Immunity to microbes

Overview of immune responses to microbes

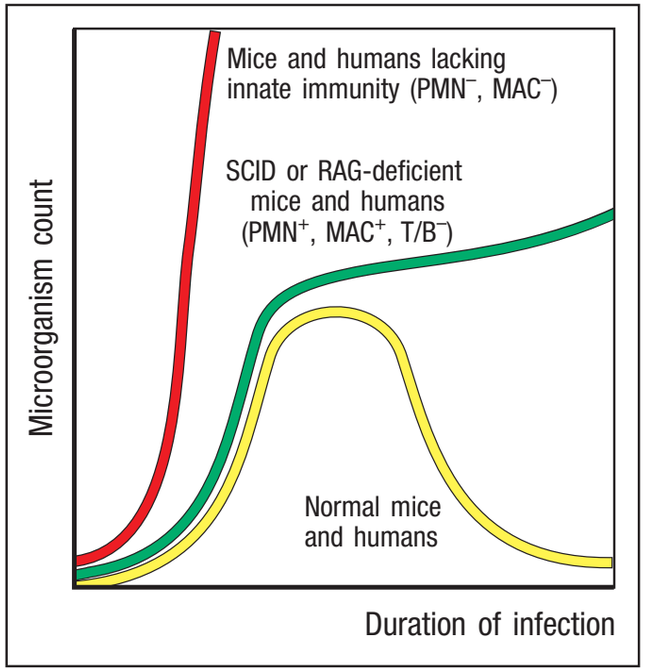
- **Specialised and distinct** responses to *different types* of microbes to most effectively combat these infectious agents

- **Survival and pathogenicity** of microbes in a host are influenced by their ability to *evade* or resist effector mechanisms of immunity

- **Latent, or persistent** infections are established by some microbes, where the immune response *controls but does not eliminate* the pathogen (e.g. herpesvirus, poxvirus and some intracellular bacteria such as the pathogen causing tuberculosis)

- **Tissue injury and disease** may be caused by the *host response* to the microbe other than by the microbe itself

- **5 main categories of pathogenic microorganisms**: extracellular bacteria, intracellular bacteria, fungi, virus, protozoan, multicellular parasites

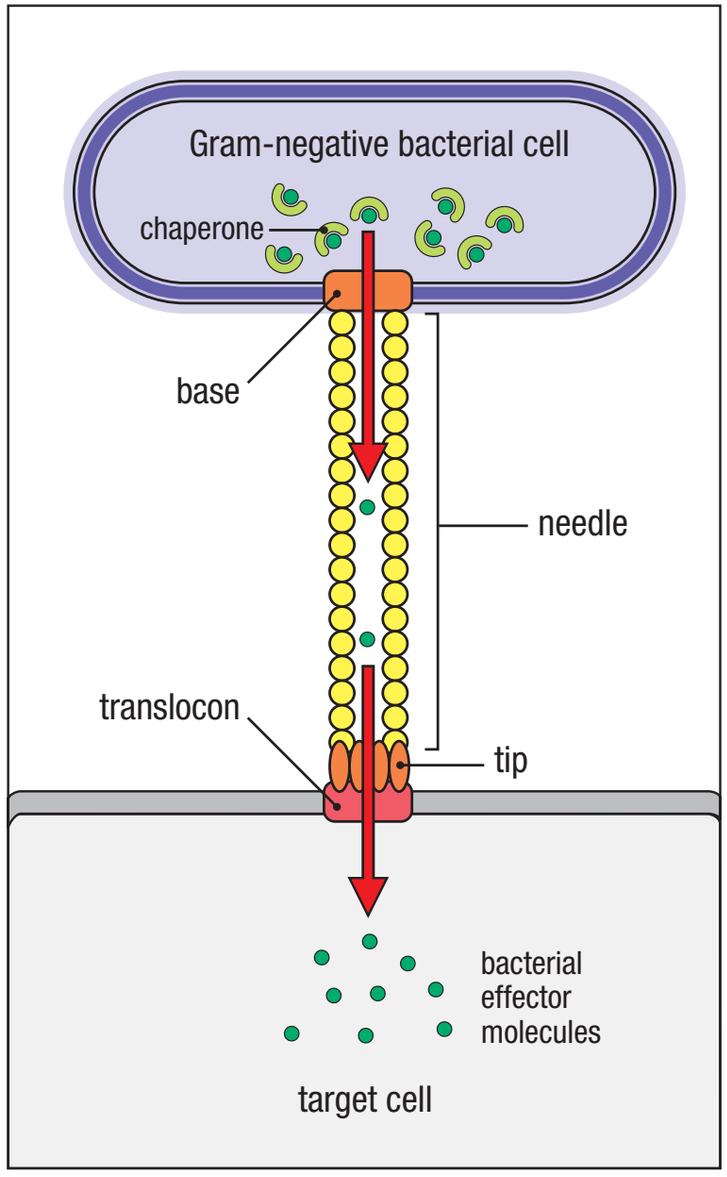


Virulence factors

Virulence factors: molecules useful for invasion of the body and proliferation within the host (pathogenicity)

- Uptake of essential nutrients
- Adherence to epithelium (binding to host cell proteins)
- Evasion of immune responses
- Toxins

Pathogenic bacteria use specialized secretion systems (T3SS/T4SS) to inject virulence factors into host cells. A prominent example is *Yersinia pestis* (agent for plague), which secrets YOPs into cells disrupting the actin cytoskeleton and, thus, inhibiting phagocytosis.



Immunity to extracellular bacteria

Can replicate outside the host cells, cause disease by:

- Inflammation-mediate tissue destruction
- Toxin production : exotoxin (whithin bacterial cell) or exotoxin (actively secrete)

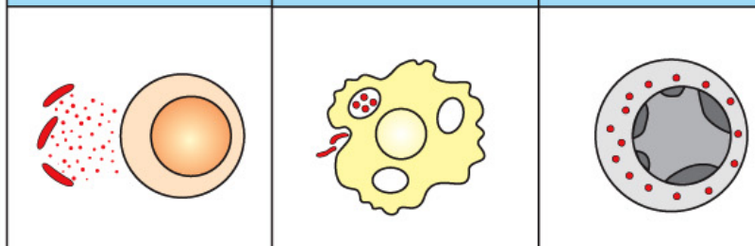
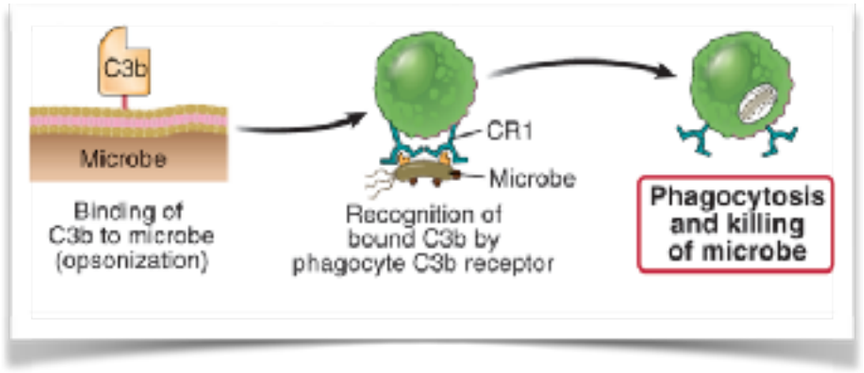
Pathogenic mechanism	Direct mechanisms of tissue damage by pathogens		
	Exotoxin production	Endotoxin	Direct cytopathic effect
			
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridium tetani* *Vibrio cholerae*	*Escherichia coli* *Haemophilus influenzae* *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)
Disease	Tonsillitis, scarlet fever Boils, toxic shock syndrome, food poisoning Diphtheria Tetanus Cholera	Gram-negative sepsis Meningitis, pneumonia Typhoid fever Bacillarydysentery Wound infection Plague	Smallpox Chickenpox, shingles Hepatitis Poliomyelitis Measles, subacute sclerosing panencephalitis Influenza Cold sores Kaposi's sarcoma

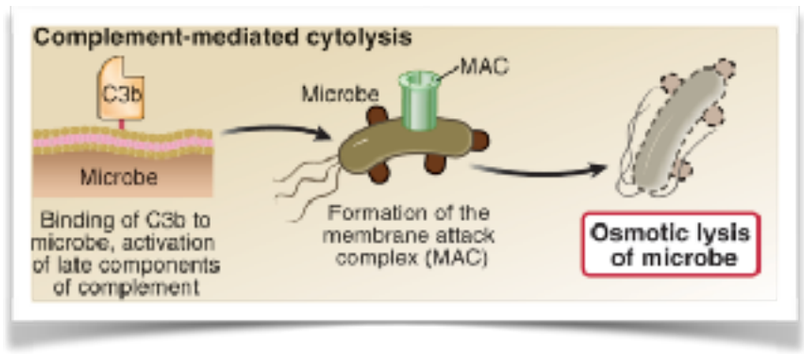
Figure 2.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

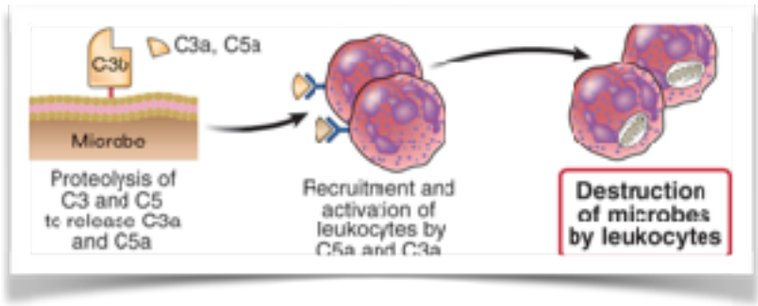
Toxins mediate various pathogenic effects and are thus often the target of antibodies produced against these pathogens (neutralize their effects)

Innate immunity to extracellular bacteria

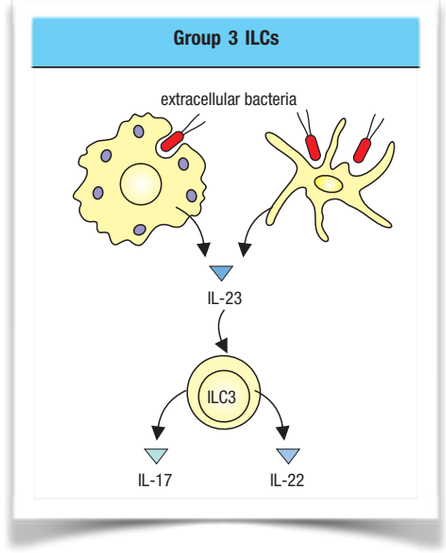
- Complement (alternative and lectin) pathway activation (peptidoglycans and LPS) facilitates bacteria *phagocytosis, lysis and inflammation*



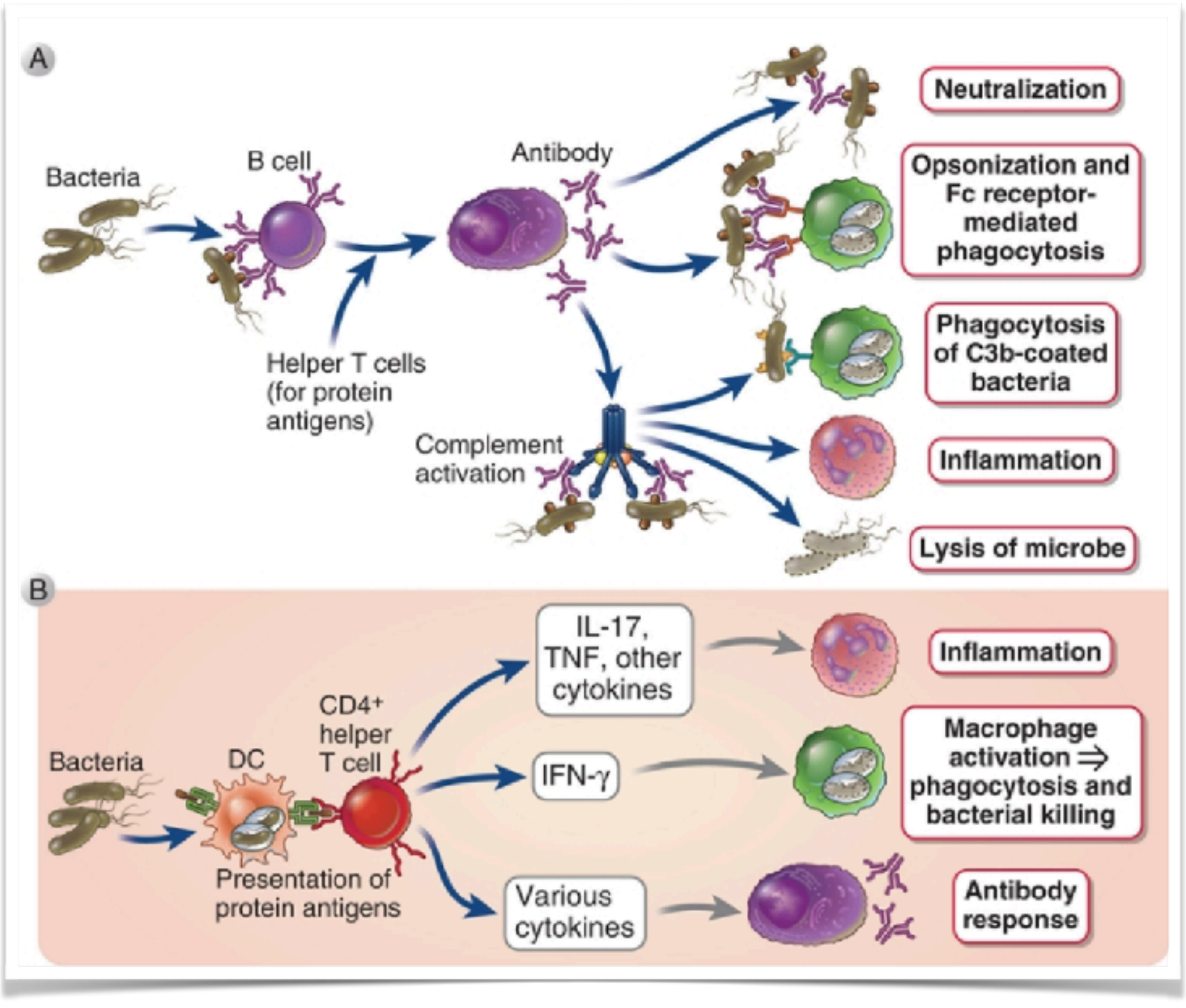




- Activation of phagocytes (Fc receptors, TLR): neutrophils and macrophages
- Macrophages activation (cytokine secretions, pro-inflammatory, local and systemic effects (fever, acute-phase proteins activators of the complement))
- Neutrophils granule secretions, extracellular traps (NETs) form a scaffold containing toxic granule proteins
- ILC3 activation enhances epithelial *barrier function* and recruits neutrophils
- NK cell cytokine secretions (IFN-y) activate macrophages (feedback)



Adaptive immunity to extracellular bacteria



Immunity to extracellular bacteria

Adaptive immunity:

- Humoral: **antibody** response directed against *cell wall antigens and toxins* to *neutralize* (high affinity IgG, IgM and IgA), *opsonise* (IgG1 and IgG3) and *phagocytose*, activate the *classical complement* pathway (IgM, IgG1, IgG3)
- Cellular: helper T cells activated by protein antigens (mainly **Th17,** also Th1) induce local *inflammation*, enhance phagocytic and microbicidal activities and stimulate *antibody production*

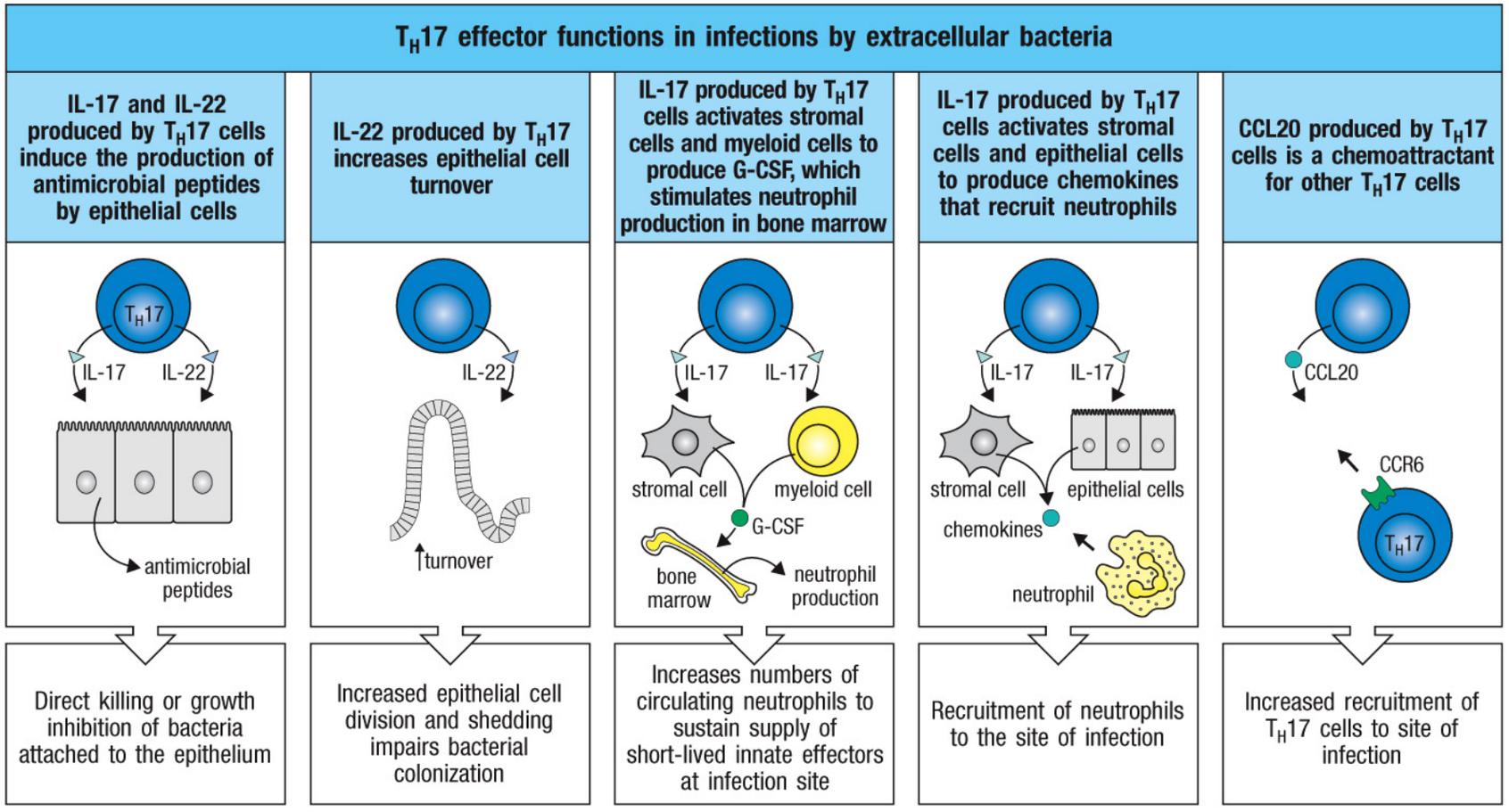
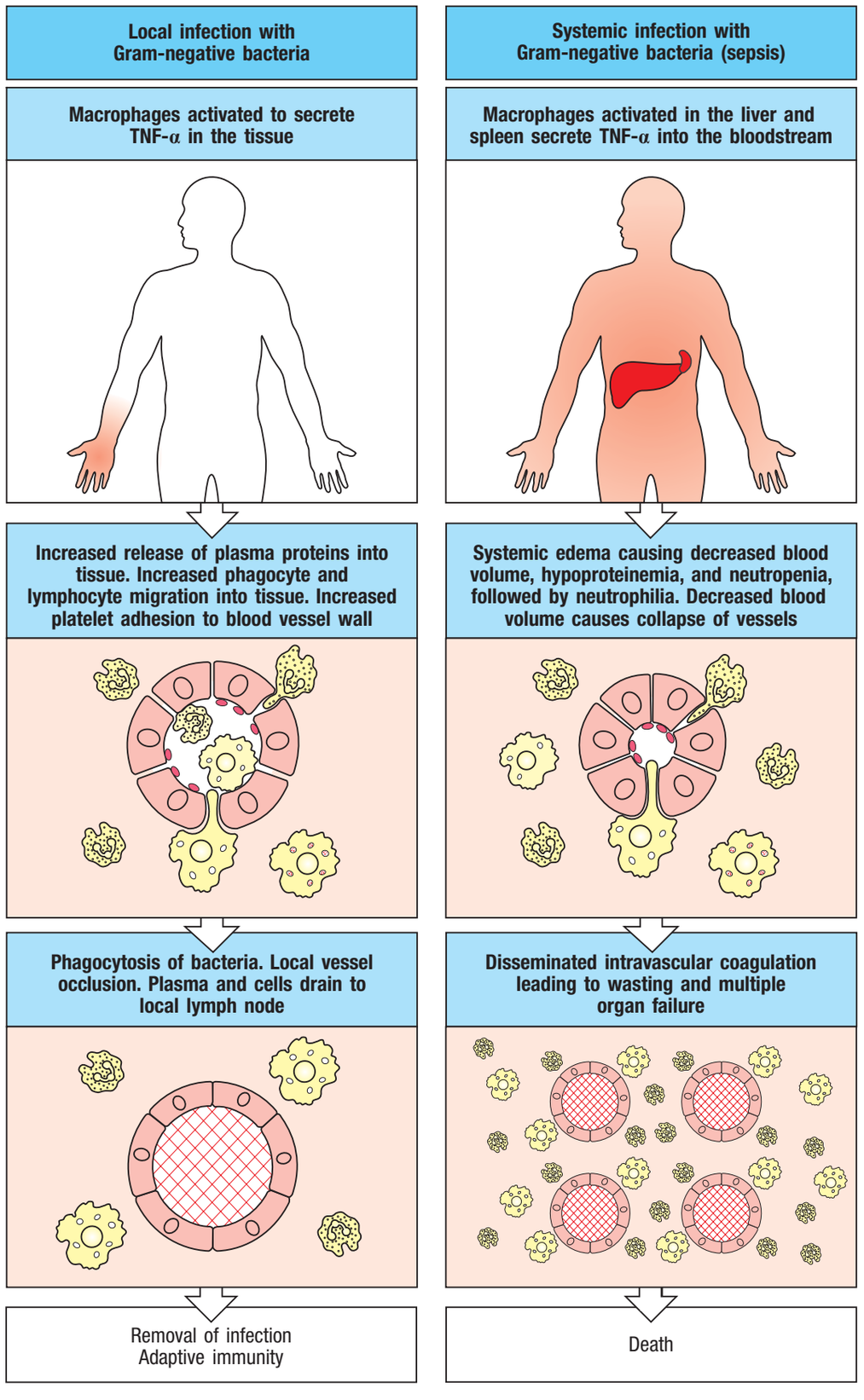


Figure 11.16 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Injurious effects of innate immunity to extracellular bacteria

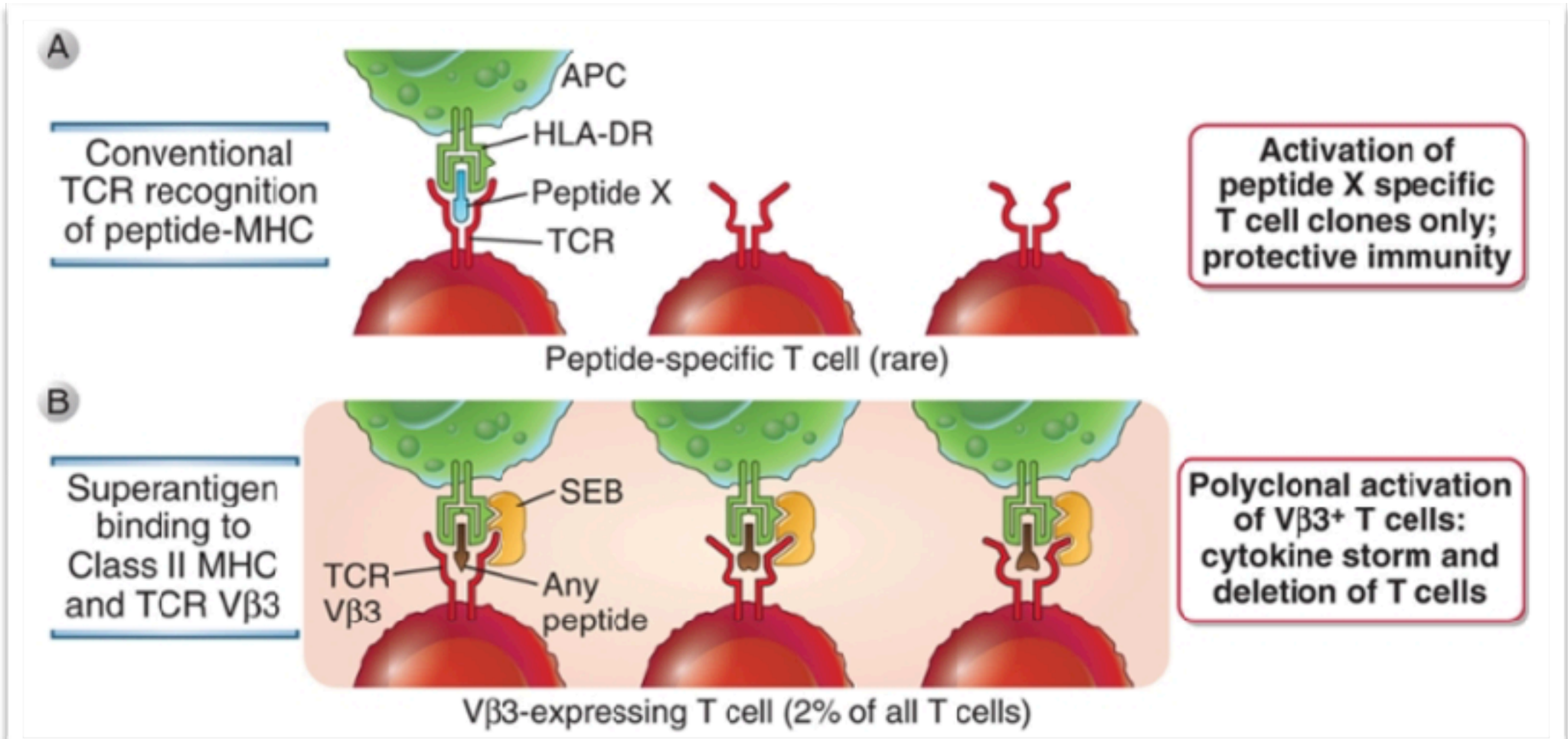
Local inflammation induced by tissue damage as a collateral effect of macrophage activation and neutrophil activation.
Sepsis refers to a condition, wherein viable bacteria or bacterial products are found in blood. Septic shock is the most severest form of sepsis with often fatal outcomes.
The initial triggers of sepsis are cytokines (IL6, IL1, TNFa) that unfold systemic effects - this phenomenon is sometimes also referred to as cytokine storm.



Injurious effects of adaptive immunity to extracellular bacteria

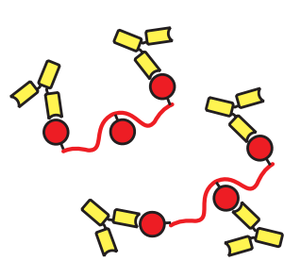
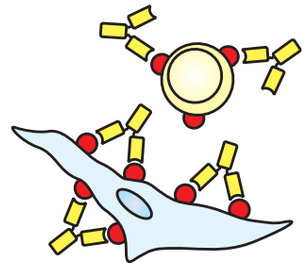
Superantigens: bacterial *toxins* that bind to TCR and also II MHC molecules but *not to the peptide-binding cleft*, thus activating *many more T cell clones* than conventional antigens

➔ induce large amounts of *cytokine* production that can cause systemic inflammatory syndromes

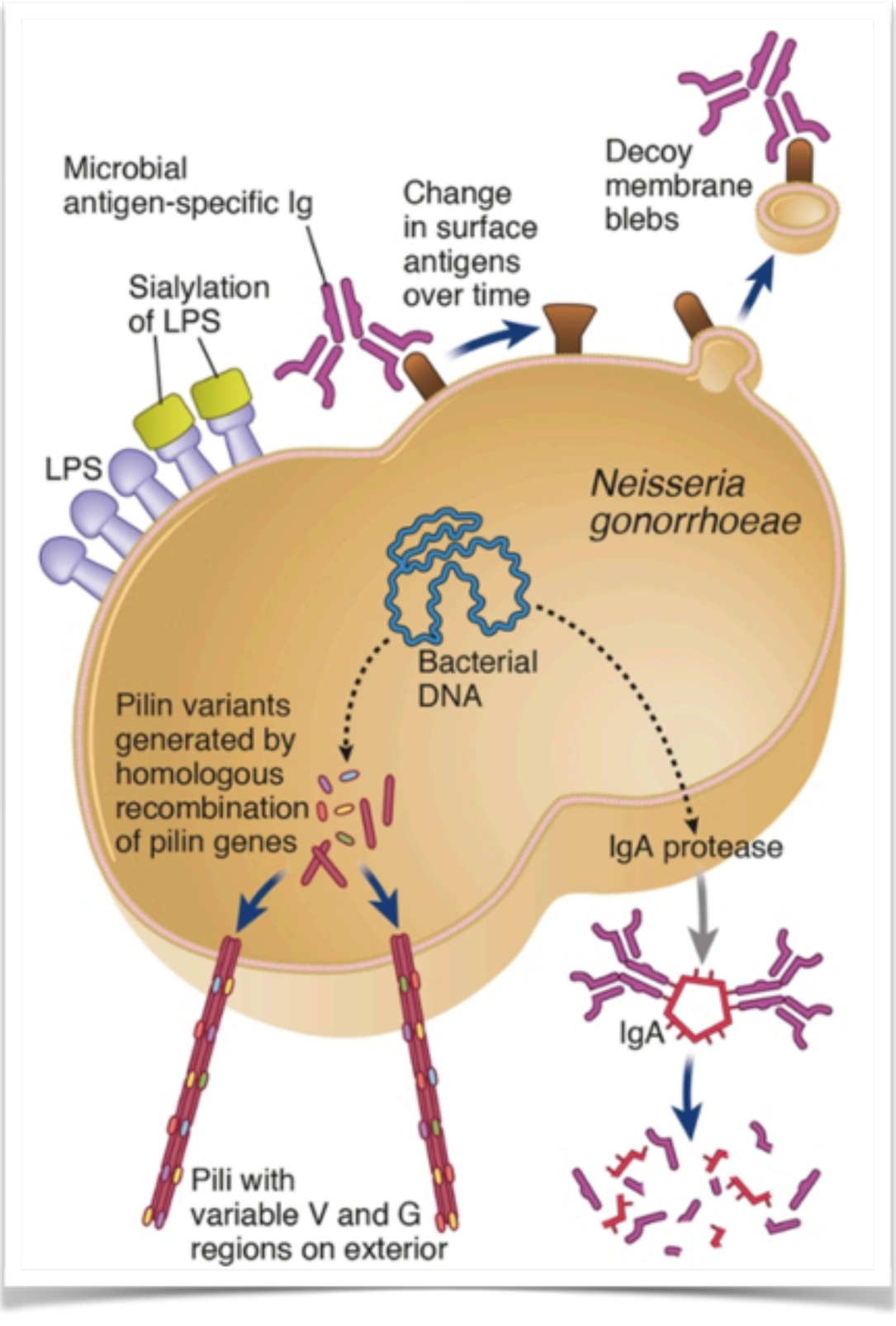


Injurious effects of adaptive immunity to extracellular bacteria

A late complication of infection can be due to the production of disease causing antibodies. Examples include rheumatic fever or post-infection nephritis.

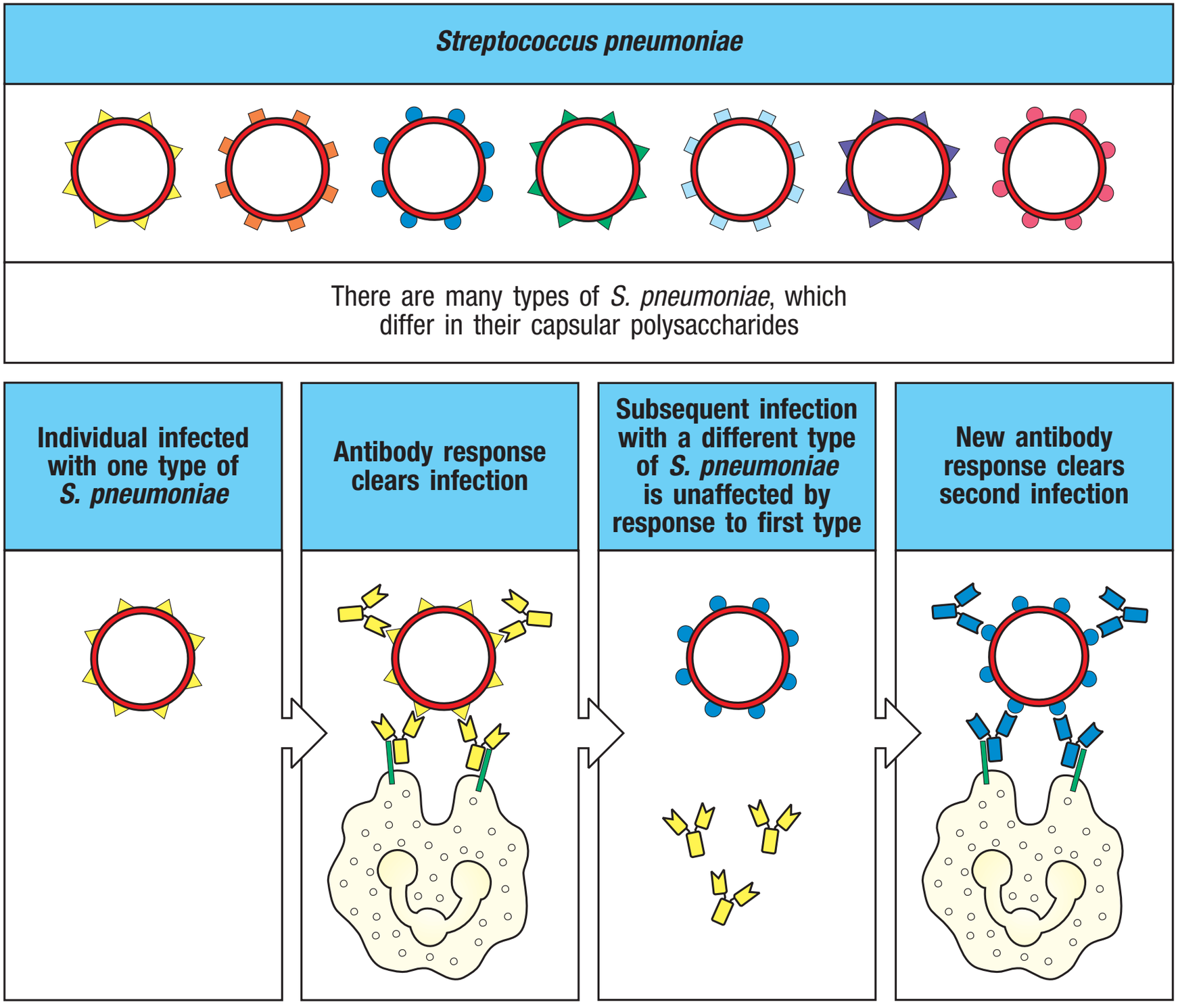
Indirect mechanisms of tissue damag	
Immune complexes	**Anti-host antibody**
	
Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*
Kidney disease Vascular deposits Glomerulonephritis Kidney damage in secondary syphilis Transient renal deposits	Rheumatic fever Hemolytic anemia

Immune evasion by extracellular bacteria

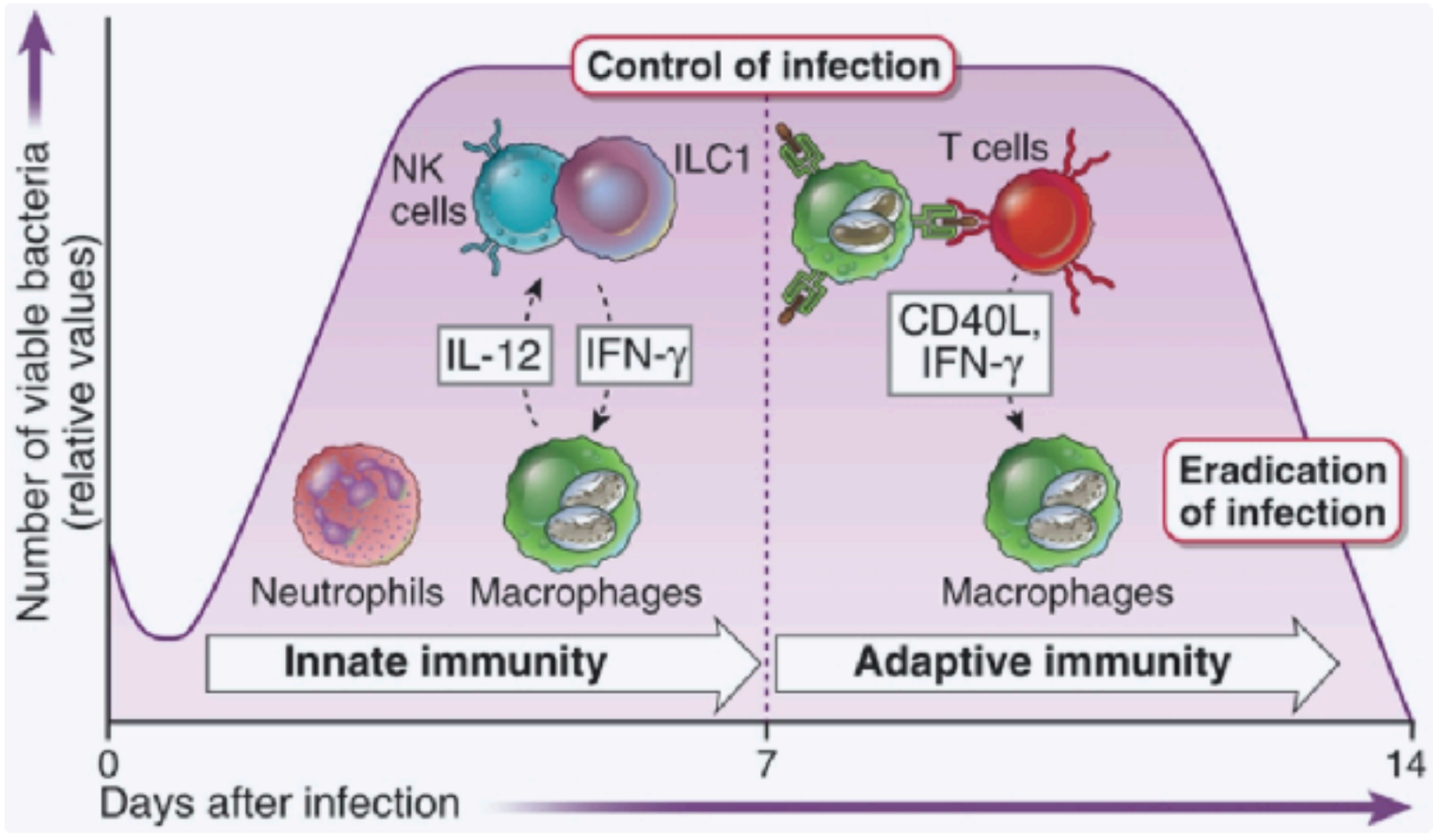


- Bacteria with **capsules** resist *phagocytosis* and are therefor more virulent
- Some capsules contain **sialic acid residues** that inhibit *complement* alternative pathway
- **Variation of surface antigens** or release of surface antigens in membrane blebs enable evasion from *humoral* responses (important for vaccination, gives rise to multiple serotypes of the same subspecies = classification based on surface molecules)

Immune evasion by extracellular bacteria



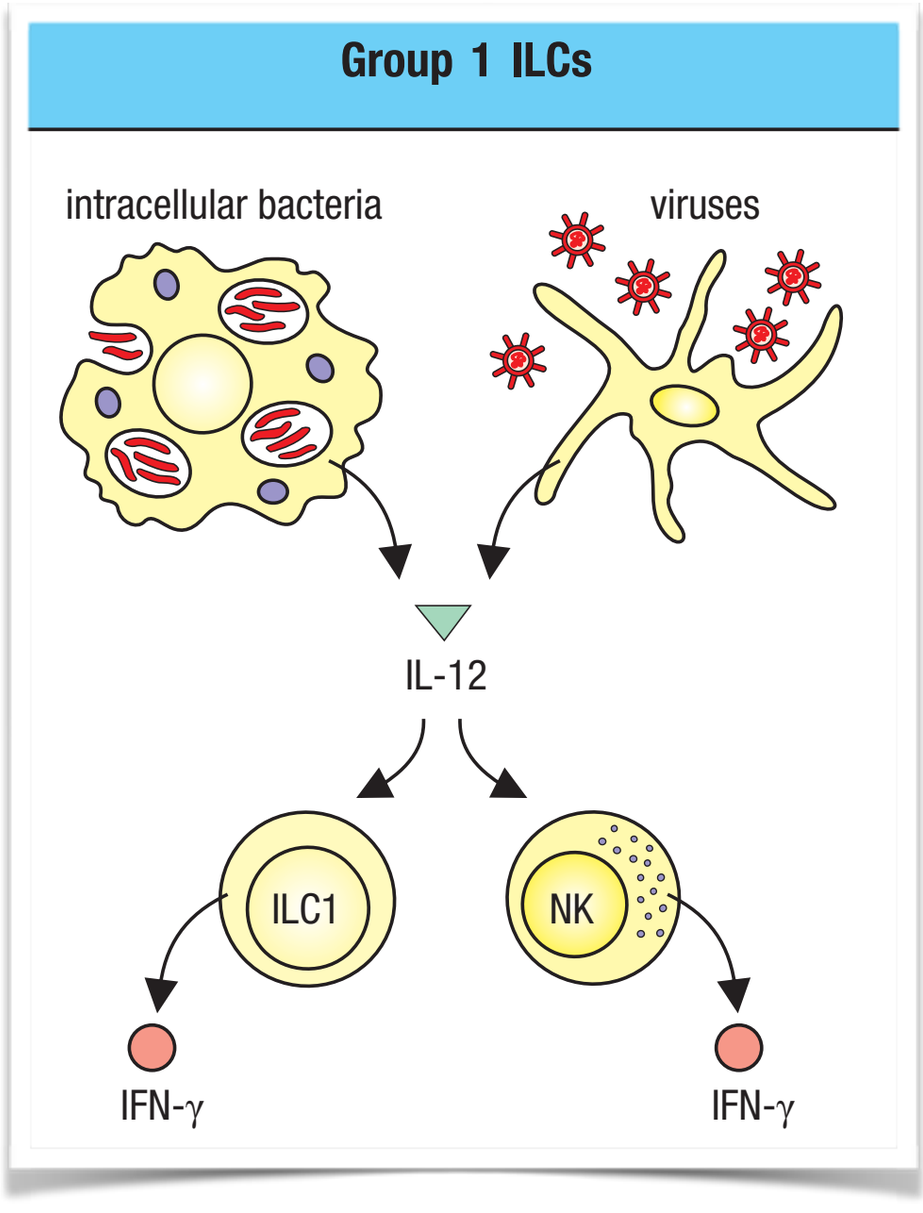
Immunity to intracellular bacteria



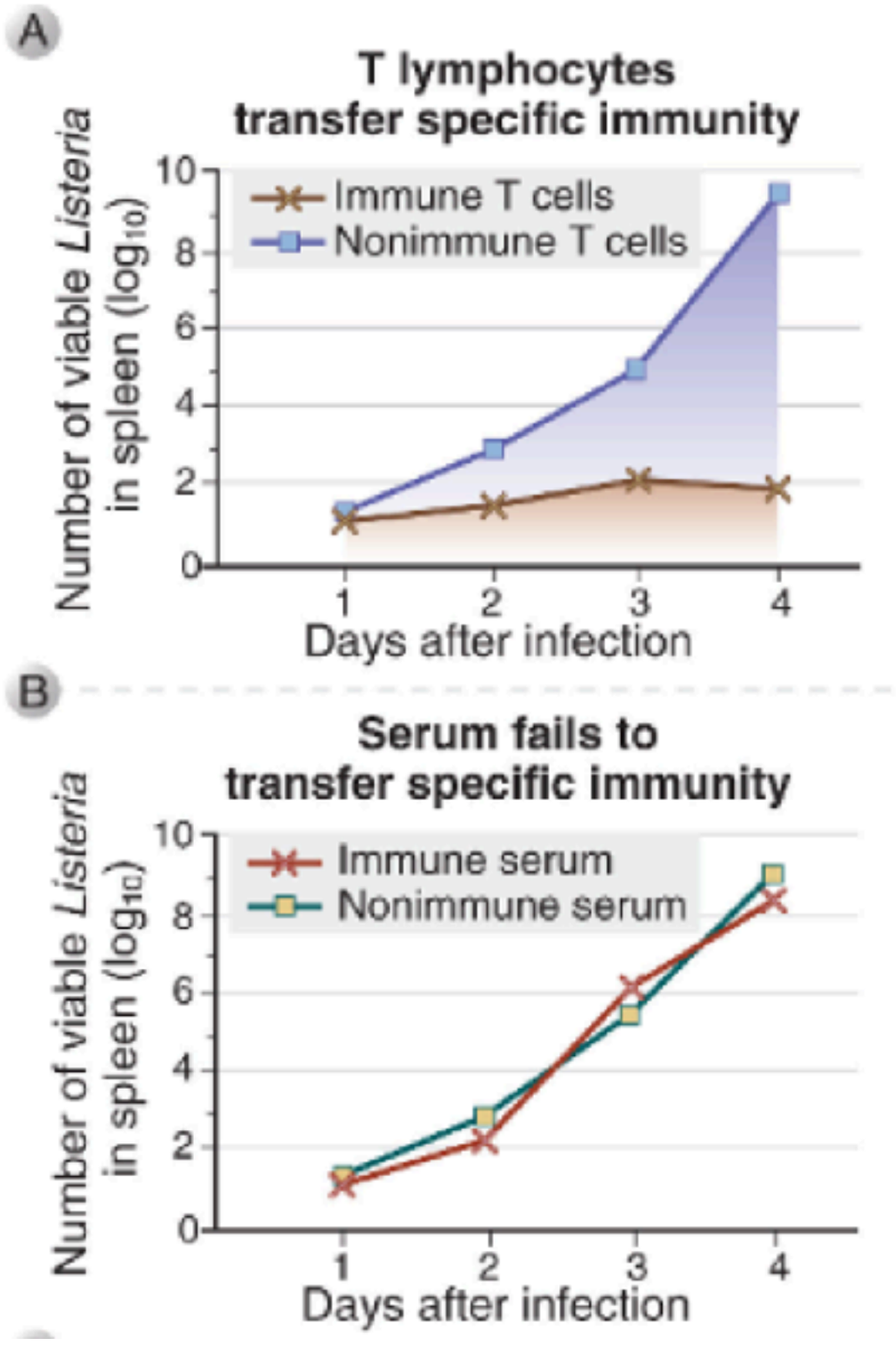
Innate immunity to intracellular bacteria

Survive *within phagocytes:* inaccessible to circulating antibodies, their elimination requires a coordinated cell-mediated immunity

- Phagocytes activation (*TLRs* and *NLRs*, bacterial DNA induces *type I interferon*)
- NK cells (infected cells express NK cell-activating ligands and cytokines) produce *IFN-γ* which activates macrophages
- ILC1 also secrete *IFN-γ and TNFa* to activate macrophages

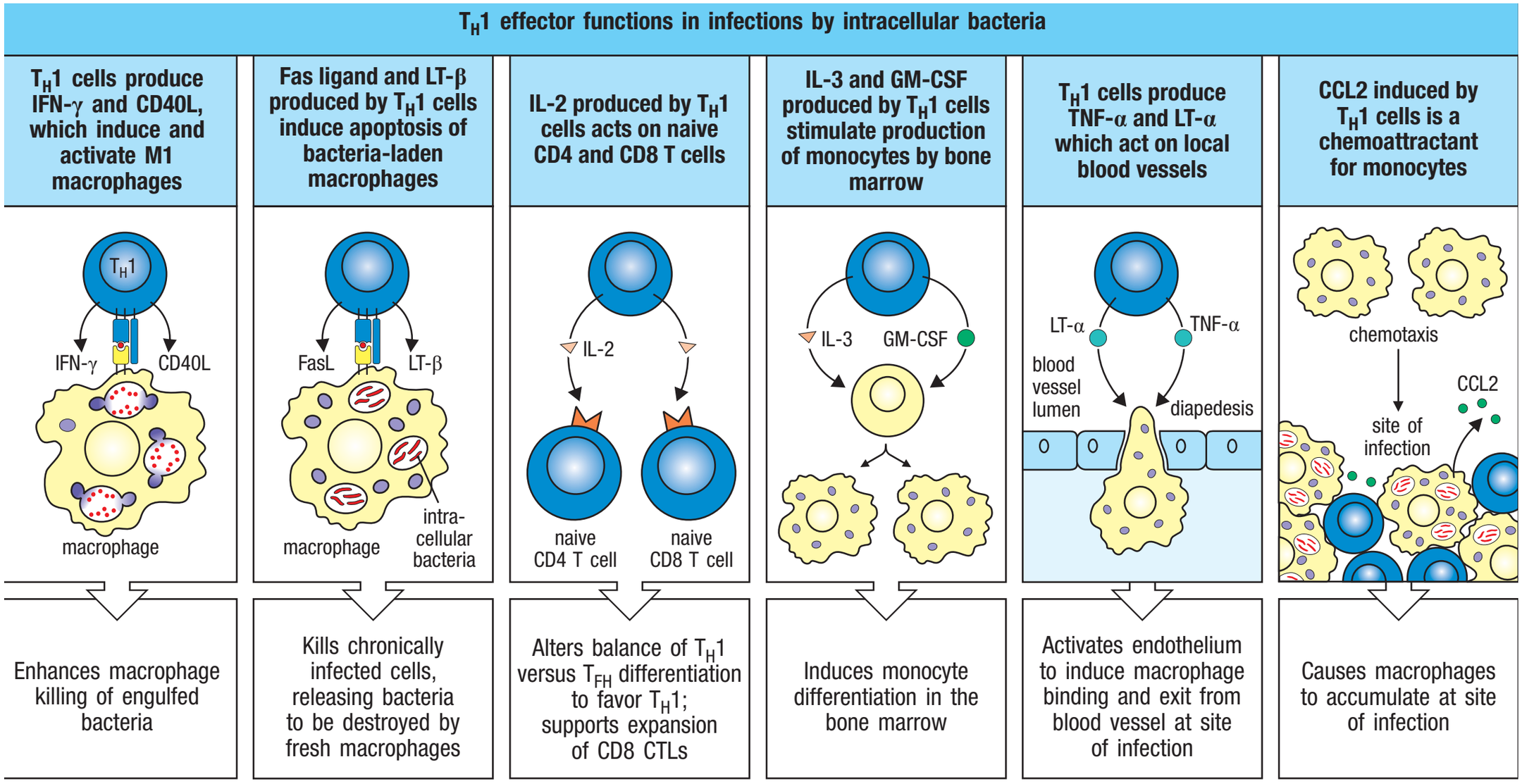


Adaptive immunity to intracellular bacteria



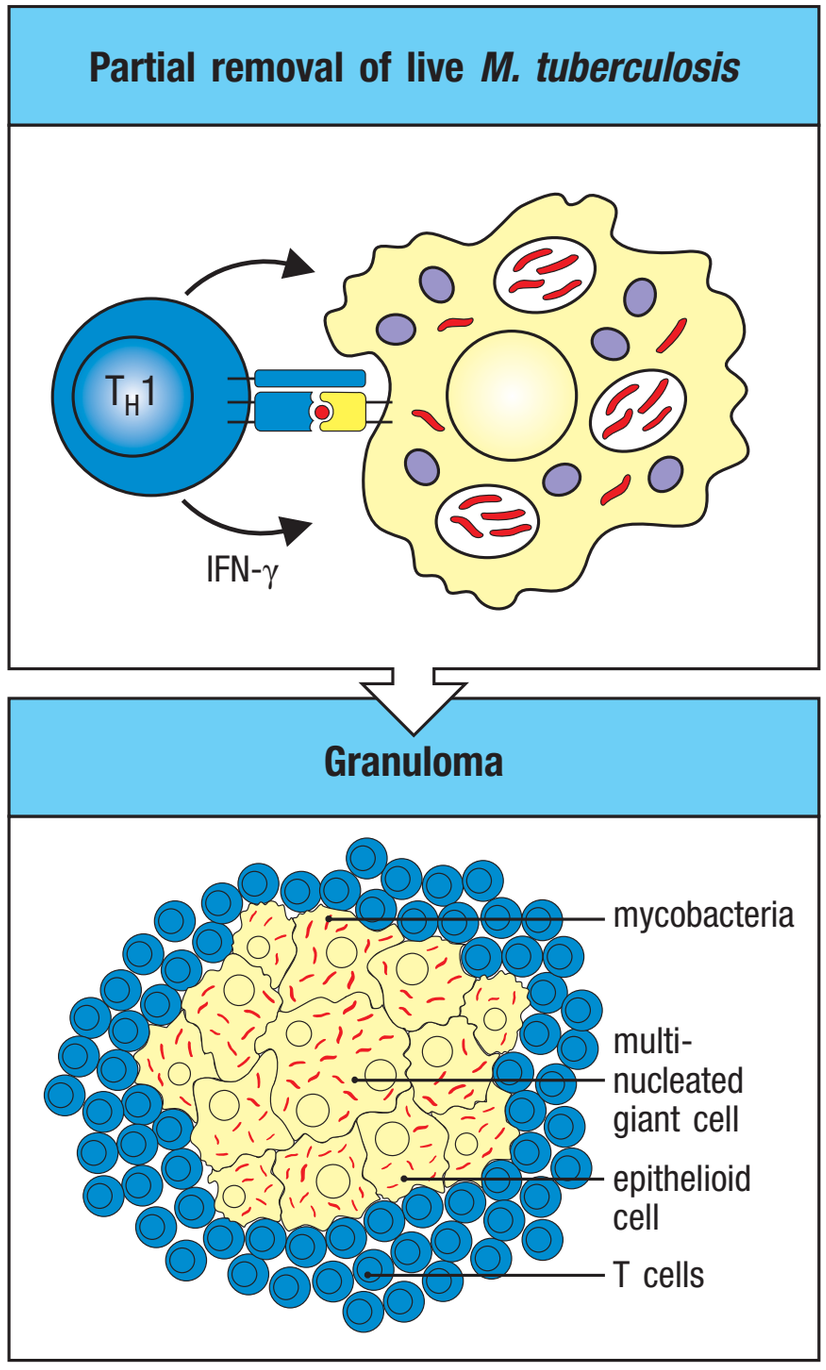
Adaptive immunity to intracellular bacteria

<u>Cell-mediated (!)</u>: IL-12 induced Th1 effector cells activate *phagocytes* (CD40 ligand, IFN-γ), $CD8^+$ CTLs *kill* infected cells (requires transport of bacterial antigens into the cytosol) and produce cytokines (IFN-y, TNFa, LTa)



Injurious consequences of immunity to intracellular bacteria

Insufficient killing of intracellular bacteria can trigger chronic activation of macrophages and Th1 cells leading to the formation of **granulomas**. Whereas granulomas can effectively contain the spread of pathogens, they are associated with severe tissue damage and reduced functionally (tuberculosis).

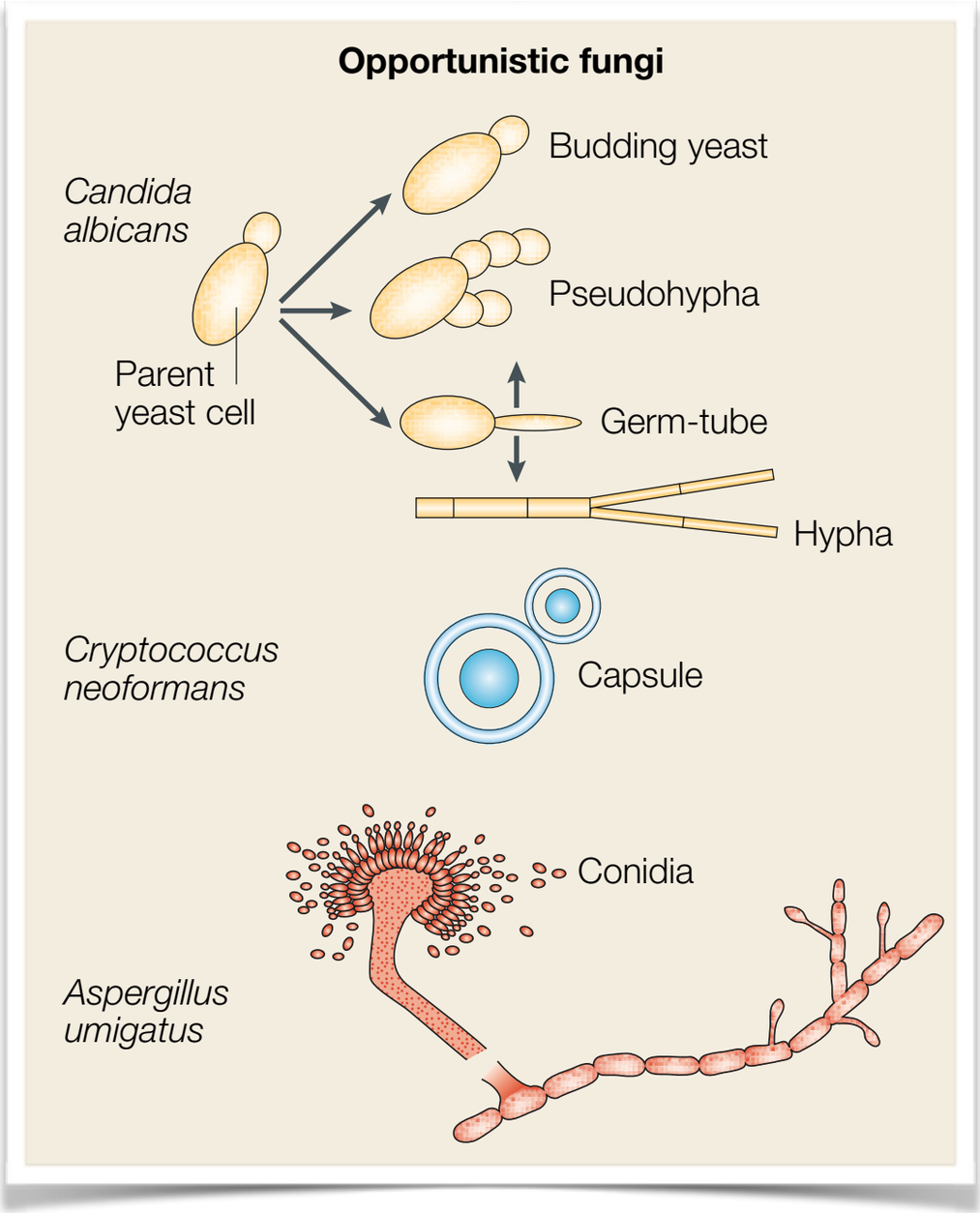


Evasion of immunity by intracellular bacteria

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.

Immunity to fungi

- Live in *extracellular tissues* or *within phagocytes*
- Some are *opportunistic* and cause mild or no disease in healthy individuals but may cause severe disease in *immunodeficient* individuals



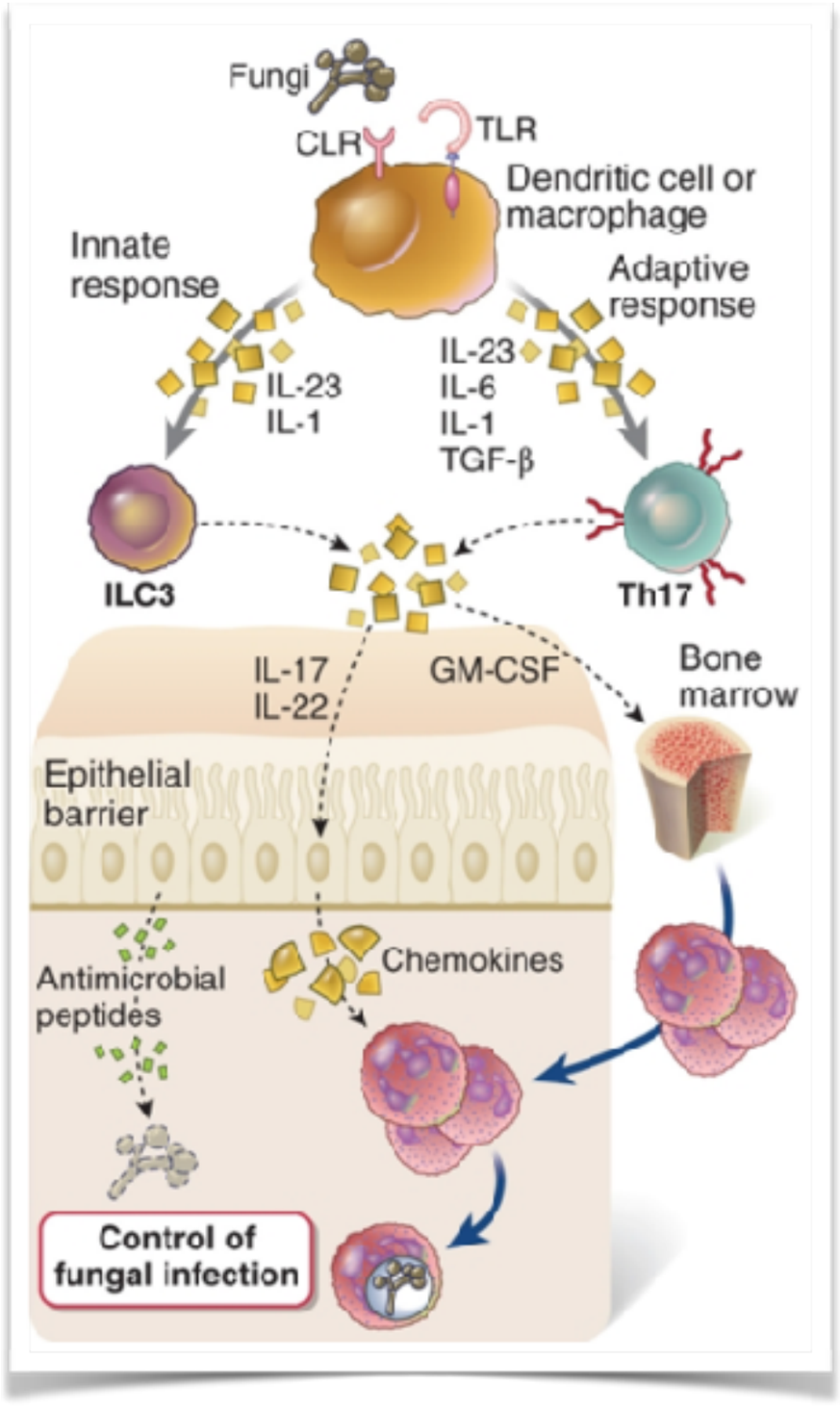
Immunity to fungi infections (mycoses)

Innate immunity:

- Macrophages and DCs sense fungi via *dectins* (receptors recognising β-glucan surface proteins) and produce *cytokines*
- ILC3 recruit and activate *neutrophils*
- Neutrophils liberate fungicidal substances (*ROS*, lysosomal enzymes)

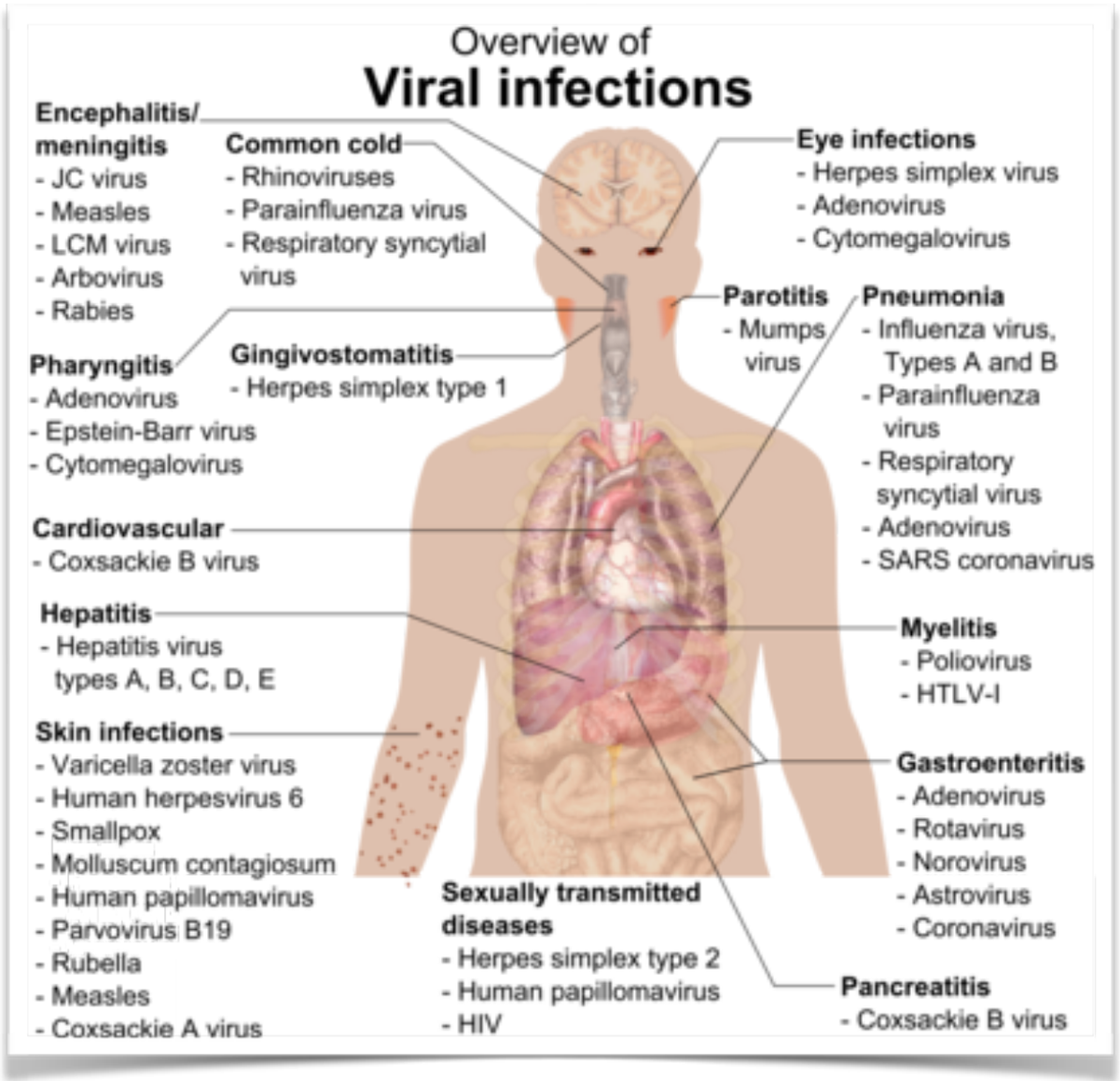
Adaptive:

- Cell-mediated (mostly): *cooperation of CD4⁺ and CD8⁺ T cells*, extracellular fungi elicit strong Th17 responses, intracellular fungi rather Th1



Immunity to viruses

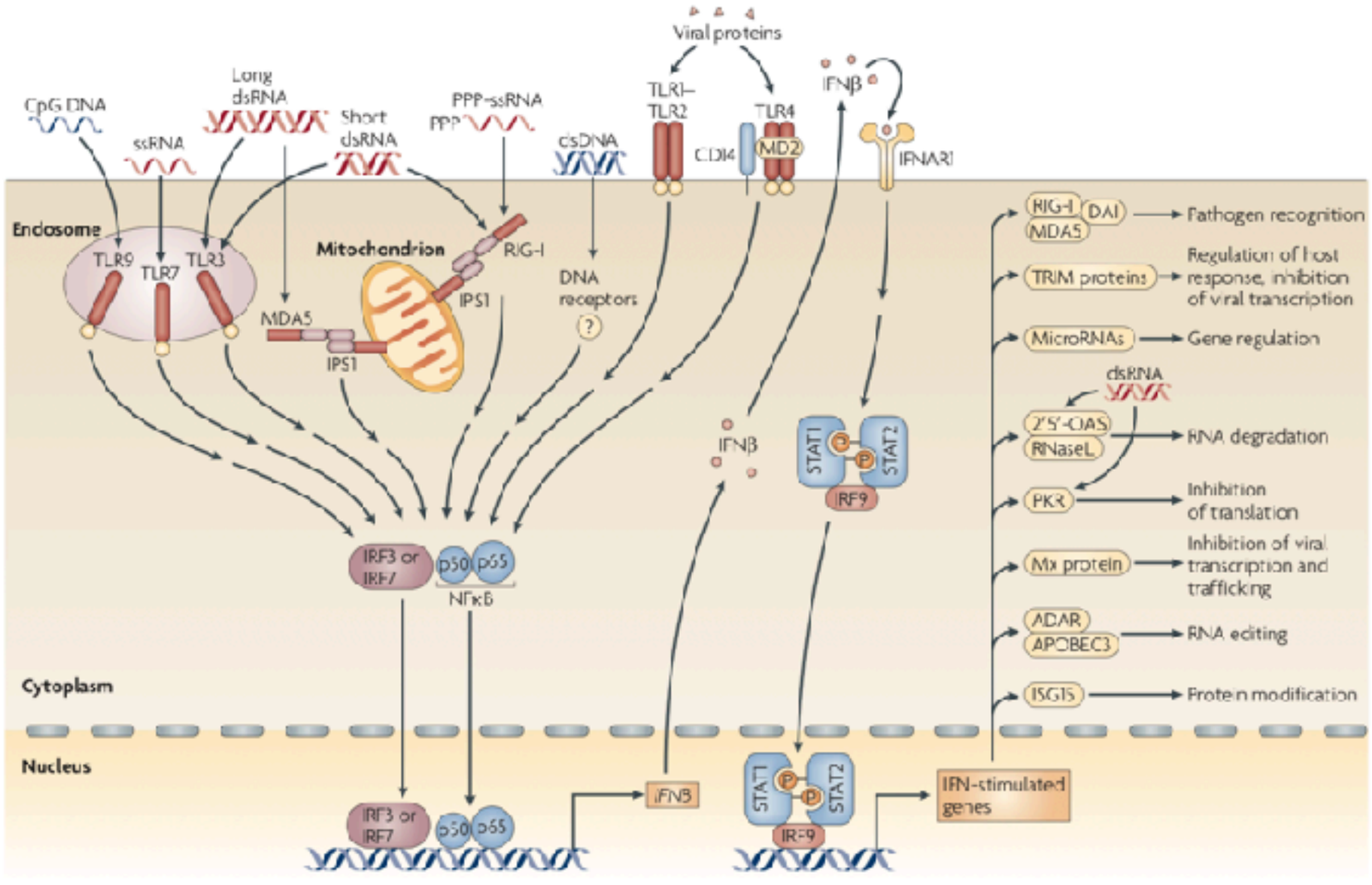
- Obligatory *intracellular* pathogens that require the host machinery to replicate
- Can infect *various cell types* by endocytosis upon binding to *surface molecules*
- Can infect via all possible body *surfaces*
- Contain either *DNA or RNA* (important in terms of detection)



Virus: Pattern recognition receptors

Converge to NFkB to elicit a strong *type I IFN* production and release and inducing many IFN stimulate genes (ISGs). IFN receptor (IFNAR) are present on almost all cells of the body.

Different receptors recognise different viruses.



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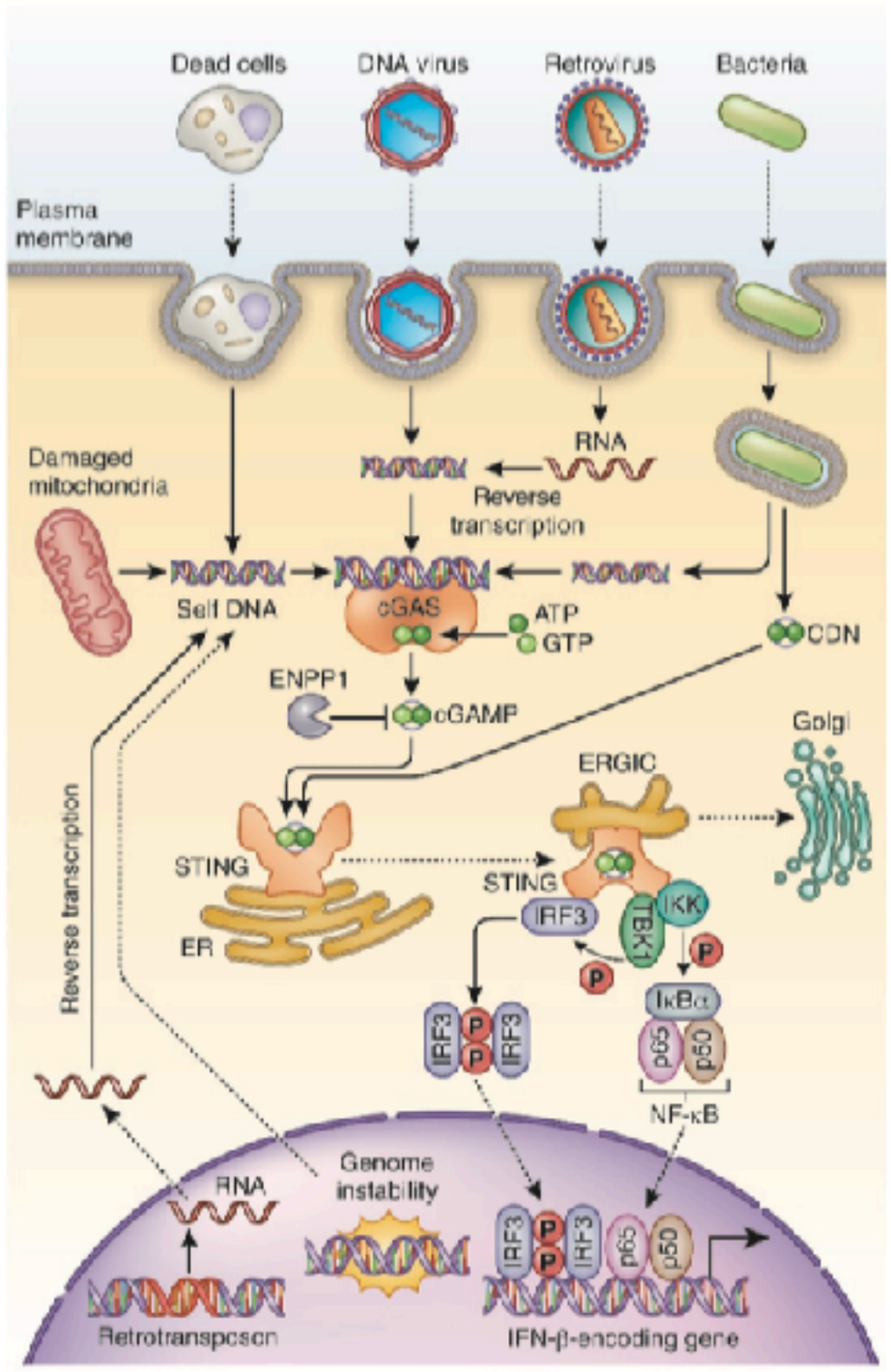
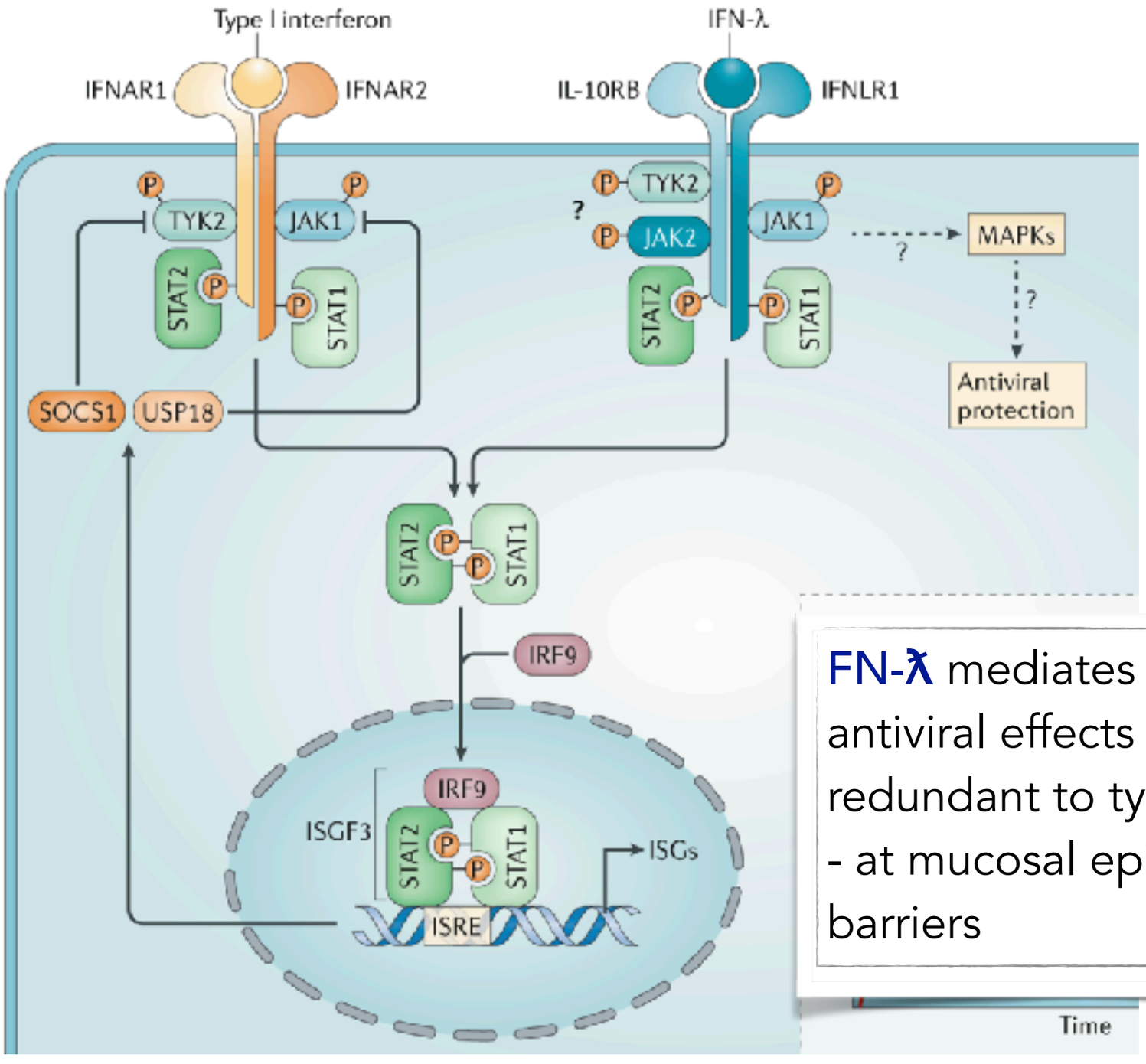
Virus recognition: STING-cGAS pathway

cGAS = sensor
cGAMP = intermediate metabolite (can signal to surrounding cells via gap junctions and other means of extracellular secretion)
STING = activation leads to strong type I IFN response (autocrine and paracrine signaling)



Type I interferons (IFNs) and IFN-ƛ

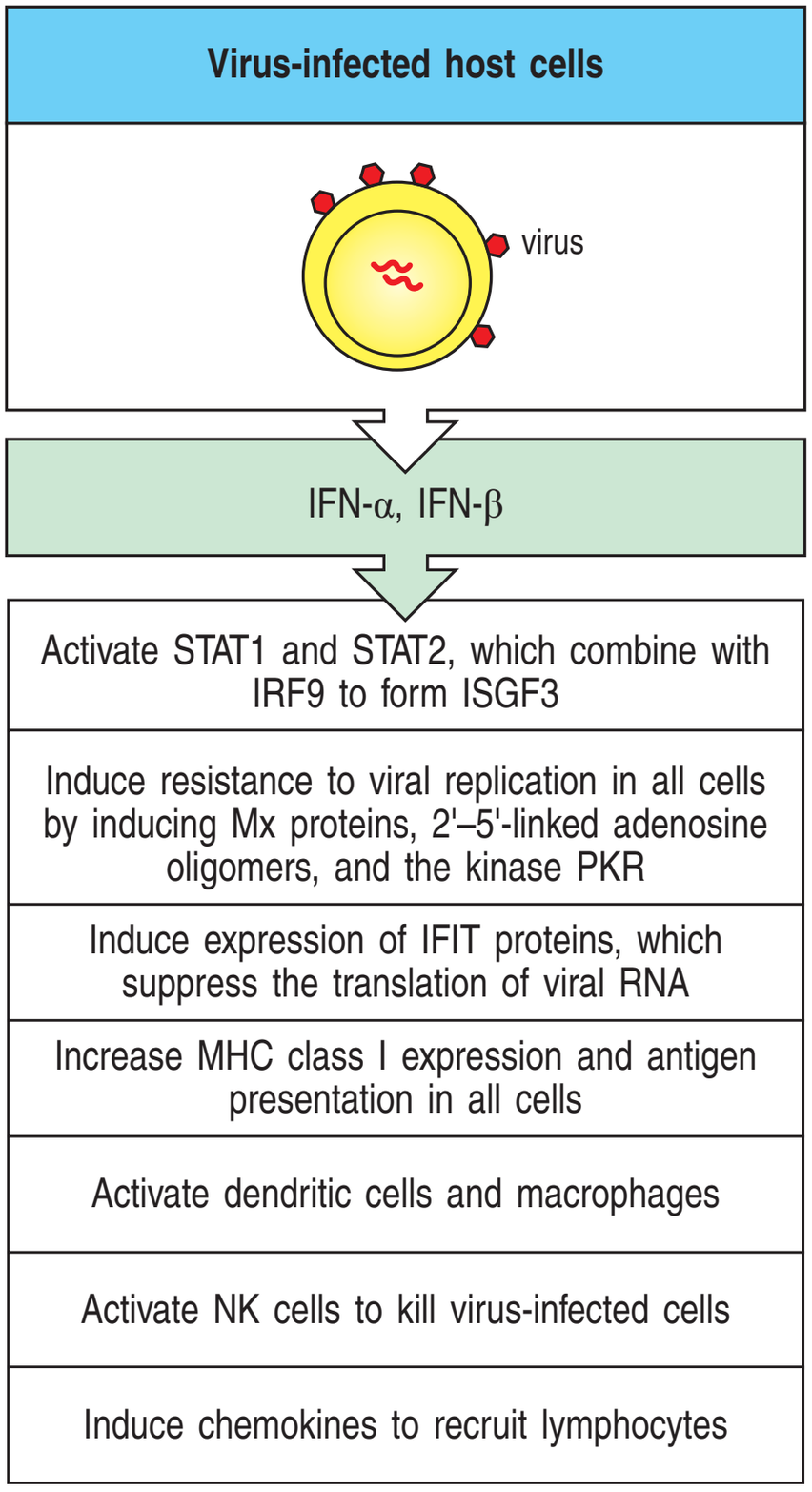


FN-ƛ mediates critical antiviral effects - non-redundant to type I IFNs - at mucosal epithelial barriers

Type I interferons (IFNs) and IFN-ƛ

Key in initiation of responses to alert the immune system with some cells more efficient producers of IFN (pDCs)

- Interferon-stimulated gene (ISG) production
- Direct antiviral action
- Block transcription
- Enhance viral recognition
- Promote the activation of innate an adaptive immune cell subsets (maturation, cytotoxicity, effector capabilities)



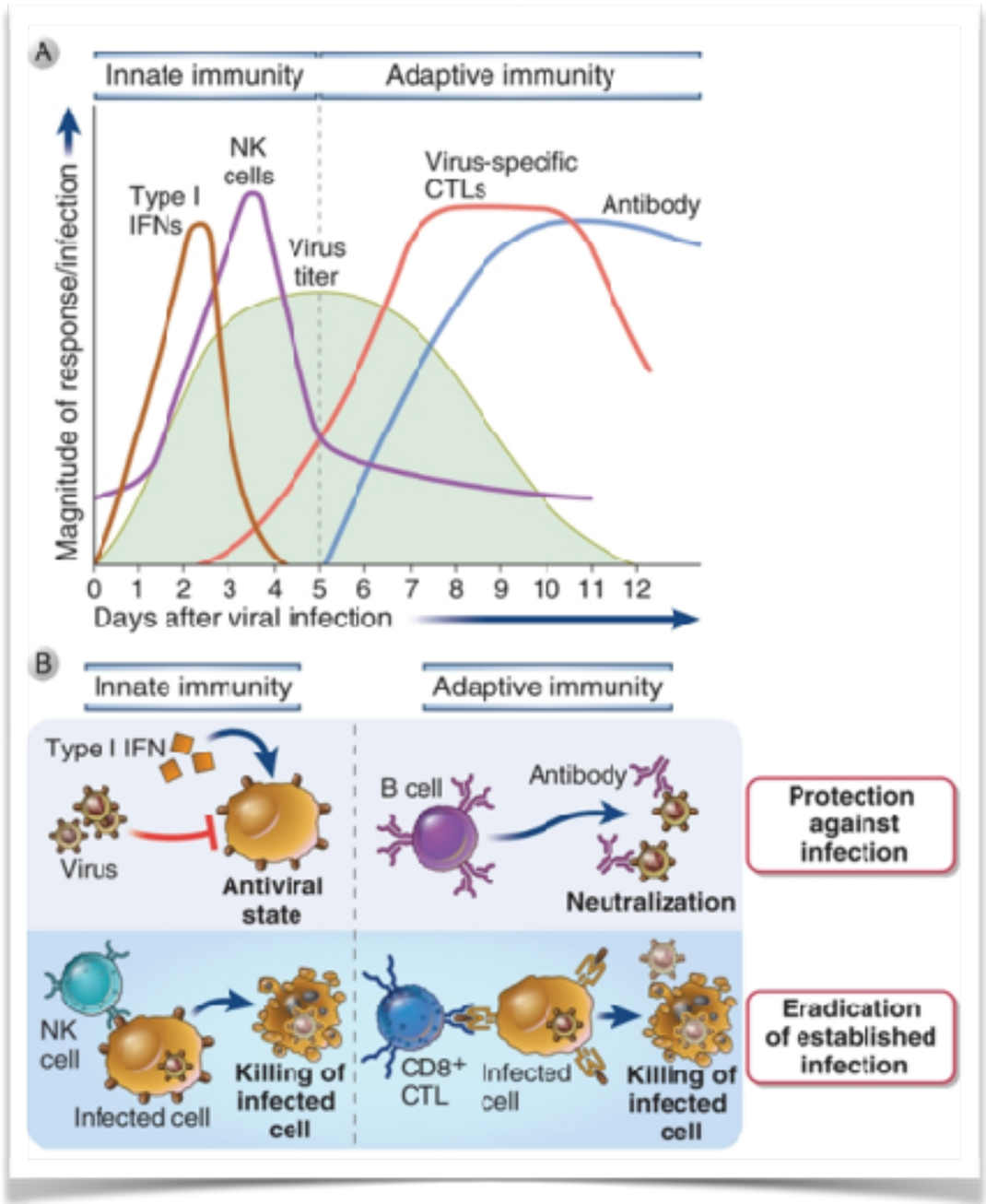
Immunity to viruses

Innate immunity:

- Infected cells and pDCs produce *type I IFNs* (TLR, RIG-like receptors and STING pathway) to inhibit viral replication
- NK cell *killing* via NK-ligand/absence of class I MHC (potentiated by IFNs)

Adaptive immunity:

- Humoral: high-affinity and T-dependent AB block effective during extracellular stages block *viral entry* in host cells (initial infection and cell-to-cell spread), *opsonise* viral particles to promote their clearance by phagocytes and activate the *complement*
- Cell-mediated: CTLs kill infected cells presenting virus antigens usually with help from *CD4⁺ helper T cells*, all nucleated cells express MHC-I (increase by interferons)



Cross-presentation activates effector T cells

Often DCs are not infected, but they can acquire exogenous antigen and load them onto their MHC-I molecules (crucial for $CD8^+$ immunity)

Transfer of antigen from the periphery onto a DCs to activate T cells.

$CD8^+$ cells: greater clonal expansion than $CD4^+$ cells, high and robust response against viruses, change surface markers to leave the LN and go the periphery, increase expression of cytokines, INF, cytotoxic granules

Immunity to viruses

Latency: state of *balance* between infection and immune response

- viral DNA persists in the host but the virus *does not replicate or kill* infected cells
- CTLs *control* but cannot eradicate the infection (e.g. Epstein-Barr virus)

Tissue injury: caused by *CTLs* in some infections

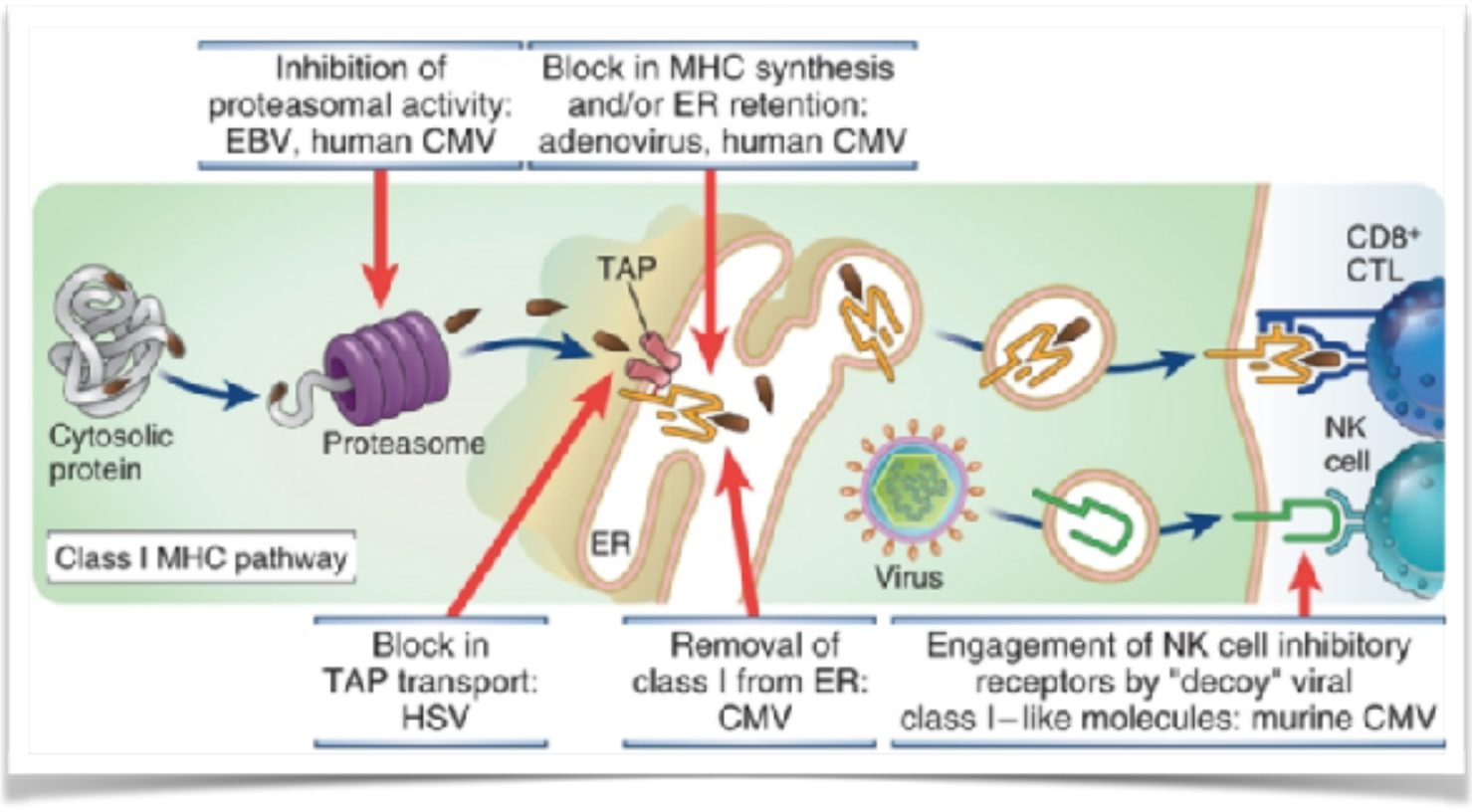
- *Persistent* infections induce the formation of *circulating immune complexes* (viral antigens + specific antibodies) that get *deposited* in blood vessels and lead to systemic vasculitis
- Some viral proteins resemble self-antigens and can lead to response to self antigens via *molecular mimicry*

Chronicity:

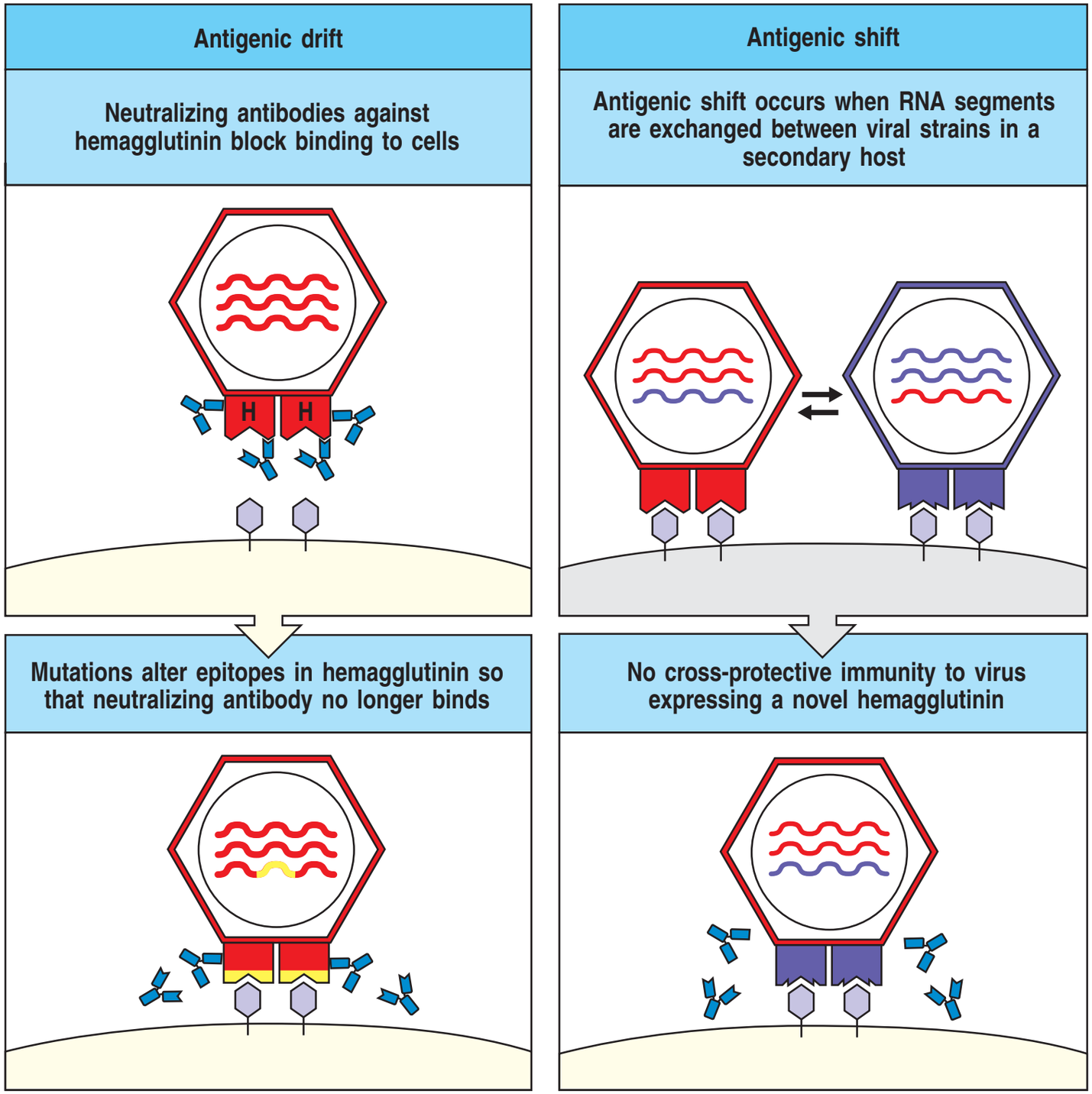
- *insufficient* immune response
- Very *aggressive* virus (hiding from the immune system)
- Interference with antigen presentation (MHC degradation, Tap blockage)
- Mutations after infections to *alter antigen motifs* for T and B cells (e.g. HIV)
- Promotes the development of T cell *exhaustion*

Immune evasion by viruses

- **Antigenic variation:** mostly surface *glycoproteins* recognised by antibodies and T-cell epitope
- **Inhibition of class I MHC** prevents protein antigens recognition by *$CD8^+$ CTLs*
- **Production of molecules** that inhibit responses (bind to cytokines, chemokines)
- **CTL response failure** called *exhaustion* occurs in *chronic* viral infections via the upregulation of inhibitory receptors (e.g. PD-1)
- Infection of **immunocompetent cells** (eg. HIV surviving in $CD4^+$ T cells and causing their gradual elimination)



Genetic variations allow repeated infection with influenza virus A



Immunity to parasites

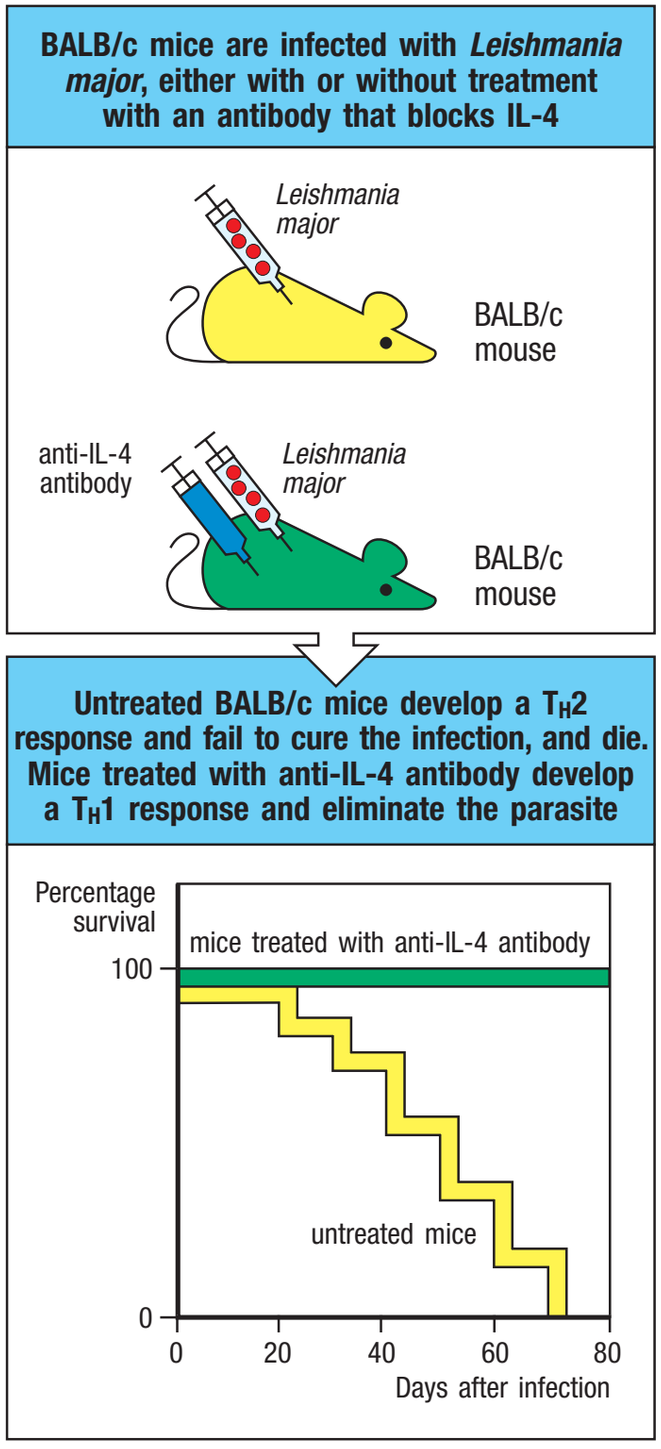
- Includes *single-celled* **protozoa**, complex *multicellular* worms (**helminths**) and *ectoparasites* (e.g. ticks and mites)
- Cause of major health problems in developing countries
- Many parasites go through *complex life cycles* (part of which occurs in humans)
- Many parasitic infections are *chronic* because of *weak innate immunity* and ability of parasites to *evade or resist elimination* by adaptive immune responses.

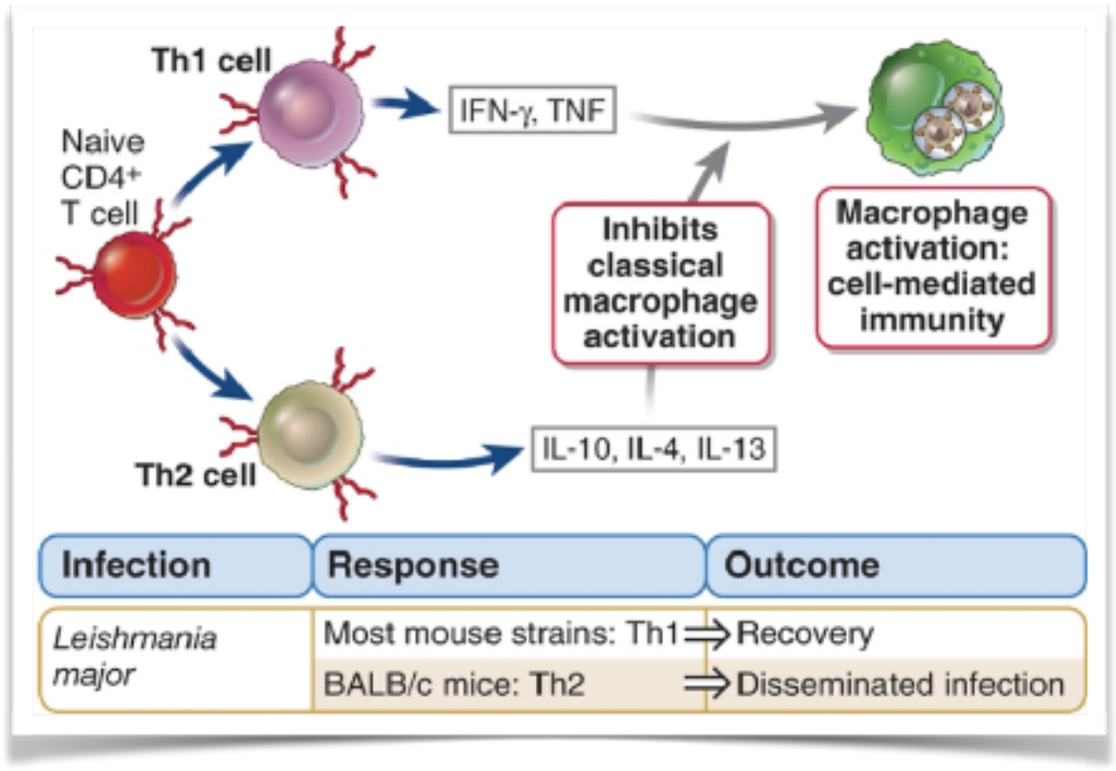
Innate immunity:

- **Phagocytes** are activated by the PRRs (TLR) sensing *surface molecules*
- **Eosinophils** release *granules* to destroy worm integuments (often resistant to cytocidal mechanisms of neutrophils and macrophages, and *too large* the be engulfed)
- May activate *alternative pathway of the complement*

Adaptive immunity to parasites

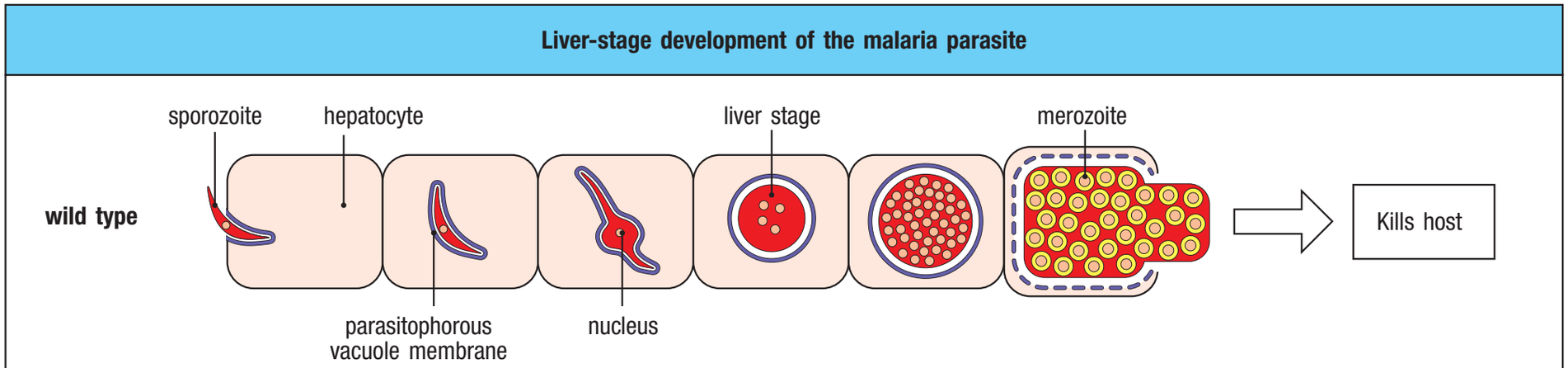
- Protazoa living within macrophages rely of *Th1* cytokines to activate *macrophages*, whereas activation of Th2 increases parasite survival
  ➔ dominance of Th1/Th2 responses determines disease resistance/susceptibility

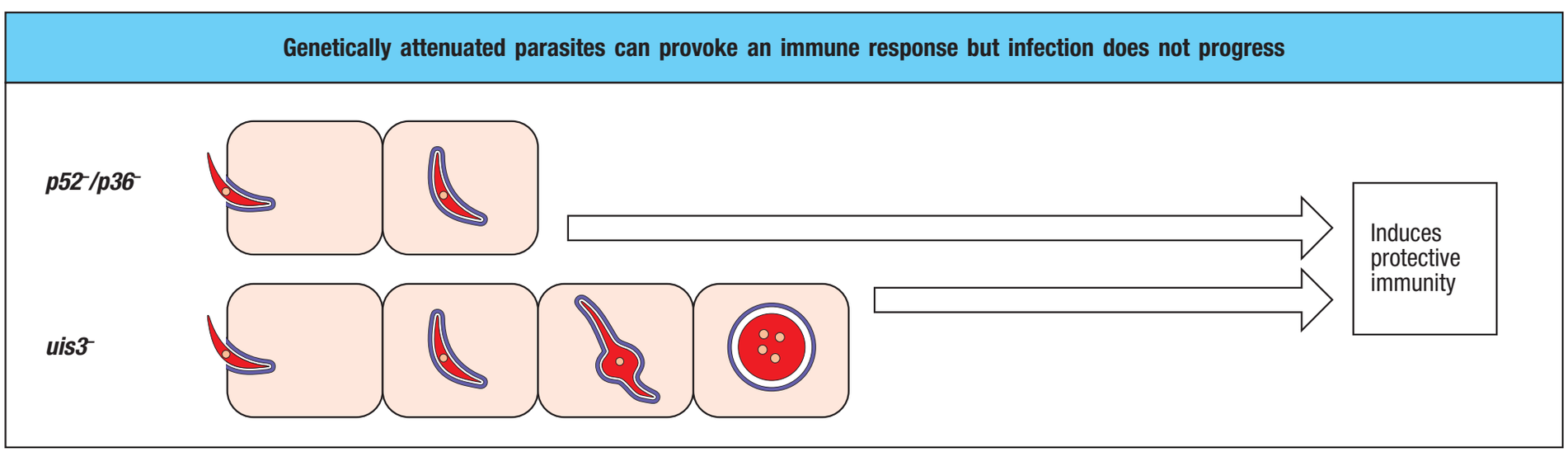




Immunity to parasites

- Cytopathic protozoa stimulate specific *antibody* and *CTL* response
- **Malaria:** parasitic infection with plasmodium species: Parasite resides in red blood cells or hepatocytes (see below). Genetically attenuated parasites can be engineered as live vaccines to provide protective immunity.

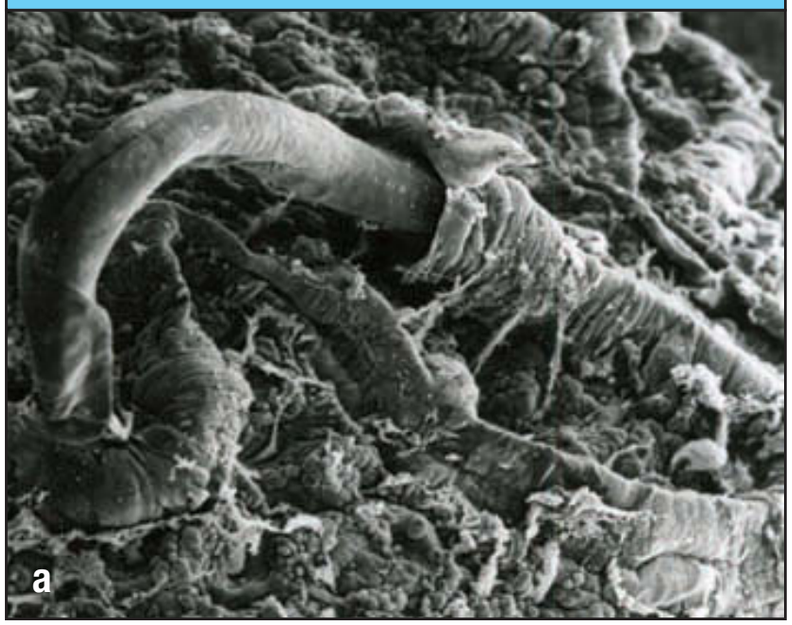




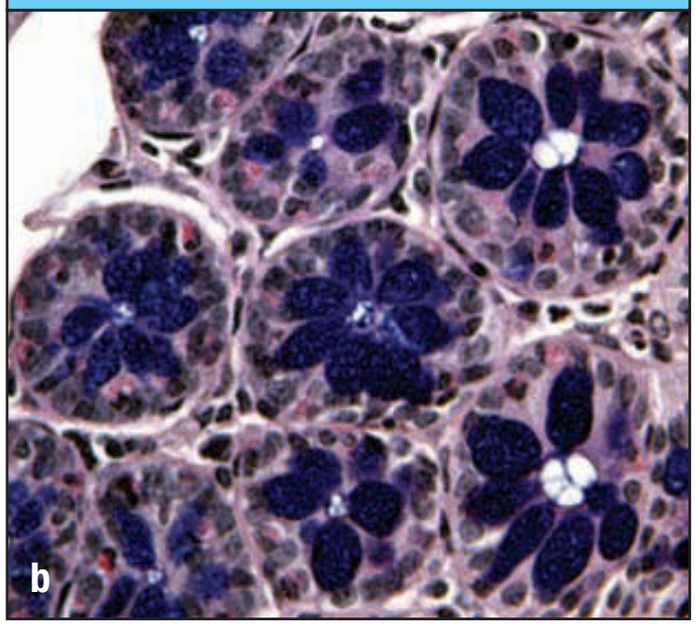
Immunity to helminths

- Mostly do not replicate in their hosts
- Multi-cellular organisms that are too large to be ingested by cells
- Infections in humans are often chronic - the host can reduce pathogen burden, but not completely
- Disease results from undernutrition (competing with the host for essential nutrients in the gut) or through tissue damage

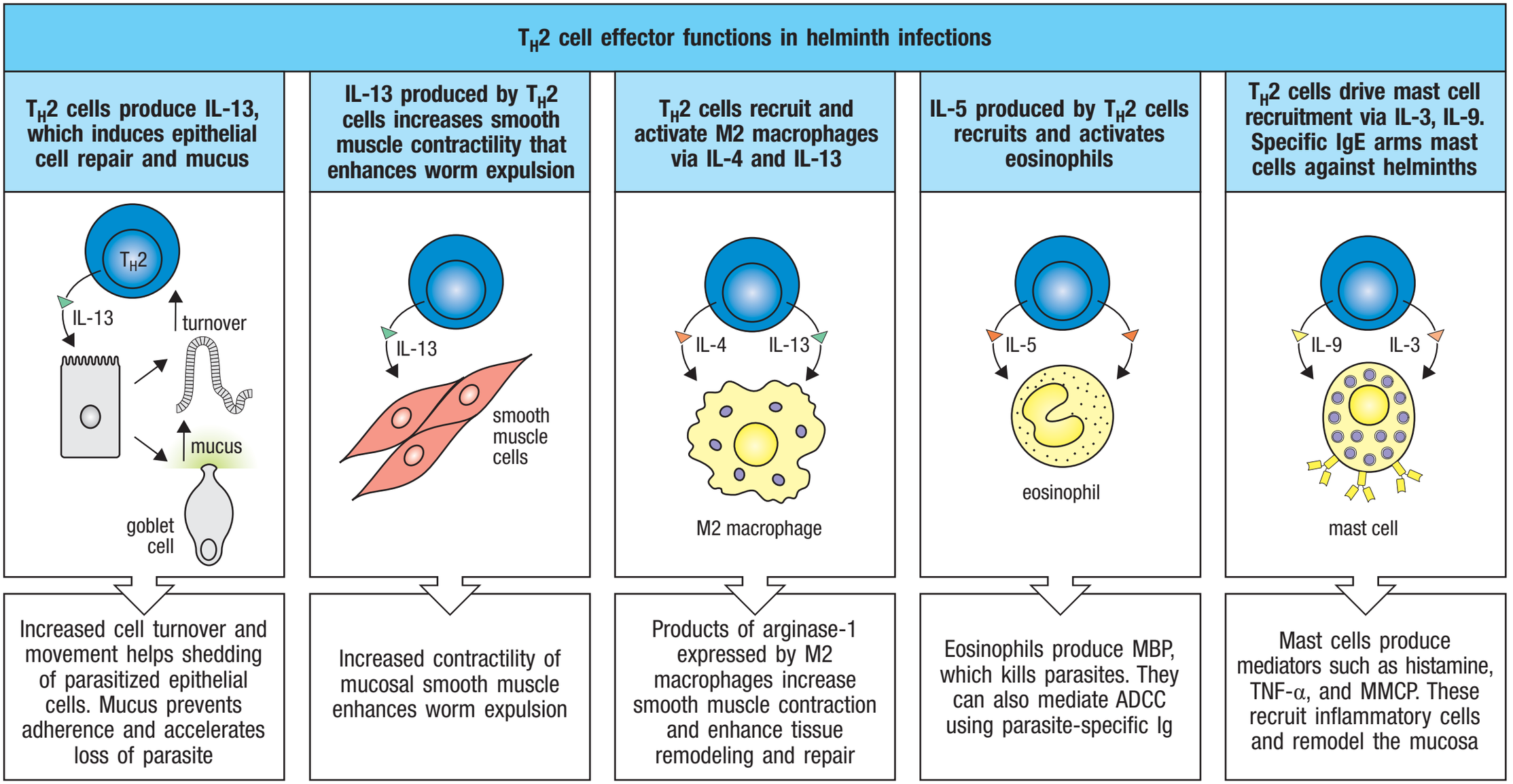
The whipworm *Trichuris trichiura* embeds in the surface epithelium of the colon, leaving its posterior free in the lumen



Infection with the whipworm stimulates mucus production in the gut



Immunity to helminths



Immune evasion by parasites

Different ways to **reduce their immunogenicity** and **inhibit host immune responses:**

- **Resistance to immune effector** mechanisms (e.g. schistosome larvae develop a *tegument resistant to damage* by complement and by CTLs)

- **Conceal** themselves from the immune system by *living inside host cells*, developing resistant *cyst*, residing in intestinal *lumen* or *shedding antigens*

- **Inhibit host immune responses:** induce *T cell anergy*, *Tregs,* generalised *immunosuppression* with immunosuppressive cytokines production and defects in T cell activation

Immune evasion by parasites

- Antigenic variation: during *life cycle* (stage specific in malaria parasite) or *continuous* variation (target surface antigens in African trypanosomes)
  ➔ challenging for vaccine development
- Trypanosomiasis (sleeping sickness):
  - Infection cause by Trypanosoma brucei
  - Antigenic variation: variant-specific glycoprotein (VSG) is expressed on the surface
  - The trypanosome genome contains 1000 VSG genes, which encodes for proteins with different antigenic properties
  - Only one gene is expressed at a time
  - Under the pressure of immunity, few pathogens with a different VSG survive and multiply
  - This leads to a recurrent disease symptoms
  - Cycles of inflammation triggers by AG-AB complexes trigger neurological damage, resulting in coma (hence sleeping sickness)