Mucosal immunology

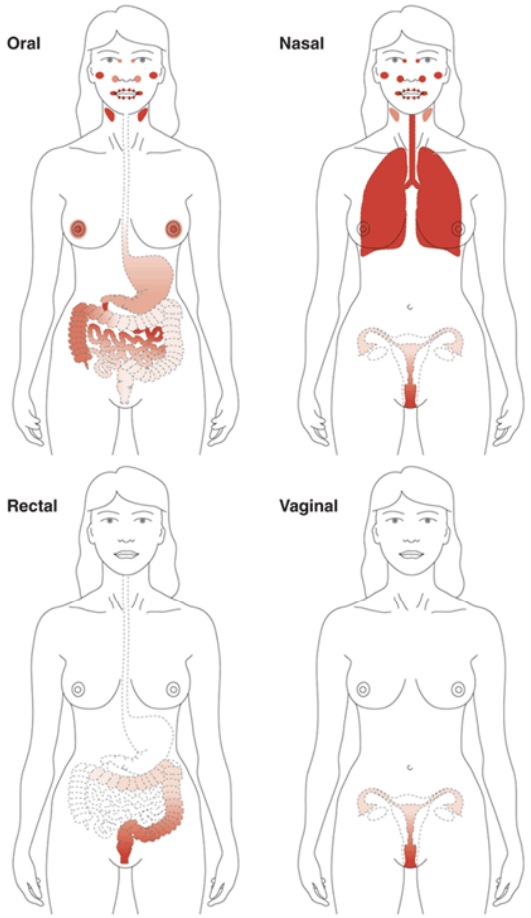
Aida Sivro

Mucosal immunology

- Mucosal surface is major portal of entry for pathogens
- Most antigents encountered by the immune system enter the body through mucosal surfaces of the respiratory, gastrointestinal and urogenital tract
- At least 90% of infectious microorganisms use the mucosae as portals of entry
  - Examples include sexually transmitted infections caused by HIV, *Chlamydia*, *Neisseria*, HSV; gastrointestinal infection caused by *Helicobacter pylori* and *Vibrio cholerae*; respiratory infections caused by RSV and influenza;

Mucosal sites

- MALT – mucosa associated lymphoid tissue
- And mucosal sites include:
- GALT – Gut Associated Lymphoid Tissue
- BALT- Broncho Associated Lymphoid Tissue
- NALT- Nasal Associated Lymphoid Tissue
- Mammary and salivary glands
- Urogenital tract



Jan Holmgren & Cecil Czerkinsky, Nature Medicine

Mucosal surfaces

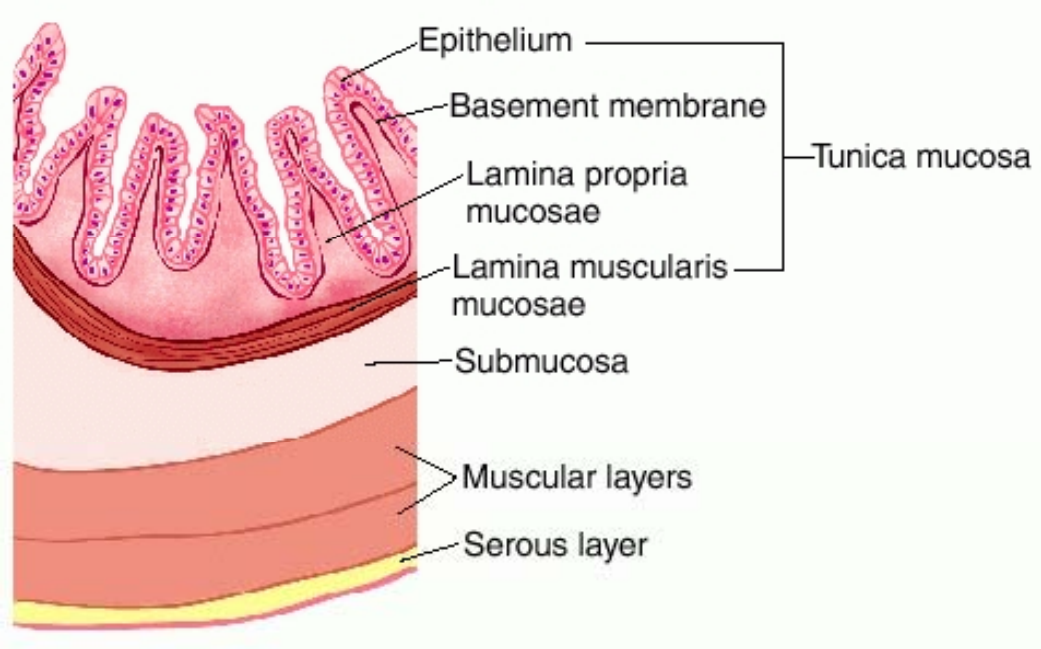
- Mucosal surfaces can generally be divided into a
  - Type I mucosal surfaces (such as those in the gut and the lungs)
  - Type II mucosal surfaces (such as those in the vagina, eyes and mouth)

Table 1 | **Comparison of the genital and rectal mucosae**

Feature	Type I mucosa	Type II mucosa
Tissues	Uterus, endocervix and upper anorectal canal	Vaginal canal, ectocervix, foreskin and lower anorectal canal
Epithelia	Simple columnar epithelium	Stratified squamous (non-keratinized) epithelium
Polymeric immunoglobulin receptor	Present	Absent
Major antibody isotype	Secretory IgA	IgG
Mucosa-associated lymphoid tissue	Present	Absent
Microfold cells	Present	Absent
Langerhans cells	Absent	Present
Mucus source	Goblet cells (in the rectum) and glands in the crypts (in the cervix)	Epithelial cells

Akiko Iwasaki, Nature Reviews Immunology

- Major components of the mucosa include
  - a single layer of epithelial cells,
  - a layer of connective tissue (the lamina propria) and
  - a thin muscle layer
- The outside of the mucosa is lined with mucus
- Mucus- made up of high molecular mass glycoproteins



- Mucosal immune system has three main functions
  - Protecting the mucus membranes against colonization and invasion by pathogens
  - Preventing uptake of foreign proteins
  - Preventing the harmful immune responses to these antigens if they do reach the body interior

- While systemic immunity normally functions in sterile environment and responds strongly to foreign invaders, MALT must economically select nature of the response in order to avoid tissue damage and immunological exhaustion

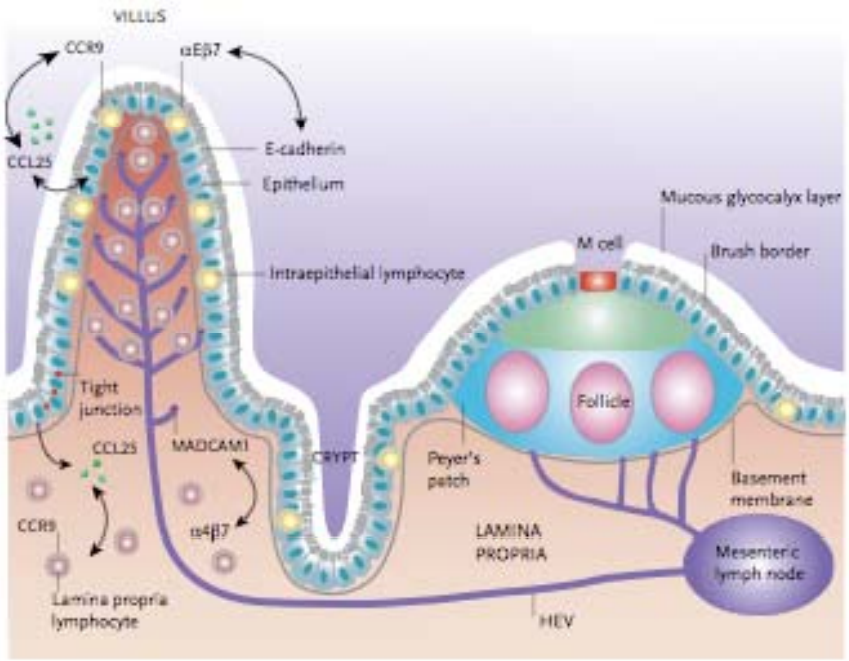
Mucosal immunology

- Mucosa have a complex immune system, functionally and anatomically different from the systemic immune system – capable of fighting pathogenic antigens and exhibiting tolerance to non-pathogenic antigens
- The combined area of the mucosal surfaces is more than 200X greater than that of the skin.
- Mucosal tissues are heavily populated by immune cells
  - Intestinal lining contains more lymphoid cells and produces more antibodies that any other organ in the body
- Mucosal IMS also includes epithelial cell barrier and other extra –epithelial defenses that the microorganism has to overcome in order to cause infection

Epithelial and extra-epithelial defenses

- The first step in the induction of the mucosal immune response is the transport of antigens across the epithelial barrier
- Besides acting as a physical barrier mucosal epithelia provides the immune system with a continuous influx of information about the external environment
- Epithelial barrier varies from one tract to the other

- single layer covers the intestinal mucosa, the airway tract varies from pseudostratified to simple epithelium
- and oral cavity, pharynx urethra and vagina have a multilayered squamous epithelial lining



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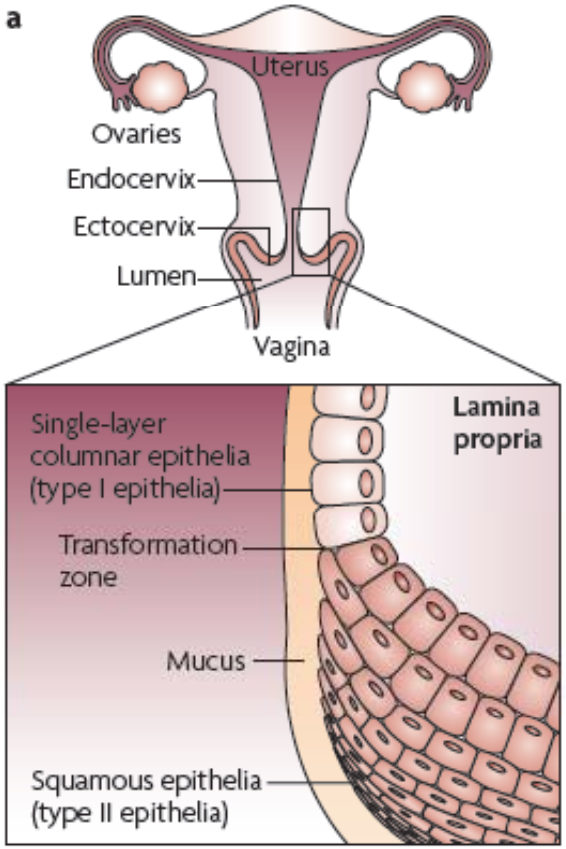

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Alternative barriers

- Mechanical washing forces and cilial action create a current that rids the mucosal surface of organisms that enter the body and fail to bond early and efficiently to the epithelium
- Mucus layer- composed of mucins, secreted by goblet cells or mucus producing epithelial cells
- Acidic pH of the stomach, enzymes (lysosime, lactoferrin, lactoperoxsidase), anti-microbial peptides secreted by the epithelial cells (defensins, cathelicidins, histatins)

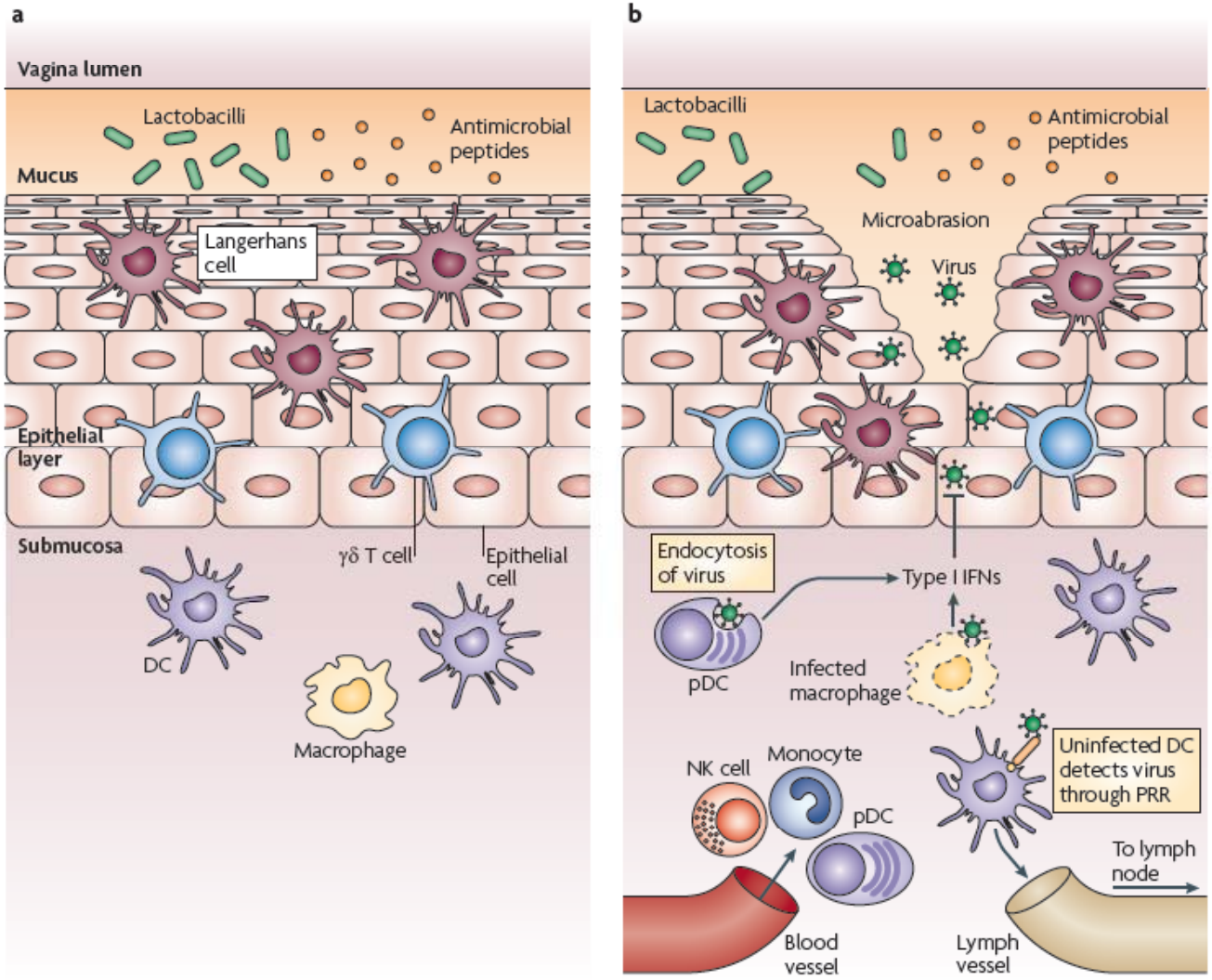
The endogenous microflora

- Colonization resistance – occupying potential binding sites, competing for nutrients, secreting inhibitory compounds (bacteriocins or metabolic products)
- More that 1000 species of bacteria are estimated to live in the gut of the humans
- In contrast to intestinal tracts normal vaginal flora is predominantly composed of the Lactobacillus species
- They provide protection against harmful pathogens by producing hydrogen peroxide and maintaining the acidic pH of the vaginal fluid by through lactic acid production

Innate defenses

- Innate immune cells in and beneath the epithelial cell layer: macrophages, Langerhans cells, dendritic cells survey the environment for the invading pathogens
- Upon infection – inflammatory responses initiate the recruitment of other immune cells (neutrophils, NK cells, monocytes) that can detect the virus and prevent further viral spread

Innate defenses at the vaginal mucosa



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Mucosa- Lymphoid tissue

Infection is detected by the APC, that take up antigens and migrate into the lymph nodes where they present antigenic peptide to the cells of the adaptive immune response

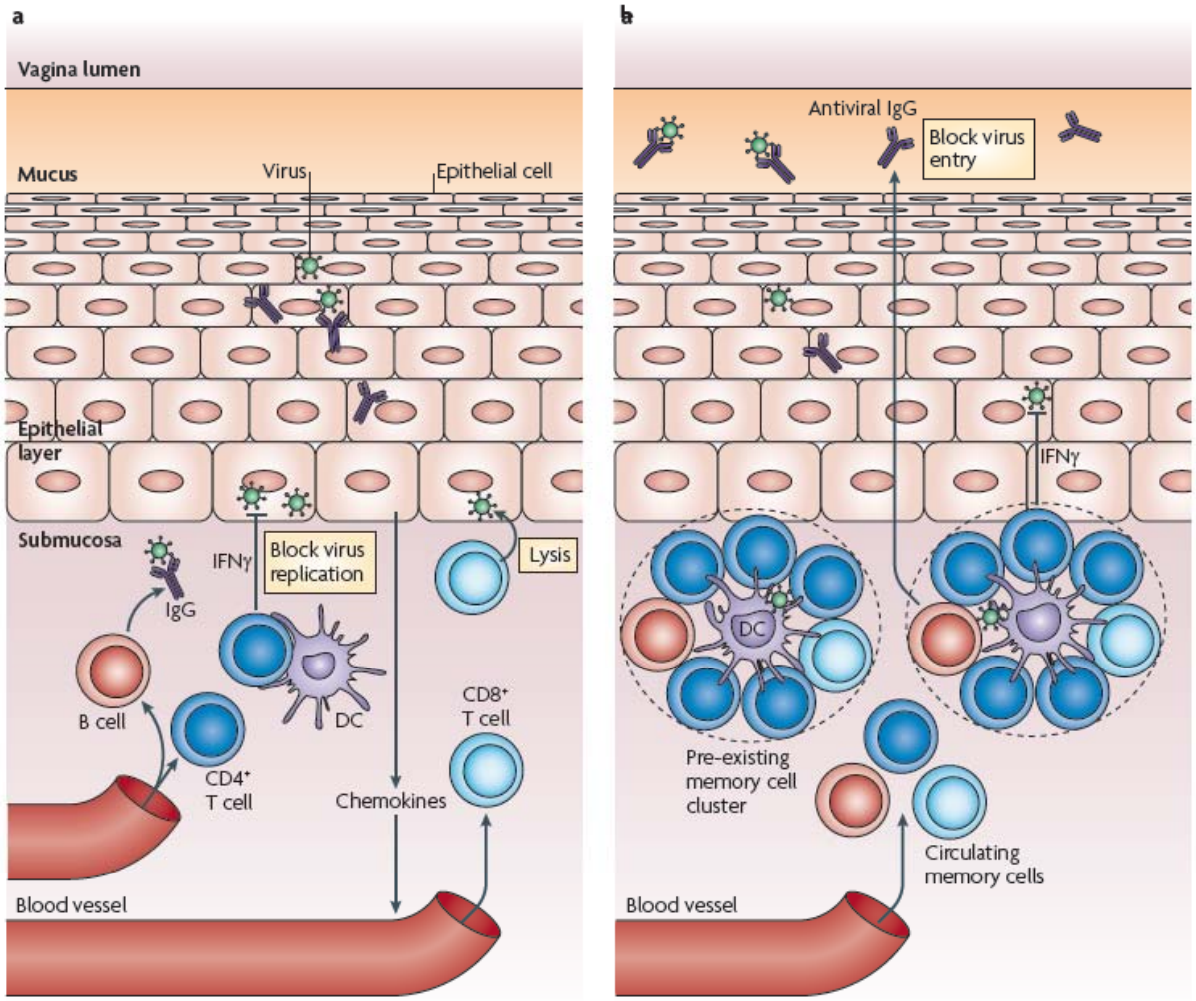
- Type II mucosa is characterized by the absence of MALT -Diffuse lymphoid tissue
  - Widespread leukocytes found throughout the epithelium and lamina propria of the mucosa. Priming of the adaptive immune response happens in the draining lymph nodes
- Type I mucosa - Organized lymphoid tissue
  - Characterized by mucosal lymphoid follicles
  - Occurs in intestines, bronchi and tonsils

Adaptive immune responses

Once primed, cells of the adaptive immune response can migrate to the sites of infection and provide protection

- Production of antibodies
  - IgA and IgM are actively produced in the mucosal tissues and transported across the mucosal cells
  - IgG is the predominant antibody in the lung and the cervicovaginal tract
- CD8+ T cell and CD4+ T cell mediated immunity and cytokine production

Adaptive immune defenses at the vaginal mucosa



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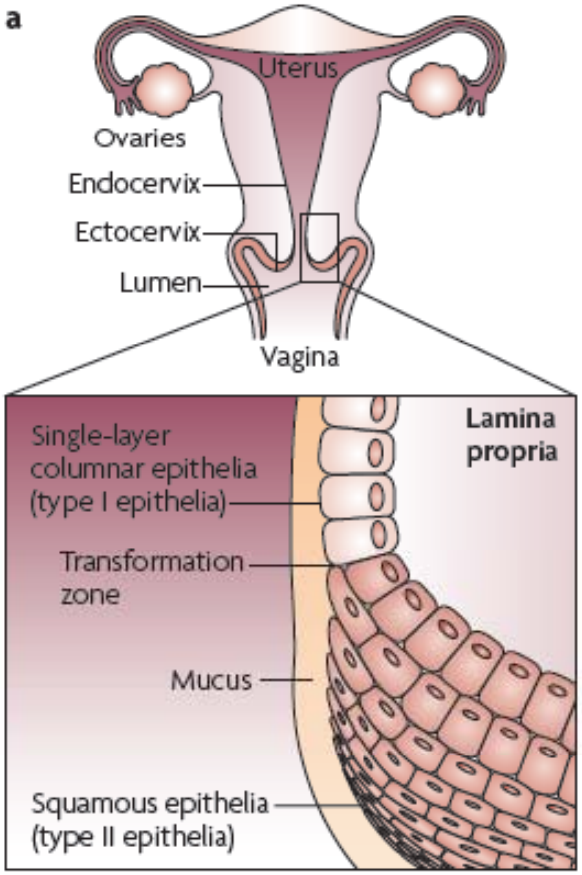
Mucosal sites – Genital tract

- **Genital tract**:
- No clear site for priming of immune responses-lack of lymphoid follicles
- Influenced by hormonal changes
- Hosts both sterile and non-sterile microenvironments
- More IgG than IgA



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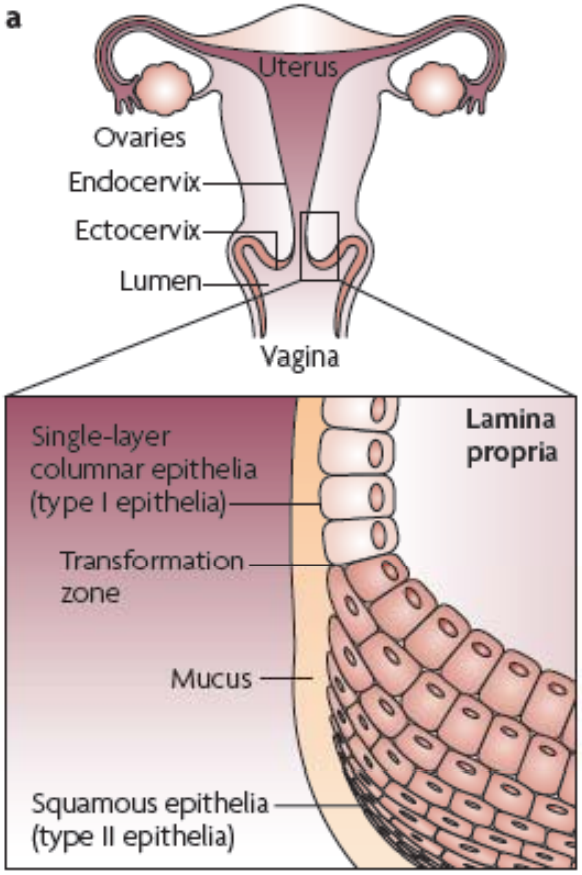
FGT and HIV

Vaginal route of transmission is estimated to be successfully between 1/200 – 1/2000 encounters

The epithelial layer acts as a first line of defense and several secreted factors including trappin/elafin and SLPI help eliminate pathogens including HIV

Co-infections with other STIs increase HIV susceptibility either by

- breaching the epithelial layer,
- recruiting HIV target cells into the site of infection or
- by creating a pro-inflammatory environment



GALT

- Thus, mucosal surfaces, particularly in the intestines, are crucial sites of innate and adaptive immune regulation.

<u>GALT and HIV</u>

HIV infection leads to severe CD4+ T cell deletion. Gut mucosa contains high number of CD4+ T cells that are potential targets for HIV.

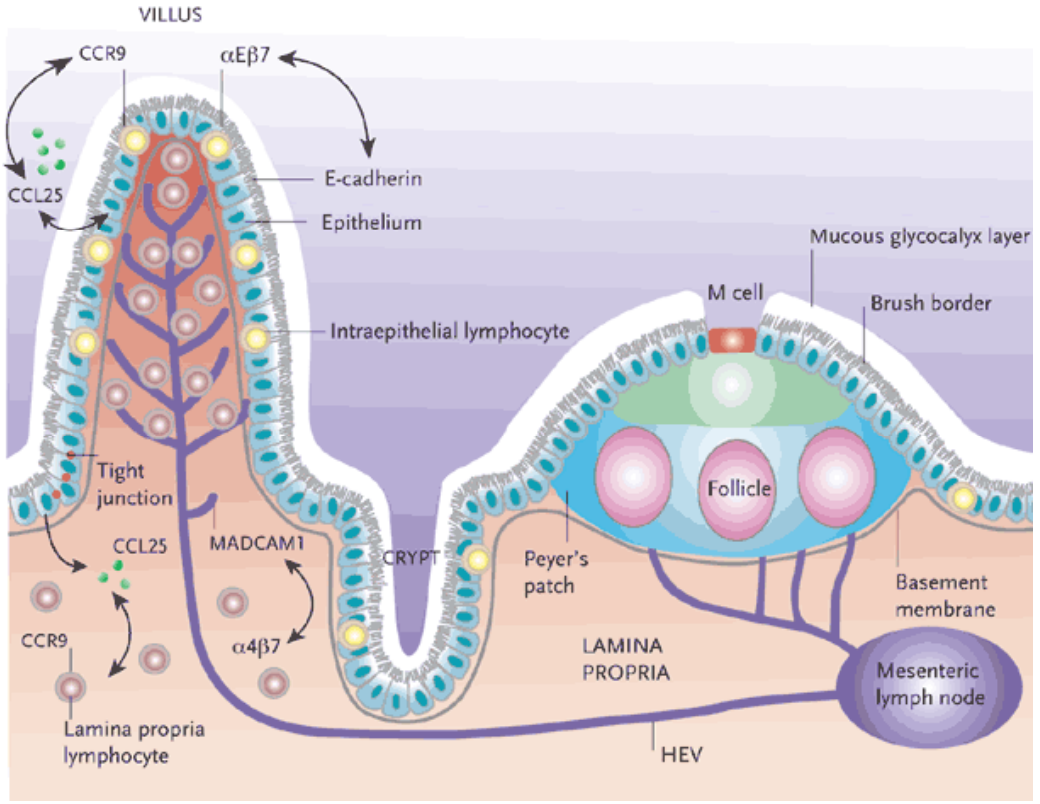
Persistent viral replication in GALT leads to replenishment and maintenance of viral reservoirs, increased levels of inflammation, immune activation, and decreased levels of mucosal repair and regeneration

GALT

GALT and HIV

Transmission rates are estimated to be as high as 1 in 10 encounters - > nature of mucosal surface

- A single layer epithelium joined by tight junctions allows the passage of water and ions
- Brush border microvilli and dense layer of glycocalyx provide additional protection
- Thick mucus coat with secretory IgA traps and expels invading microorganism
- The effector compartment consist of IEL and scattered lamina-propria lymphocites



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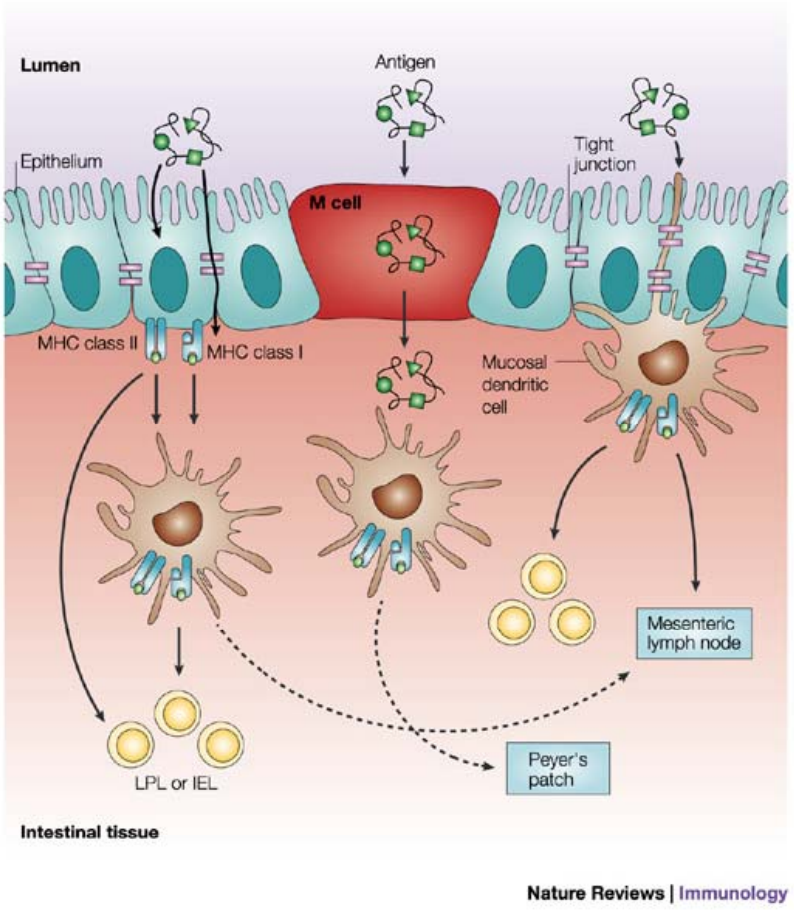
M cells

- The role of the M cells is absorption, transport, processing, and presentation of antigens to sub-epithelial lymphoid cells
- Antigens are released to cells of the immune system beneath the epithelium where antigen processing and presentation and stimulation of specific B and T lymphocytes takes place.



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Challenges of studying mucosal immunology

- Sample collection and availability
- Person to person variation
- Mucosal sites variation
- Interaction of various pathogens and normal flora,
- Non-sterile sites, hard to create in-vitro conditions
- Still and unexplored field
  - Limited understanding of the innate and adaptive immune responses

Why study mucosal immunology?

- Mucosal surface is major portal of entry for pathogens
- Mucosa contains highest concentration of lymphocytes
- Mucosal immunization
  - Provides both mucosal & systemic immunity
  - prevents infection
- Systemic immunization –
  - no mucosal immunity
  - resolves infection before disease develops

Thank you!!!

- And now Were …