Bacterial Infections: TB, Pneumococcus, Staph Aureus

Unit 5

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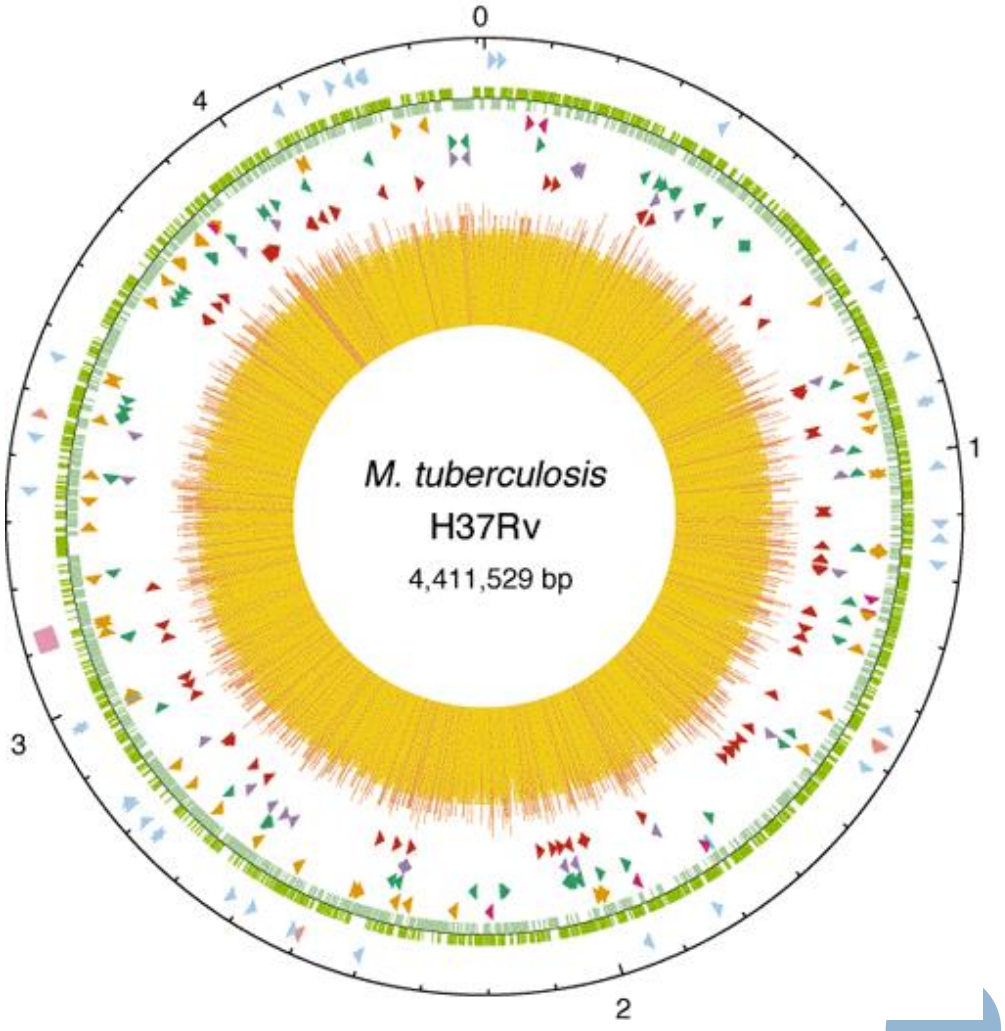
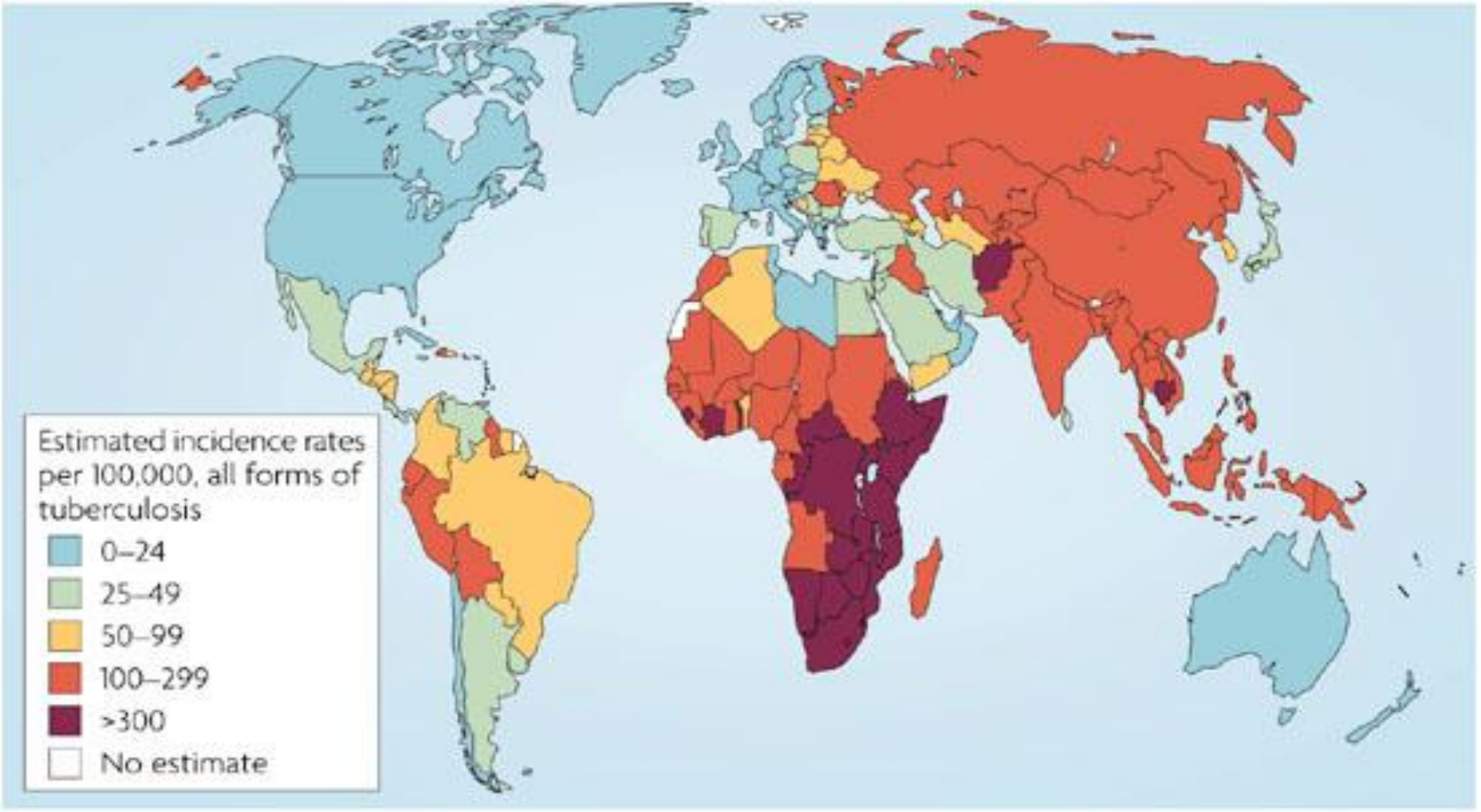
Immune Control of *Mycobacterium tuberculosis*

Mycobacterium Tuberculosis (Mtb)

- Acid-fast, rod-shaped bacillus
- Unique wax-rich cell wall composed of long chain fatty acids and glycolipids
- 250 genes dedicated to fatty-acid metabolism
- Slow, 20 hour replication time



MTB INFECTION WORLDWIDE



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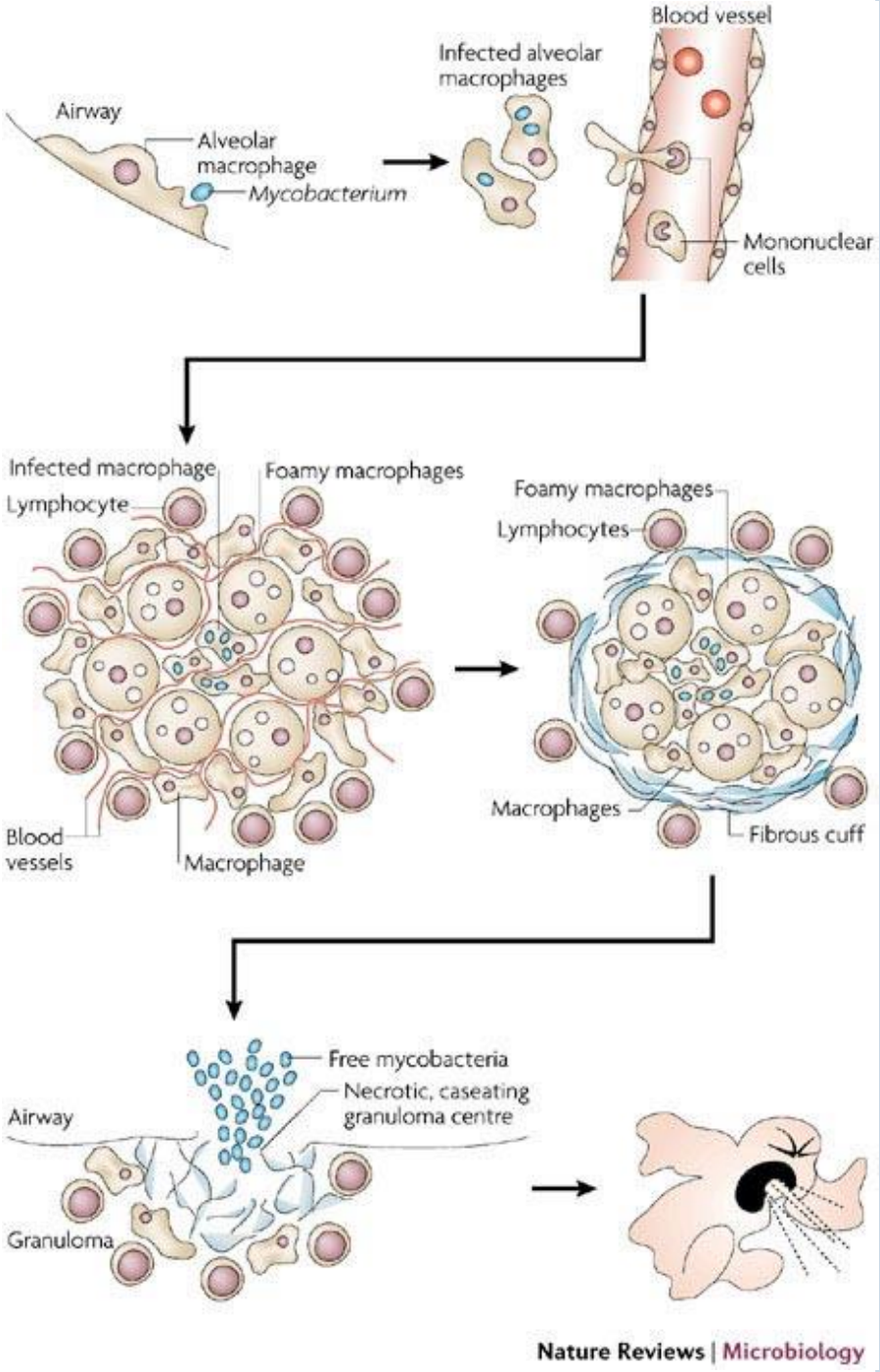
MTB IMPACT

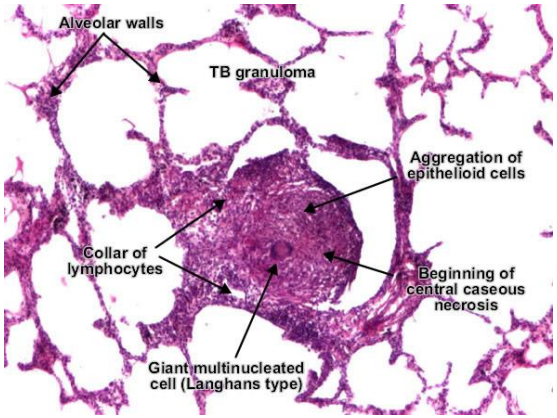
- 2.2 million deaths/year
- Burden of diseases in DALY (disability-adjusted life years)
- Total Disability Adjusted Life Years: 45 million (3.1%).
- 2 billion individuals infected with M. tuberculosis
  - 10% risk of developing disease following infection
  - Untreated, disease mortality is 50%
- 8 million new tuberculosis cases per year (1 new case every 4 seconds)
- 10–15 individuals infected annually by a single untreated patient

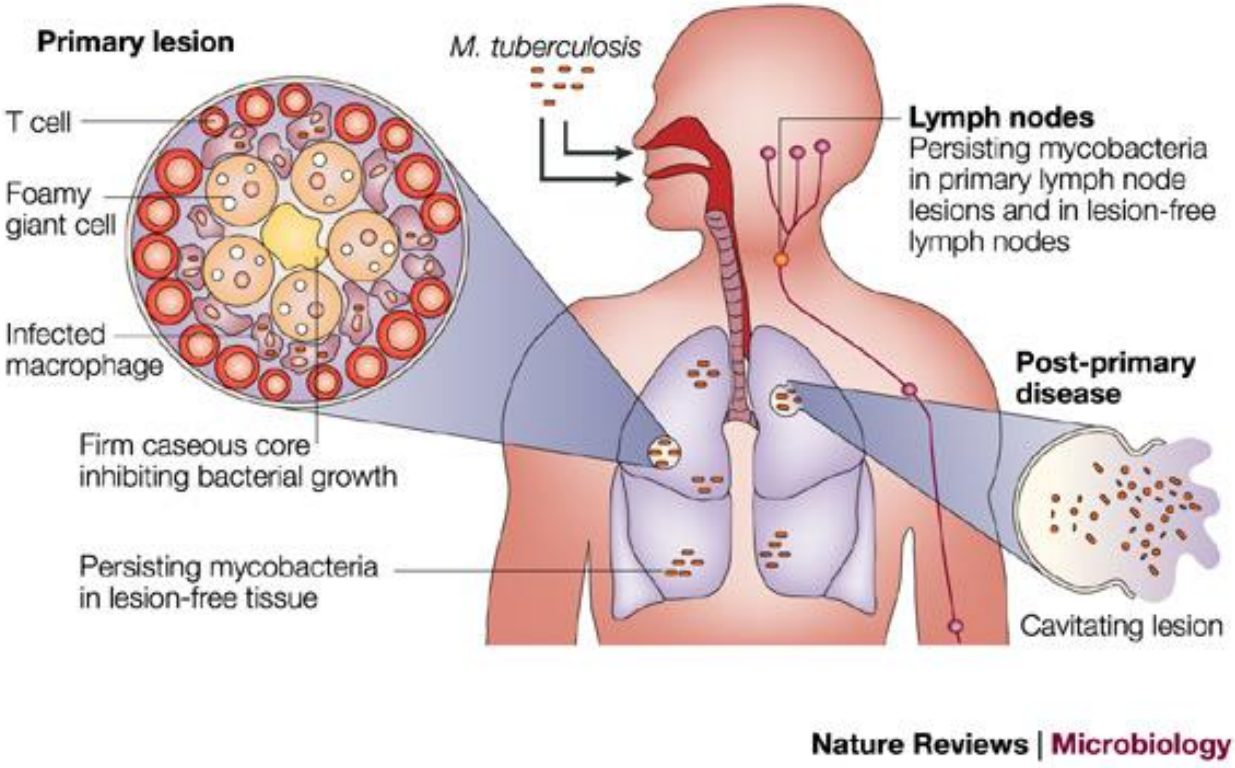
MTB LIFE CYCLE

- MTb replicates in and accumulates in macrophages, mostly in the lung (though other tissue sites are possible)
- The accumulation of infected macrophages, surrounded by other leukocytes forms a unique structure called the granuloma, the characteristic feature of MTb-associated lung damage

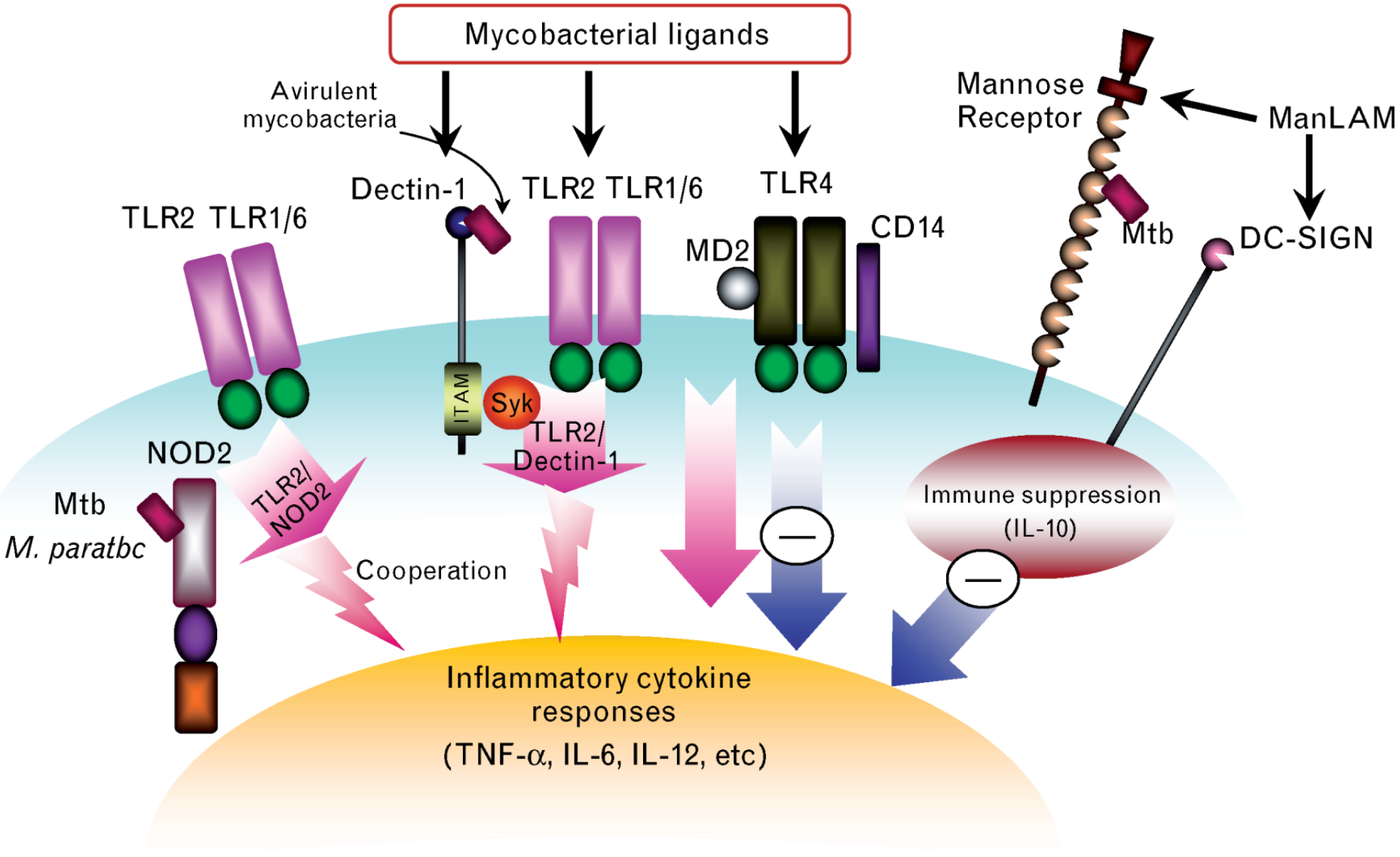


MTB LIFE CYCLE PART 2



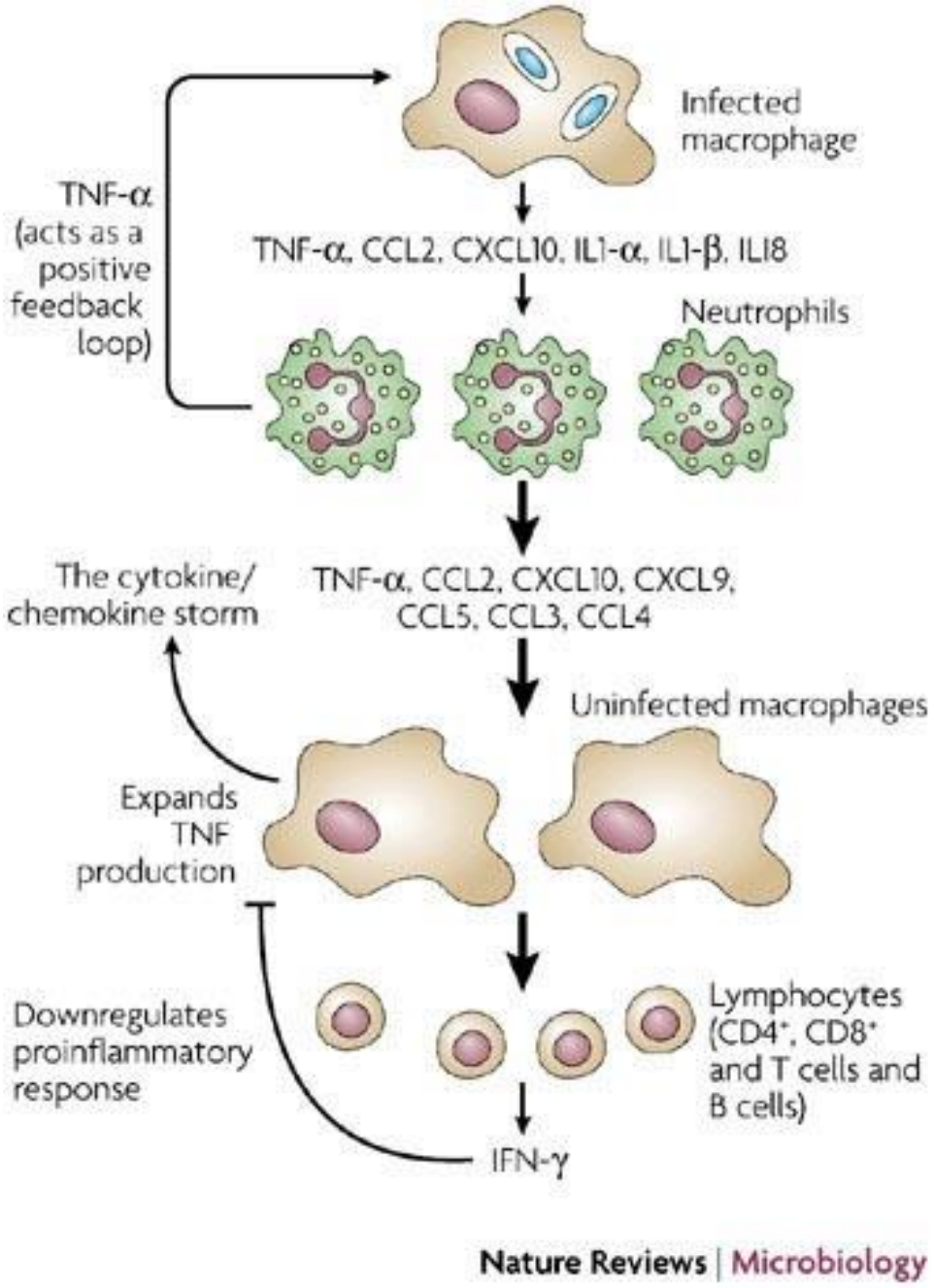


Innate Recognition of Mtb



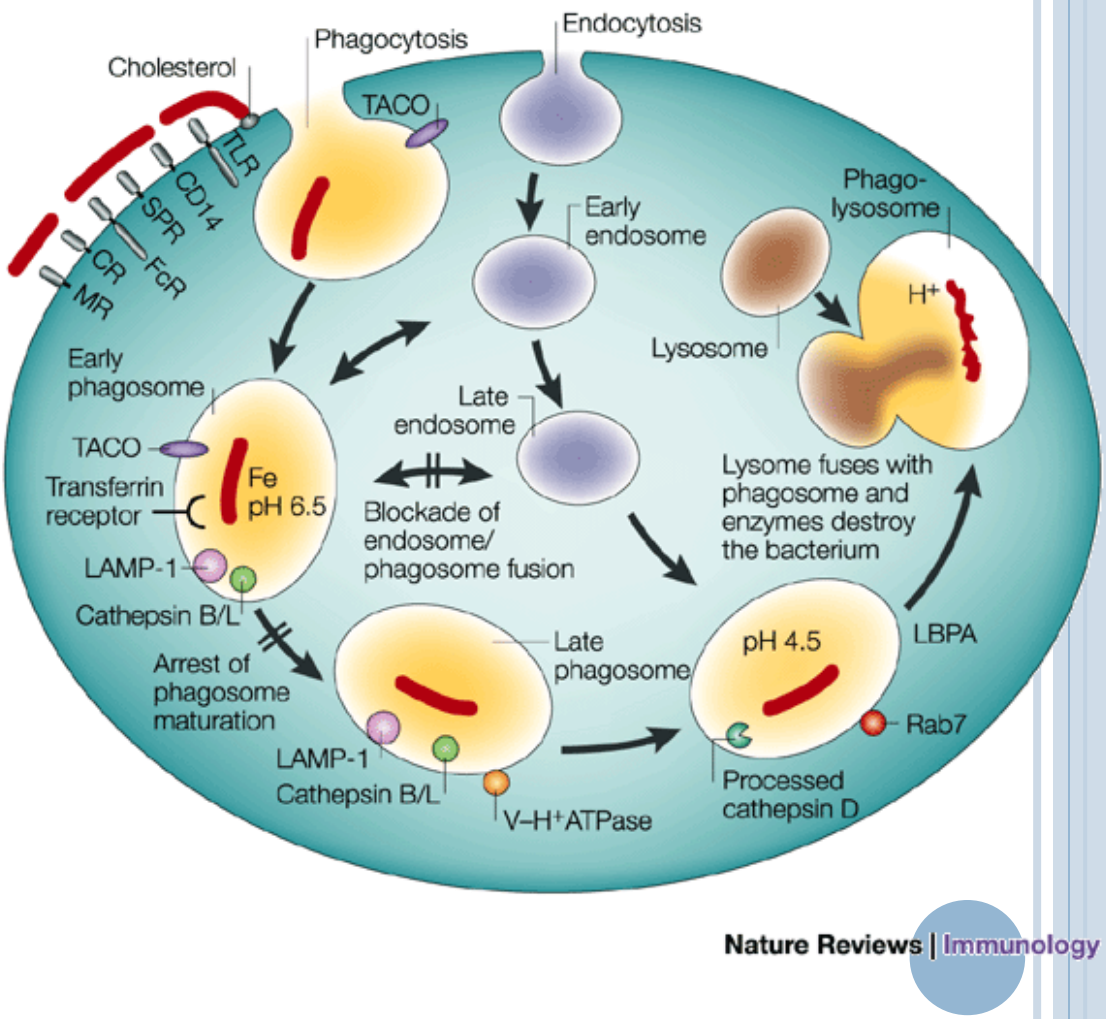
Activation of Cytokine Storm

- Macrophages do respond to the infection, even if they fail to clear
- Recruitment of other monocyte/macrophages/inflammatory cells to the lesion, promoting granuloma formation and enhancement of cytokine signaling
- Eventually recruits adaptive response which acts through "traditional" cell-mediated clearance and regulation of macrophage effector function



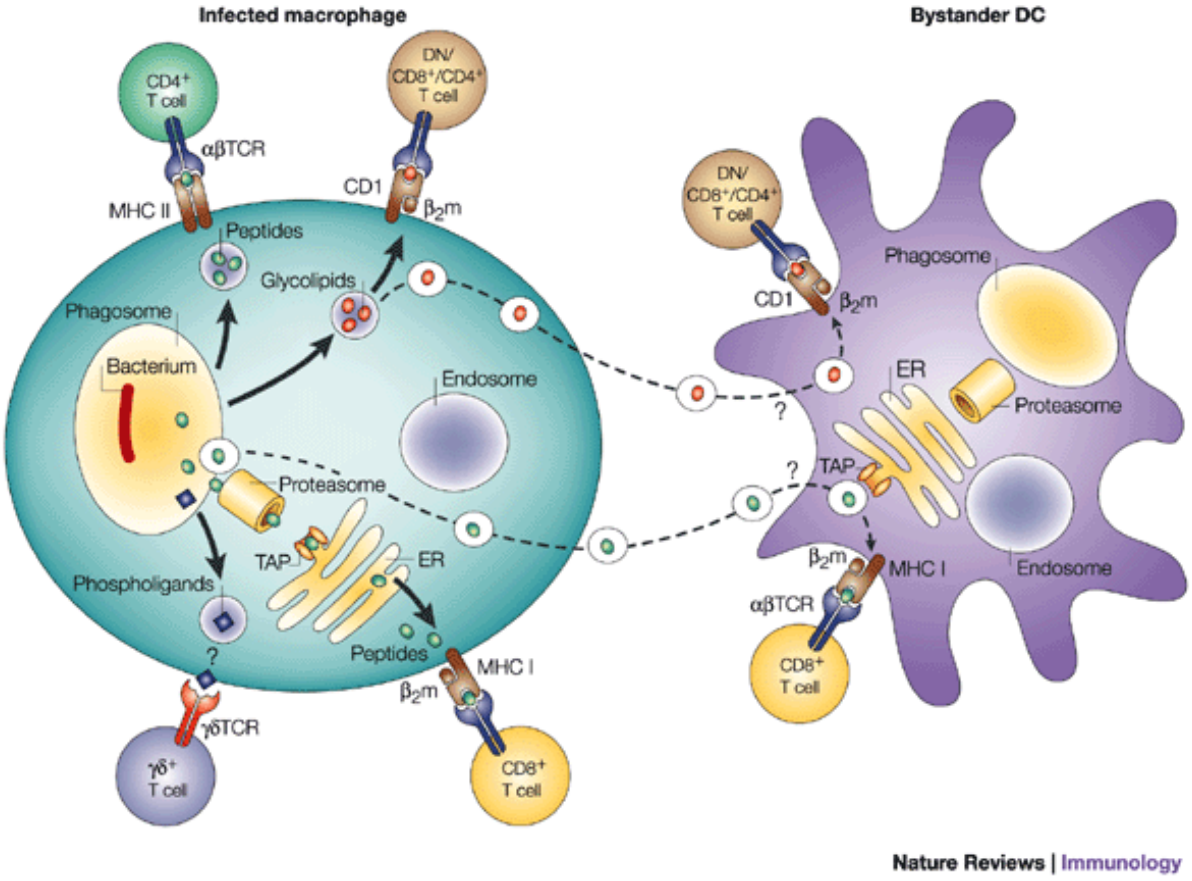
Endosomal/Lysosomal Dysregulation

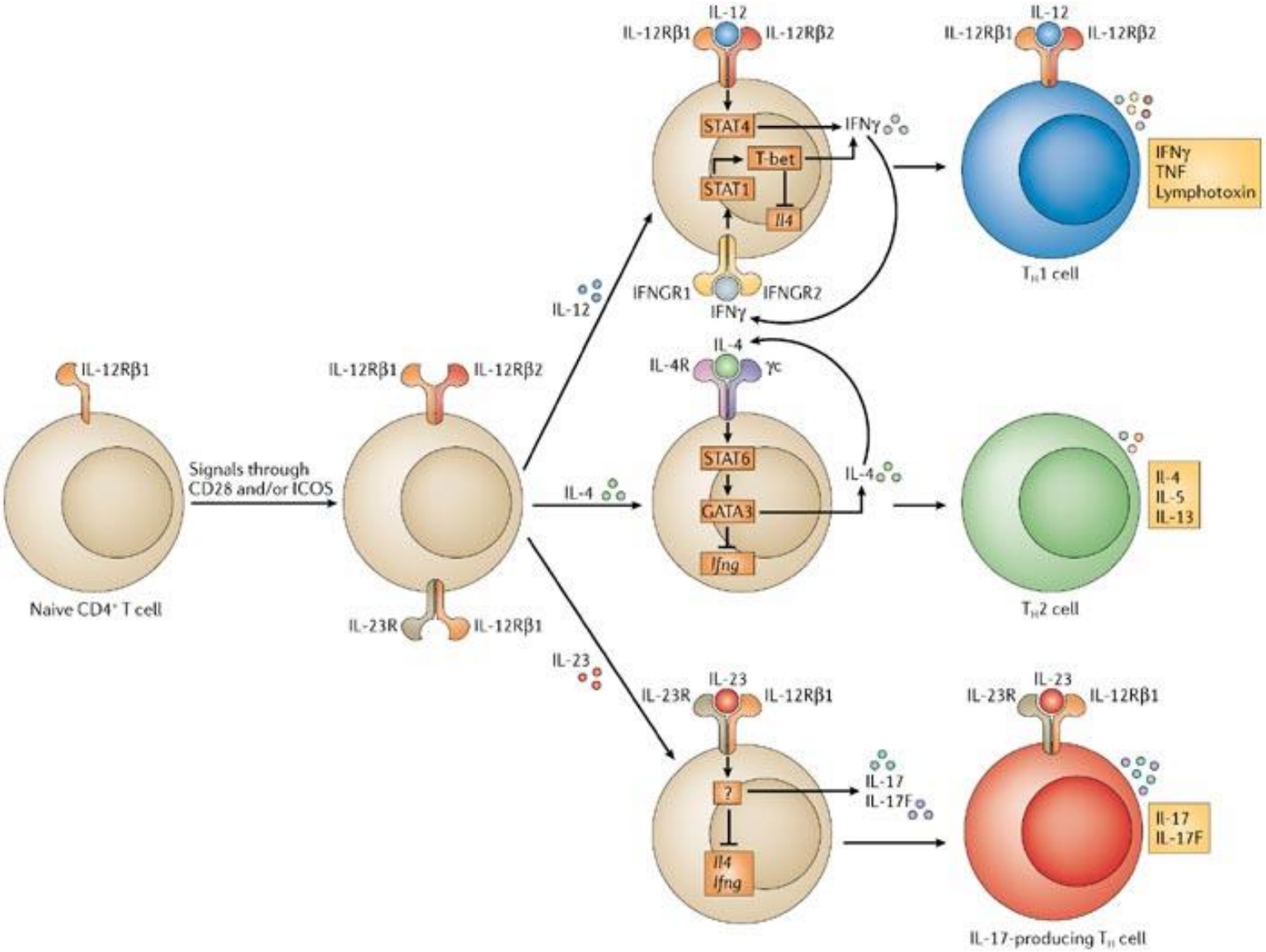
- After uptake by scavenger receptors, MTb arrests the maturation and fusion of the phagosome with the endosome
- Highly activated macrophages (IFN-g stimulation) can complete maturation and destroy the bacteria—otherwise, the bacteria remain latent or can grow



Initiation of the Adaptive Response

- The cytokine storm initaited by the innate response determines the character of the ensuing adaptive response
- Non-classical T cells (gamma-delta, CD1 restricted) play an important role in MTb control, but are not conserved between humans and mice, making their study difficult (one reason why guinea pigs are often used in MTb studies)
- Both CD_4 and CD8 functions (cytokine regulation and direct cell clearance) are associated with protection from disease





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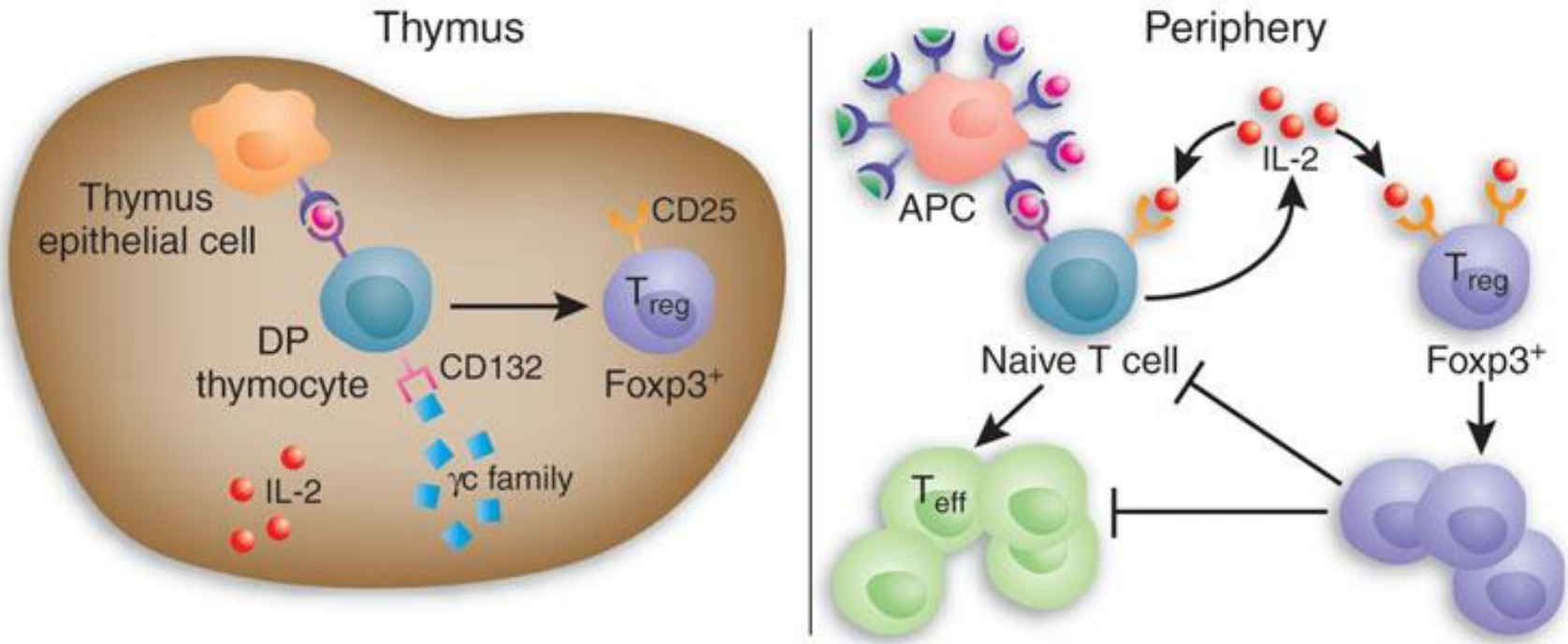
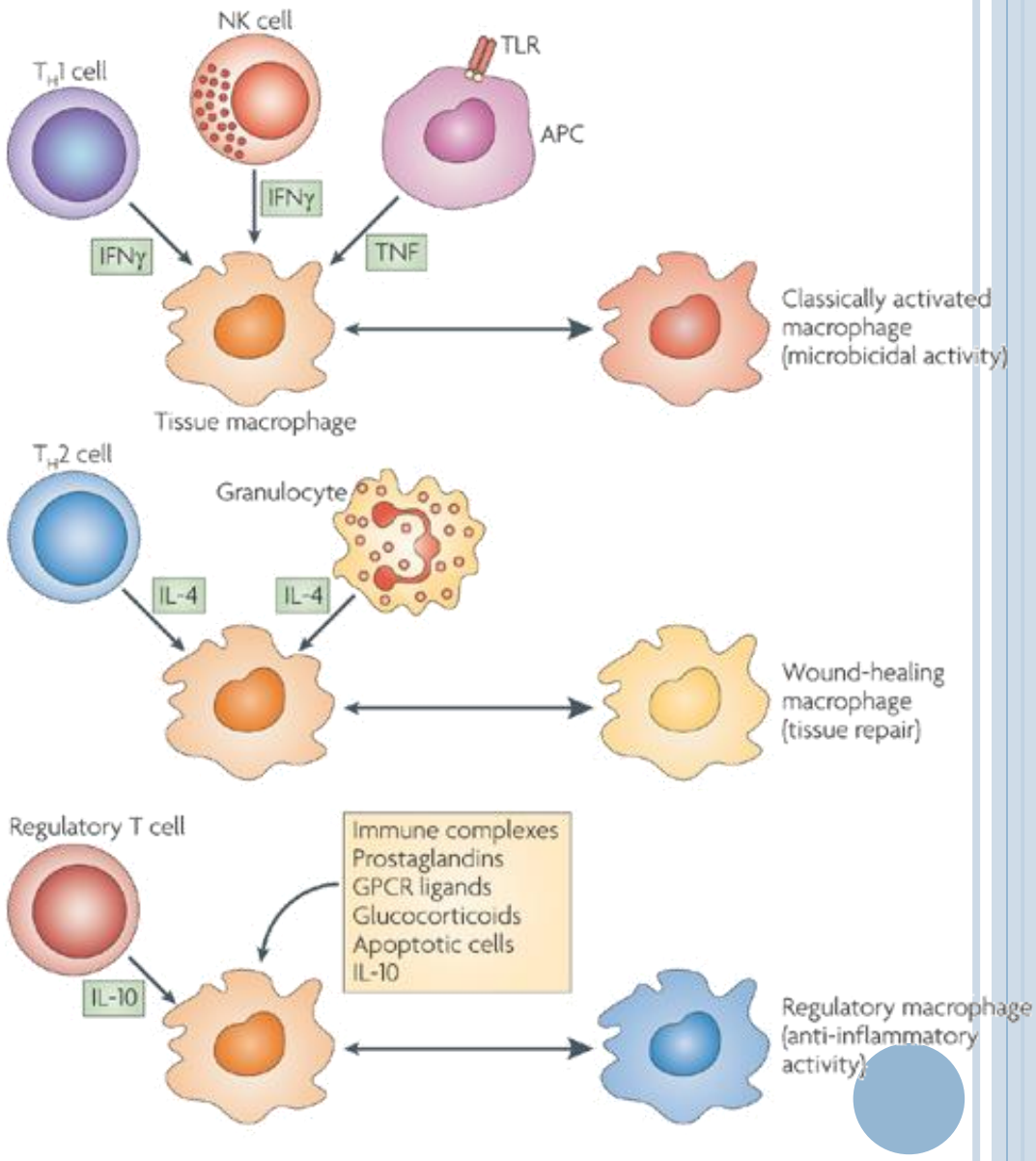
Generation of Antigen-Specific Regulatory T cells



T cell regulation of Macrophage effector Function

- The balance of regulatory vs. effector signals (and the various types of those signals) determine the activation mileu of the granuloma and the infected macrophage
- Immune-associated pathology is also a risk, so some regulatory balance is required to maintain the lung physiology while achieving clearance or control



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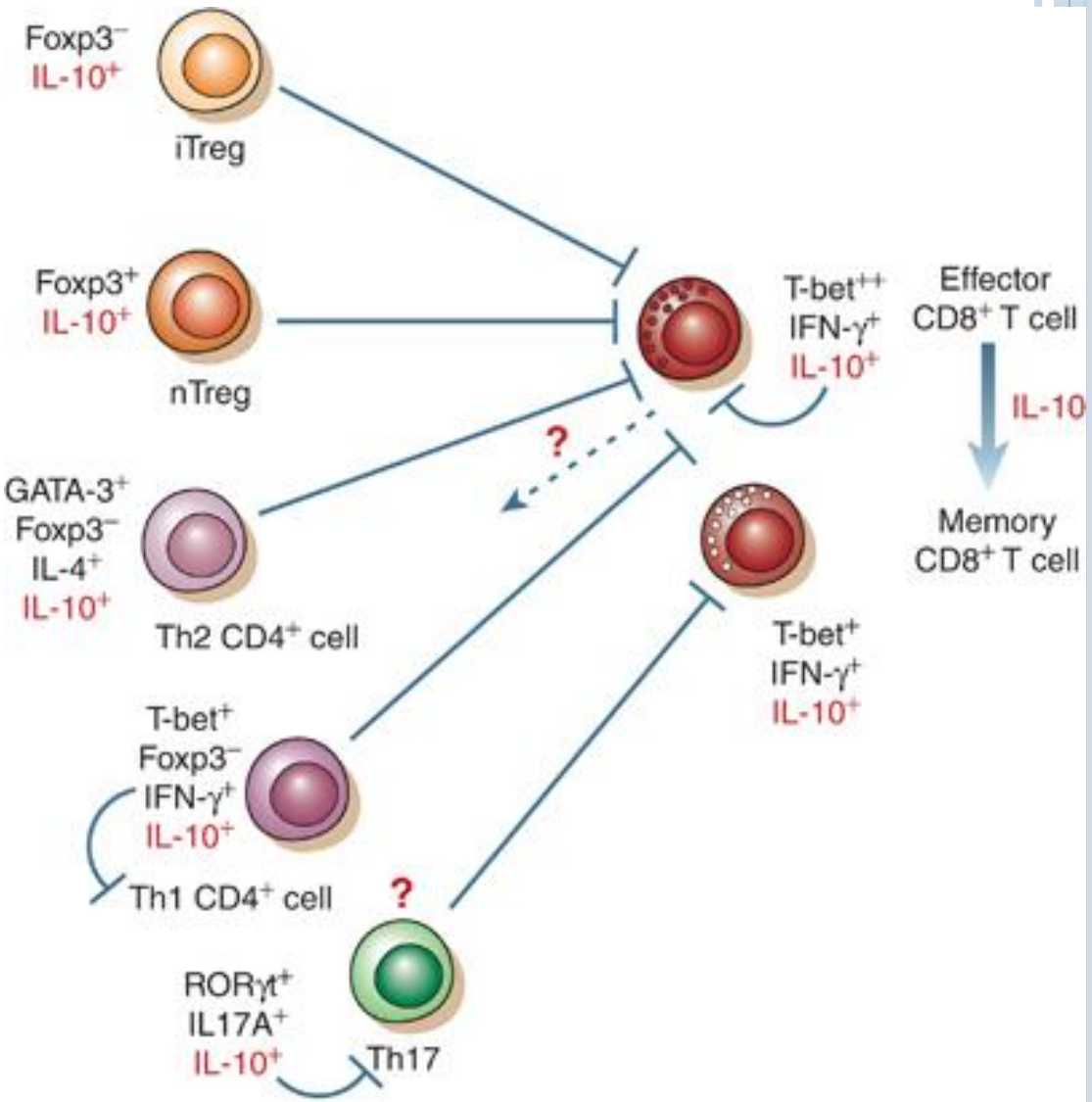
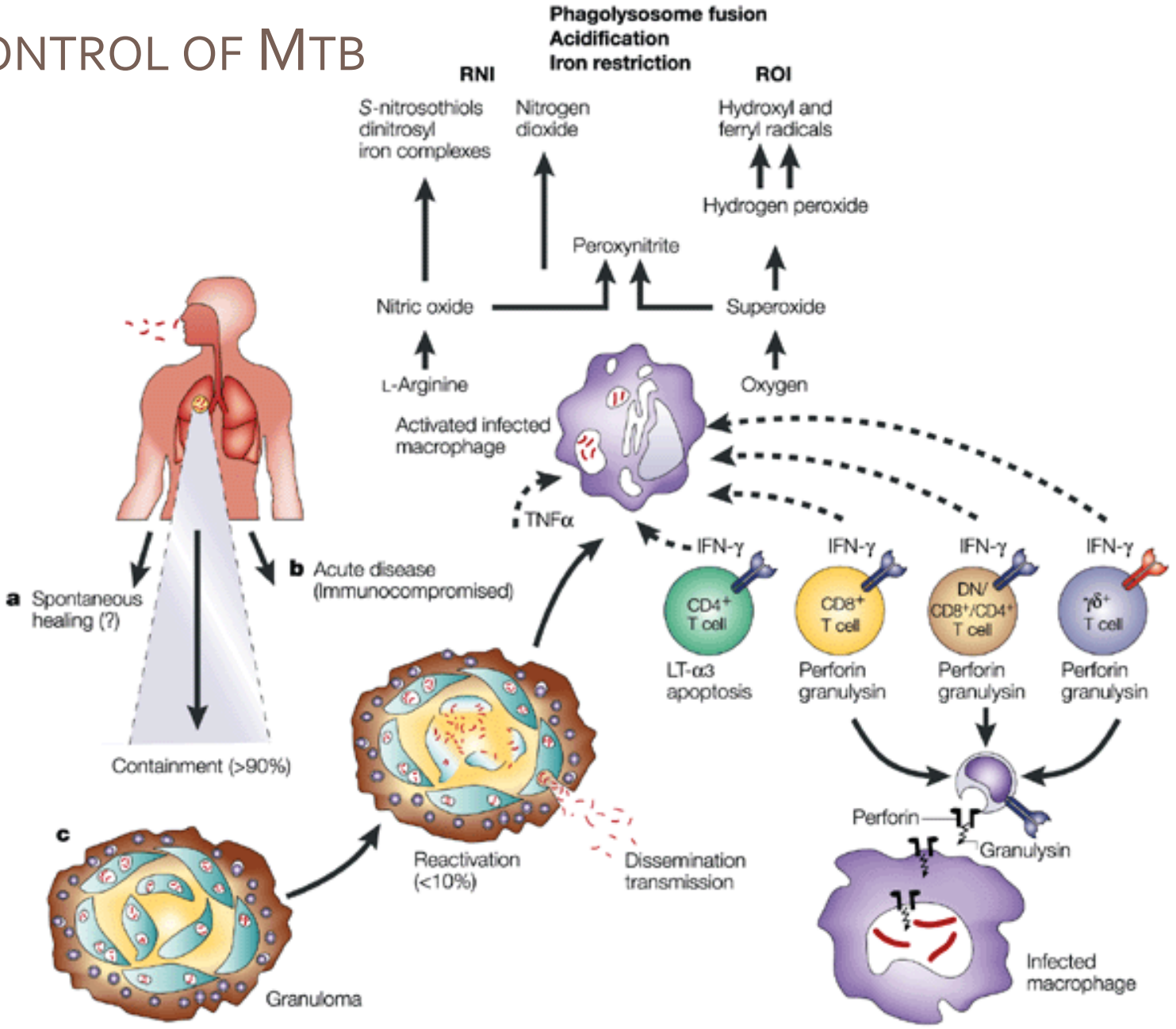
IL-10 REGULATION OF LUNG PATHOLOGY

- IL-10 has been shown in multiple infections to be a key regulatory of pathology
- In influenza, IL-10 produced by multiple cell types is required for survival in certain models of infection
- The pleiotropic effects of this cytokine are still poorly understood at a mechanistic level



Control of Mtb



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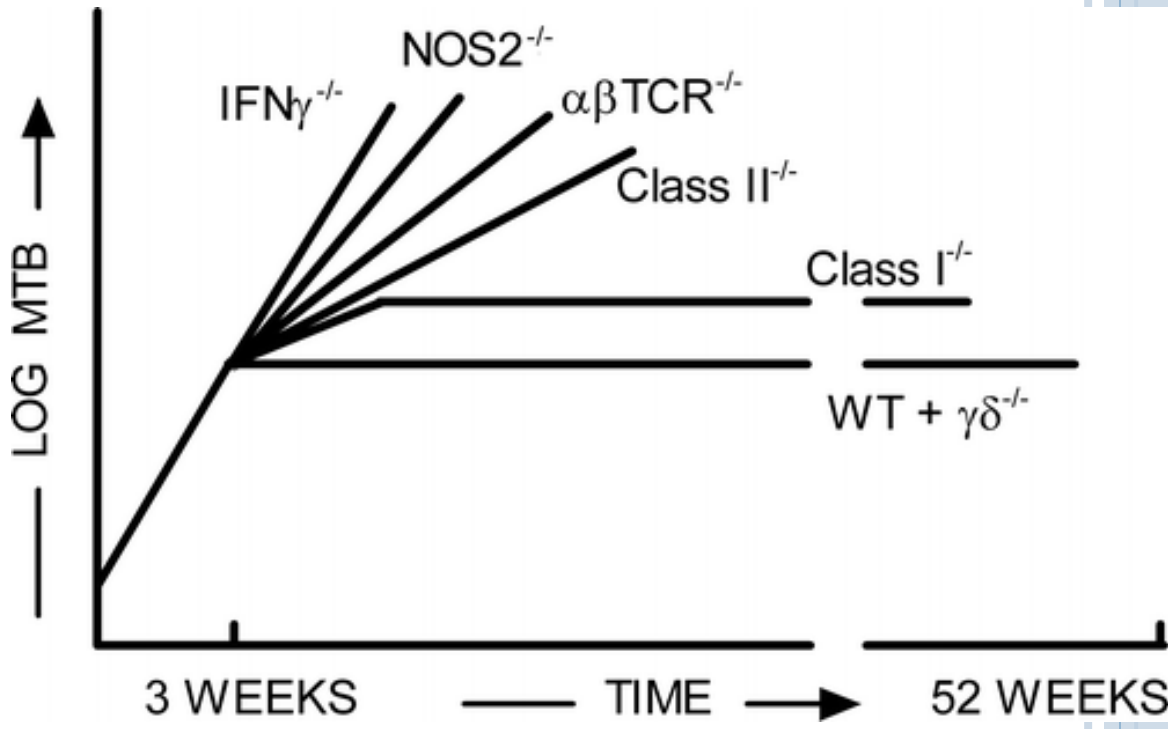
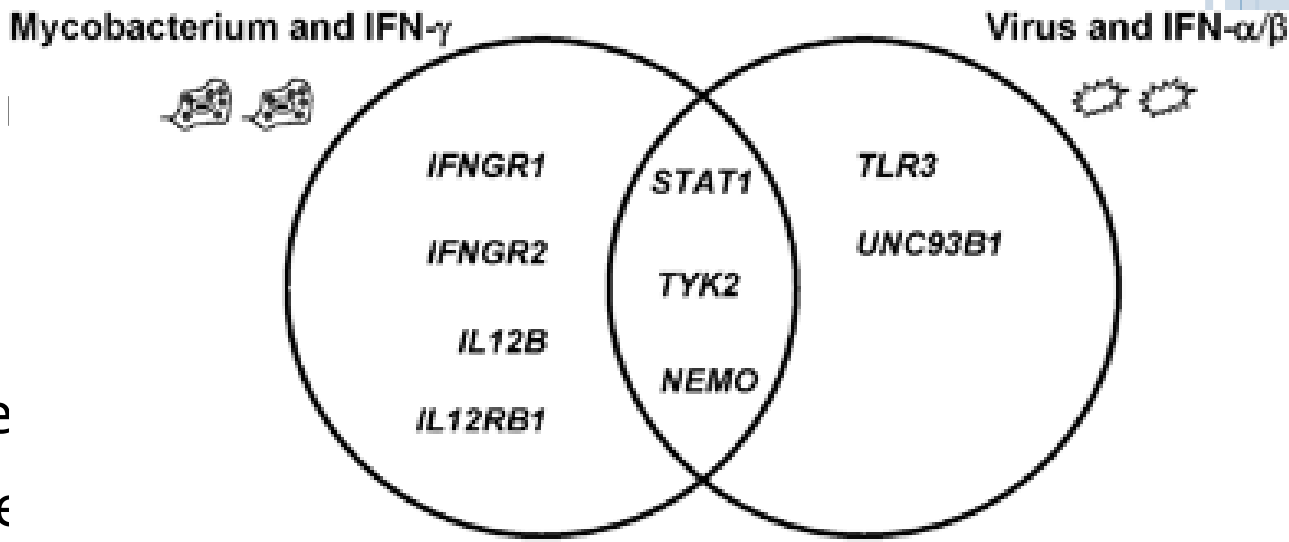
Summary of Control mechanisms

- Phagolysosomal destruction is the most important mechanism for removing bacteria
- IFNg stimulates the maturation of the phagolysosome, overcoming the inhibitory signals used by MTb
- The most effective form of this killing involves ROI and RNI
- Adaptive immunity is important for regulating the cytokine environment and, to a smaller extent, for cytolytic killing



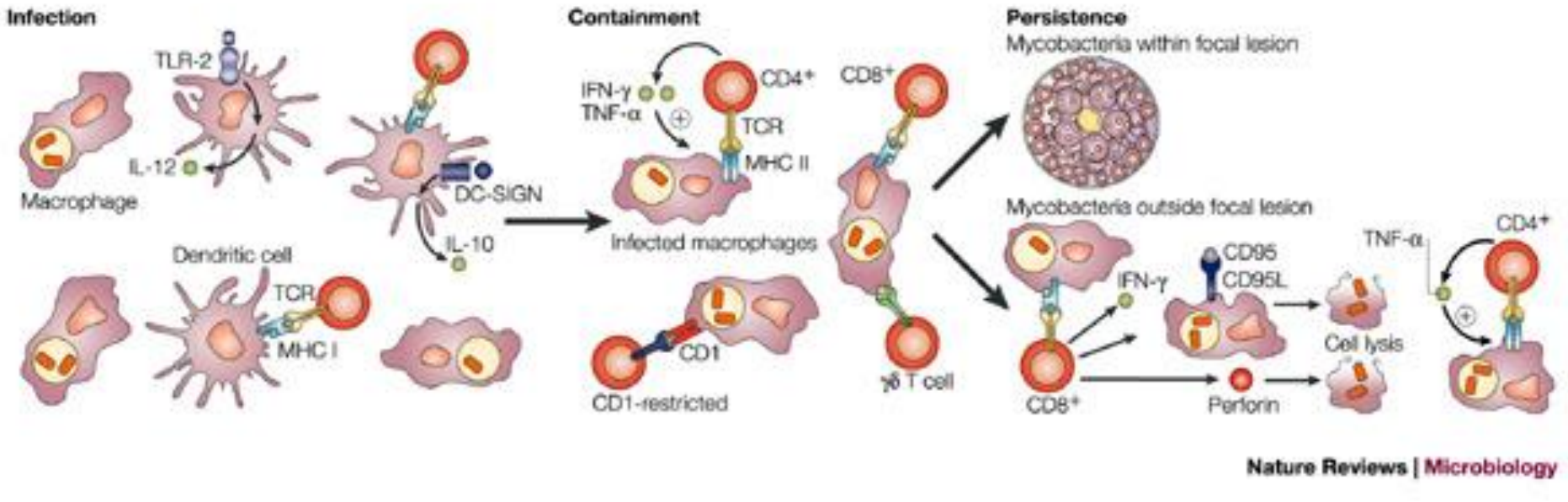
Human Genetic Deficiencies

- The primary phenotype of individuals with genetics deficiencies i IFN-g signaling or activation is susceptibility to Mycobacterial disease
- In contrast, deficiencie in Type I IFNs result in viral susceptibilities



Summary and Perspectives

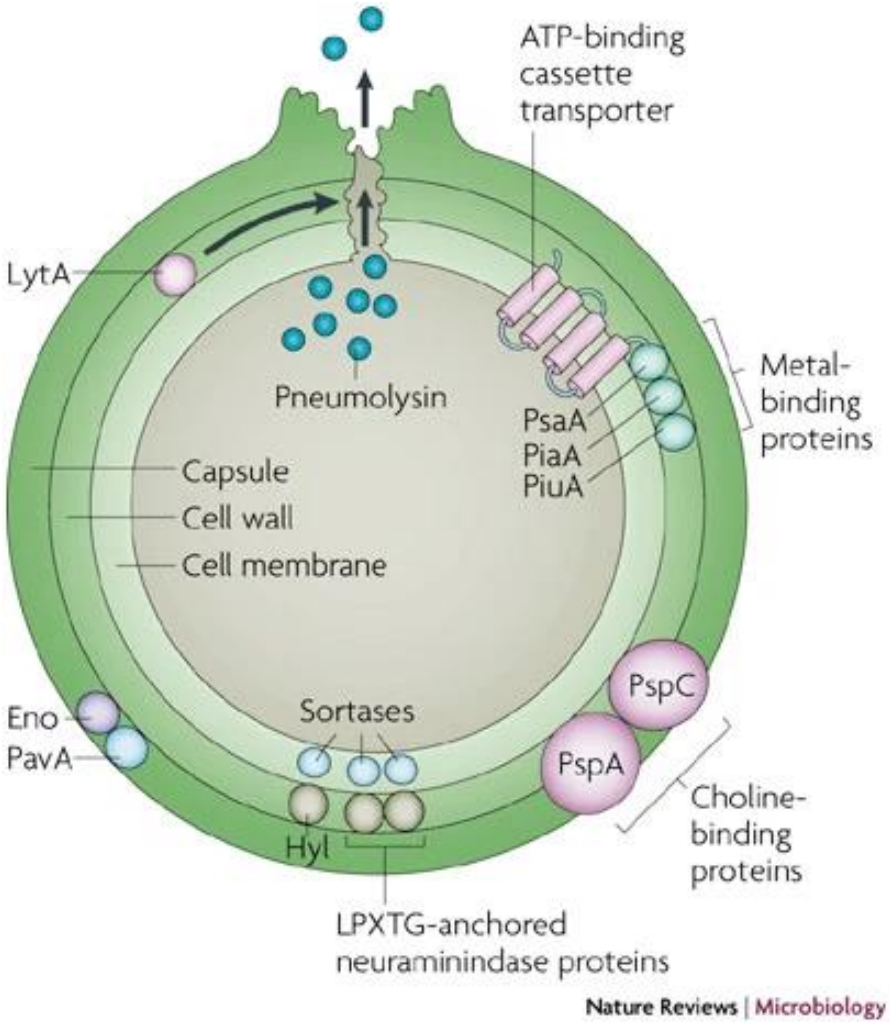
- MTb is never completely cleared following initial infection
- The primary effector mechanisms are macrophage bactericidal functions, but their success is determined by the cytokine and cellular regulatory environment
- Small subtle shifts over time or dramatic short-term changes lead to reactivation and disease



Streptococcus Pneumoniae (Pneumococcus)

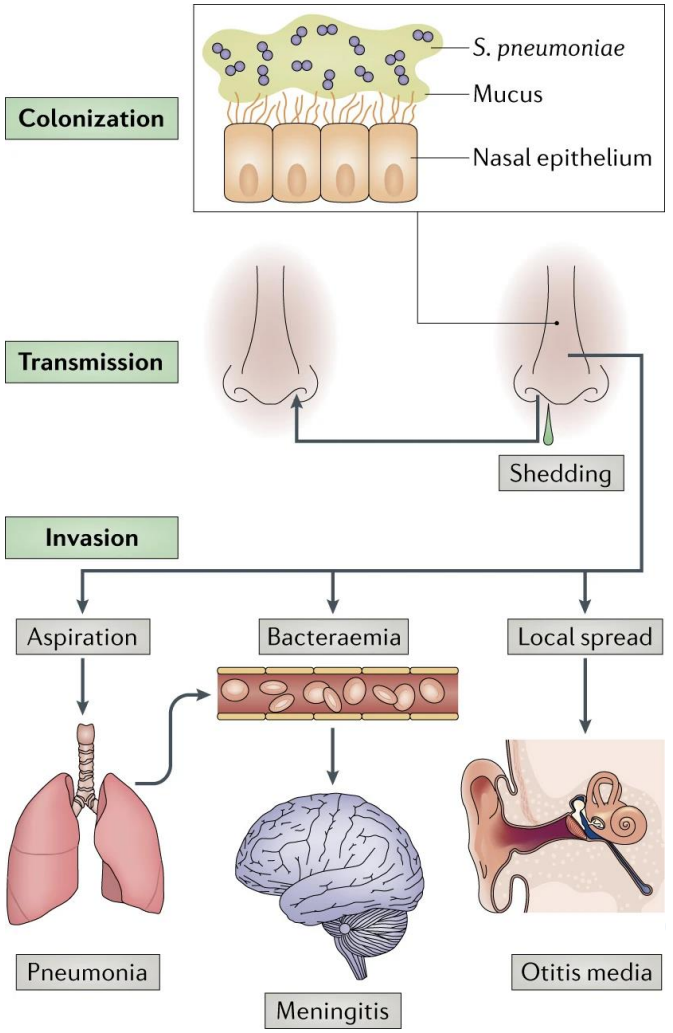
Streptococcus Pneumoniae

- Gram-positive, extracellular, opportunistic pathogen
- Varying degrees of carriage among population—up to 65% of children, <10% of adults (higher in schools and hospitals)

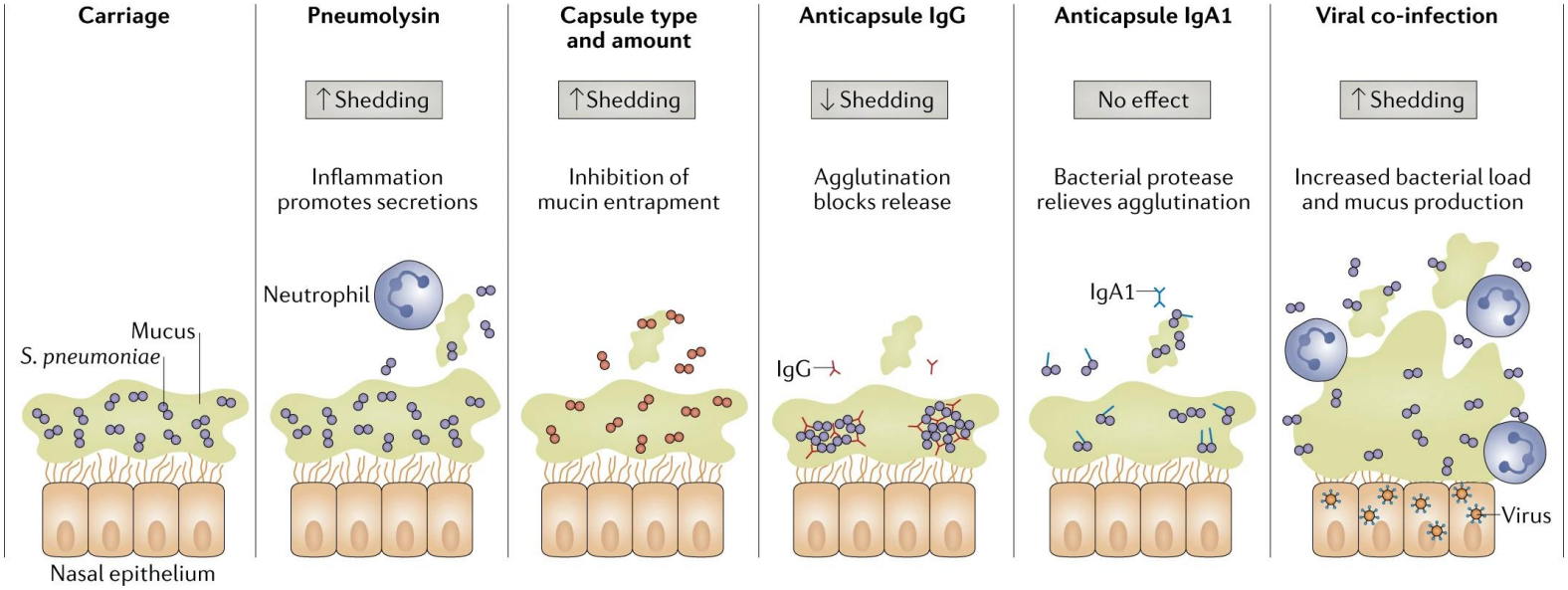


Life Cycle of Strep Pneumoniae

- Colonization/carriage is a prerequisite to disease, but is not itself a disease state
- Colonized individuals can transmit to others, and suffer invasive infection and subsequent disease within themselves



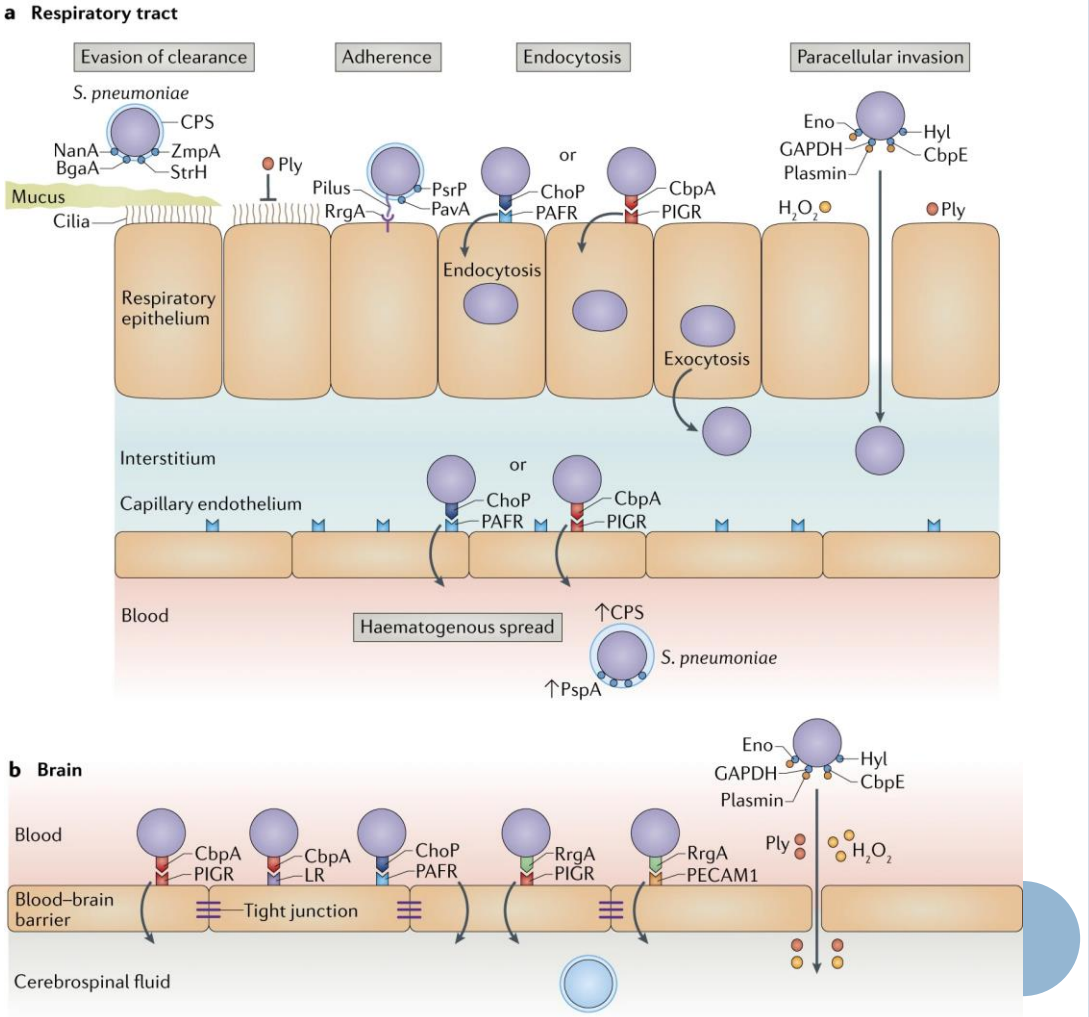
Conversion from carriage to invasion



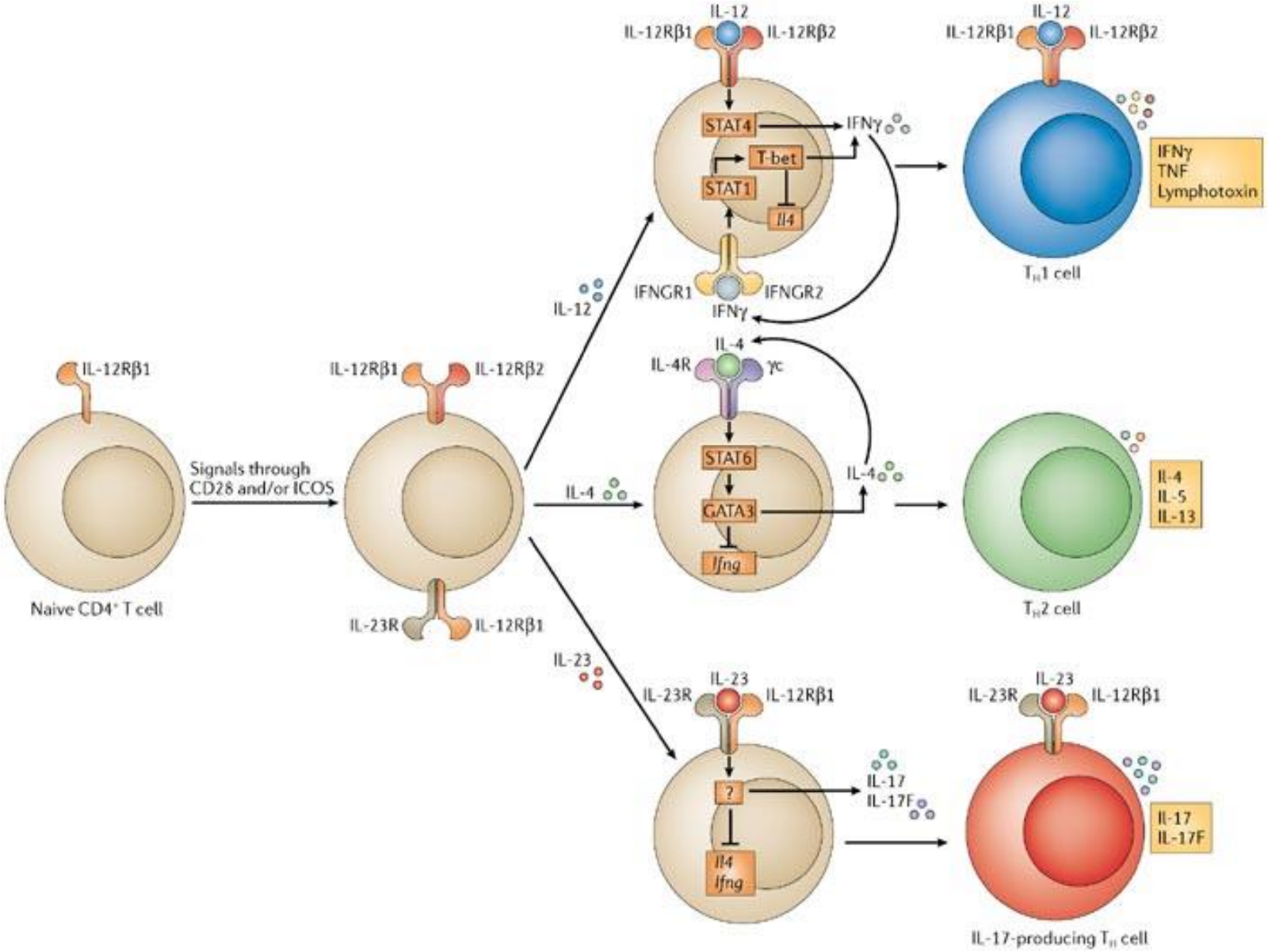
Inflammation can cause an increase in shedding, bacterial load, and disease manifestation

Invasion of the Bacteria

- Pneumococcus evade entrapment in mucus by the charge of the capsule
- Barriers (epithelial barrier, blood brain barrier) are broken down through a number of virulence factors



CD4 Cells Can Differentiate into multiple Types of "Helpers"



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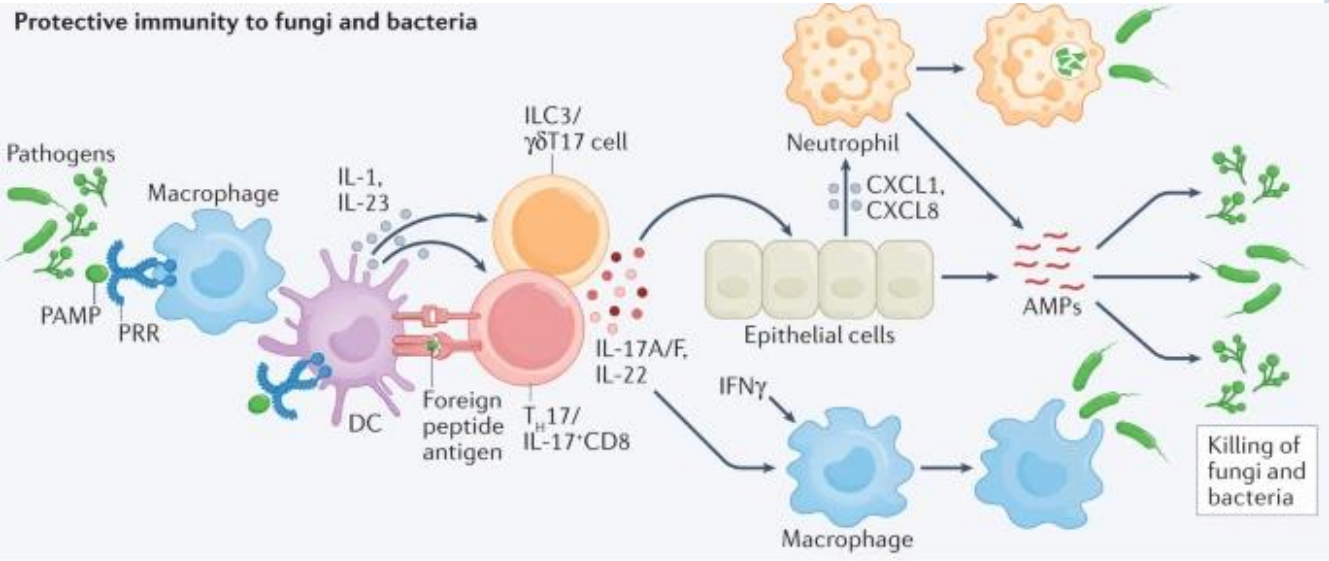
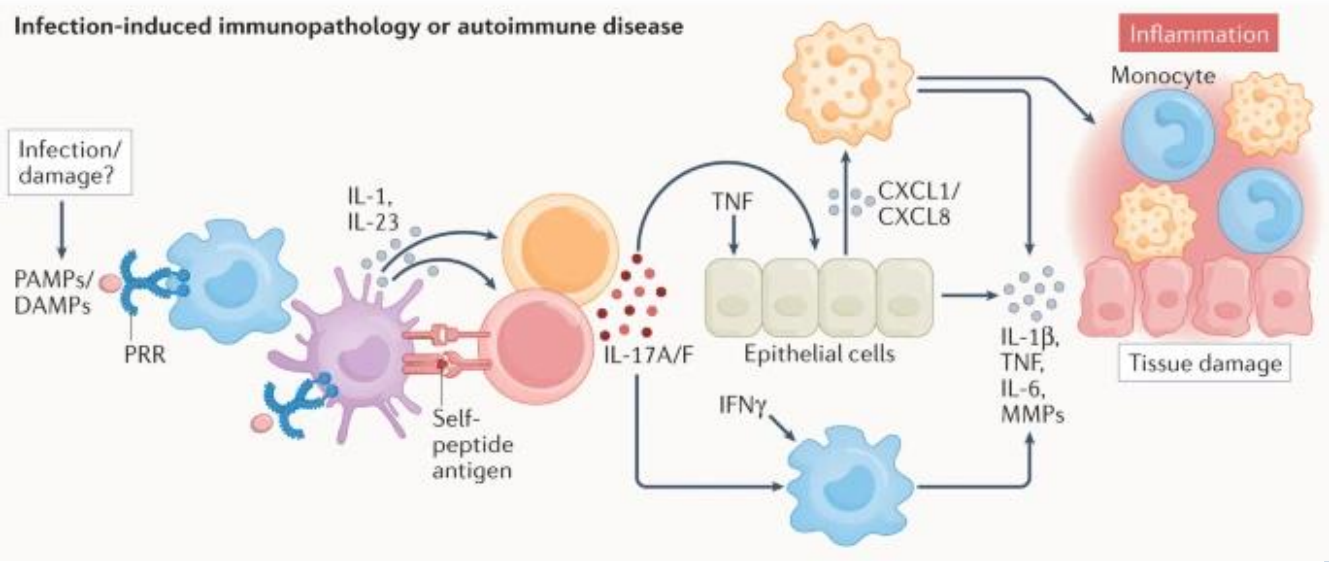
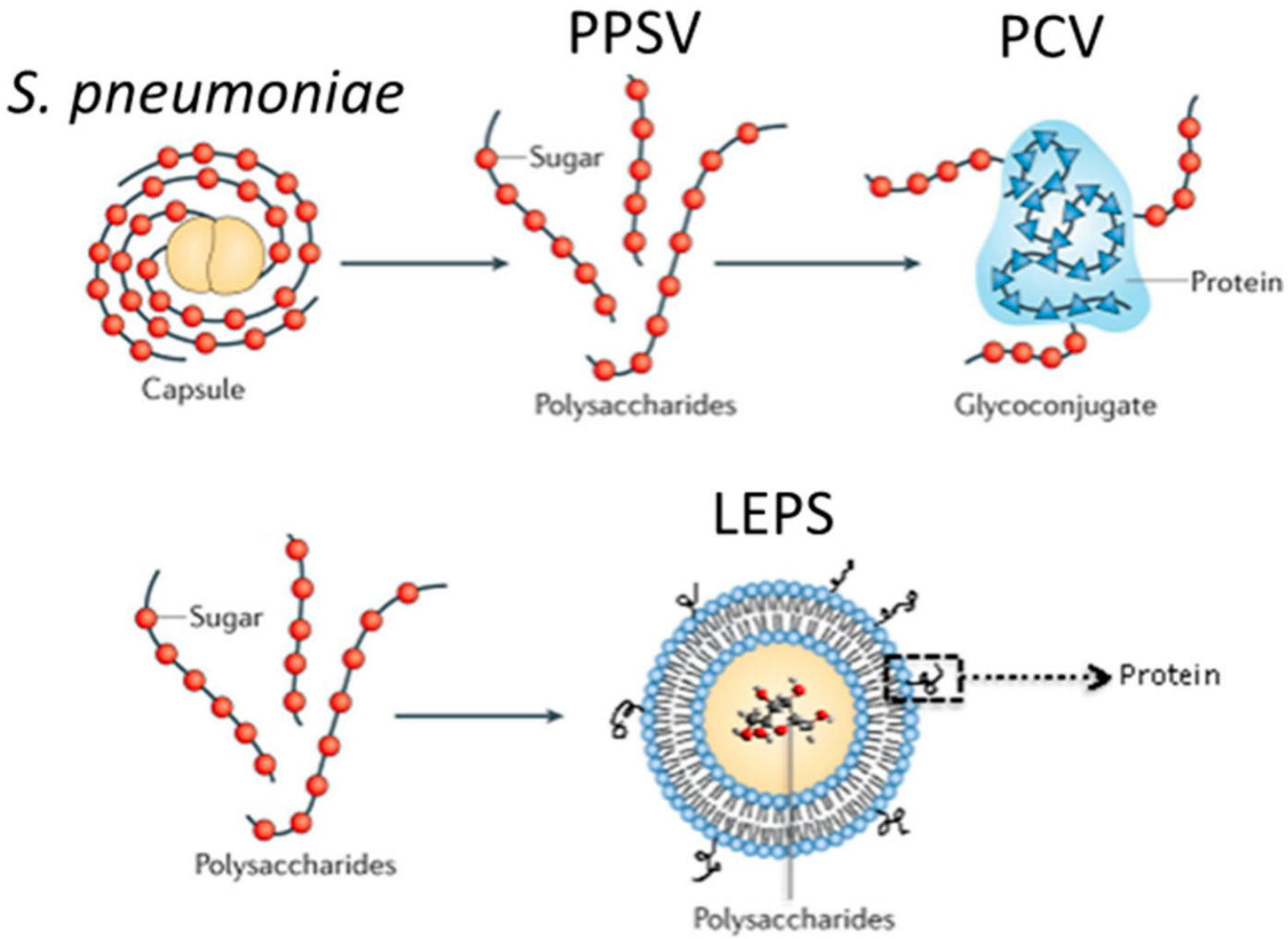
Combined innate and adaptive responses provide protection

- Innate responses can be enforced and amplified by the differentiation of adaptive immune regulators





Pneumococcal vaccines rely on specific polysaccharides



Multiple pneumococcal vaccine platforms

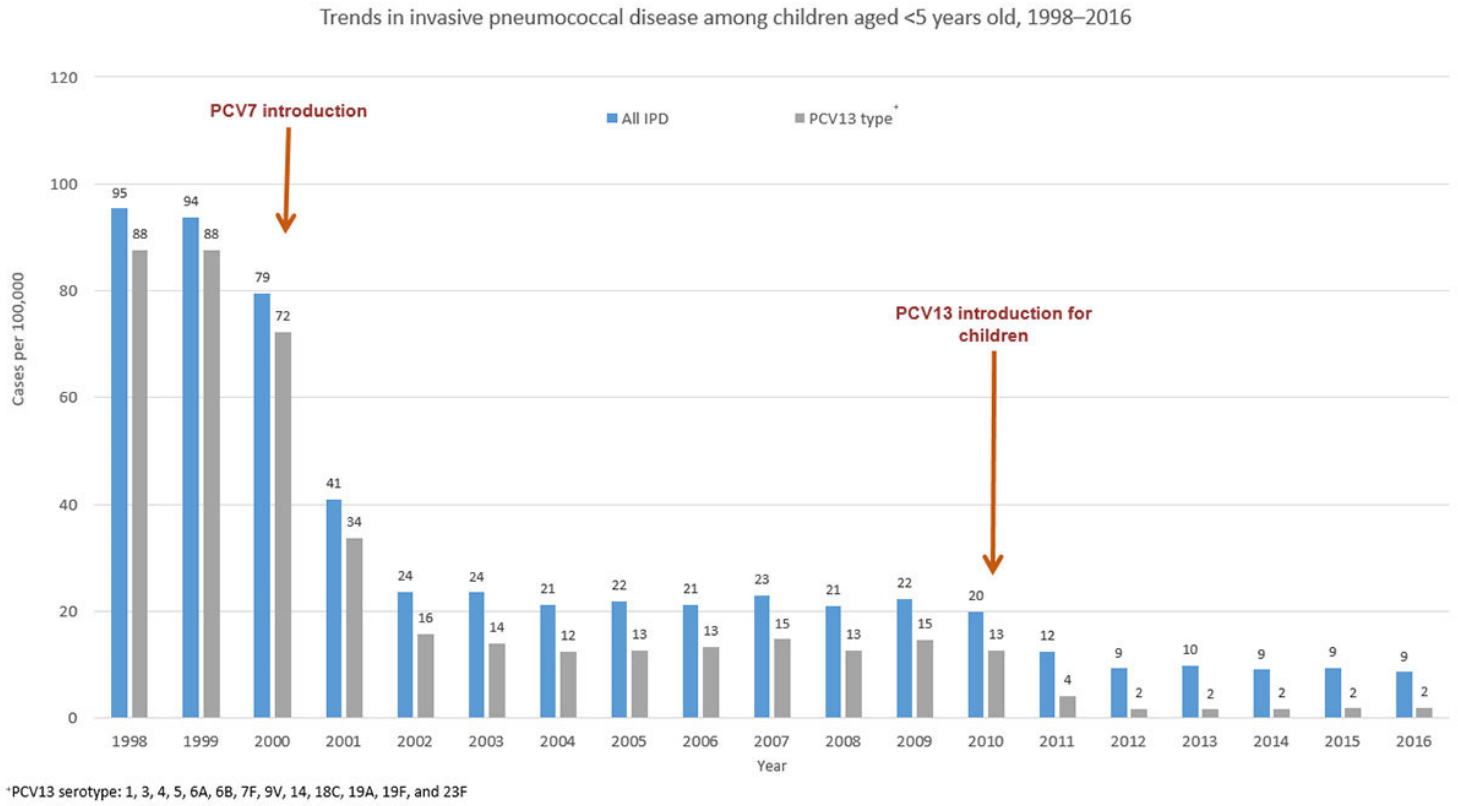
PCVs

- Prevnar 13® : Doctors give this vaccine to children at 2, 4, 6, and 12 through 15 months old and to older children who need it. The vaccine helps protect against 13 types of pneumococcal bacteria that can cause serious infections in children and adults.
- Vaxneuvance® : Doctors give this vaccine to adults 65 years or older and other adults who need it. This vaccine helps protect against 15 types of pneumococcal bacteria that commonly cause serious infections in adults.
- Prevnar 20® : Doctors give this vaccine to adults 65 years or older and other adults who need it. The vaccine helps protect against 20 types of pneumococcal bacteria that commonly cause serious infections in adults.

PPSV23

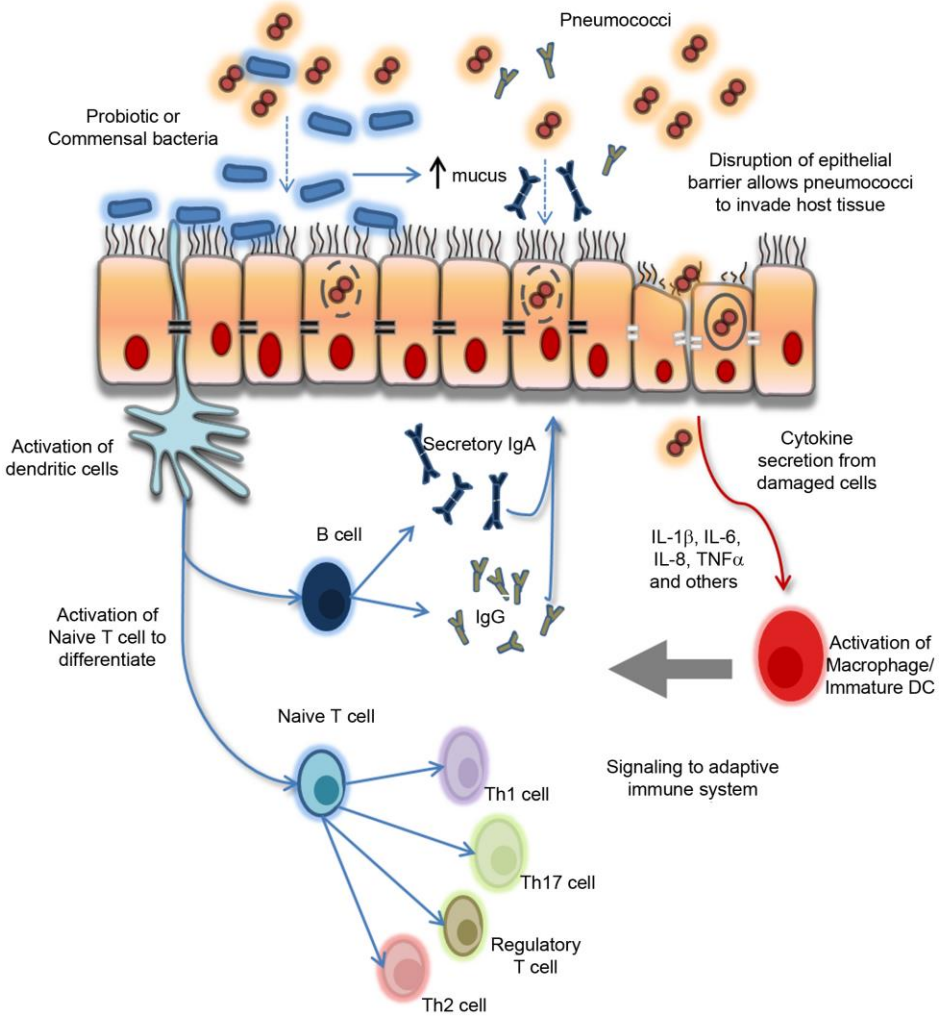
- Pneumovax23® : Doctors give this vaccine to children 2 through 18 years old who need it. Doctors also give it to adults who receive PCV15 or who have received PCV13. This vaccine helps protect against serious infections caused by 23 types of pneumococcal bacteria.

Overall Disease burden reduced, with focus on included strains



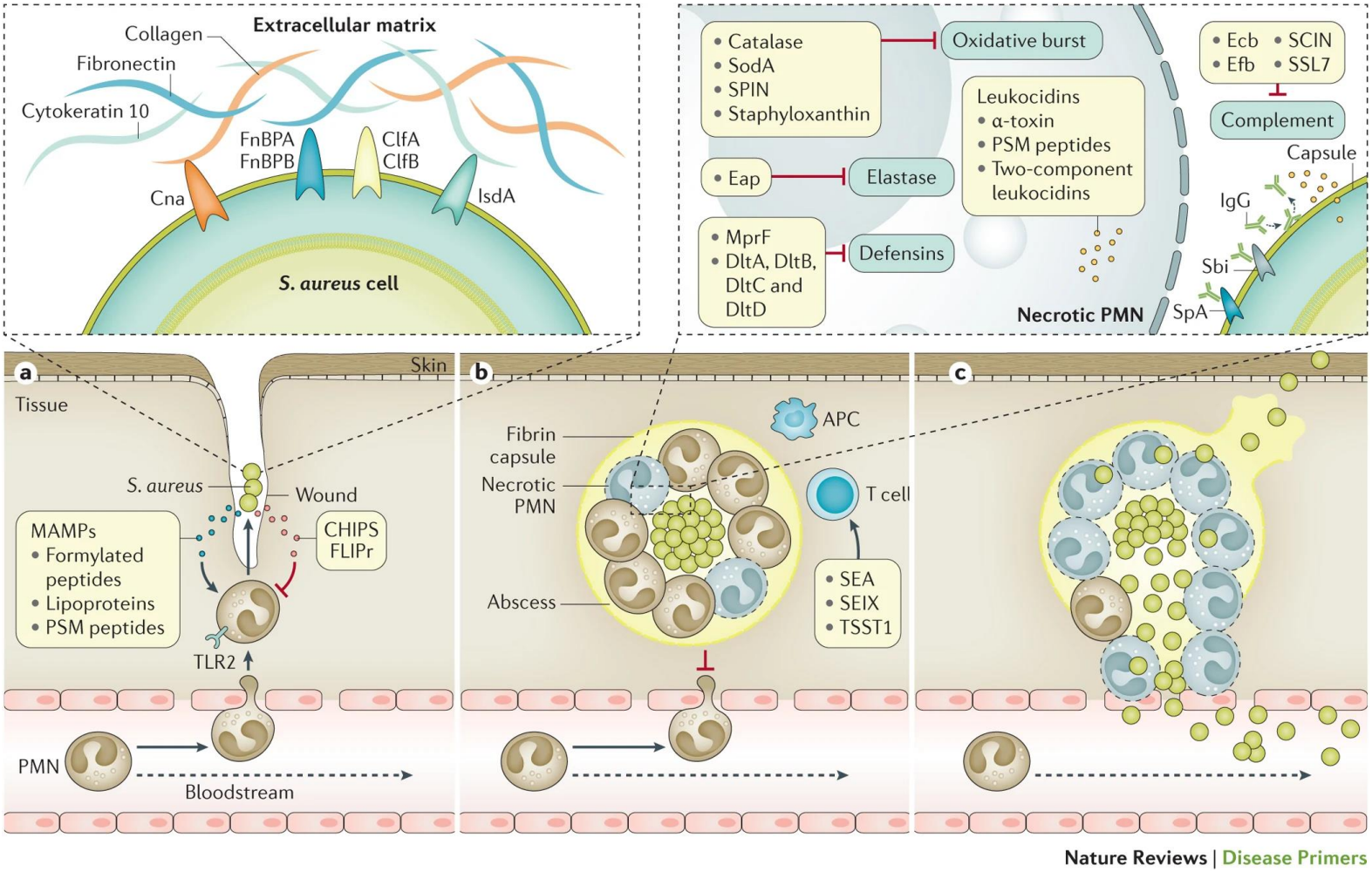
*PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Secretory IgA molecules provide protection against invasion

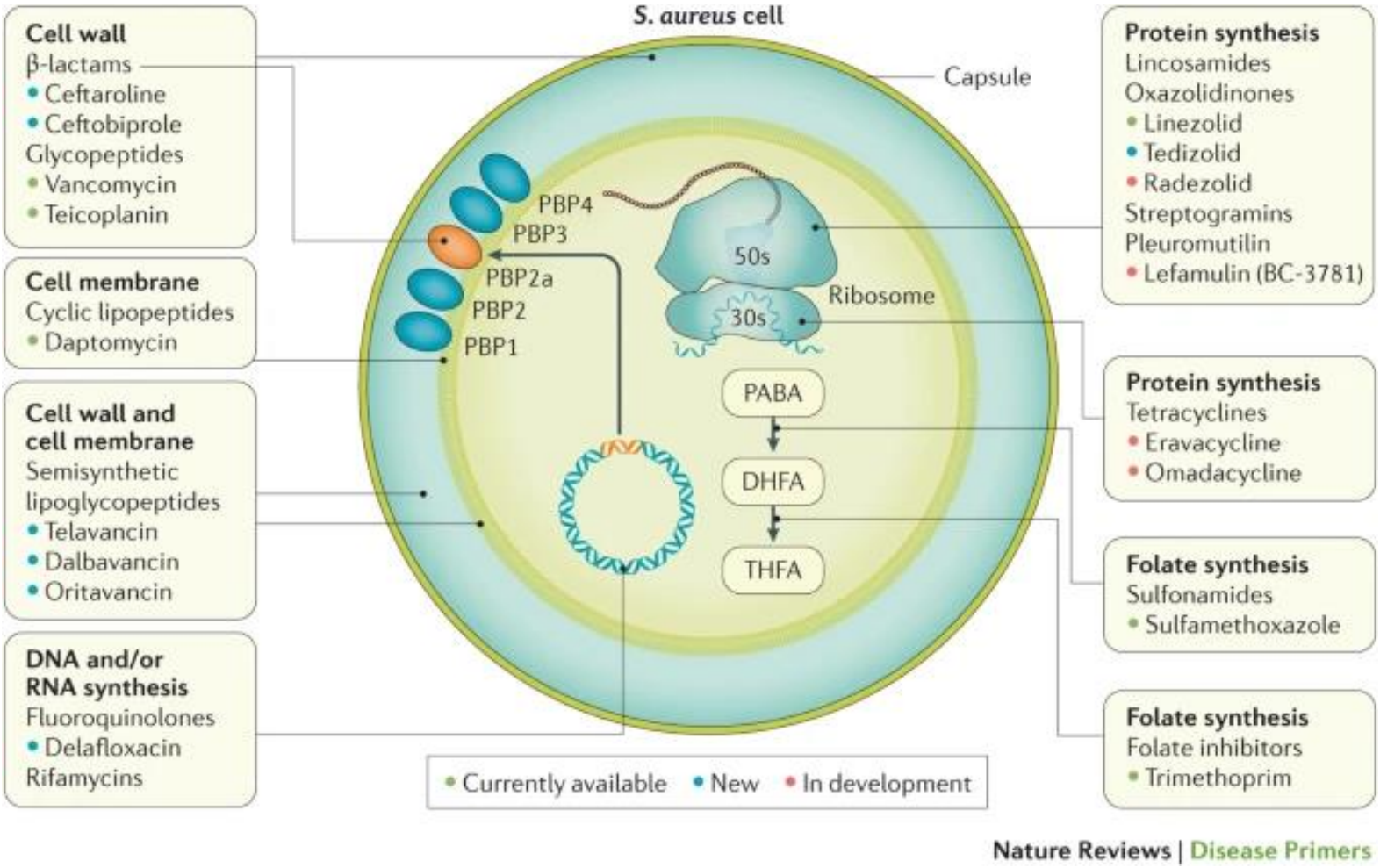


Staphylococcus Aureus

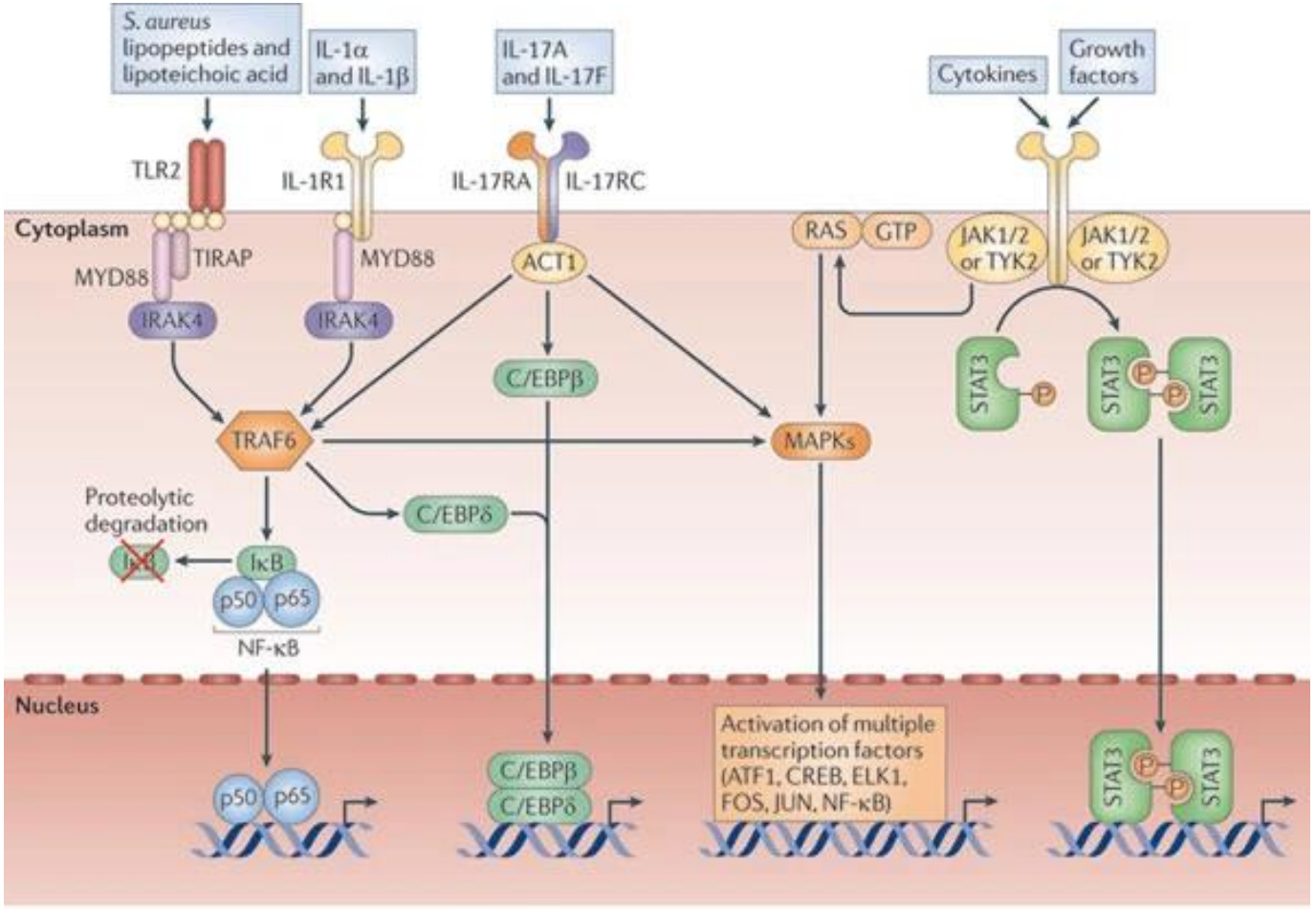
Stages of Staph Aureus infection



MRSA-Methicillin Resistant Staph Aureus



Innate Signaling is Critical for STAPH recognition



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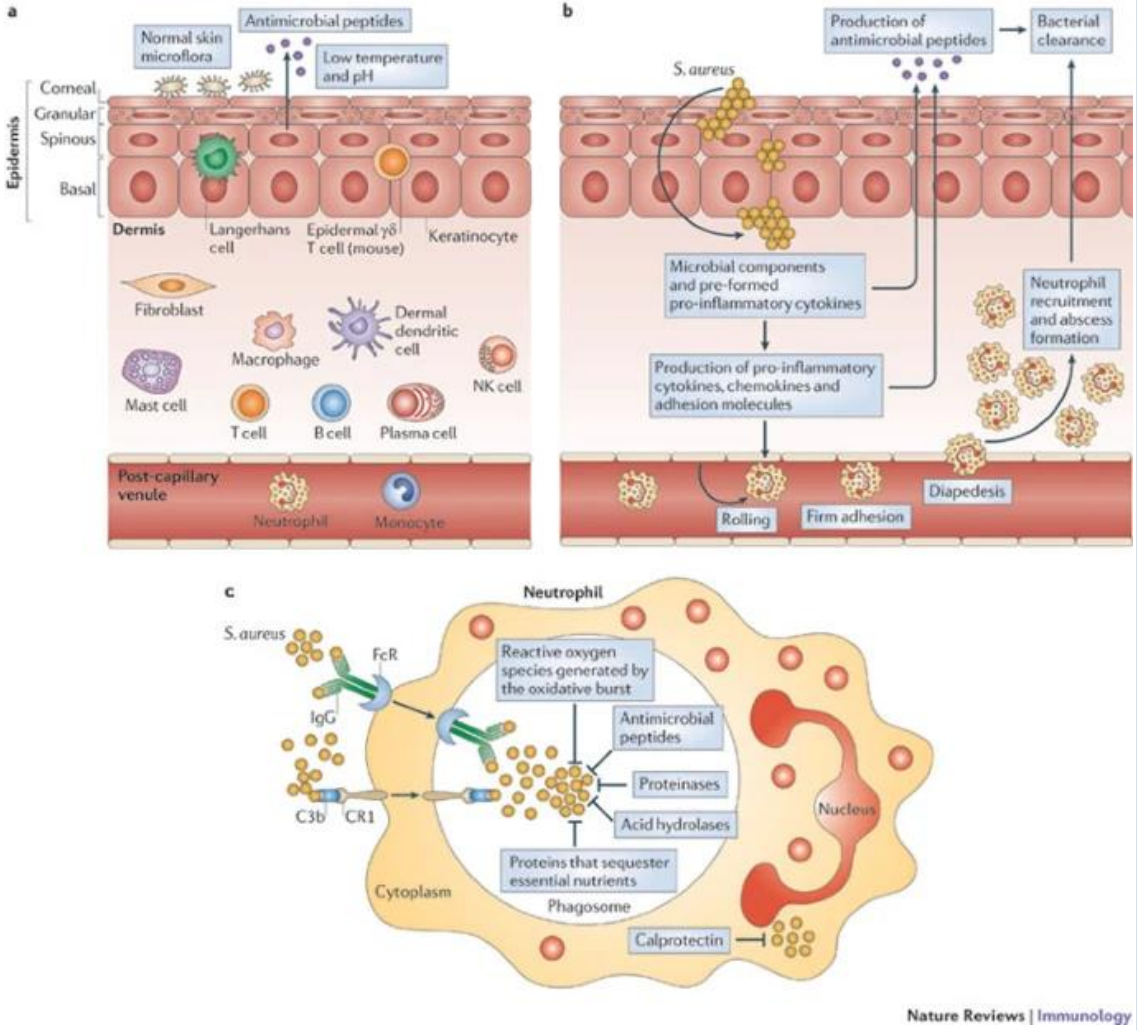
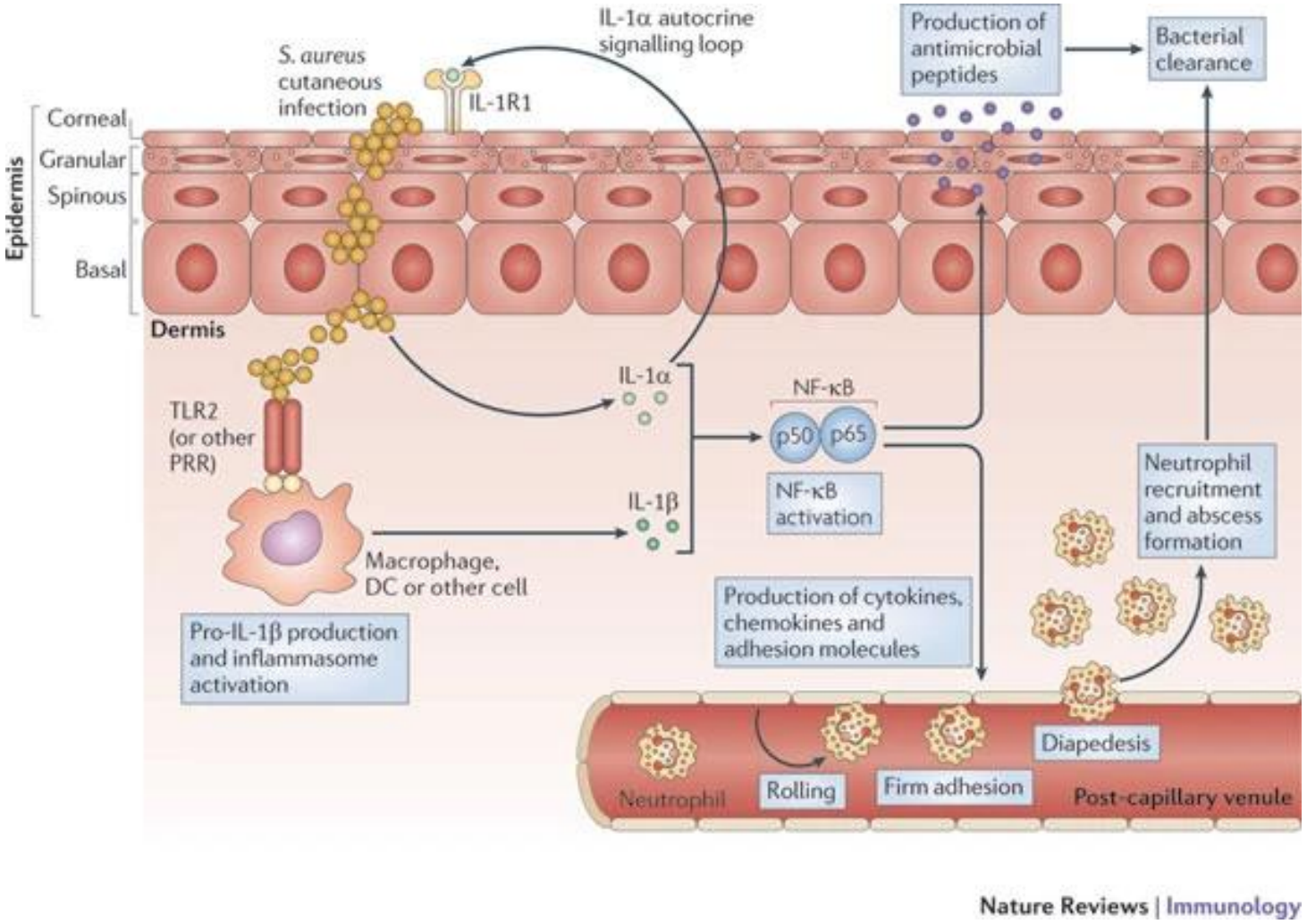
Anti-Staph Immunity in the Skin

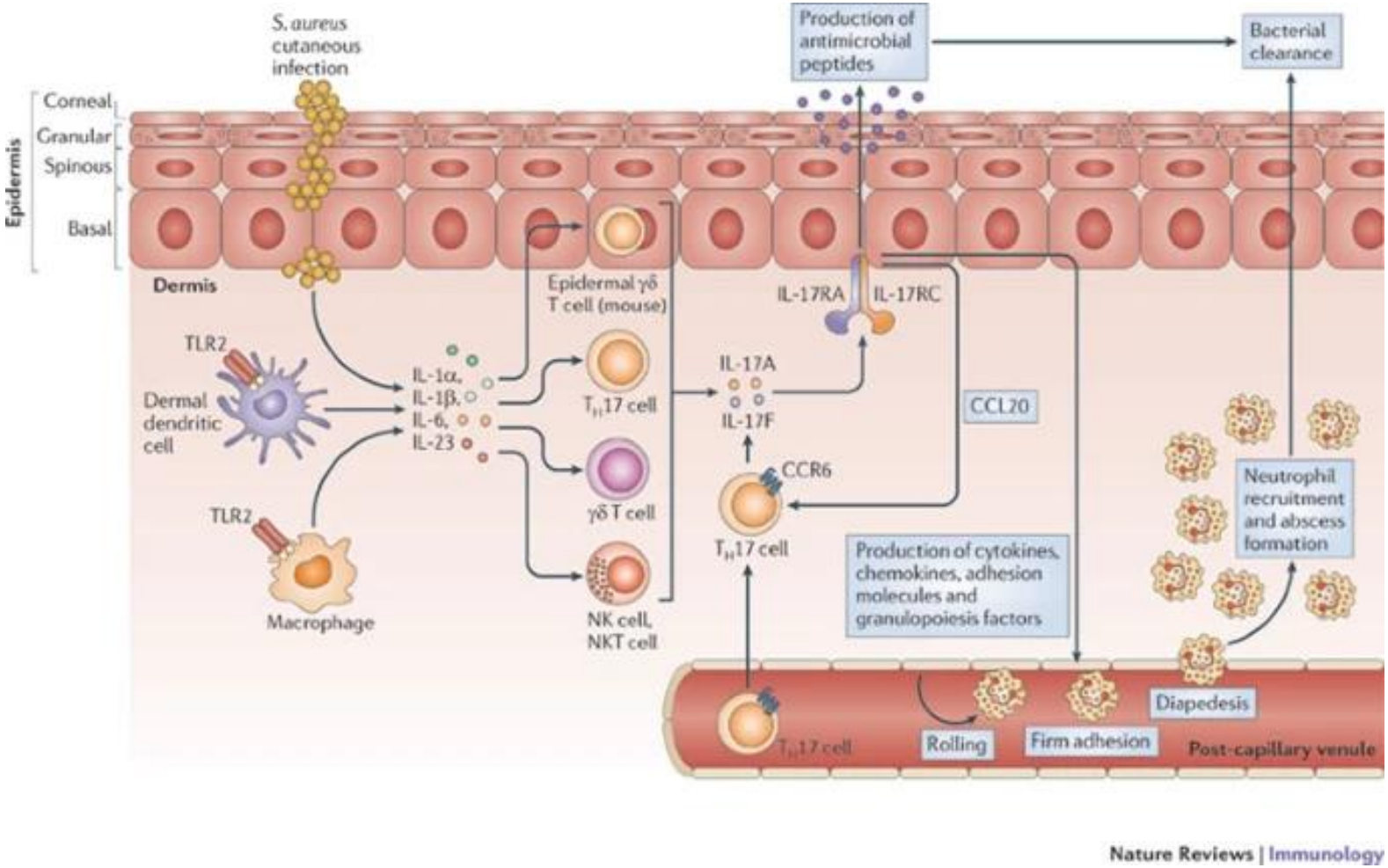
- Innate responses at mucosal surfaces are critical to limit bacterial invasion—high rates of Staph colonization!
- Innate responses can be boosted by well-formed adaptive immunity



Innate Control of Staph



Innate-Adaptive collaboration



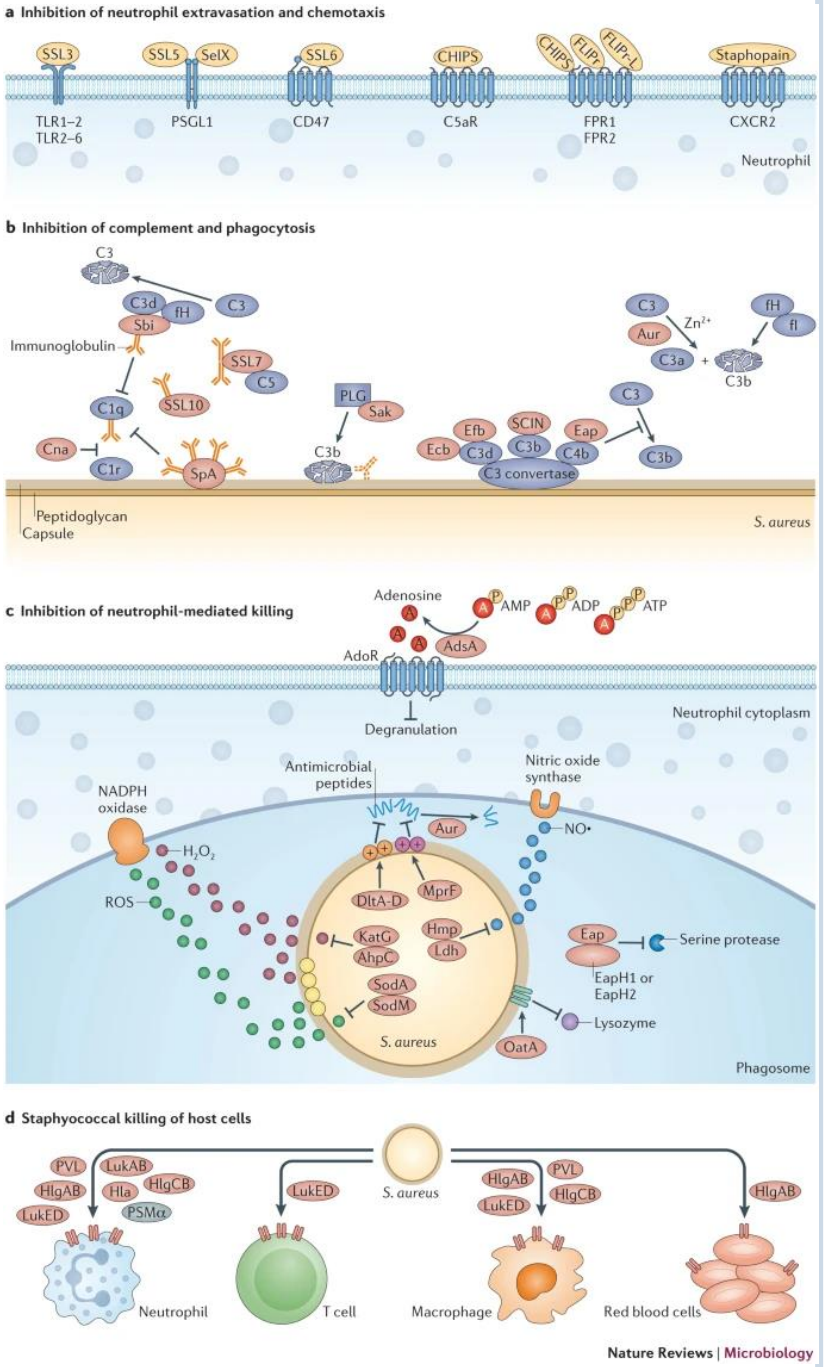
Immunological Deficincies promote susceptibility to STAPH

Immune defect	Diseases
Neutrophils	
Neutropenia	Severe congenital neutropenia and neutropenic patients (such as patients undergoing chemotherapy)
Defective oxidative burst	Chronic granulomatous disease, myeloperoxidase deficiency and G6PD deficiency
Defective chemotaxis	Leukocyte adhesion deficiency type I, Wiskott–Aldrich syndrome and RAC2 deficiency
Granule disorders	Neutrophil-specific granule deficiency and Chediak–Higashi syndrome
Combined defects in oxidative burst, chemotaxis and phagocytosis	Diabetes mellitus and renal insufficiency (in particular, patients on haemodialysis)
Signalling	
Defects in IL-1R or TLR signalling	MYD88 deficiency and IRAK4 deficiency
T cells	
Decreased T_H17 cell numbers	Hyper-IgE syndrome (caused by *STAT3* and *DOCK8* mutations that render patients deficient of T_H17 cells)
	Atopic dermatitis (caused by skin barrier defects, including filaggrin mutations, that lead to decreased levels of antimicrobial peptides, increased T_H2 cell responses and decreased T_H17 cell responses)
	HIV/AIDS (which results in decreased numbers of $CD4^+$ T cells, including T_H17 cells)
IL-17F and IL-17RA deficiency (or patients with autoantibodies specific for IL-17A, IL-17F and IL-22)	Chronic mucocutaneous candidiasis (in which patients have increased susceptibility mainly to mucocutaneous *Candida* infections, but also to *S. aureus* skin infections)

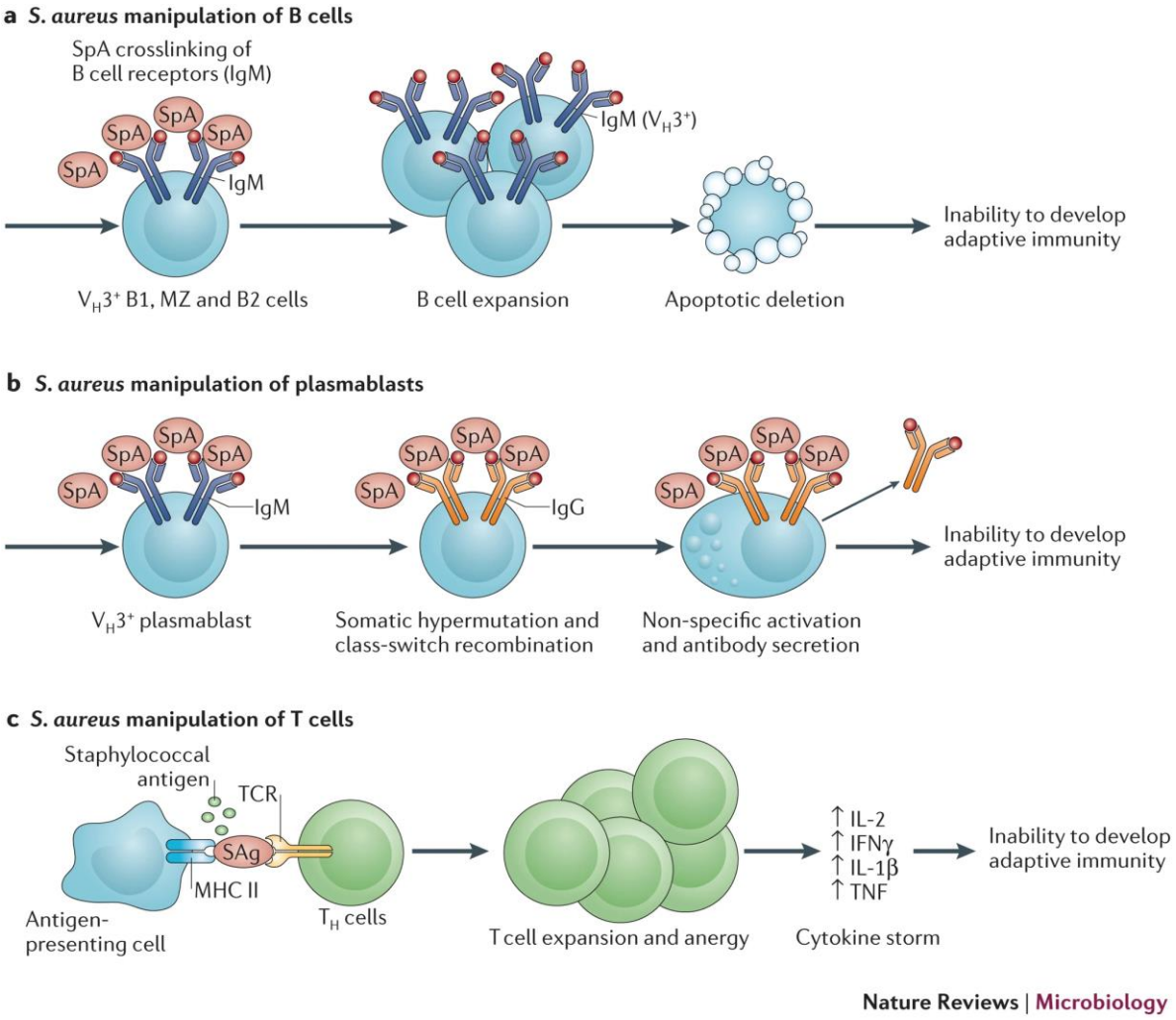
DOCK8, dedicator of cytokinesis 8; G6PD, glucose-6-phosphate dehydrogenase; IL, interleukin; IL-1R, IL-1 receptor; IL-17RA, IL-17 receptor A; IRAK4, IL-1R-associated kinase 4; MYD88, myeloid differentiation primary response protein 88; STAT3, signal transducer and activator of transcription 3; T_H, T helper; TLR, Toll-like receptor.

Mechanisms of Immune Evasion from Staph Aureus

- Staph has multiple virulence factors to limit anti bacterial immunity
  - Enzymes to restrict effects of ROI/RNI
  - Metabolic disruptors to limit functionality of responding neutrophils
  - Direct mechanisms to kill host cells
  - Subtle disruptors of cell trafficking
  - Complement disruptors

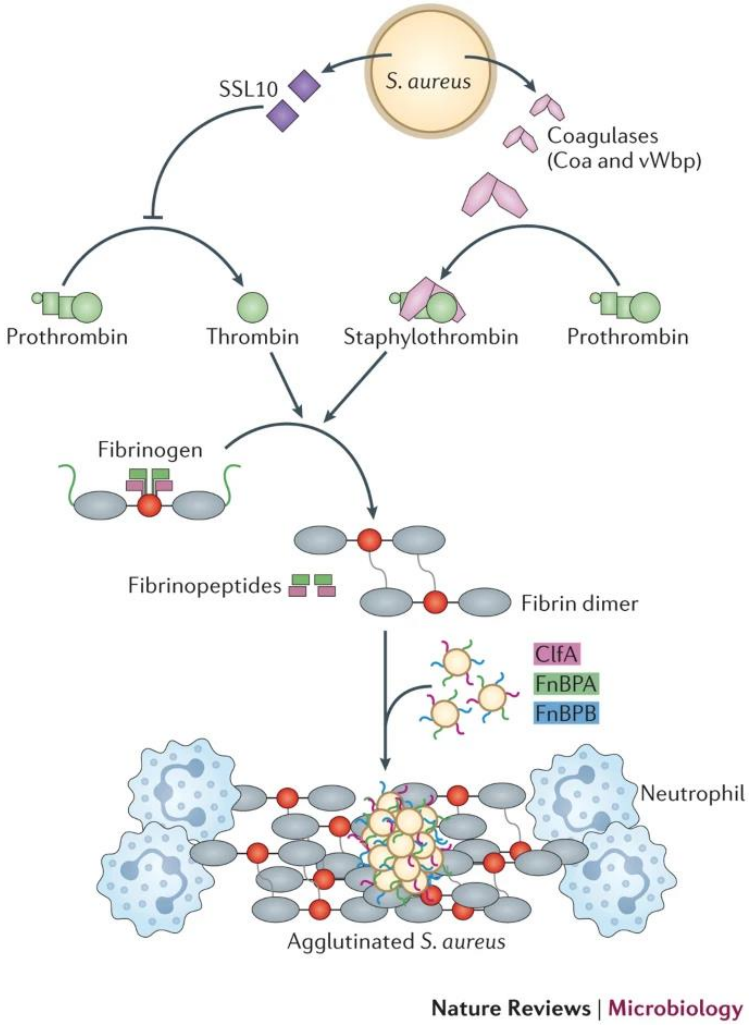


Manipulation of Host Immune responses



STAPH CAN COAGULATE BLOOD

- Staphs unique ability to coagulate blood creates opportunities for virulence and immune evasion
- The fibrin coat acts as a shield, and the large clumps generated block efficient phagocytosis



Bacterial Infections are Potentiated by Virus

- Viral infections provide ideal environments for bacterial colonization to convert to invasive infection
- Compromised immune function, barrier degradation, and immunoregulatory environments all contribute to decreased bacterial surveillance