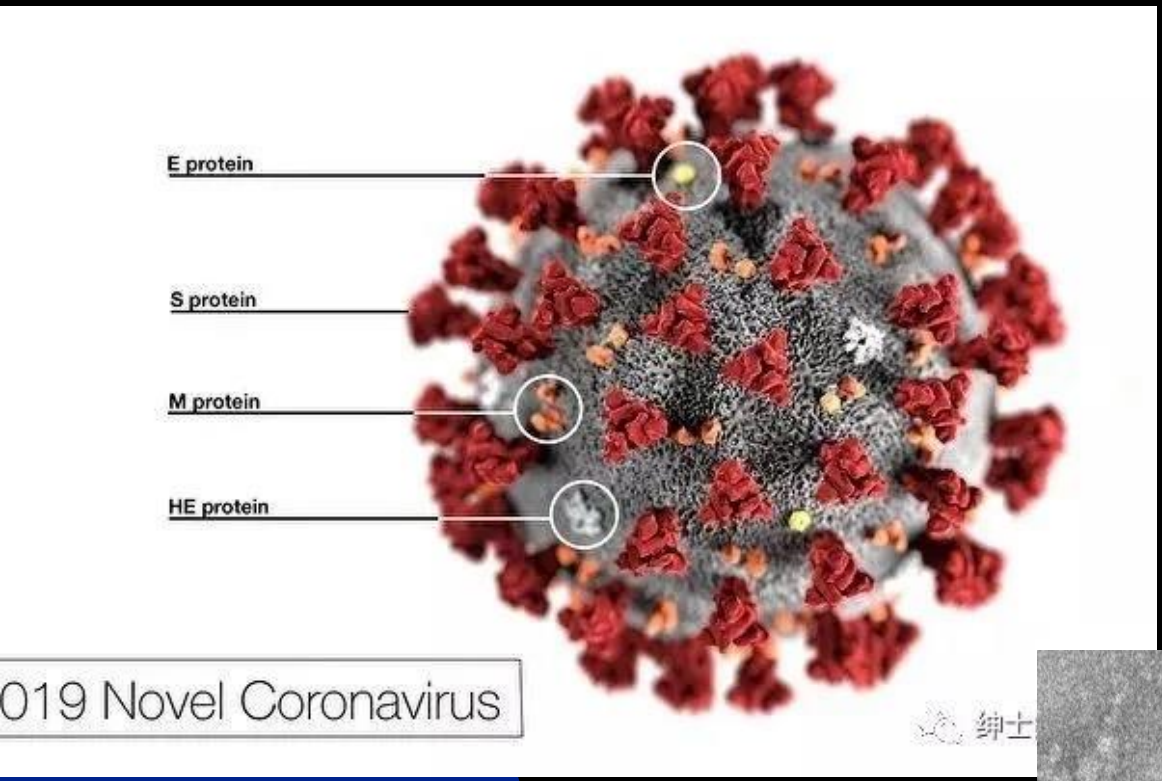
pneumonia. B cells or plasma cells produce SARS-CoV-2 specific antibodies that may help neutralize viruses. Lymphopenia caused by viral infections such as SARS-CoV-2 can occur with three mechanisms: The first mechanism is the reduction of lymphocyte production or impaired lymphopoiesis. The second mechanism is apoptosis and destruction of lymphocytes. The third mechanism that reduces lymphopenia without decreasing production or increasing degradation is lymphocyte redistribution, such as lymphocyte attachment to the vascular endothelium (a phenomenon similar to neutrophil marginalization)

that can lead to decrease in circulating lymphocytes. SARS-CoV-2 infection induces IgG production against N protein that can be detected by serum as early as day 4 after the onset of disease and with most patients seroconverting by day 14. Based on immuno- fluorescence assays and ELISA, in 89% of the recovered patients, IgG-specific and neutralizing antibodies were detected 2 years after SARS infection. In addition, peak specific IgM on the ninth day after disease and the class switching to IgG in the second week were detected.

Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol*. 2020. Feb 27[Online ahead of print]

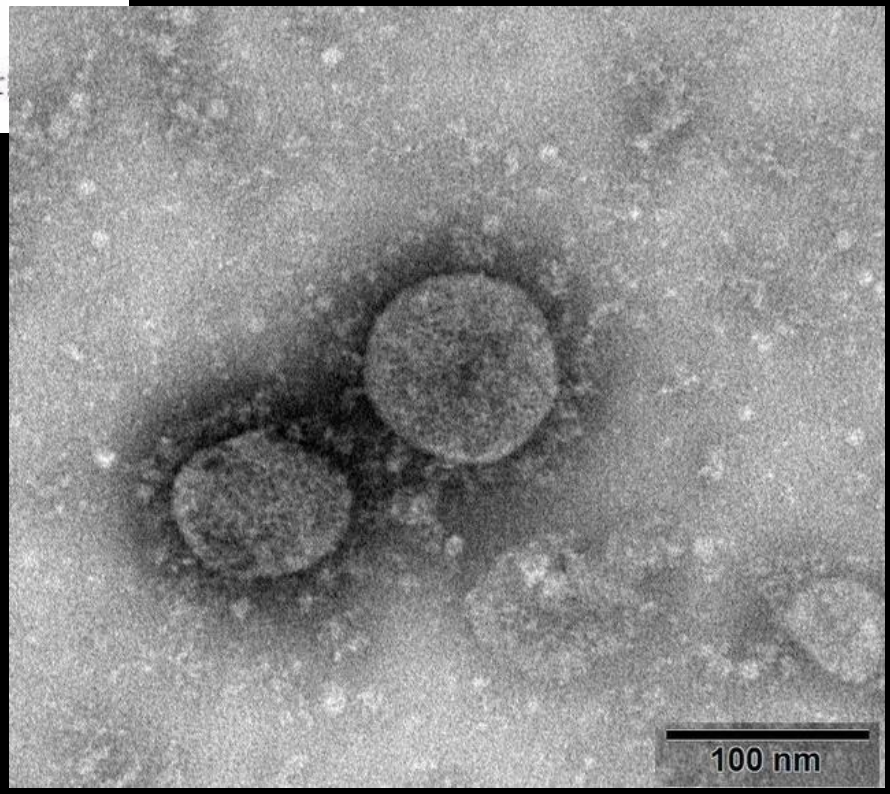
Laboratory evidence of clinical patients showed that specific T-cell responses against individuals SARS-CoV-2 is important for the recognition and killing of infected cells, particularly in the lungs of infected. The results of a study with 128 cases showed that the number and function of $CD8^+$ T cells were greater than $CD4^+$T cell responses, although whether the memory T-cell response is sufficient to protect from reinfection needs further study.

Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. *J Med Virol*. 2020; **92**(4): 424- 432.

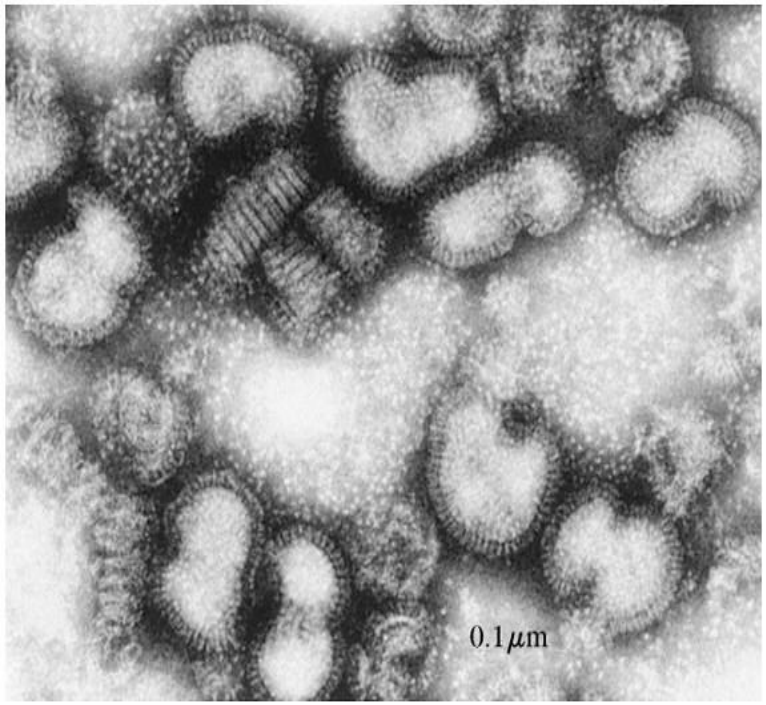


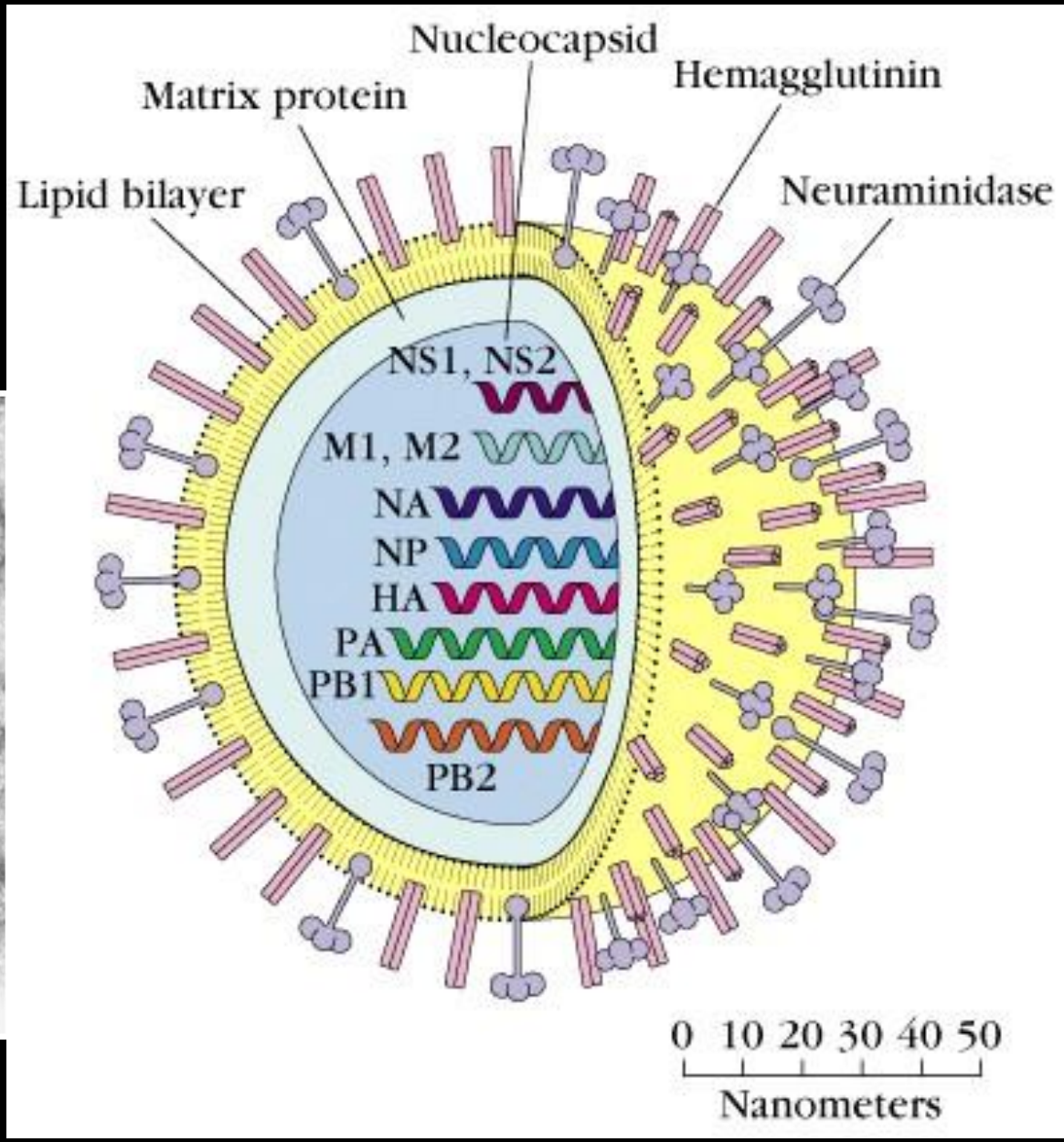
CDC网站刊出新型冠状病毒NovelCoronavirus）示意图

2020年1月27日，国家病原微生物资源库再次发布了由中国疾病预防控制中心病毒病预防控制所成功分离的我国第一株从环境样本中分离的新型冠状病毒毒种中英文名称、编号（NPRC 2020.00002）

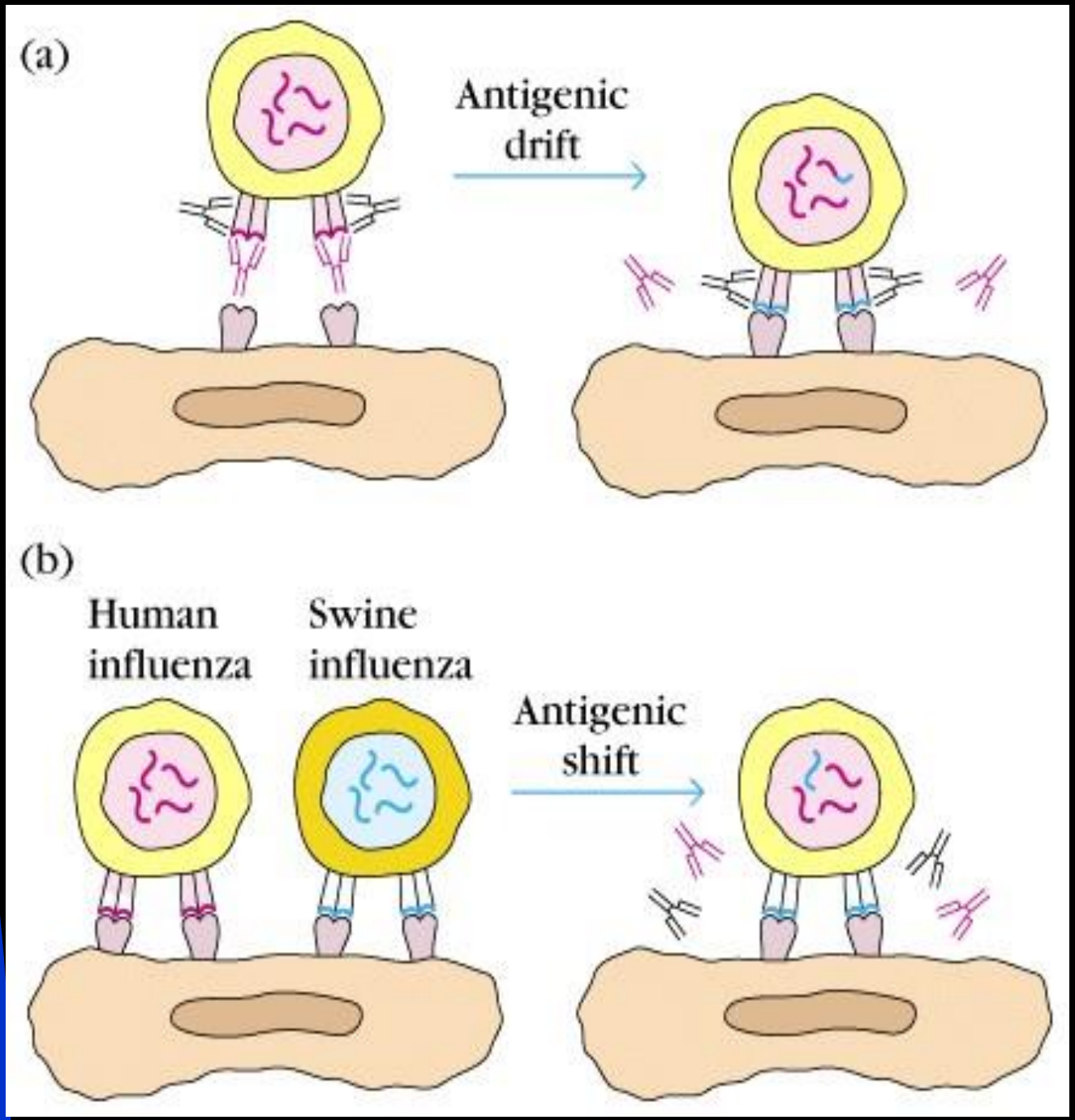


Influenza Virus





Drift and Shift



- **The studies have revealed that during evolution they have found a balance of "live and let live" with their host.**

- **Understanding the interactions of these viruses with the host will certainly help to achieve the goal of eradicating latency viruses.**

IMMUNITY IN BACTERIAL INFECTIONS

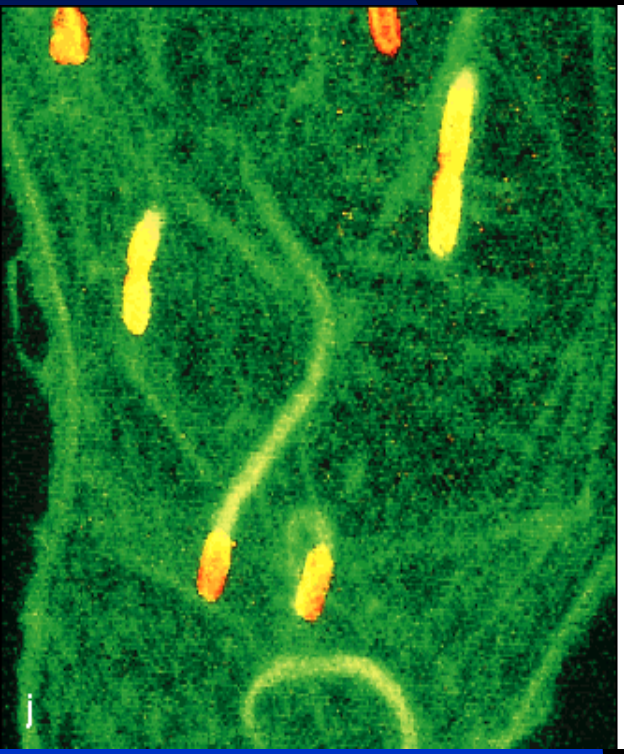
- **The host response to invading bacteria depends upon the infectious agents where it is encountered.**
- **Bacteria enter the body either through a number of natural routes (e.g. the mucous membrane respiratory tract, the gastrointestinal tract and the genitourinary tract) or through broken skin and mucous membrane.**

- **Different levels of host defense are enlisted depending on the number of microorganisms and their virulence.**

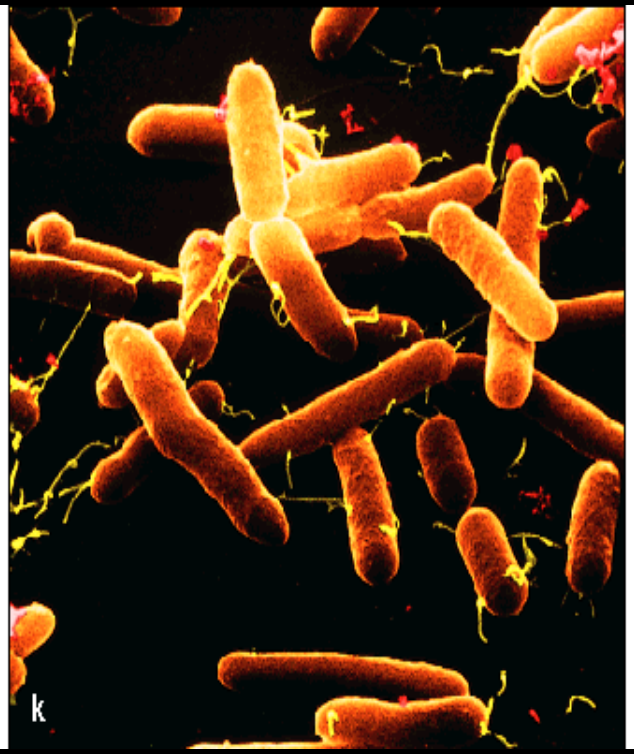
- **If the invading bacteria size is small and the virulence of the bacteria is low, they can be eliminated by phagocytic cells of the innate immune system.**

IMMUNITY IN BACTERIAL INFECTIONS

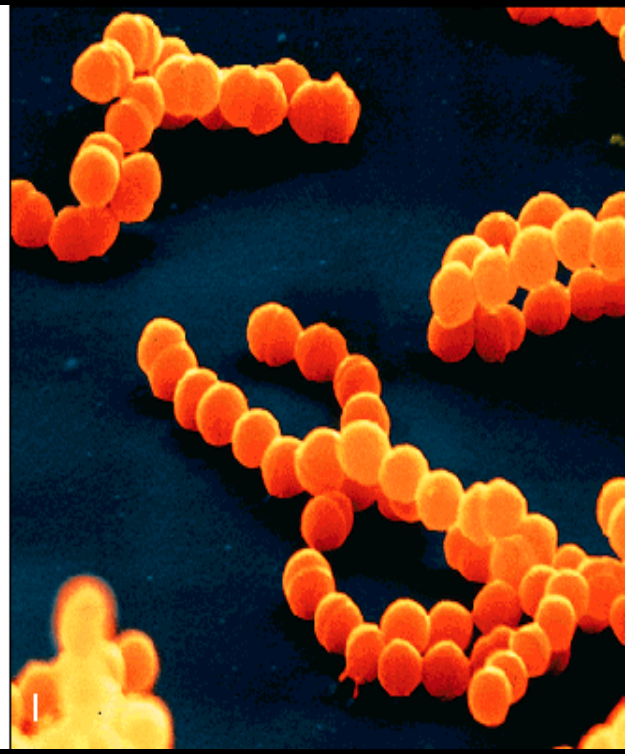
Some Bacterial Pathogens



Listeria

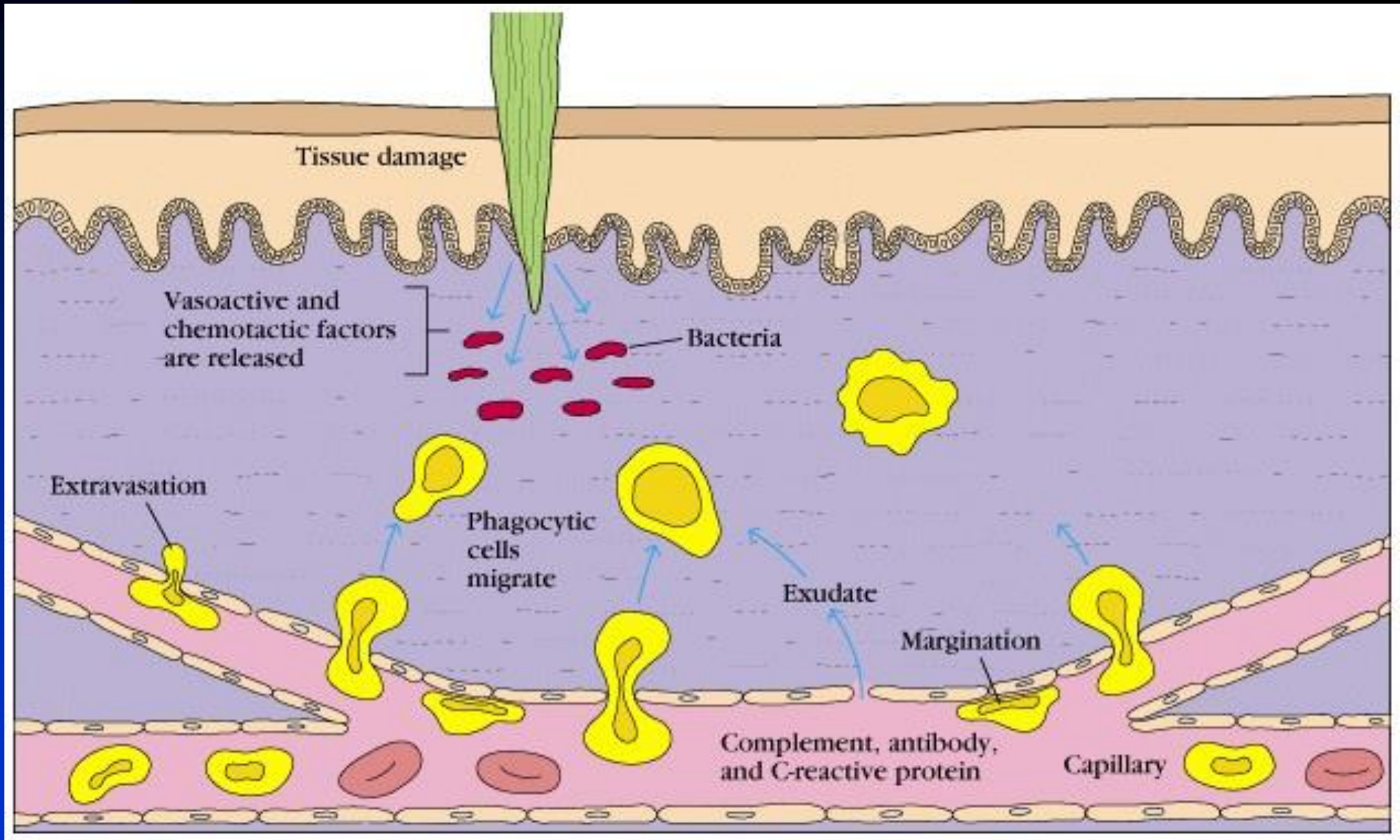


Salmonella



Streptococcus pyogenes

Perception of Invasion and Inflammation

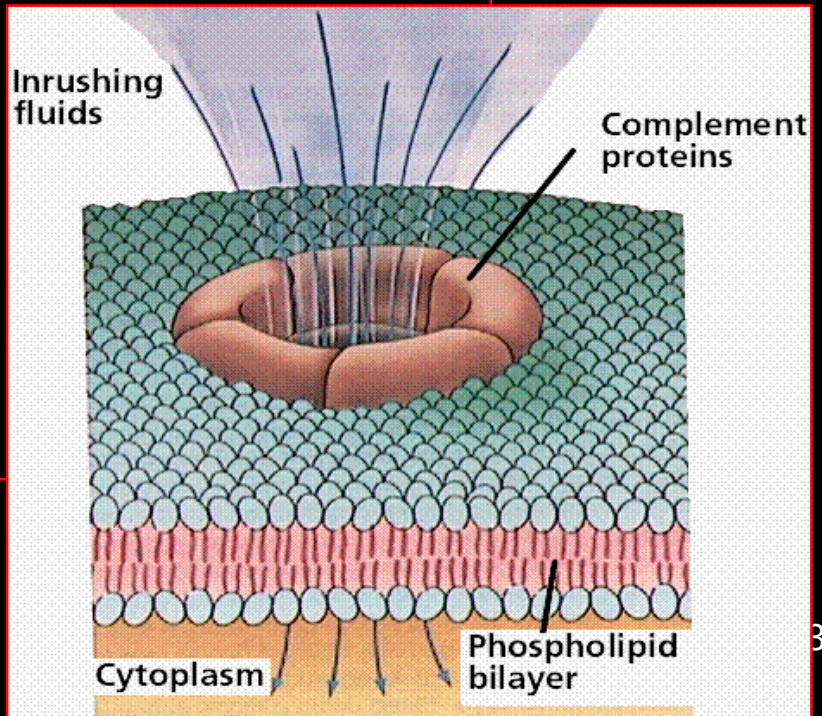


Basis for Inflammation

"Tripwires" (or Sentinels) for Inflammation

- **Complement:**
  - a complex group of proteins in plasma and cells
  - kills bacteria, attracts and assists phagocytes

"MAC"



Phagocytes: neutrophils, monocytes/Mϕs kill microbes, release cytokines for communication, express integrins.

Mϕs process and present antigens to T cells.

Cytokines and chemokines produced in response to infection act on cells to regulate adhesion and activation.

Host Defenses

- Very few microorganisms can penetrate the intact skin, because of various innate defense mechanisms. Whenever, the bacteria gain access to the tissues, the ability to fight the microorganisms and to eliminate depends upon the immune response generated against the microbial antigens (Ags).

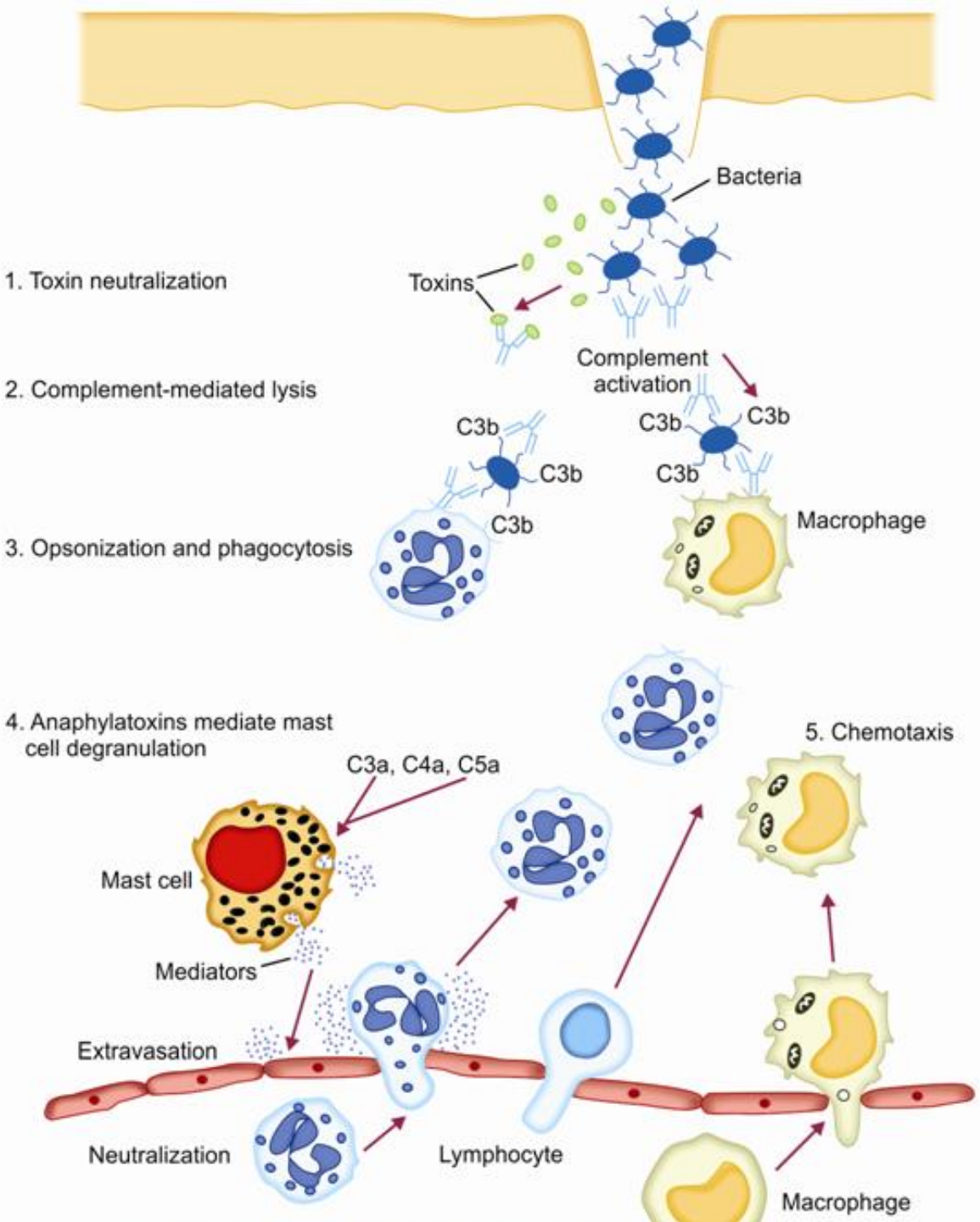
- **In most cases, the immune response is generated against the components of the bacteria and the molecules secreted by them. Immune response is generated against the flagella's motility , the fimbriae's adhesion as well as the capsules.**

- **Specific Abs to flagella and fimbriae also affect their ability to function properly. Abs also can inactivate various bacterial enzymes and toxins.**

- **Humoral Immunity**

- **Attachment and invasion are important processes, which pathogenic bacteria adopt to establish the infection. sIgA, interfere**
- **with the attachment molecule and prevent colonization of pathogenic bacteria. Diphtheria, tetanus, botulism, etc. produce disease through their exotoxins.**

- **Abs acquired by either immunization or previous infection or given passively, neutralize the bacterial exotoxins. The toxin-antitoxin complexes are phagocytosed.**
- **Many bacterial exotoxins are enzymes. The Abs against enzymes interferes with the ability of the enzyme to interact with substrates.**


Bacteria
1. Toxin neutralization
Toxins
Complement activation
2. Complement-mediated lysis
C3b
C3b
C3b
C3b
C3b
C3b
3. Opsonization and phagocytosis
Macrophage
4. Anaphylatoxins mediate mast cell degranulation
C3a, C4a, C5a
5. Chemotaxis
Mast cell
Mediators
Extravasation
Neutralization
Lymphocyte
Macrophage

- **Fig. 16.3 Ab-mediated mechanisms for combating infection by extracellular bacteria.**
- **1. Ab neutralizes bacterial toxins;**
- **2. Complement (C) activation on bacterial surface leads to C -mediated lysis of bacteria;**
- **3. Ab and the C split product C3b bind to bacteria, serving as opsonins to increase phagocytosis;**
- **4. C3a and C5a, generated by Ab-initiated C activation, induce local mast cell degranulation, releasing substances that mediate vasodilation and extravasation of lymphocytes and neutrophils;**
- **5. Other complement split products are chemotactic for neutrophils and Mϕs.**

Cell-mediated Immunity

- Ultimately, all bacteria will be engulfed by Mϕs either to kill the bacteria or to remove after extracellular killing. The microbial products (muramyl dipeptide and trehalose dimycolate) and chemotactic factors (formyl methionyl peptide) are the stimuli to activate Mϕs and monocytes. The endotoxin present in the cell wall of gram-negative bacteria and various carbohydrate polymers, such as β-glucans, are also potent Mϕs activators.

- **While innate immunity as well as humoral immunity are not very effective against intracellular bacterial pathogens, it can activate NK cells, which inturn provides early defense against intracellular bacteria.**

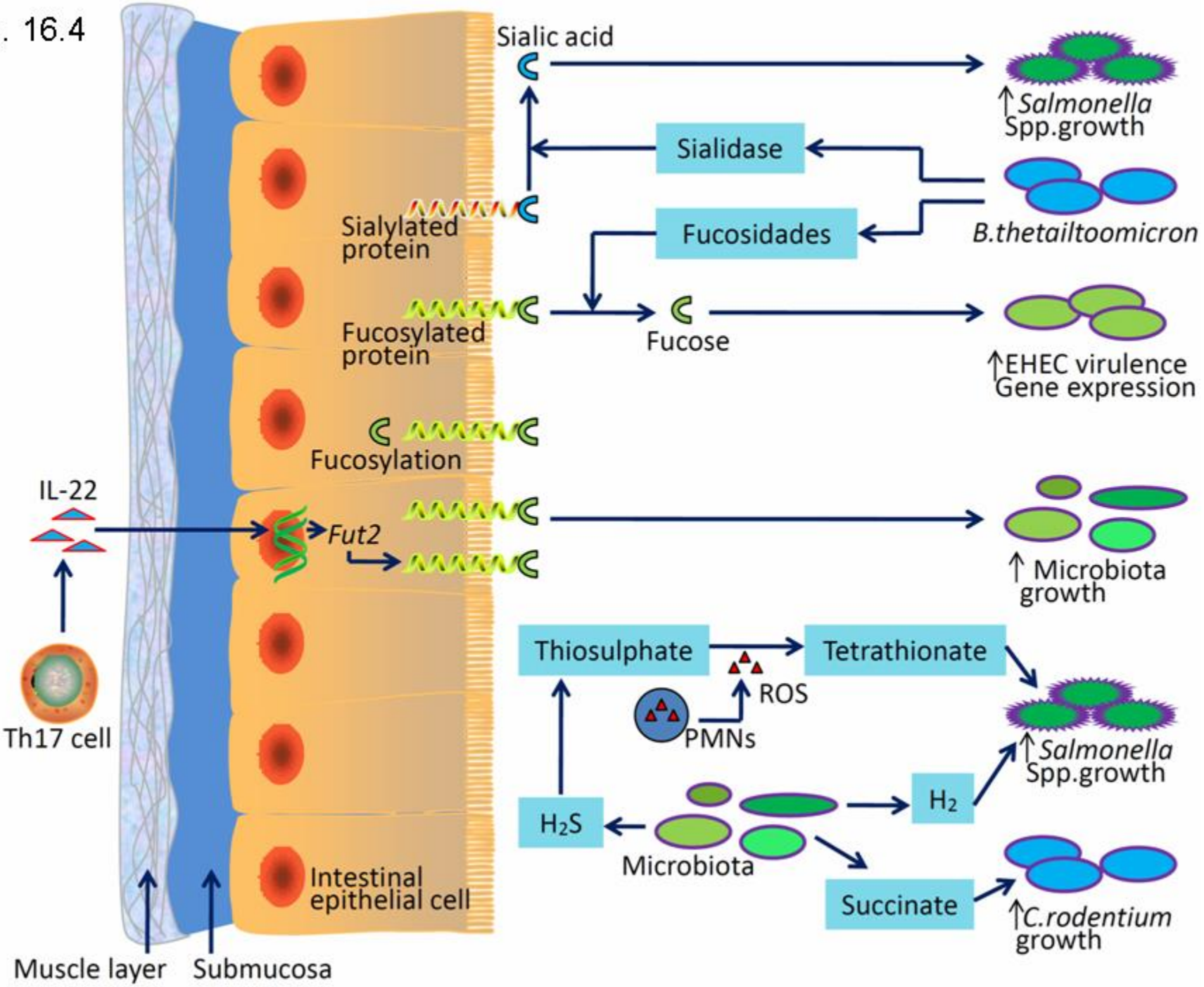
- **The bacteria induce a cell mediated immune response, specifically delayed type of hypersensitivity. The cytokines secreted by $CD4^{+}T_h$ cells are important, notably IFN-γ though TNF-β and CSF activate Mϕs to kill ingested pathogens more effectively.**

- **Mucosal Immunity**
- The mucosa is a particularly dynamic environments. There are the mucous membrane systems of respiratory tract, the genitourinary tract and the gastrointestinal tract, and particularly the gastrointestinal tract mucous membrane in which the host constantly interacts with trillions of commensal microorganisms. The surface area of the gut is an order of magnitude larger than that of the skin and approaches

- the size of the surface area of another major mucosal surface, the lungs. The **epithelial surface of the digestive tract** constitutes a physical barrier against the ‘outside’, thereby providing a **first layer** of defence against infection.
- **A second layer of defence** is mucus layer, which consists of a complex web of mucin and antimicrobial proteins that cover epithelial surfaces of the gut, thereby impeding microorganisms from reaching epithelial cells.

- **A third layer of defence is the numerous immune cells in the gastrointestinal tract.**
- **The mucus layer, epithelial cells and immune**
- **cells (Peyer's patches and mesenteric lymph nodes, or scattered throughout the intestinal epithelium and lamina propria), together constitute the intestinal mucosal barrier and prevent the trillions of commensal microorganisms (bacteria, fungi or viruses) living in host intestines from reaching systemic sites without causing harm to hosts.**

Fig. 16.4


Sialic acid
Salmonella Spp.growth
Sialidase
B.thetailtoomicron
Sialylated protein
Fucosidades
Fucosylated protein
Fucose
EHEC virulence Gene expression
Fucosylation
IL-22
Fut2
Microbiota growth
Thiosulphate
Tetrathionate
ROS
PMNs
Th17 cell
Salmonella Spp.growth
H2S
H2
Microbiota
Succinate
C.rodentium growth
Intestinal epithelial cell
Muscle layer
Submucosa

- **Fig. 16.4 Pathogens exploit the microbiota to colonize the gut.**
- ***Salmonella* spp., *Citrobacter rodentium* and enterohaemorrhagic *Escherichia coli* (EHEC) use microbiota-generated products such as enzymes, sugars and inorganic compounds as carbon or energy sources to thrive in the gut. The microbiota produces hydrogen sulphide (H_2S), which is then converted to thiosulphate by enterocytes. During inflammation, polymorphonuclear cells (PMNs) are recruited to the gut, where they release reactive oxygen species (ROS) and generate an oxidative environment.**

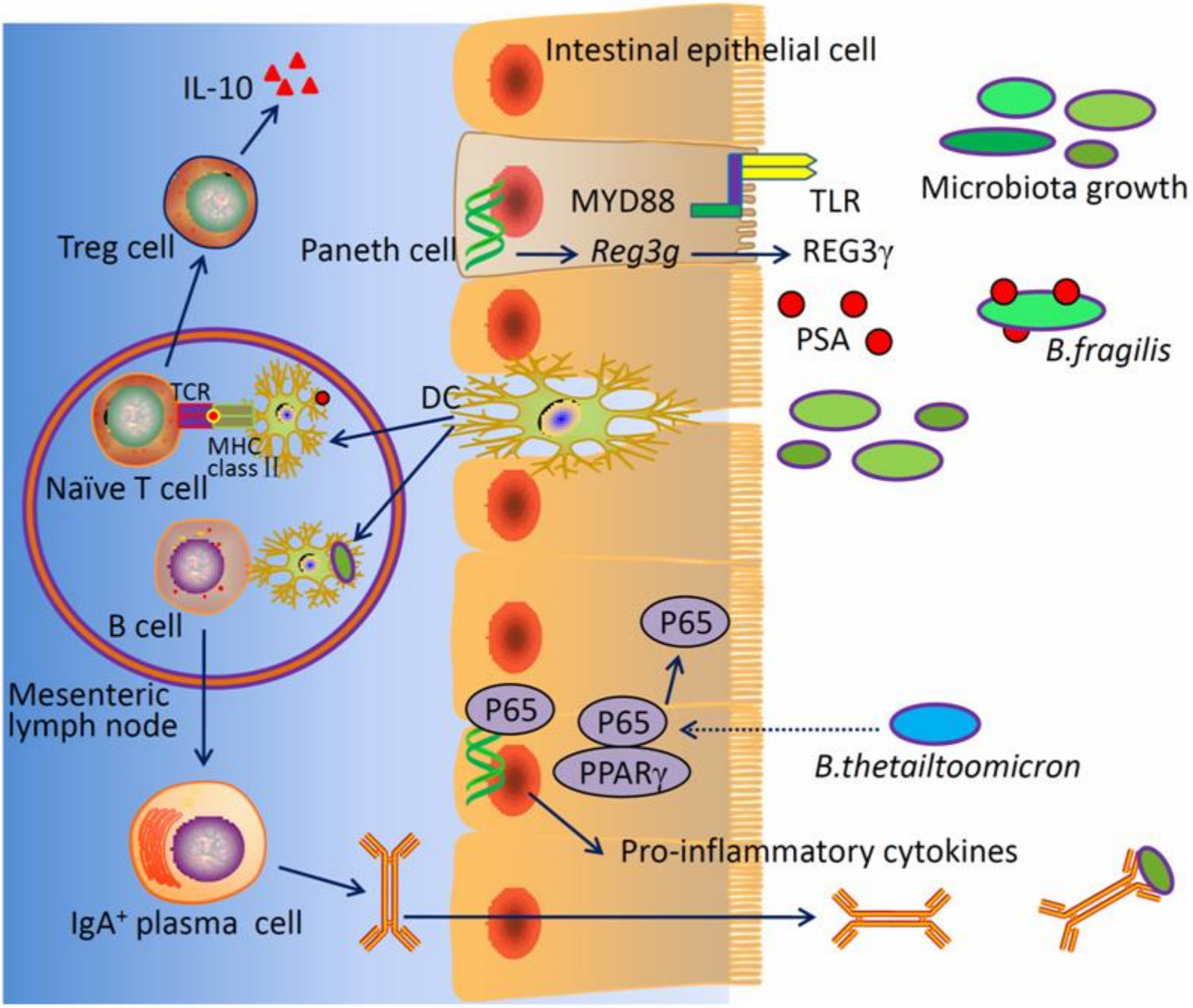
- **Thiosulphate is then oxidized to tetrathionate,**
- **which *Salmonella* spp., but not the microbiota, can anaerobically respire.**
-
- ***C. rodentium* uses succinate, another product produced by the microbiota, as a carbon source. Pathogens also indirectly benefit from members of the microbiota that have a high metabolic activity; for example, enzymes produced by *Bacteroides thetaiotaomicron* are beneficial for both EHEC and *Salmonella* spp. growth.**

- ***Salmonella*** **spp. can grow on sialic acid, which is liberated from mucosal glycoconjugates through the activity of sialidase produced by *B. thetaiotaomicron*. This commensal microorganism also expresses fucosidases that liberate fucose. Upon sensing fucose, EHEC upregulate the expression of virulence genes.**
- **Fucose not only benefits pathogens but also the microbiota itself.**
- **For instance, Th17 cell-derived IL-22 induces the expression of the α1,2-fucosyltransferase *Fut2* in**

- epithelial cells, which results in an increase of fucosylation on their surface. The increase in fucose functions as a carbon source for the microbiota and stabilizes it during inflammatory conditions.
- Sampling of commensal bacteria by the immune system is another mechanism through which the microbiota provides colonization resistance to pathogens.
- In this context, expression of CX3C chemokine receptor 1 allows a subset of myeloid derived

- mucosal DCs to extend their dendrites between epithelial cells and to engulf bacteria in the intestinal lumen.
- Commensal bacteria are then transported from the intestines to the mesenteric lymph nodes, where the bacteria selectively induce the production of sIgA
- by plasma cells. These Abs subsequently bind to and modulate the composition of the gut
- microbiota, thus limiting inflammatory responses and preventing the penetration of commensal and pathogenic bacteria.

Fig. 16.5


Intestinal epithelial cell
IL-10
Treg cell
Paneth cell
MYD88
TLR
Reg3g
REG3γ
Microbiota growth
PSA
B.fragilis
TCR
MHC class II
DC
Naïve T cell
B cell
Mesenteric lymph node
P65
P65
P65
PPARγ
B.thetailtoomicron
Pro-inflammatory cytokines
IgA+ plasma cell

- **Fig. 16.5 Commensal microorganisms modulate intestinal immunity.**

- **Commensal bacteria induce the expression of the antimicrobial lectin regenerating islet-derived protein 3γ (REG3γ) by stimulating Toll-like receptor (TLR) signalling in Paneth cells. Polysaccharide A (PSA) from *Bacteroides fragilis* is captured by intestinal DCs and transported to the mesenteric lymph nodes (MLNs) where Treg cells are induced through conventional antigen presentation**

- **pathways and TLR2 signalling; the Treg cells then migrate to the gut where they carry out their regulatory functions.**
- **CX3C-chemokine receptor1(CX3CR1)$^{+}$DCs sample commensal bacteria, which are transported from the intestines to the MLNs, where they induce the production of IgA from naïve B cells; these IgA Ab, in turn, modulate the composition of the microbiota. In epithelial cells, *Bacteroides thetaiotaomicron* modulates the expression of pro-inflammatory cytokines by inducing the export of**

- **p65 (encoded by *RELA*) from the nucleus through**
- **its association with the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ).**

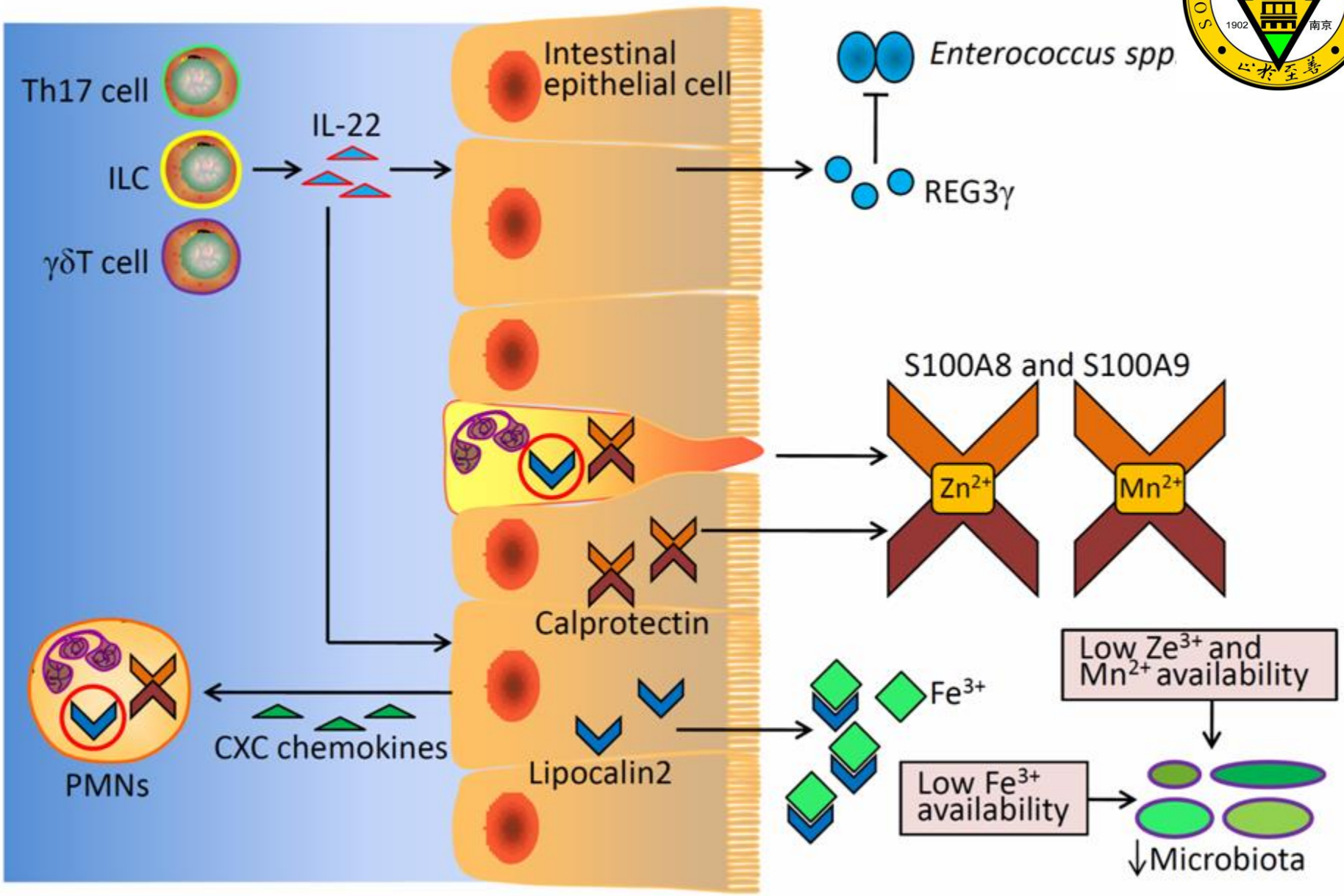
- **The host uses a range of innate immune sensors of PRRs to detect PAMPs. PRRs are expressed by immune and nonimmune cells of the intestinal mucosa, which are either located on the cell membrane (in the case of TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10) or inside vesicles (in the**

- **case of TLR3, TLR7, TLR8, TLR9, TLR11 and**
- **TLR13. TLR activation has an important role in both the course and outcome of infection with pathogens that cause inflammatory diarrhea.**
- **For example, during infection with *S. enterica* subsp. *enterica* serovar Typhimurium, activation**
- **of both TLR2 and TLR4 is important for the elimination of the pathogen.**

- **In addition, TLR signalling is also important for maintaining mucosal integrity after bacterial infection.**

- **The host initiates processes to resolve the infection following the detection of pathogenic bacteria. To achieve this, a common strategy the host uses is to recruit and/or to activate additional cells by communicating through cytokines, such as IL-23, IL-17 and IL-22. IL-23 is produced in the gut by DCs and other mononuclear cells in response to infection with pathogens. A variety of cell types including Th17 cells, natural killer T (NKT) cells,**
- **γδT cells and innate lymphoid cells (ILCs) express the IL-23 receptor.**

Fig. 16.6


Th17 cell
ILC
γδT cell
IL-22
Intestinal epithelial cell
Enterococcus spp.
REG3γ
S100A8 and S100A9
Zn2+
Mn2+
Calprotectin
PMNs
CXC chemokines
Lipocalin2
Fe3+
Low Ze3+ and Mn2+ availability
Low Fe3+ availability
↓Microbiota

- **Fig. 16.6: Antimicrobial responses induced by IL-22.** High level of IL-22 is produced by intestinal immune cells on infection with enteric pathogens, and it upregulates epithelial cell expression of antimicrobial proteins, including regenerating islet-derived protein 3γ (**REG3γ**), **lipocalin 2** and the two subunits of **calprotectin**, S100A8 and S100A9. **REG3γ** kills Gram-positive bacteria such as *Enterococcus* spp. and helps to maintain a microorganism-free zone adjacent to the epithelial layer.
- **Lipocalin 2** binds to the bacterial siderophore enterochelin and limits iron availability in the gut.

- **Calprotectin, a heterodimer of the proteins S100A8 and S100A9, sequesters zinc and manganese from microorganisms. IL-22 induces epithelial cell production of CXC-chemokines, which recruit PMNs to the site of infection; these recruited neutrophils are also a major source of calprotectin and lipocalin 2. ILC, innate lymphoid cell; PMNs, polymorphonuclear cells. Siderophore: A low molecular weight, high-affinity iron-binding molecule that is secreted by bacteria and fungi to acquire iron from the surrounding environment.**

- **One of the consequences of IL17 production is the**

- induction of potent CXC-chemokines that recruits neutrophil and translocate to the intestinal lumen, which represents a hallmark of inflammatory diarrhea.
- Neutrophils, in turn, counter these pathogens by using a vast repertoire of effector mechanisms including their phagocytic activity, their release of degradative enzymes, their production of ROS and their release of neutrophil extracellular traps
- (NETs) and antimicrobial peptides, and produced T_h1 and $T_h17$cytokines such as IFN-γ, IL-17 and
- IL22.

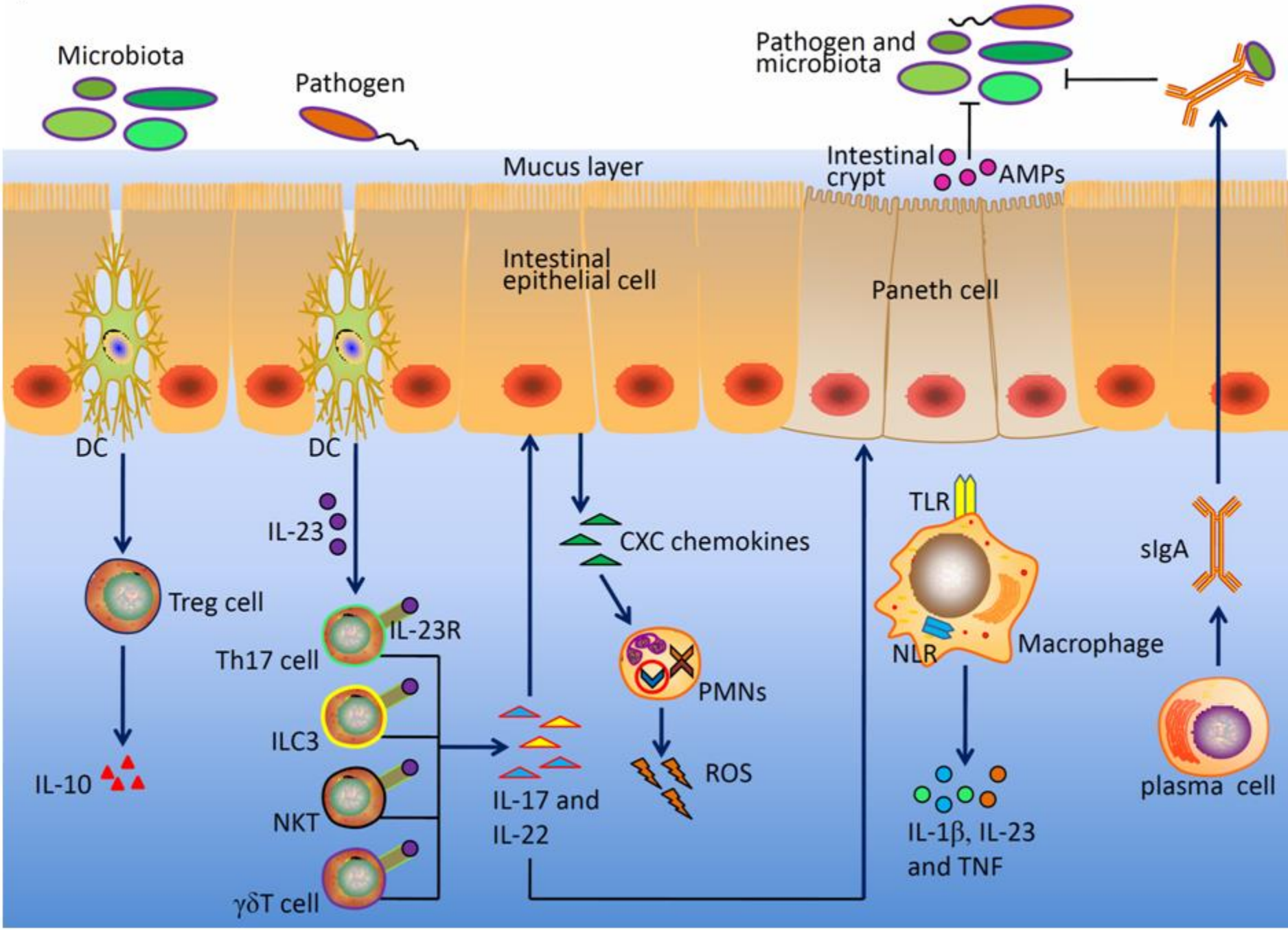
Thus, neutrophils may have additional functions beside killing microorganisms and could be important regulators of the mucosal response to pathogens.

NETs
Chaput C. and Zychlinsky A.Nat Med. 2009;15:1245-6.

- **The sIgA is also plays pivotal roles in promoting barrier protection against enteric pathogens by binding to surface molecules expressed by pathogens and by neutralizing their toxins. These secretory Abs are important to mitigate**
- **colonization of the mucosa by noninvasive pathogens such as *V. cholerae*.**

- **High serum titers of sIgA that is specific to cholera toxin, the major virulence factor of *V. cholerae*, correlate with protection against infection.**

Fig. 16.7


Microbiota
Pathogen
Pathogen and microbiota
Mucus layer
Intestinal crypt
AMPs
Intestinal epithelial cell
Paneth cell
DC
DC
IL-23
CXC chemokines
TLR
sIgA
Treg cell
IL-23R
Th17 cell
ILC3
NKT
γδT cell
PMNs
ROS
NLR
Macrophage
IL-10
IL-17 and IL-22
IL-1β, IL-23 and TNF
plasma cell

- **Fig. 16.7: General overview of mucosal immunity**
- **to intestinal pathogens and commensal micro-organisms. DCs sample intestinal microorganisms.**
- **Upon sampling the resident microbiota, DCs induce**
- **a tolerogenic response by activating Treg cells to secrete IL-10. Resident Mϕs and DCs are activated by pathogens and secrete IL-23, which stimulates several subsets of T cells including Th17 cells, γδT cells, NK cells, NKT cells and group 3 innate lymphoid cells (ILC3s) to secrete IL-17 and IL-22. These cell subsets promote amplification of the**

- host response by stimulating the intestinal epithelium to secrete CXC-chemokines that attract PMNs for secreting ROS.

- In addition to chemokines, IL-17 and IL-22 induce the production of AMPs which, in turn, modulate the microbial composition of the intestinal lumen. Plasma cells also control the microbiota and pathogens via sIgA. NLR, NOD-like receptor; AMPs, antimicrobial peptides.
- Upon sampling the resident microbiota, DCs induce

- a tolerogenic response by activating Treg cells to secrete IL-10.
- Resident Mϕs and DCs are activated by pathogens and secrete IL-23, which stimulates several subsets of T cells including Th17 cells, γδT cells, NK cells, NKT cells and group 3 innate lymphoid cells (ILC3s) to secrete IL-17 and IL-22. These cell subsets promote amplification of the host response by stimulating the intestinal epithelium to secrete CXC-chemokines that attract PMNs for secreting ROS.

Evasion of Host Defense Mechanisms

- Establishment of bacterial infection involves four primary steps.
- They include attachment to host cells, proliferation, invasion of host cells, and toxin-induced damage to host cells.
- Host defense mechanisms act at each of these steps and many bacteria have evolved ways to circumvent some of these host defenses (Tab. 16.2).

Table 16.2 Host immune responses to bacterial infection		
Infection process	Host defenece	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory	Secretion of proteases that cleave secretory IgA antibodies, IgA dimers (Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae)
		Antigenic variation in attach-ment structures (pill of N. gonorrhoeae)
Cell-mediated	Phagocytosis (Ab and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cell
		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

- **Intracellular Bacteria**

  The bacteria can survive and replicate inside the cells in an advantageous condition, because the antibodies have no access on them. *Mycobacterium leprae (M. leprae)* adopts an intracellular environment, for example, Listeria monocytogenes, the causative organism of listeriosis, multiply in normal Mϕs, but fail to survive in activated Mϕs.

- **Listeriosis occurs mostly in immunocompromised subjects, pregnant women and neonate in whom probably the T cell-dependent Mϕs activating factors (IFN-γ, TNF-β, etc.) are deficient. Salmonella species and Brucella species can also survive intracellularly. They owe their resistance to glycolipid that is resistant to destruction.**

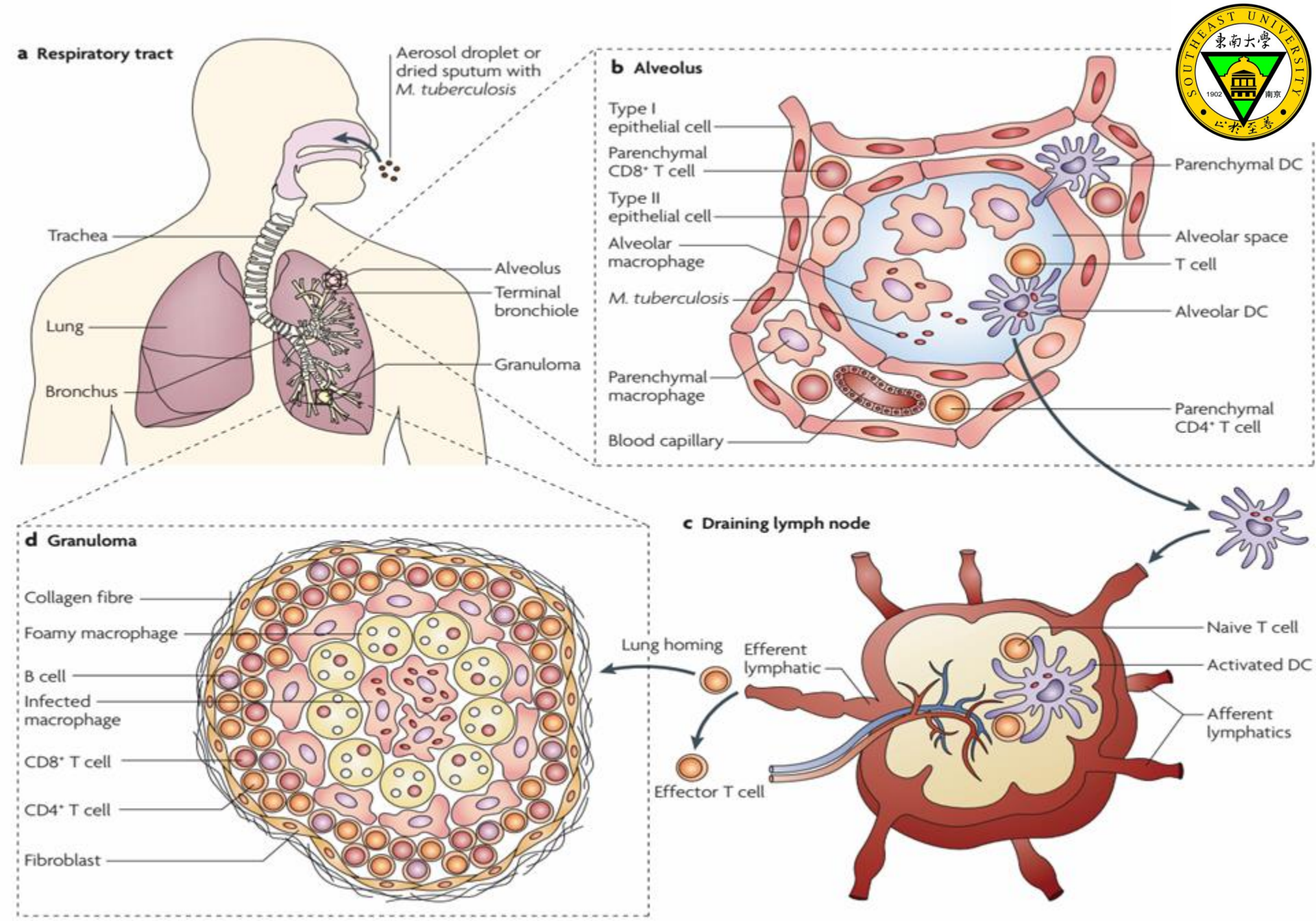


Fig. 16.8 引自：**Gareth Griffiths, et al. Nature Rev Microbiol. 2010;8 :827-834**

- **Fig. 16.8: *Mycobacterium tuberculosis* infection and granuloma formation.**

- **a. *M. tuberculosis* infection starts with the inhalation of bacilli, either as an aerosol droplet generated by the cough of a patient with TB or as a dust microparticle of dried sputum, followed by deposition of the bacteria in the lung alveolar space.**
- **b. The alveoli are lined by type I and type II epithelial cells and are separated by thin walls of interstitium containing pulmonary capillaries. In the alveolar cavity, the main hosts for the bacilli are alveolar Mϕs.**

- **After initial bacterial multiplication in alveolar Mϕs, the bacteria are taken up by DCs, which carry *M. tuberculosis* to the draining thoracic lymph nodes. Alternatively, DCs sampling the alveolar mucosa may carry bacilli to the lung parenchyma, leading to initiation of the local inflammatory foci.**

- **c. In the draining lymph nodes, DCs carrying bacilli undergo apoptosis, and the mycobacterial antigenic peptides that are released are presented by the activated lymph node-resident DCs to the specific naive cells through cross-presentation.**

- **The activated T cells proliferate, become effector T cells and leave the lymph node to reach the blood circulation through the efferent lymphatics and the thoracic duct.**

- **d. Effector T cells originating in the draining lymph nodes home back from the blood through pulmonary capillaries to the site of inflammation under the influence of chemokines and other mediators. Extravasations of the mononuclear cells thus initiate the formation of granuloma.**

- **The classic TB granuloma is made up of a central core of infected Mϕs surrounded by epithelioid and foamy Mϕs and a peripheral rim of lymphocytes (B cells, $CD4^+$T cells and $CD8^+$T cells) in association with a fibrous cuff of extracellular matrix laid by fibroblasts. The formation of the granuloma at the site of infection, resulting in containment of the infection.**

IMMUNITY IN FUNGAL INFECTIONS

- **Fungi are eukaryotes with a rigid cell wall consisting of complex polysaccharides such as chitin, glucans and mannan. Among 70,000 or so species of fungi, only a small numbers are pathogenic for humans. However, one can no longer ignore fungi with the ever-increasing risk for fungal infections. It is imperative that clinical manifestations "presume fungus" with their epidemiologic and pathogenic features when evaluating a potentially infected patient.**
- **In the high-risk patient groups, fungi with intrinsic**

- resistance to antifungal agents already exist, with
- a tendency to emerge as **opportunistic pathogens**.

- **The fungi can exist as:**
- 1. Single cells (**yeasts**), which can easily be phagocytosed because of small size.
  2. Long sender branching **hyphae**, which require extracellular killing processes.
- **Innate Immune Response**
- Intact skin and normal commensal flora play important roles in preventing the entry and colonization of fungi.

- Certain antifungal and antibacterial substances such as defensins, mannose-binding lectin, surface protein ‘A' and ‘D', coats over the fungal elements and opsonize them for phagocytosis. Immunity to mycoses is principally cellular, involving neutrophils, Mϕs, lymphocytes and probably by NK cells (for extracellular killing).

- Many of the inflammatory cells and molecules actively participate in the fungi elimination, such as

- **Mϕs, neutrophils, eosinophilic granular cells, soluble factors and MHC molecules.**

- **1. Degranulation and release of the toxic materials on to indigestible hyphae.**
  2. Ingestion of the yeasts or conidia.
- **The oxidative bursts, following ingestion, play an important role in destruction of fungi. The phagocytic response is dependent on the recognition of PAMPs in the fungal cell wall by either soluble**

- or cell bound pattern recognition molecules.
- TLR2 recognizes fungal phospholipid mannan of Candida (C.) albicans, yeasts, hyphae and conidia, etc.
-
- T Cell-mediated Specific Immune Response
- Most fungi are highly immunogenic. They induce Ab production, as well as T cell mediated immunity, which can be detected by serology and skin test (delayed hyper-sensitivity), respectively.

- **Abs are seldom protective. Considerable evidence suggests that T_h1-Mϕ activity plays dominant role**
- **in eliminating fungal pathogens.**

- **Immunity against most pathogenic fungi(including dermatophytes and most systemic mycoses such as C. neoformans, Histoplasma (H.) capsulatum, etc. but not Aspergillus species) is dependent on T cell mediated immunity particularly, $CD4^+T_h1$ cell secreting IFN-γ.**

- **Evasion Strategies**

  Many fungi have evolved the ways to circumvent, some of the host defense for their survival:

- **1. C. neoformans, ordinarily, inhibits phagocytosis because of its polysaccharide capsule, but can be overcome by the opsonic effect of complement and antibody.**
  2. Dermatophytes suppress host T cell responses
- **and delay the cell-mediated destruction.**
  3. H. capsulatum, an obligatory intracellular pathogen, evades killing by Mϕs as well as by entering through CR3, and alters the normal pathway of phagosome maturation.

- **IMMUNITY IN PARASITIC INFECTIONS**

- **General Features**

  Parasites infect, very large number of people and present major medical problems, especially in tropical countries. The diseases caused are diverse and the immune responses, which are effective against the different parasites vary considerably. Parasitic infections do, however, share a number of common features.

- **Protozoan parasites (unicellular eukaryotic organisms) and the worms (multicellular organisms) are considerably larger than the**

- bacteria and viruses, not only more in quantity, but also in variety. The parasites, unlike bacteria and viruses, undergo a life cycle in the hosts and exhibit different antigenicity at different stages of life, besides some species also change their surface Ags, a process known as antigenic variation, such as Protozoa evolve different mechanisms to enter inside the cell to have their intracellular survival.

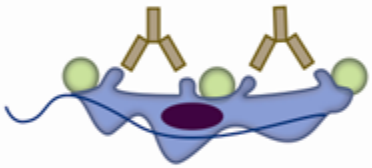
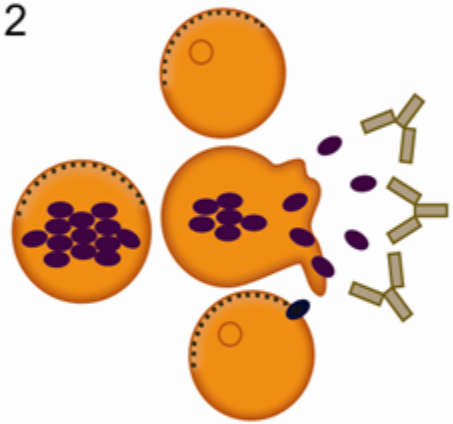
- The invasive merozoite attaches itself to the receptor on erythrocytes and uses the cells.

- **On the other hand, Leishmania species use the complement receptor on Mϕs to be engulfed by Mϕs, where ultimately they reside and multiply. The host resistance to parasite infection may be genetic and controlled by immune response genes situated in the MHC II area.**

- **Effector Mechanisms**
- **After the entry of the parasite into the host, before it faces the specific immune response, it has to overcome the host's pre-existing defense mechanisms. Complement plays role in eliminating or causing lysis of many parasites, including certain adult worms and infective larva of Trichinella (T.) spiralis, schistosomules of Schistosoma (S.) mansoni, S. Japonicum, S. haematobium, which are large multicellular organisms and major human pathogens. NK cells also may be active in imparting innate immunity against parasitic infection initially.**

- **Mϕs**

  Apart from acting as APCs in initiating adaptive immune response, Mϕ affects the course of parasitic infection in two ways:
- **1. Mϕs secrete molecules, which act to regulate the inflammatory response. IL-1, TNF and CSF may enhance immunity by activating other cells or stimulating their proliferation. Mϕs releases prostaglandins, which may be immunosuppressive. 2. Mϕs act as effector cells, which inhibit the multiplication of the parasite or they may destroy them.**
- **Granulocytes, Eosinophils, Mast Cells, T cells……**

Parasite	*Plasmodium* sporozoite, intestinal worms, trypanosome	*Plasmodium* sporozoite and merozoite, *Trypano-soma cruzi*, *Toxoplasma gondii*	*Plasmodium*, *Trypanosoma*	Schistosomes, *Trichinella spiralis*, Filarial worm larvae
Mechanism	1 Complement protein 	2 	3 	4 
Effect	Direct damage or complement-mediated lysis	Prevents spread by neutralizing attachment site, prevents escape from lysosomal vacuole, prevents inhibition of lysosomal fusion	Enhancement of phagocytosis	Antibody-dependent cell-mediated cytotoxicity (ADCC)

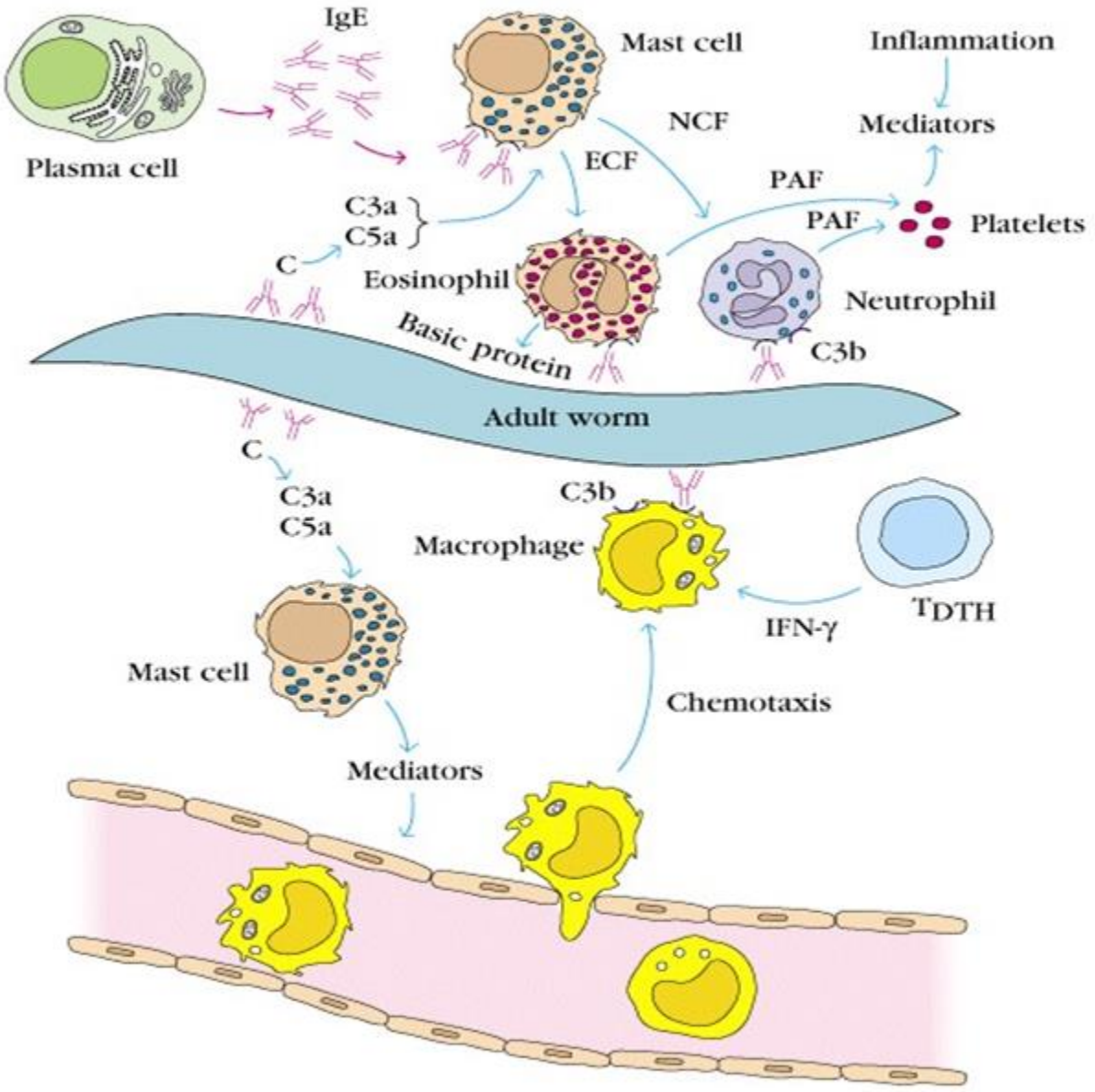
- **Fig. 16.9 Antibody-mediated defense of parasitic infections, direct damage**
- **1. Antibody activates the classical complement pathway, causing damage to the parasite**
- **membrane and increasing susceptibility to other mediators;**

- **2. Neutralization: Parasites such as Plasmodium species spread to new cells by specific receptor attachment; blocking the merozoite binding site with antibody prevents attachment to the receptors on the erythrocyte surface and hence prevents further multiplication;**

- **3. Enhancement of phagocytosis: Complement C3b deposited on parasite membrane opsonizes it for phagocytosis by cells with C3b receptor. Mϕs also have Fc receptors;**

- **4. Eosinophils, neutrophils, platelets and Mϕs may be cytotoxic for some parasites when they recognize the parasite via specific antibody (ADCC). The reaction is enhanced by complement.**

Fig. 16.10


IgE
Mast cell
Inflammation
Plasma cell
NCF
Mediators
ECF
PAF
C3a
C5a
PAF
Platelets
C
Eosinophil
Neutrophil
Basic protein
C3b
Adult worm
C
C3a
C5a
C3b
Macrophage
TDTH
IFN-γ
Mast cell
Chemotaxis
Mediators

- **Fig.10 Immune responses to Schistosoma mansoni.**
- **ADCC by Eosinophils, Mϕs and neutrophils as well as complement play roles in eliminating or causing lysis of S. mansoni. ECF: eosinophilic chemotactic factor; NAF: neutrophil chemotactic factor; PAF: platelet activating factor; T_{DTH}: delayed-type hypersensitivity T cells.**

- **Escape Mechanisms**
  There are various mechanisms, how the parasites evade the host immune system and establish infections.

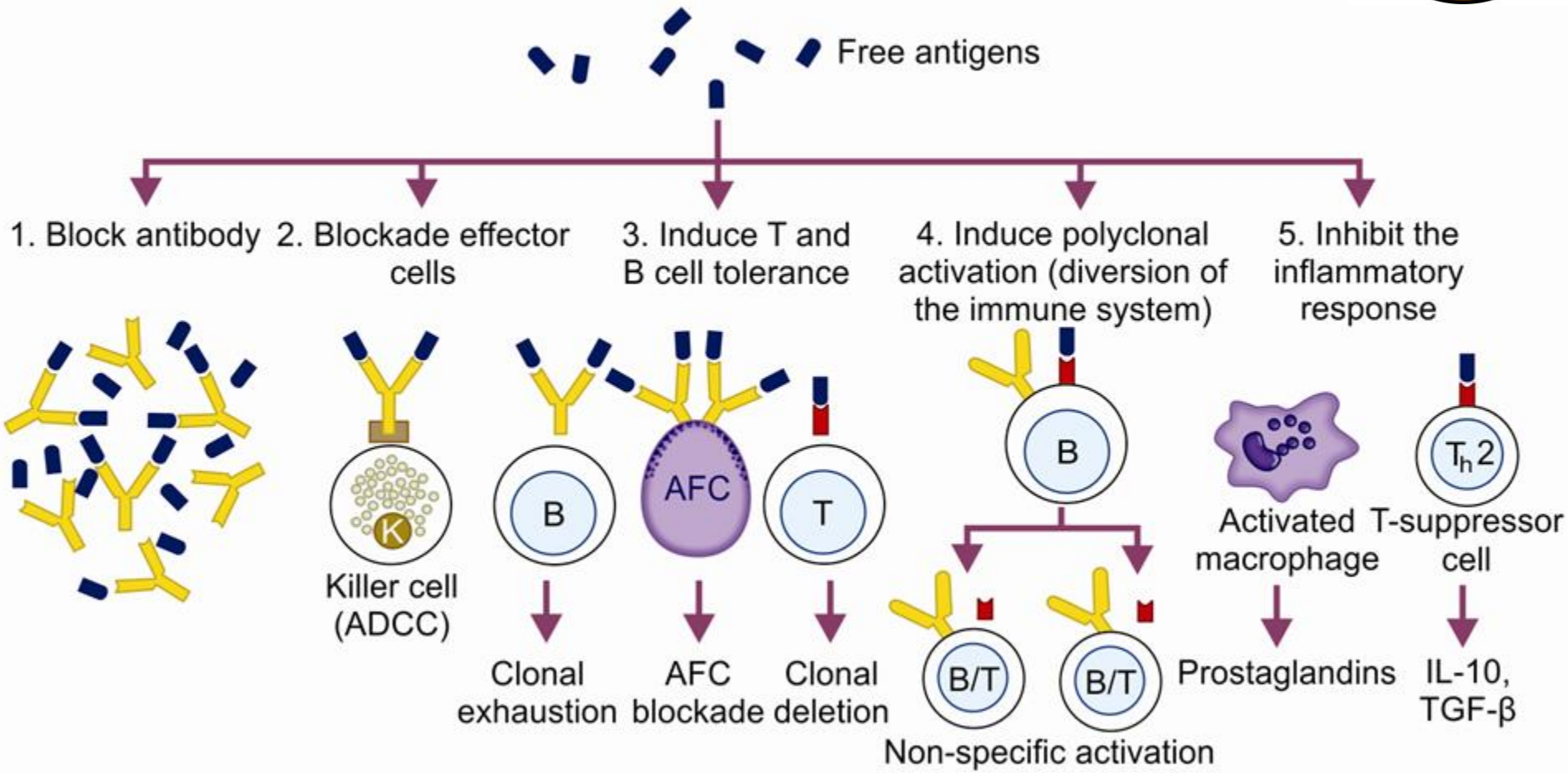
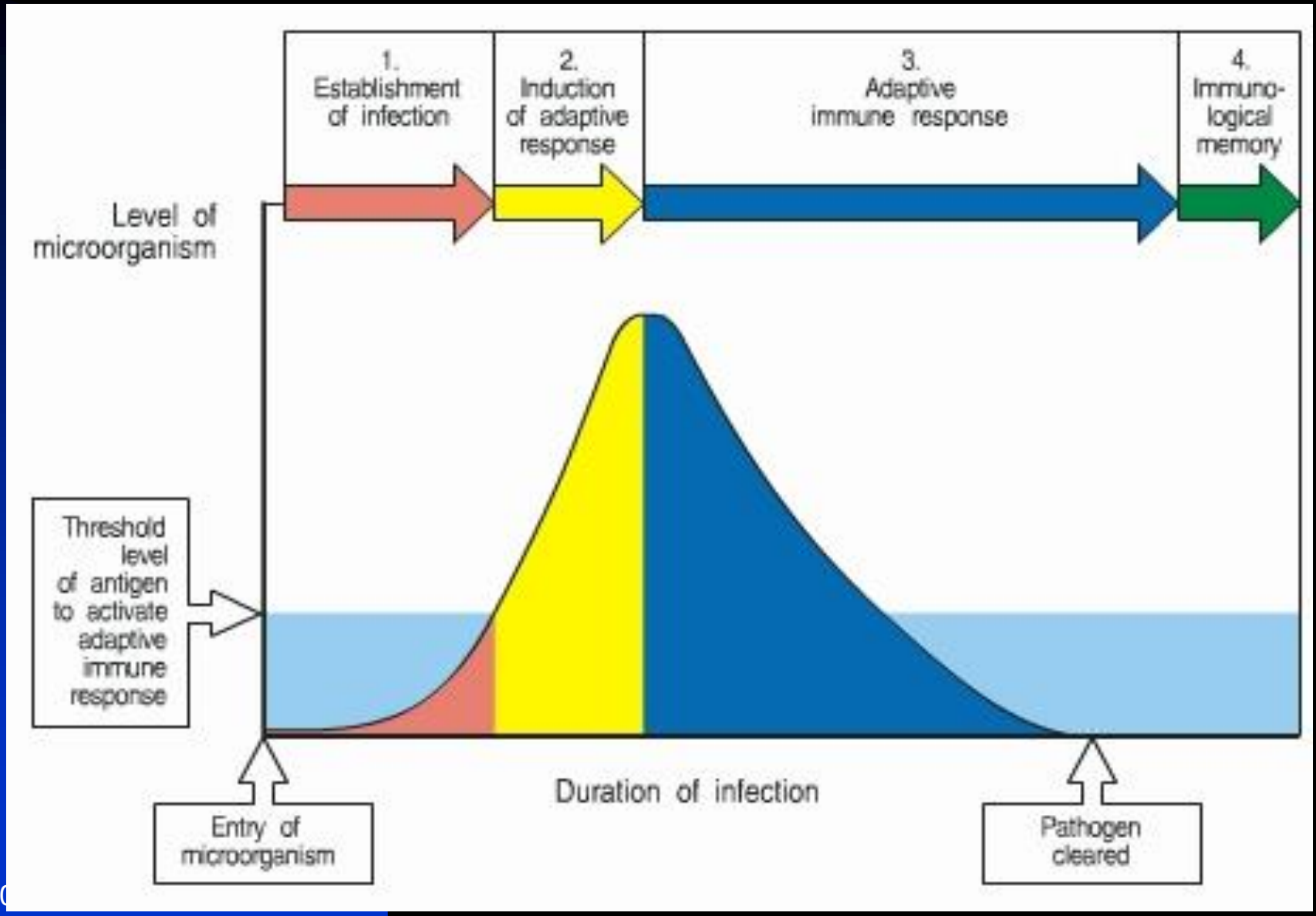


Fig. 11 Free Ags

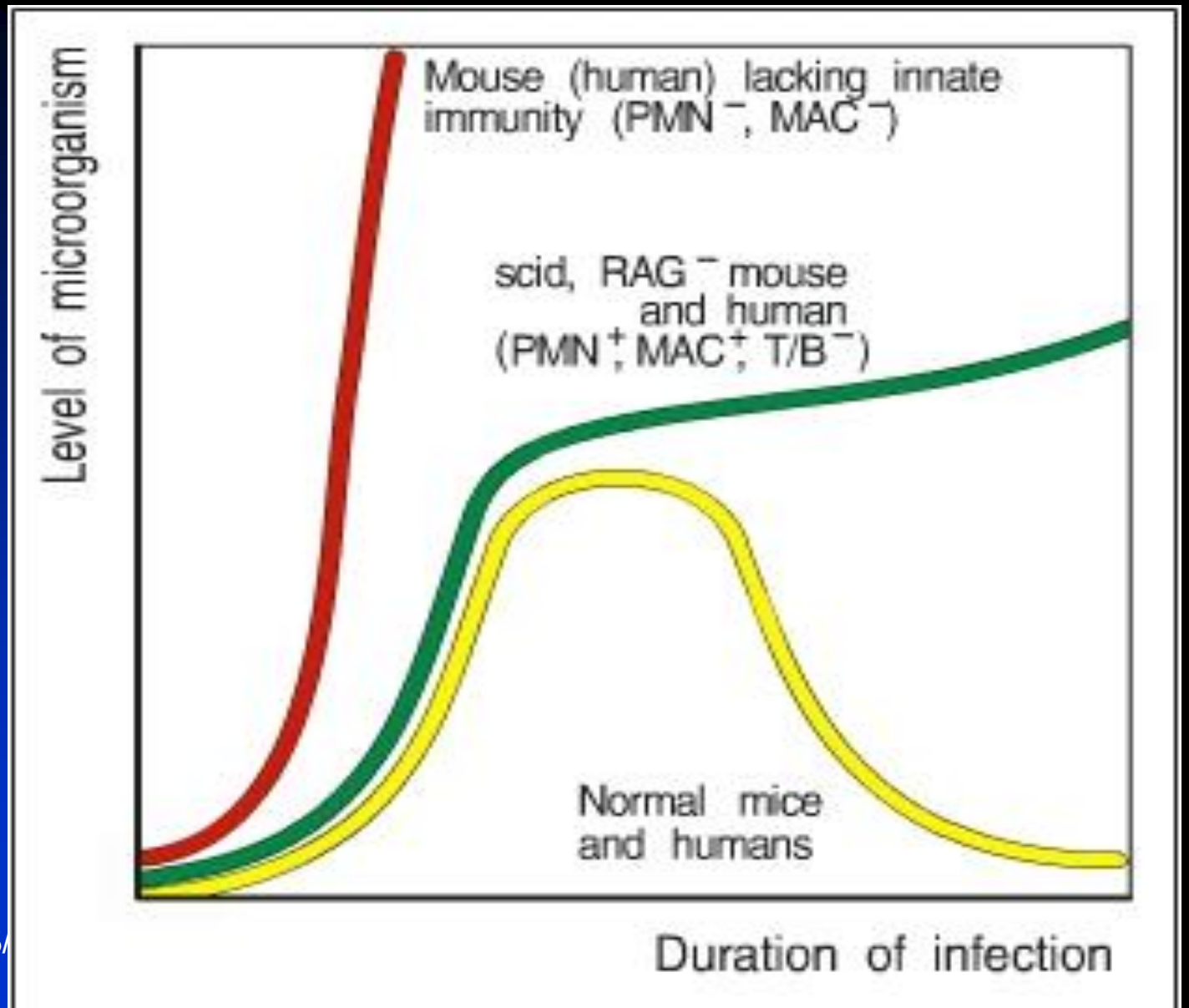
- 1. Combine with Abs and divert it from the parasite. The variant surface glycoprotein of Trypanosoma brucei and the soluble Ags of Plasmodium falciparum, which are also polymorphic and contain repetitive sequences of amino acids, are thought to act in this way as a smokescreen or decoy;
- 2. Blockade effector cells, either directly or as immune complexes. Circulating complexes, for example, are able to inhibit the action of cytotoxic cells active against Schistosoma mansoni;
- 3. Induce T or B cell tolerance, presumably by blockage of antibody-forming cells (AFC) or by

- depletion of the mature antigen specific lymphocytes through clonal exhaustion;
- 4. Cause polyclonal activation. Many parasite products are mitogenic to B or T cell and the high serum concentrations of non-specific IgM (and IgG) commonly found in parasitic infections probably result from this polyclonal stimulation. Its continuation is believed to lead to impairment of B cell function, the progressive depletion of antigen-reactive B cells and thus immunosuppression;
- 5. Activate T cells, especially T_h2 cells or Mϕs or
- both, to release immunosuppressive molecules.
-

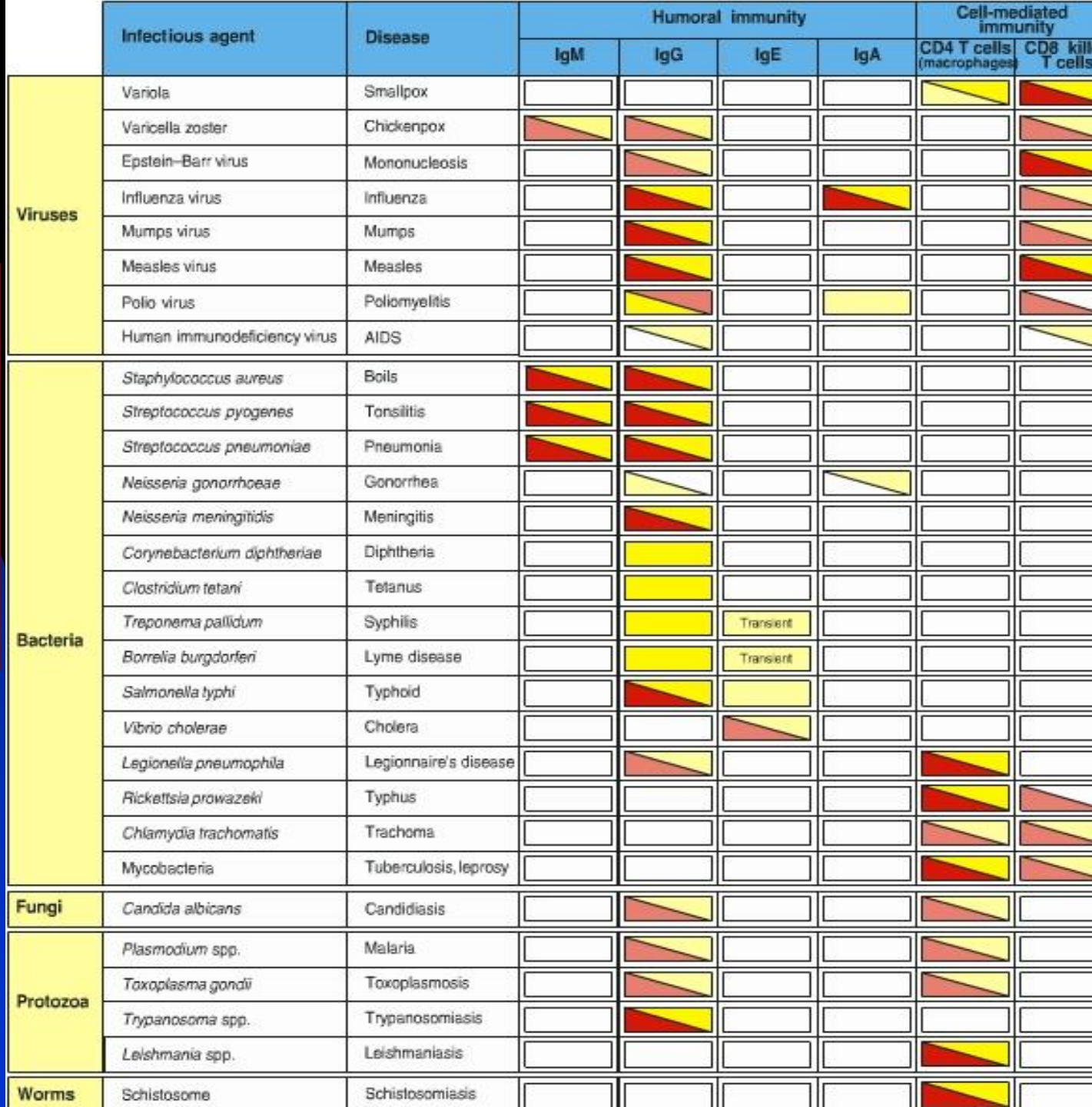
Time Course of Infection



Infection and Immune Defense



Mechanisms used to clear infection vary with the Pathogen



	Infectious agent	Disease	Humoral immunity				Cell-mediated immunity	
			IgM	IgG	IgE	IgA	CD4 T cells (macrophages)	CD8 kill T cells
Viruses	Variola	Smallpox						
	Varicella zoster	Chickenpox						
	Epstein–Barr virus	Mononucleosis						
	Influenza virus	Influenza						
	Mumps virus	Mumps						
	Measles virus	Measles						
	Polio virus	Poliomyelitis						
	Human immunodeficiency virus	AIDS						
Bacteria	*Staphylococcus aureus*	Boils						
	Streptococcus pyogenes	Tonsilitis						
	Streptococcus pneumoniae	Pneumonia						
	Neisseria gonorrhoeae	Gonorrhea						
	Neisseria meningitidis	Meningitis						
	Corynebacterium diphtheriae	Diphtheria						
	Clostridium tetani	Tetanus						
	Treponema pallidum	Syphilis			Transient			
	Borrelia burgdorferi	Lyme disease			Transient			
	Salmonella typhi	Typhoid						
	Vibrio cholerae	Cholera						
	Legionella pneumophila	Legionnaire's disease						
	Rickettsia prowazeki	Typhus						
	Chlamydia trachomatis	Trachoma						
	Mycobacteria	Tuberculosis, leprosy						
Fungi	*Candida albicans*	Candidiasis						
Protozoa	*Plasmodium spp.*	Malaria						
	Toxoplasma gondii	Toxoplasmosis						
	Trypanosoma spp.	Trypanosomiasis						
	Leishmania spp.	Leishmaniasis						
Worms	Schistosome	Schistosomiasis						

Infection and Immunity

Avoid it.

Keep it out.

Kill it if it gets in

If can't kill it, isolate it.

If can't kill it, keep it from replicating.

If can't control it. Surrender.

Die and don't pass it on.

- **SUGGESTED READING**

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4. Thao Doan, Roger Melvold, Susan Viselli, et al. Lippincott's illustrated reviews: Immunology. 1st Indian print. Baltimore, USA: Lippincott Williams and Wilkins; 2008.

- 5. Perez-Lopez A, Behnsen J, Nuccio SP, Raffatellu M. Mucosal immunity to pathogenic intestinal bacteria. **Nat Rev Immunol.** 16(3):135-148; 2016.

Questions:

1. How does the innate immune response "sense" bacteria?
2. Discuss briefly the humoral and cell mediated immune responses to viruses, for example, 2019-nCoV/SARS-Cov-2 infection, please!
3. How viruses evade the host defense mechanisms?
4. Discuss the host immune responses to bacterial infections, please!
5. How to understand the general overview of mucosal immunity to intestinal pathogens and commensal micro-organisms?

- **6. How to understand the *Mycobacterium tuberculosis* infection and granuloma formation?**

- **Short Notes**

1. Role of eosinophils in parasitic infection.

2. Immunity against intracellular bacteria.

3. Mucosal immunity against viral infections.

- **4. Mucosal immunity against bacterial infections.**

5. T cell-mediated immune response against fungal infections.