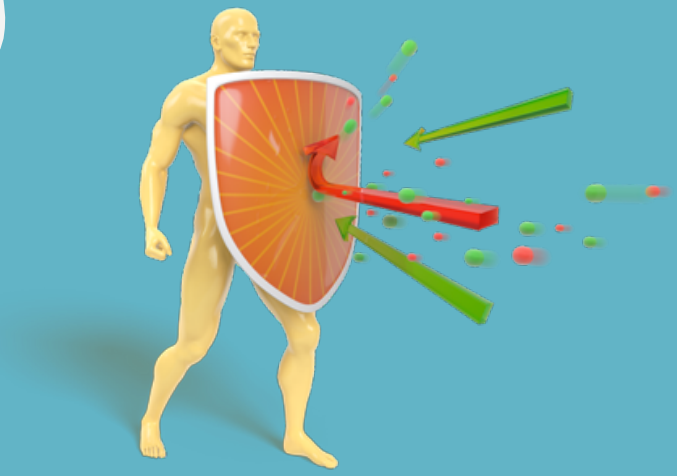
THE IMMUNE RESPONSE QUESTIONS

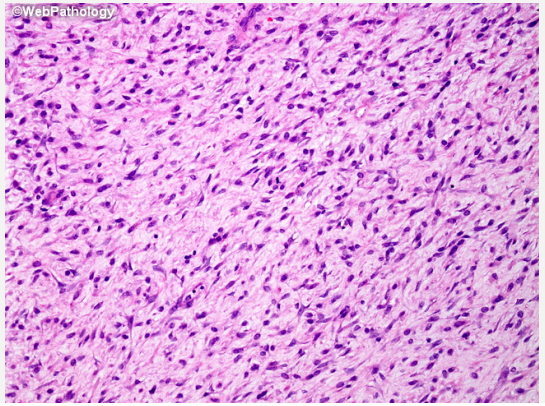


BY STEVEN CHO

THE INNATE IMMUNE SYSTEM

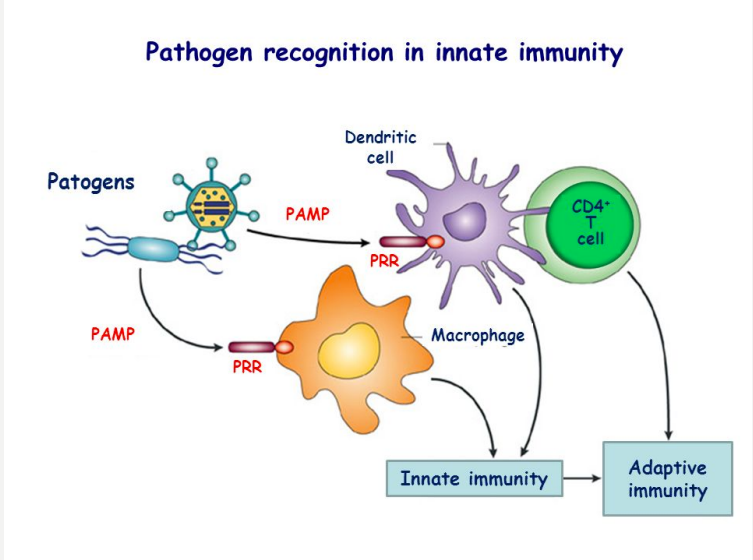
Physical Barrier

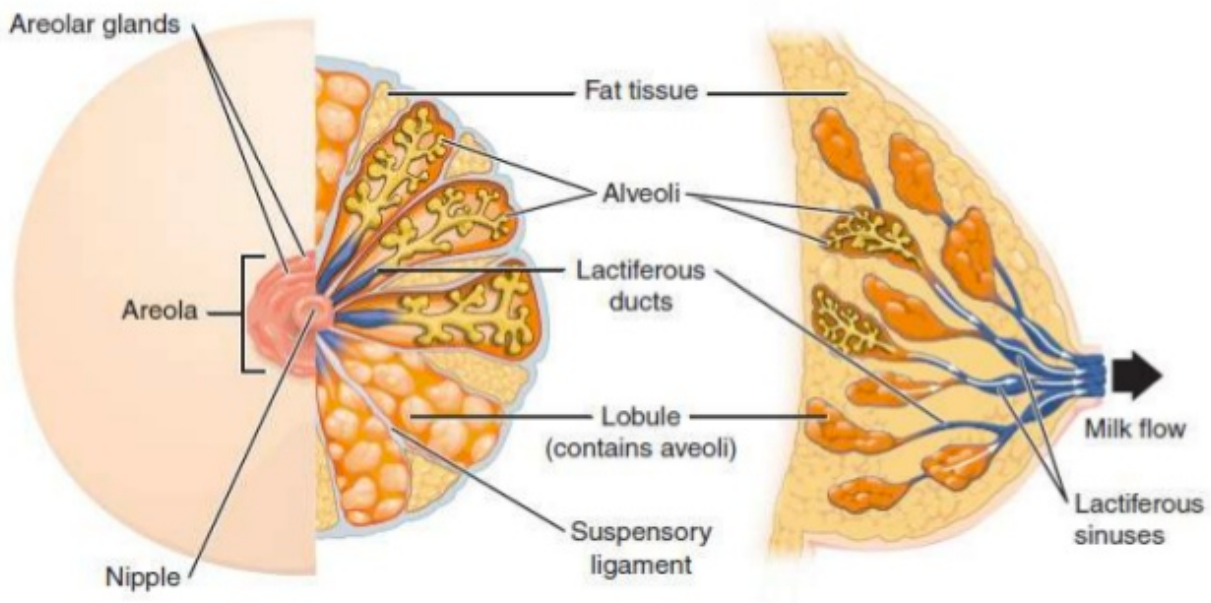
Teat Sphincter – tightly closed and blocks entrance
Squamous epithelium – plug creation with **keratin**/ also chemically attacks pathogens



PRRs and PAMPs

Types of PAMPs – depends on type of bacteria
- Gram negative bacteria – TLR4
- Gram positive bacteria – TLR 2
- Staphylococcus aureus – MBL (Mannose binding lectin), ficolins, and complement molecules





THE INNATE IMMUNE SYSTEM

Mammogenesis

Proliferation of mammary glands – due to increased estrogen

- Increase in interleukin IL-10 and tumor necrosis facter α (TNFα) – upregulates other factors

INFLAMMATION

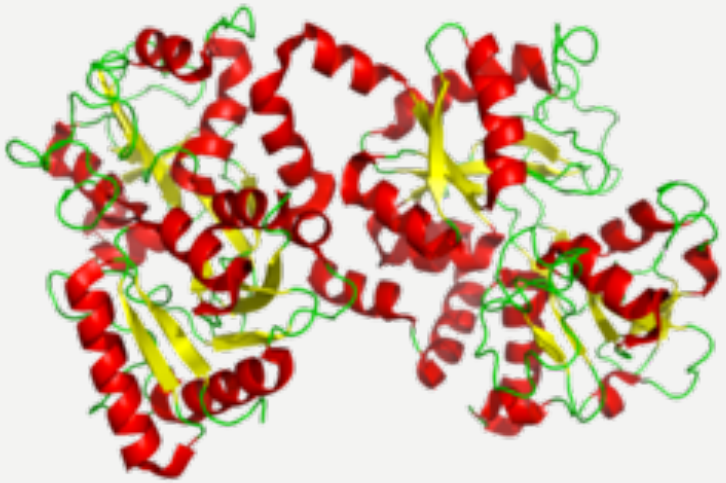
Eicosanoids, prostaglandin E2, prostaglandin F2 α, are increased during mastitis – induces inflammation
- Increases vaso-permeability – leukocyte recruiting/ Induces fever

Eicosanoids, prostaglandins D2 and 15-Deoxy-Delta-12,14-prostaglandin J2 (15 d-PGJ2) - inhibits inflammation
- Block nuclear factor kappa beta (NFKB) – proinflammatory cytokines (inhibited)

BREAST MILK COMPOSITION

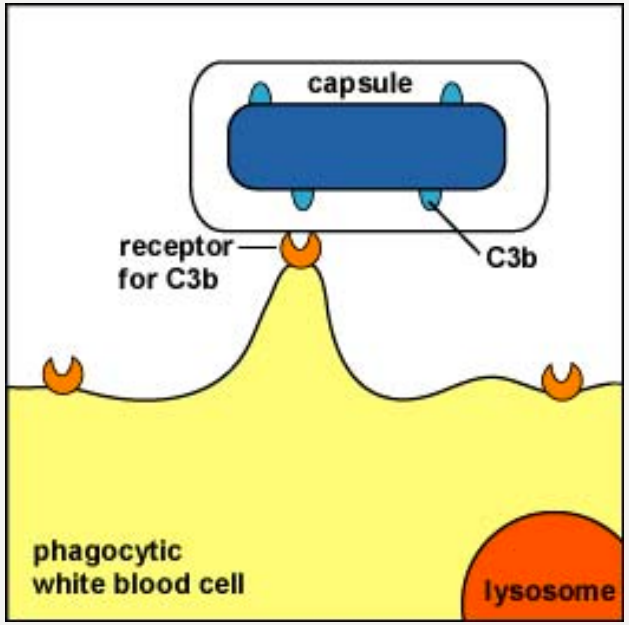
Neutrophils	Lymphocytes	Macrophages	Mammary epithelial cells
• First to be recruited by **C5a and C3a** • Release **defensins**, **oxygen** species, **proteases** and **lysozymes** to attack pathogens • Also take part in increasing inflammation by releasing **prostaglandins and leukotrienes**	• **B Cells** – Antibodies produced by B cells kill and neutralize pathogens • **T Cells** – kills infected cells	• **Phagocytose** bacteria and **release cytokines** to induce inflammation such as TNF- α and Il-1 β	• Also release TNF- α, Il-6, Il-8 after bacteria adhesion • **Upregulate cellular adhesion molecules** - E-selectin • ICAM-1 – intercellular adhesion molecule, and vascular cellular adhesion molecule 1 – **entry of immune cells**

ADDITIONAL INNATE COMPONENTS



Lactoferrin

- Antimicrobial factor in the breast milk – increased when pathogen is present
- Will deplete iron source for the bacteria
- Produced by epithelial cells and leukocytes



Complement System

- C3b and C3bi – major role in opsonization of the bacteria – create pores

ADAPTIVE IMMUNE RESPONSE

Major Histocompatibility Complex – specifically MHC II

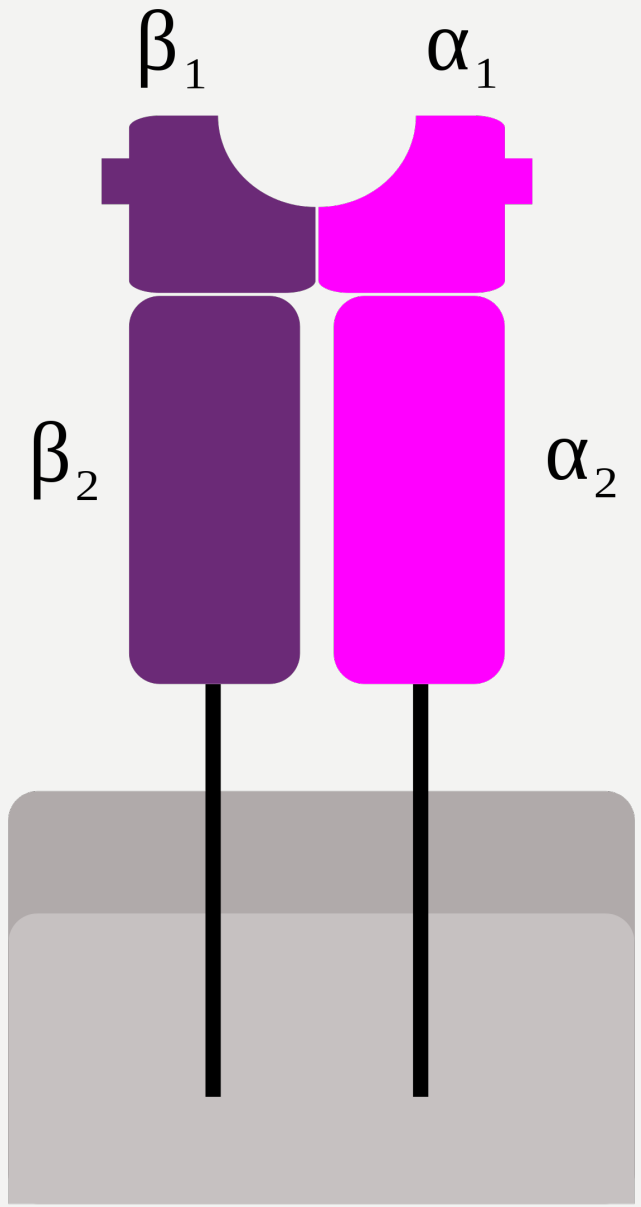
Activates CD4+ helper cells

- Facilitate B cell differentiation – release of Il 2
- Activate more CD8+ cytotoxic cells
- Memory B cells

Th1 – Switches neutrophils to the IgG2 isotope with enhanced phagocytosis

Th2 – Drive antibody-mediated immunity

Th17 – Produce IL-17, IL-21, IL-22, and IL-26, which recruit neutrophils and form abscesses



HOST DAMAGES

Most damage is done by the **Host Immune Response**

Macrophages

M1 macrophages – Secrete IL-12 and IL-23 to promote an inflammatory Th-1 response

- Can produce **reactive oxygen species (ROS)** using **nicotinamide adenine dinucleotide phosphate (NADPH)** oxidase
- Also produces **reactive nitrogen species (RNS)** using **Nitric Oxide Synthase 2 (NOS-2)**

Neutrophils

- Elastase (type of protease) – may damage host cell

STAPHYLOCOCCUS AUREUS –EVASION FROM THE INNATE IMMUNE SYSTEM

Staphylococcal superantigen-like proteins

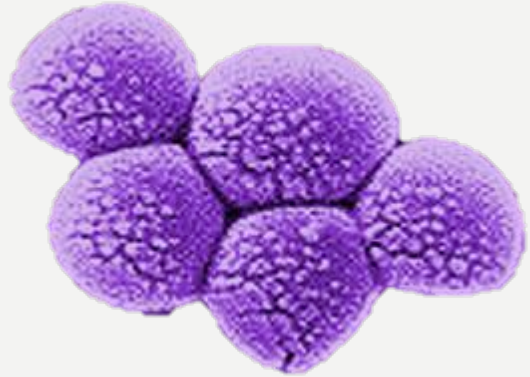
- Slow down clearance and phagocytosis of bacteria
- SSL-7 bind to C5 and IgA

Extracellular adherence protein

- Prevents leukocyte migration – associating with I-CAM-1 – prevents neutrophil squeezing through endothelial cells

Aureolysin

Cleaves C3 to generate C3a and C3b



Self-protection

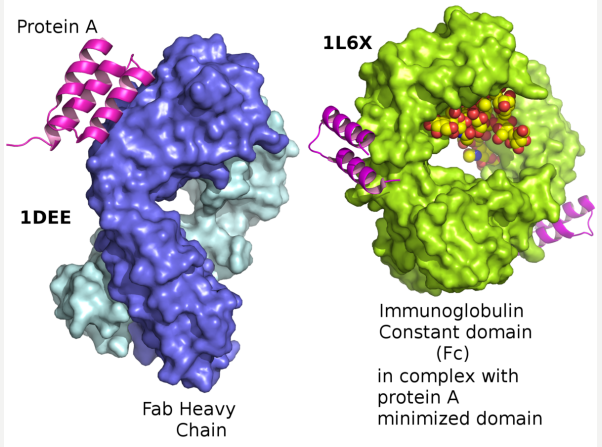
- Express **Capsular polysaccharide** – escape digestion
- **Peptidoglycan acetylation** and **D-alanylation** or **teichoic acids** – against lysosome killing
- **Siderophores** – acquire iron from host

STAPHYLOCOCCUS AUREUS –EVASION FROM THE ADAPTIVE IMMUNE SYSTEM

Manipulate humoral response

Staphylococcal protein A (SpA) – down regulation of receptors

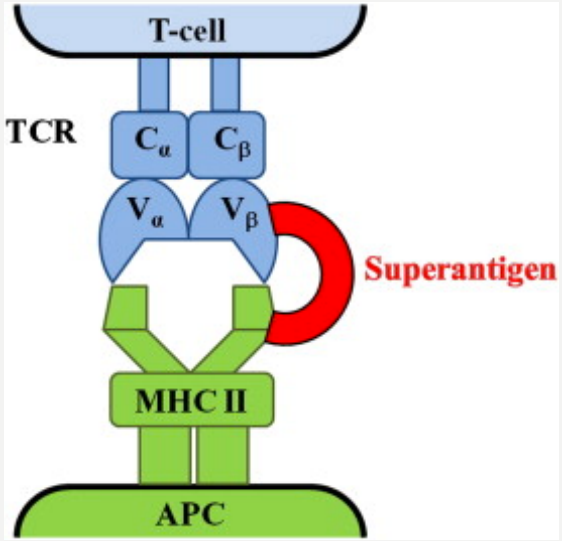
- Binding to the **Fcy domain** of Igs – prevents opsonophagocytic killing
- Binding to the **Fab domain** of Igs – clonal activation of B cells



Manipulate T cell response

Secrete **superantigens** (i.e Toxic shock syndrome toxin and enterotoxins)

- Bypass conventional MHC antigen presenting and processing
  - Promotes Th1 cell proliferation – delayed production of antigen specific antibodies.



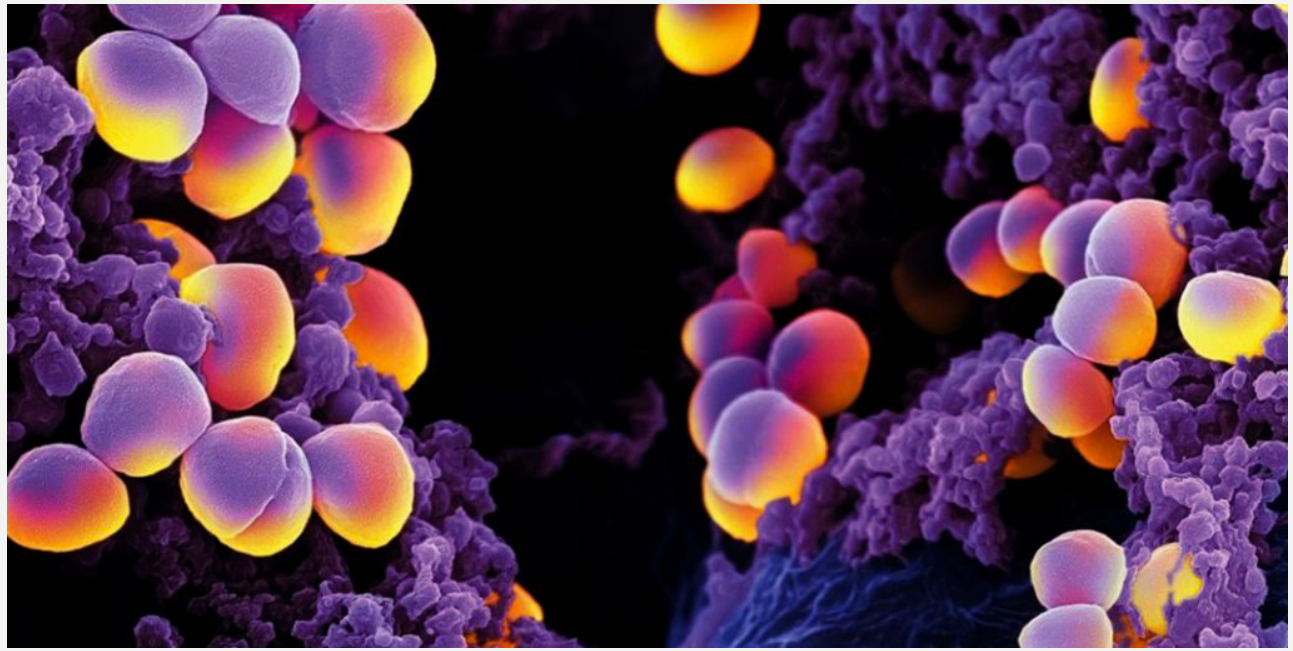
Virulence factors that promote adherence to host cell

Examples - Fibronectin-binding proteins, collagen-binding proteins, iron-regulated surface determinants, ECM-binding proteins, and surface proteins

CLEARANCE OF THE BACTERIA

Most of the time
No need for antibiotics – breast drainage and immune system will suffice

For the case with S. aureus
Bacteria may remain causing risks of relapse or chronic mastitis
Results in **subclinical mastitis** and **chronic infection**



STAPHYLOCOCCUS AUREUS AND IT'S PERSISTANCE

Induction of a weak immune response

- Less **NF-kB** signaling and a delayed secretion of inflammatory cytokines like **TNF-α** – establish colonies or biofilms that resist

Increased expression of Immune dampeners

- **Transforming Growth Factor Beta 1** (TGFB1) and **IL-10**

Small colony variants (SCV)

- Deficient metabolic pathways – more persistence and can more readily avoid of immune cells – less immune response
- May be able to switch back and forth/ may also avoid antibiotics

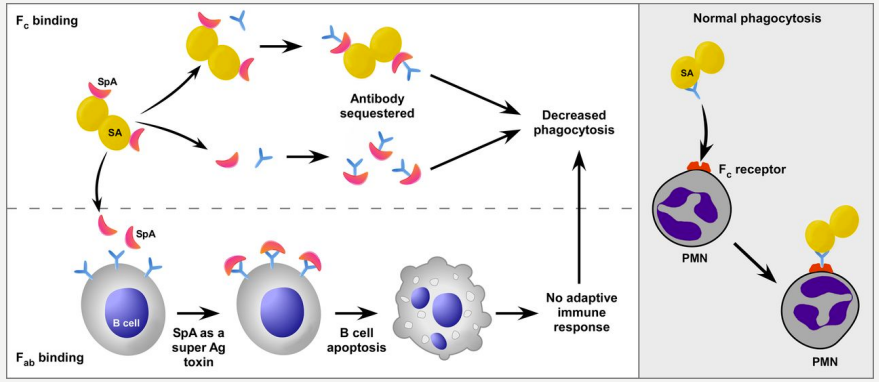
Intracellular surviving

- Help them avoid **antibody mediated immune responses**

Loss of capsular polysaccharide expression

- Greater persistence in the mammary glands by avoiding immune clearance **neutrophil and leukocyte** infiltration

RECOVERY AND IMMUNITY



Following the infection

- **IgG and IgA** subsequently follows after the infection
- Clearance is mostly done by the the **host immune syst**em/ rarely – usage of antibiotics
- Relapse may occur (Intracellular S. aureus)

Prevention

- Breastfeeding technique – also helps for recovery and prevention of milk stasis

Immunity?

- Immunity is not well formed – **SpA** decreases long lived **plasma cells** and binds to **B cells** and **down regulates** them.