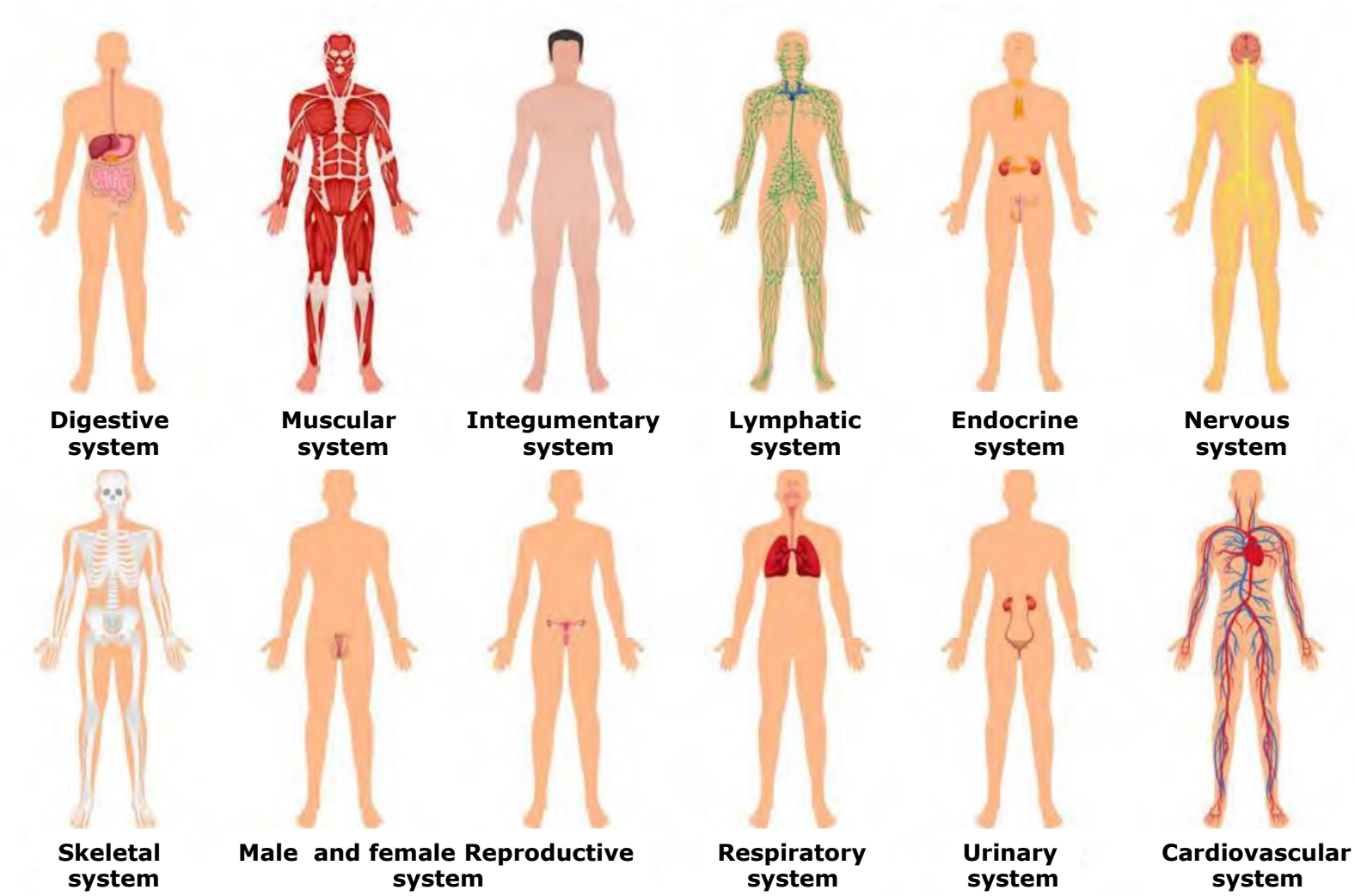
Host : Microbiota interactions

THE HUMAN BODY

A series of 11 integrated systems. Each system carries out one major role or task.



Each system depends directly or indirectly, on all of the others.

From Lumen Learning

Humans are Meta-organisms

- 37.2 × trillions (10^{12}) cells of the macroscopic host (https://doi.org/10.3109/03014460.2013.807878).

- 100 trillions (10^{14}) of symbiotic commensal microbiota.
  - At least 10-fold more unique genes than their host's genome.
  - Include bacteria, fungi, viruses, and other microbial and eukaryotic species.
  - Provide a tremendous enzymatic capability and play a fundamental role in controlling many aspects of host physiology.

- Humanity is estimated at 7.5 billions humans x 10^{14} =**$7.5\ 10^{23}$ microbial cells.**
- The world's oceans contain an estimated **10^{29} cells**.

Humans are born germ free

The microbes that populate our intestinal tract must come from the outside.

- Inherited vertically from mothers
- Stable enough over time
    - Kinship relationships are reflected in community composition

Microbial diversity on our planet is vast:

- 55 divisions (deep evolutionary lineages) of Bacteria
- 13 divisions of Archaea

The intestine is remarkable for its exclusivity:

Gut microbiota in adults is dominated by members of only two divisions of bacteria—the Bacteroidetes and Firmicutes and one member of Archaea

Microbiota Immunity and inflammation

The microbiota play a fundamental role in the, induction, education, and function of the mammalian immune system.

The immune system a network of innate and adaptive components.

- Extraordinary capacity to adapt and respond to highly diverse challenges.
- Regulator of host homeostasis that sustain and restore tissue function in the context of microbial and environmental encounters.

Acquisition of adaptive immunity has coincided with that of a complex microbiota.

- A large fraction of adaptive immune system may has evolved as a means to maintain a symbiotic relationship with these highly diverse microbial communities.

Microbiota Immunity and inflammation

In turn, the microbiota promote and calibrate multiple aspects of the immune system.

- Pathologies such as allergies, autoimmune diseases, and inflammatory disorders arise from a failure to control misdirected immune responses against self, microbiota-derived, or environmental antigens.

- Alteration of the composition and function of the microbiota as a result of antibiotic use, diet evolution, and recent elimination of constitutive partners such as helminth worms, has affected the function of these microbial allies.

Microbiota-Immune System Interaction during Development

- Under normal conditions, the foetal gastrointestinal tract is sterile

- First exposure of the immune system to commensals occurs at birth.

- These early interactions set the tone of the mucosal and systemic immune system.

Factors from maternal milk shape both the microbiota and the early IS.

- Colostrum and breast milk contain live microbes, metabolites, IgA, immune cells and cytokines.
  - Maternal IgA restricts immune activation and microbial attachment
  - Milk metabolites, (oligosaccharides) promotes the expansion of defined subset of the microbiota such as Bifidobacterium.

Microbiota-Immune System Interaction during Development

The capacity to accept the microbiota can be explained by:

- The immaturity of the neonate immune system
  - Blunted inflammatory cytokine production
  - Skewed T and B cell development in favour of regulatory cells.
  - Suppression of iNKT cells involved in inflammatory response.
    - Mediated by inhibitory commensal-derived sphingolipids.

- The tolerogenic environment that defines early mammalian life.
  - A population of neonate erythroid cells maintaining the immunoregulatory environment.

Consequence:

- High susceptibility to infections of the new born.
- Establishment of microbiota without over inflammation.

Microbiota-Immune System Interaction during Development

Host - microbiota interaction is mediated by the recognition of microbial-associated molecular patterns (MAMPs).

Neonate innate IS integrate these signals to promote healthy microbial colonization.
Neonate TLR engagement

- Impaired inflammatory mediator production.
- Increase production of regulatory cytokine (IL-10)
- Microbial LPS renders gut epithelial cell hyporesponsive to subsequent TLR stimulation (epigenetic modification).

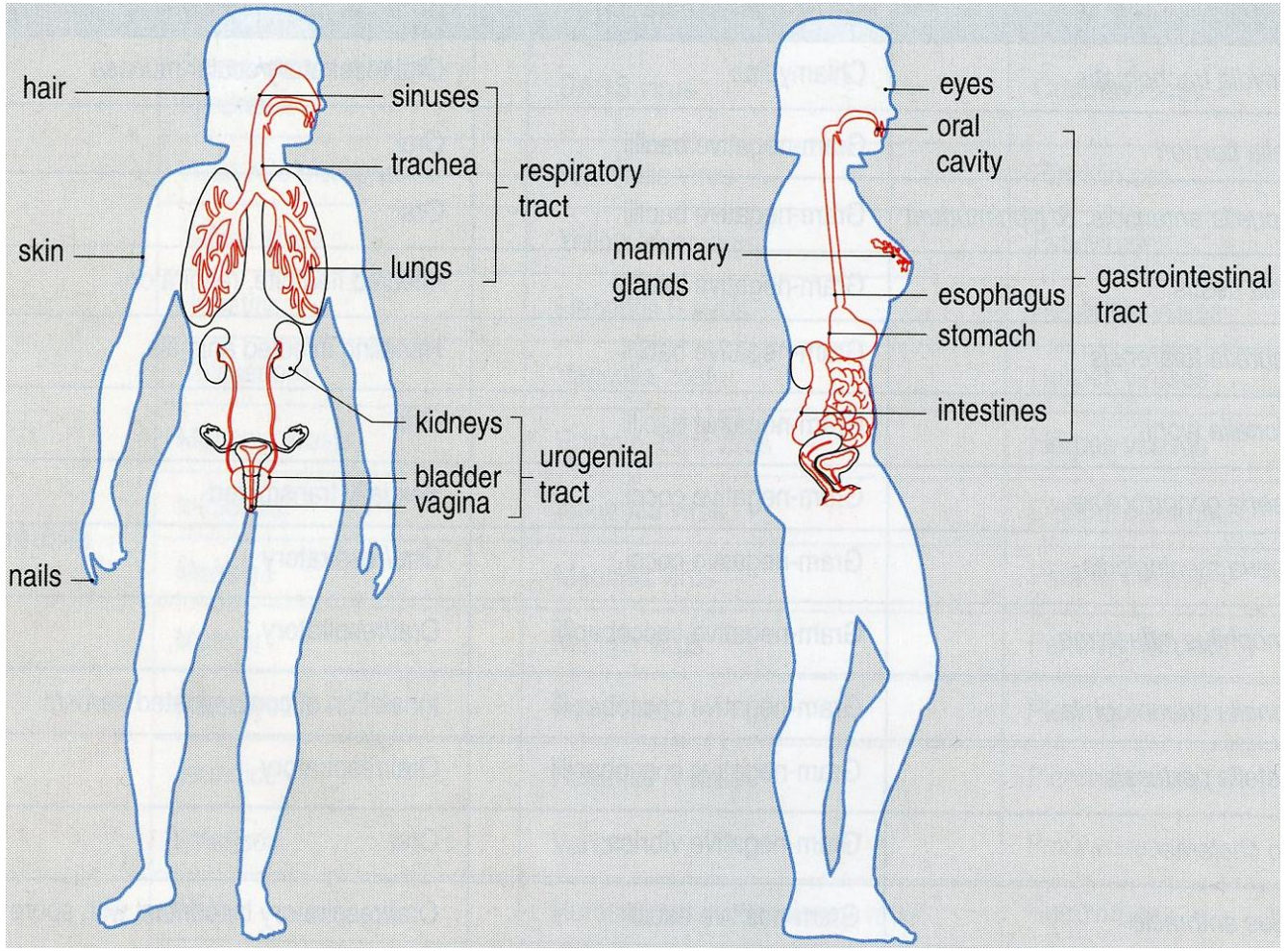
Reciprocally microbiota allow:

- Development of secondary lymphoid structures to favour IS development.
- Fortify the intestinal barrier by various mechanisms (promotion of epithelial cell maturation and angiogenesis).

Both the neonate IS highly regulatory tone + the action of commensals

- Establishment of a durable and homeostatic host/commensal relationship.
- Profound and long-term implications for human health.

Microbiota-Immune System Interaction



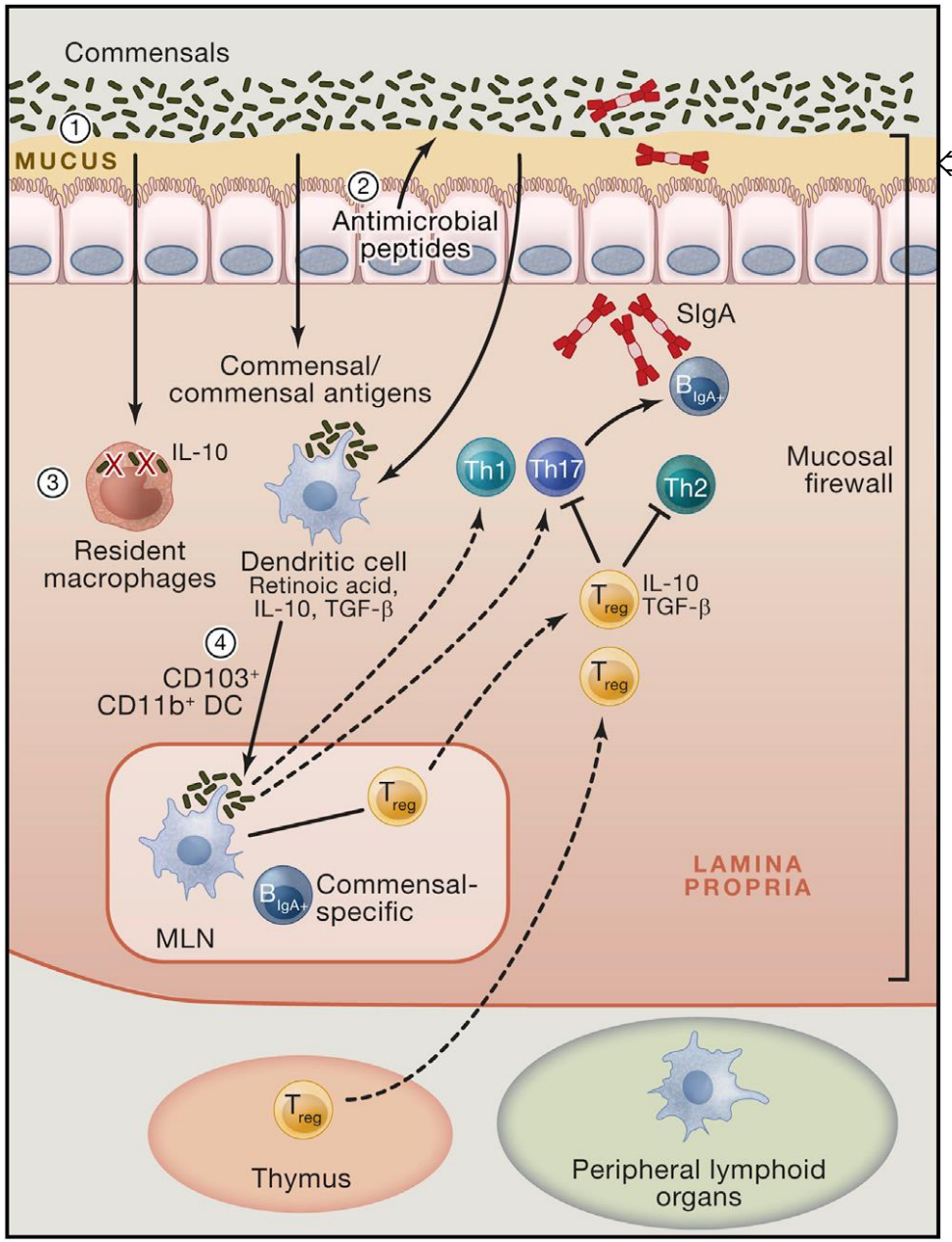
- Skin: Epithelium protected by a layer of keratinized cells (robust and impermeable)

- Mucosae: respiratory track, oro-gastro-intestinal, urogenital, and mammary glands.
  - Not keratinized epithelia specialized in the communication (less impermeable, more vulnerable).

From Parham 4th edition

Host ⇔ microbiota: The Mucosal Firewall

- Part of the IS function is to control the interaction with the microbiota.
- The largest number of immune cells is located at sites colonized by microbiota
  - GALT: Gut-associated lymphoid tissues
  - BALT: Bronchus-associated lymphoid tissue
  - NALT: Nasal-associated lymphoid tissue
  - CALT: Conjunctival-associated lymphoid tissue
  - LALT: Larynx-associated lymphoid tissue
  - SALT: Skin-associated lymphoid tissue
  - VALT: Vulvo-vaginal-associated lymphoid tissue
- Minimize interactions: The Mucosal Firewall
  - Limits tissue inflammation
  - Limits microbial translocation



⇐ demilitarized zone

Mucosal IgA responses lack classical memory characteristics: Established IgA-producing clones are outcompeted by novel antibacterial responses.

From Belkaid, Y. et al. 2014

Host ⇔ microbiota: Immune Regulation

In homeostatic condition:

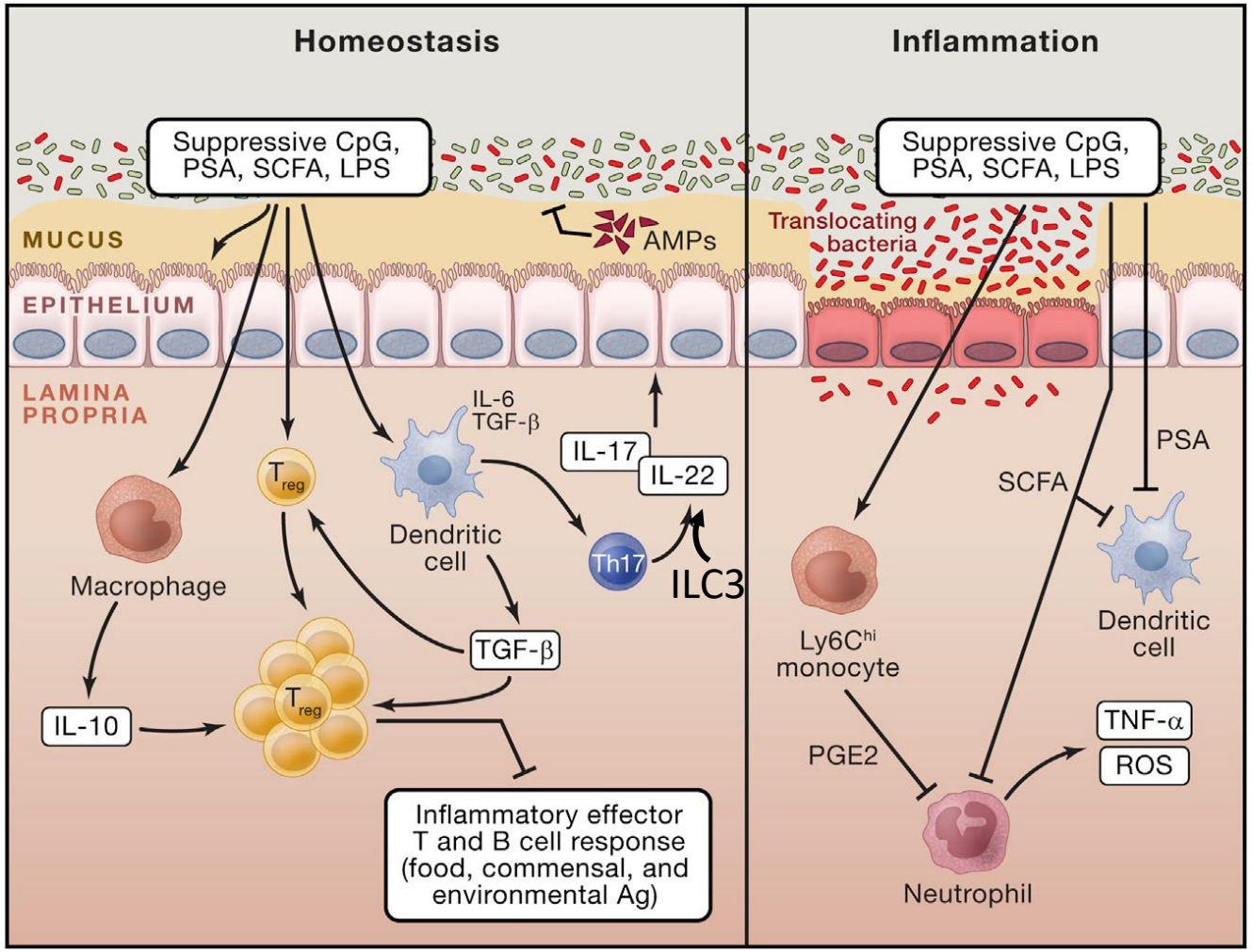
Promote the induction of regulatory T cells via direct sensing of microbial products or metabolites by T cells or dendritic cells.

Promote the induction of Th17 cells that can regulate the function and homeostasis of epithelial cells.

During inflammation

Commensal-derived metabolites can also have a local and systemic effect on inflammatory cells. SCFA can inhibit neutrophil activation.

Inflammatory monocytes can also respond to microbial-derived ligands by producing mediators such as PGE2 that limit neutrophil activation and tissue damage.



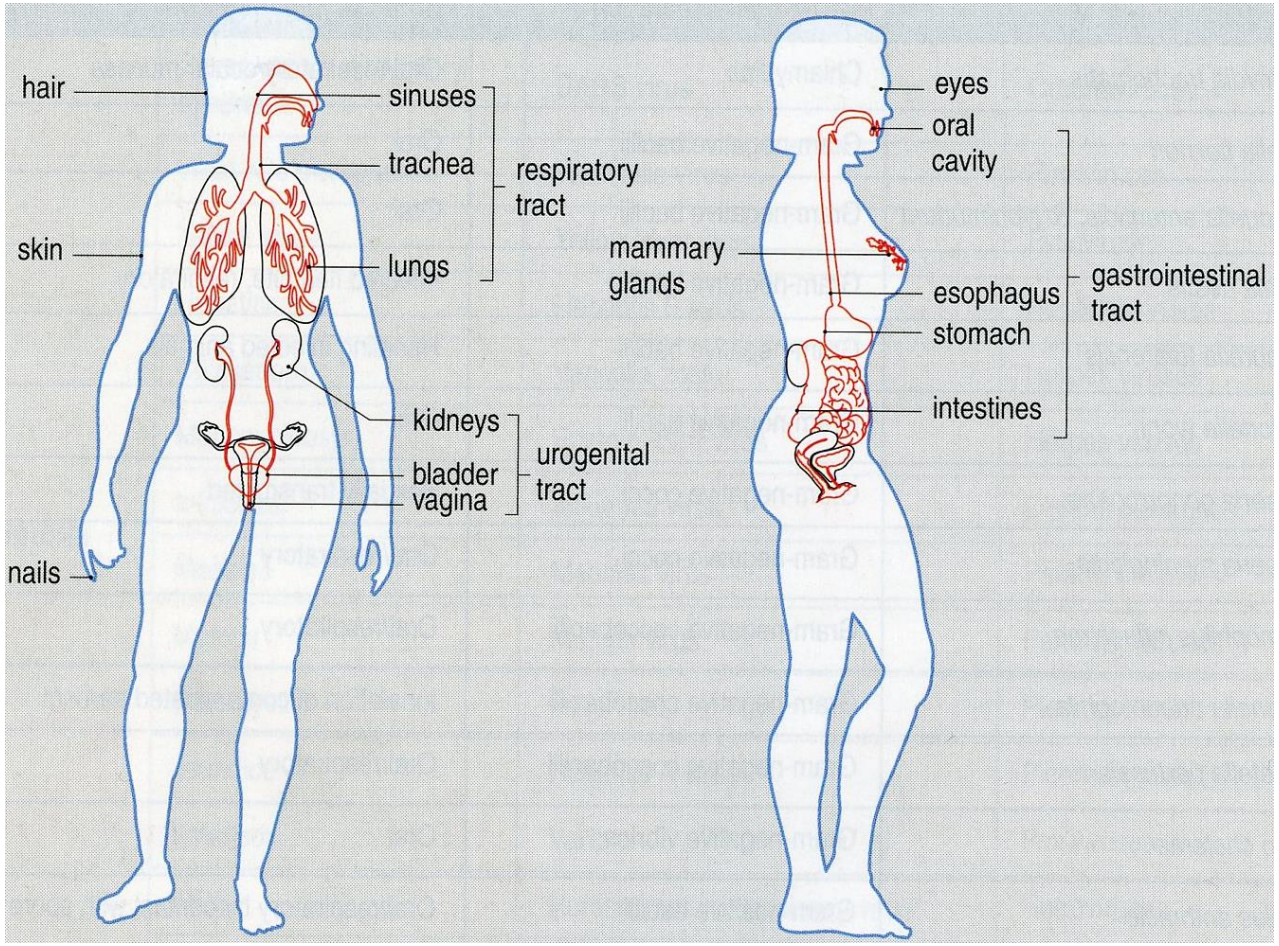
From Belkaid, Y. et al. 2014

A major role for the microbiota is to shape the repertoire, number, and activation of tissue-resident T regulatory (Treg) cells to maintain host-microbe mutualism at barrier sites.

Based on the fundamental role of Treg in maintaining mucosal homeostasis, it is likely that a large fraction of any given microbiota or microbiota metabolism may have evolved to favour the emergence of T reg.

Because of the diversity of the flora, opportunity for cross reactivity between commensals, pathogenic, and environmental antigens is high. Thus, commensal-induced Treg may also contribute to the systemic control of immune responses.

Induction of Protective Responses by Commensals



Tissues that are natural habitats of the flora are also the portals by which pathogens access the host and, are often, the primary site of infections.

Initial encounter of pathogens with the IS occurs in an environment conditioned and regulated by its endogenous microbiota.

Commensals directly and dynamically interact with pathogens and IS.

The results of this interaction define the pathogenesis and outcome of the infection.

From Parham 4th edition

Induction of Protective Responses by Commensals

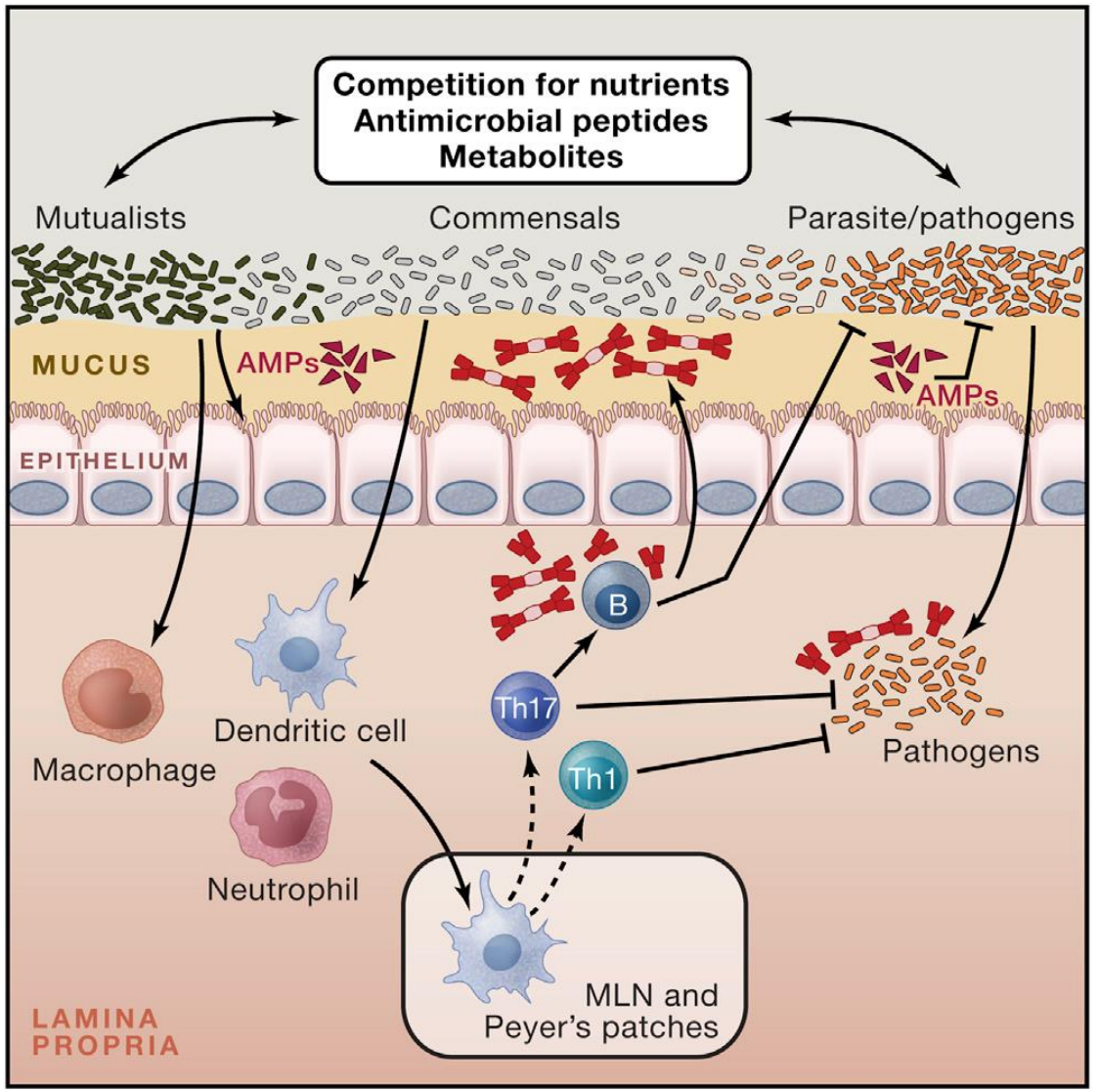
Colonization resistance:

1) both compete for the same ecological niche. Competition for the same resources (nutrient & metabolites) alteration of growth rate of pathogenic cells and expression of virulent factors.

2) Commensal derive metabolites such as SCFA, directly downregulates the expression type 3 secretion system in Salmonella enterica and typhimurium.

3) Lactobacilli protect vaginal environment from pathogenic colonization via reduction of the local pH.

4) Production of antimicrobial peptides that directly affect pathogen growth or survival. E. coli bacteriocins—proteinaceous toxins inhibit the growth of the same or similar bacterial strains enterohemorrhagic E. coli. Staphylococcus epidermidis produces antimicrobial proteins and proteases to limit the biofilm of Staphylococcus aureus (skin & heart valve infections, pneumonia).



From Belkaid, Y. et al. 2014

Induction of Protective Responses by Commensals

Promote and calibrate innate and adaptive immunity:

4) keystone species, unique microbes or groups of bacteria with non-redundant functions. Segmented filamentous bacteria (SFB) a Gram-positive spore-forming anaerobic bacteria colonizes the terminal ileum of mice establishing tight adhesion to Peyer's patches and epithelial cells, inducing cytoskeletal reorganization in these cells promoting the accumulation of both Th17 and Th1 cells in the small intestine and driving the production of IgA.

Both inflammatory and regulatory signals are constantly integrated—the sum leads to the establishment of an immune tone compatible with tissue immunity.

keystone species

Systemic Control of Protective Immunity

Reduction of gut commensals results in blunted T and B cell response against influenza as microbiota promote the inflammasome-mediated induction of IL-1b and IL-18 secretion. Broad decrease of genes associated with antiviral immunity.

Adjuvant effect:

- The tonic sensing of commensal products or metabolites in the blood stream contributes to steady-state hematopoiesis and monocyte egress from the bone marrow.

- Radio- and/or chemo- therapies altering epithelial barrier favour this adjuvant effect.

Interdependence of Diet, Commensals, and the IS

There is a multidirectional interaction between the diet, IS, and commensal microflora. The IS and commensal microbiota are sensitive to changes in diet

Dietary control of immune cells is mediated both by their metabolic requirements and direct sensing of food-derived metabolites.

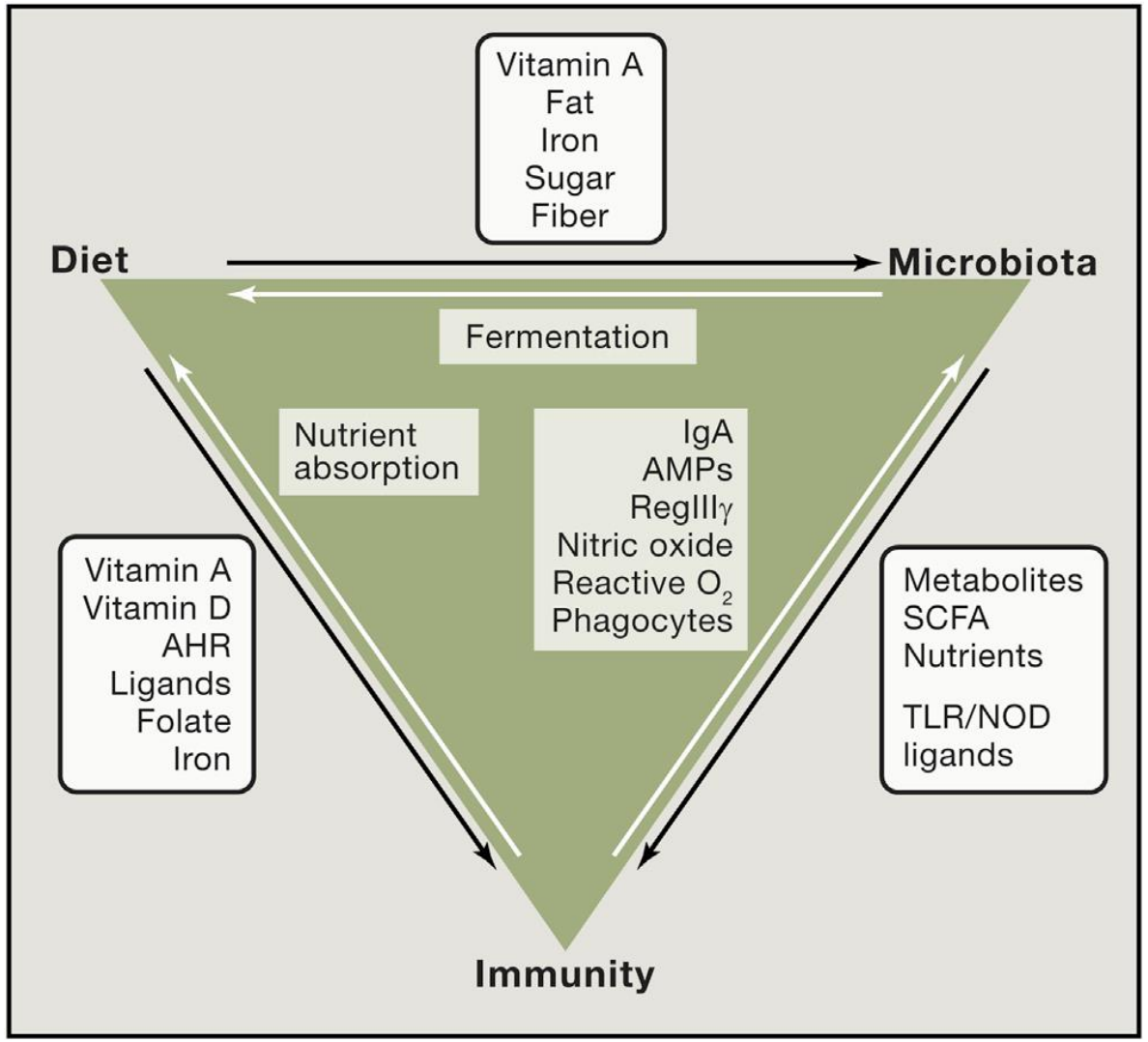
Metabolite of vitamin A, retinoic acid directly control the capacity of lymphocytes to respond to antigen and to migrate to the gastrointestinal tract.

dietary-derived aryl hydrocarbon receptor (AHR) ligands from cruciferous vegetables are important signals for intestinal immune development and immune responses.

These observation are highly generalizable to all micronutrients explored thus far, including iron, folate, zinc, selenium,and vitamins C, D, and E.

The diet has highly dynamic impact on the composition and function of the microbiota.

Interdependence of Diet, Commensals, and the IS



From Belkaid, Y. et al. 2014

The Immune System

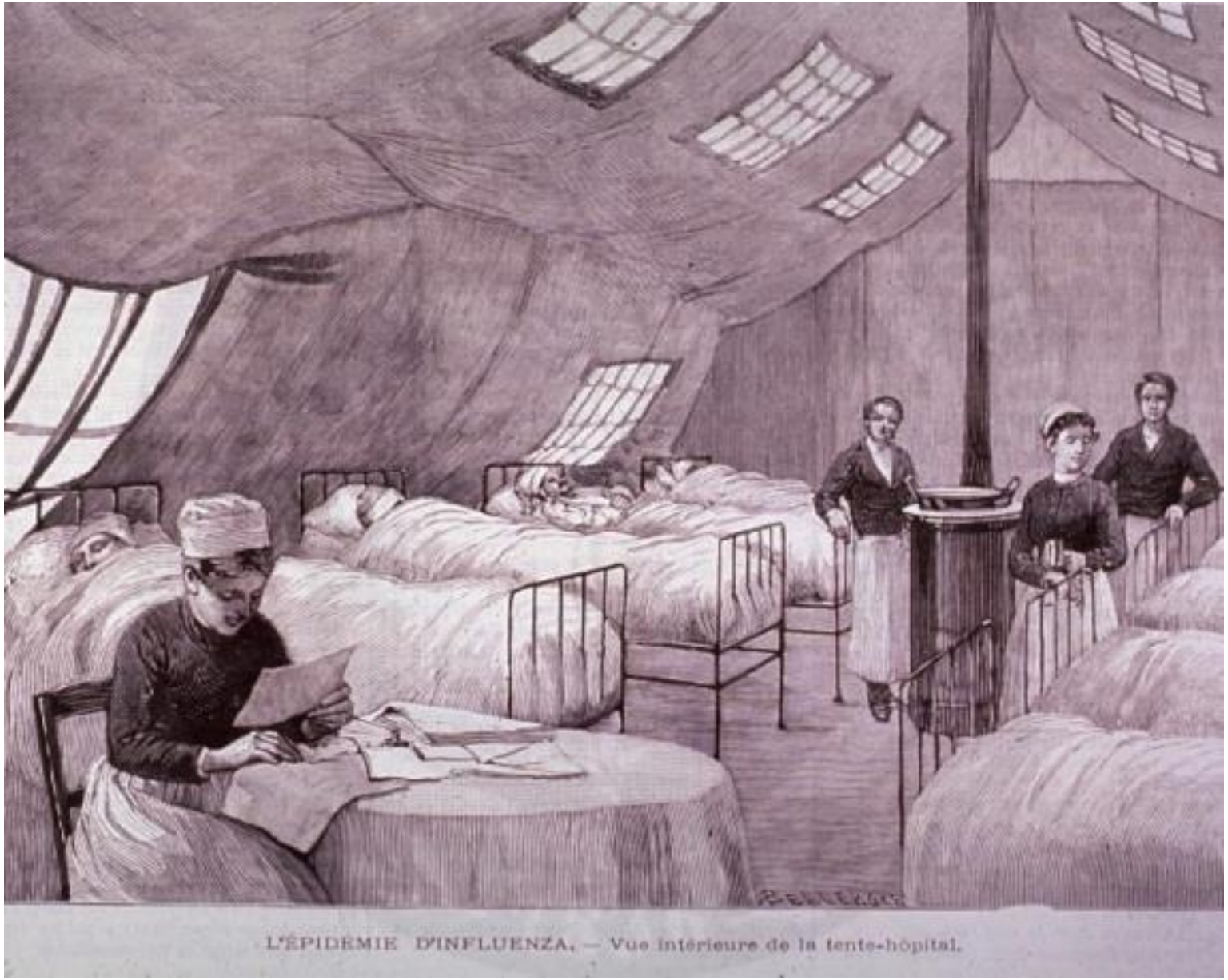
The immune system (1)

Topic 5 Innate immunity

- ✓ Basic aspects of defense mechanisms

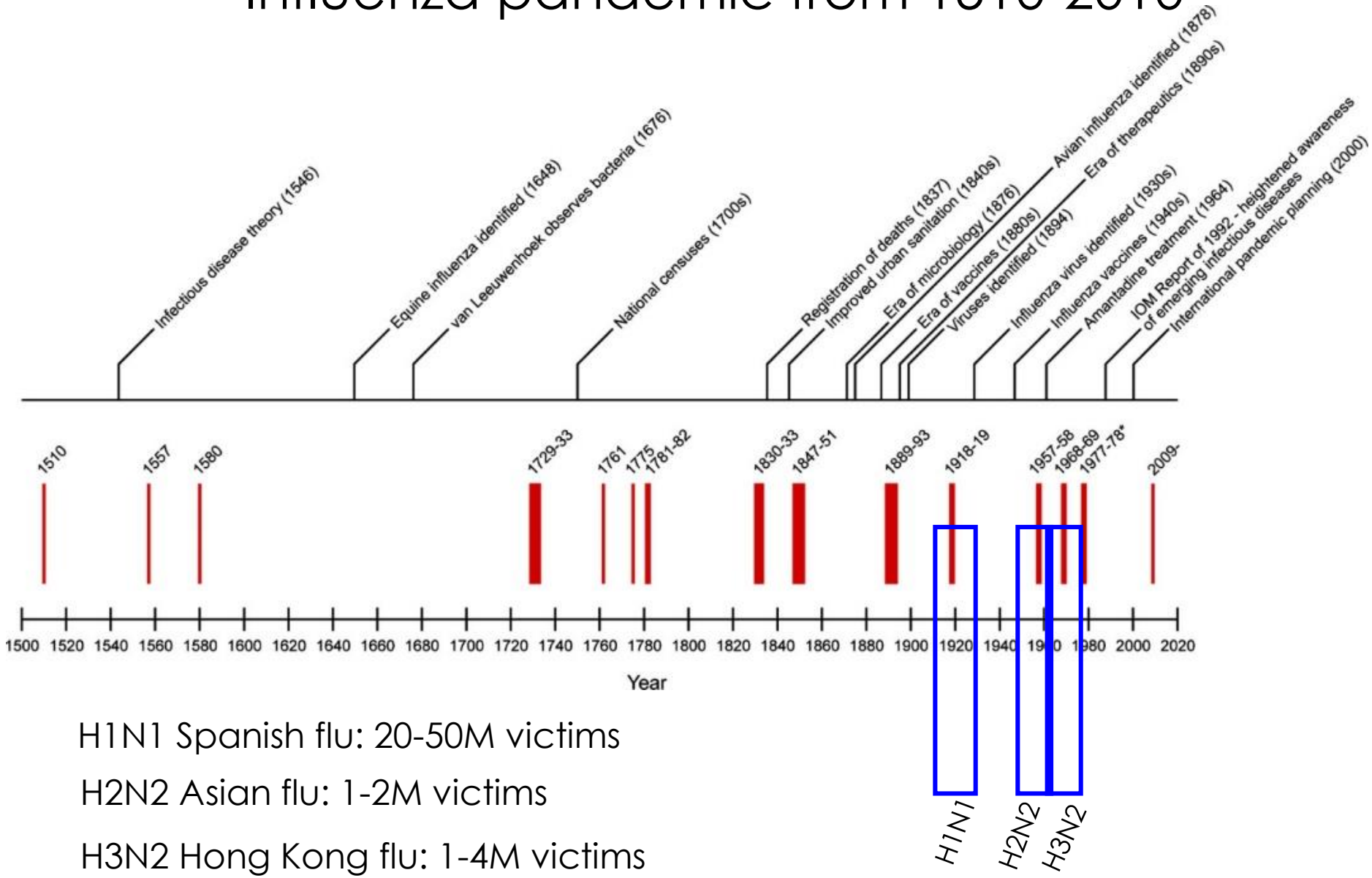
- ✓ Innate immunity
  - ➢ The self
  - ➢ The non self
  - ➢ Lymphoid organs
    - ➢ Cells
    - ➢ Complement
    - ➢ Phagocytosis
    - ➢ Receptors
    - ➢ Cytokines

Mechanism



Morens, Taubenberger, Folker, & Fauci, 2010.
Placed in public domain https://contagions.wordpress.com/2010/12/31/pandemic-influenza-1510-2010/

Influenza pandemic from 1510-2010



H1N1 Spanish flu: 20-50M victims

H2N2 Asian flu: 1-2M victims

H3N2 Hong Kong flu: 1-4M victims

Morens, Taubenberger, Folker, & Fauci, 2010.
Placed in public domain https://contagions.wordpress.com/2010/12/31/pandemic-influenza-1510-2010/

Immunology:

- Physiological mechanism that organisms use to defend their bodies from invasion by all sort of other microorganisms or substances.

- Historical observation (survivors of pandemic diseases).

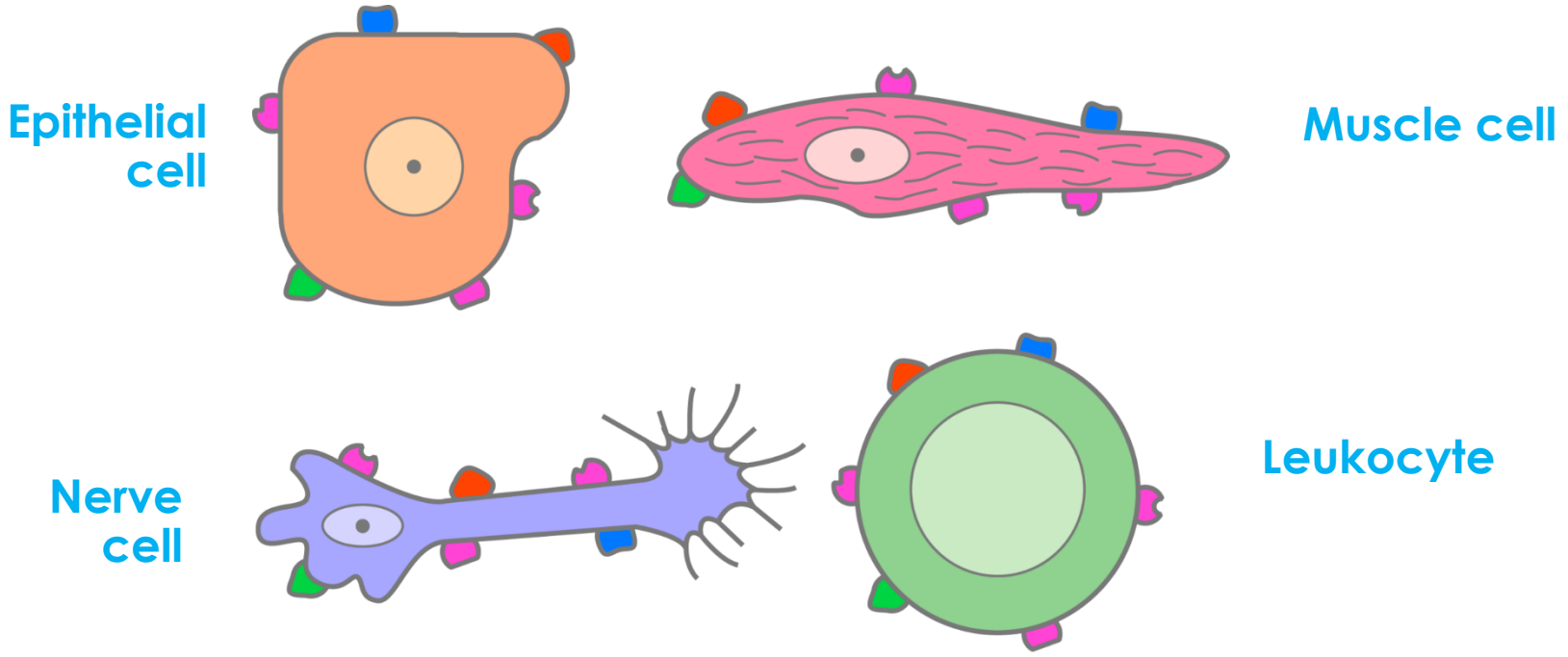
- Crucial for survival
  - Even minor infection become lethal
  - Children born without an immune system die in early childhood.

- Even with normally functioning immunity we still suffer from infection
  - take time to build up the most robust response.

The immune system protects from: pathogens, abnormal host cells and toxins.

- Discriminate self from non self.
  - Self must be tolerated
    - Host cells
    - Commensal microorganisms (microbiota)
  - Non self must be rejected
    - Exogenous cells (pathogens, organ transplant)
    - Exogenous substances (toxins, venoms, allergens)
    - Modified self (cancer)

Markers of Self

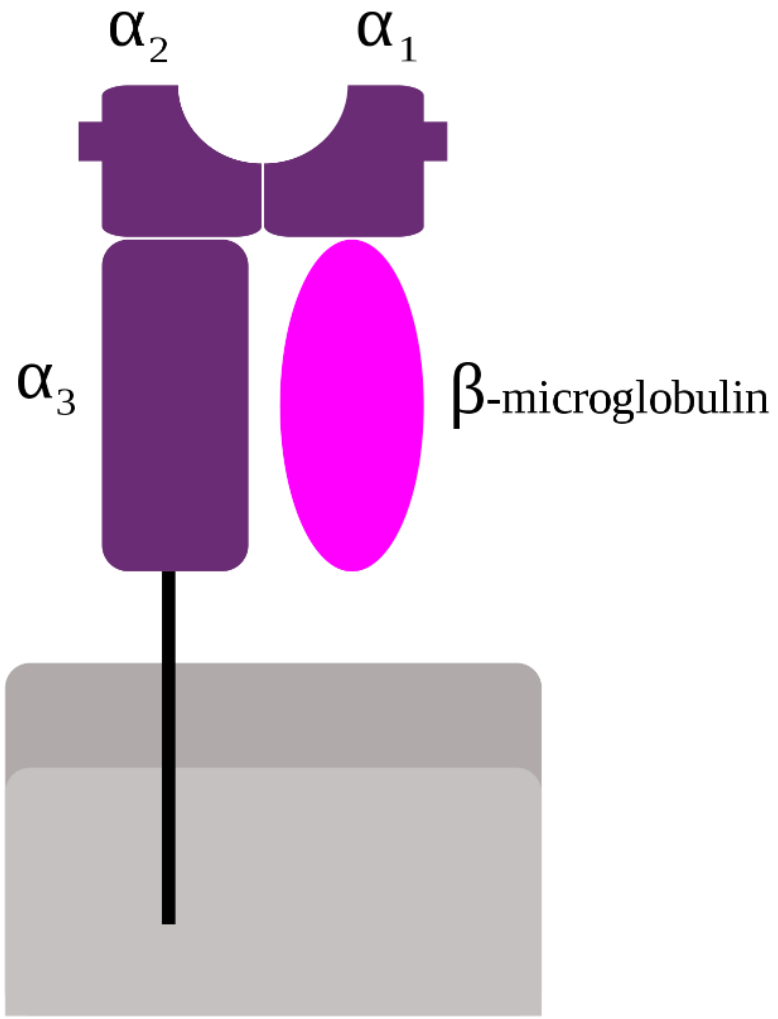


Major histocompatibility complex (MHC) also called
Human Leukocyte Antigen (HLA)

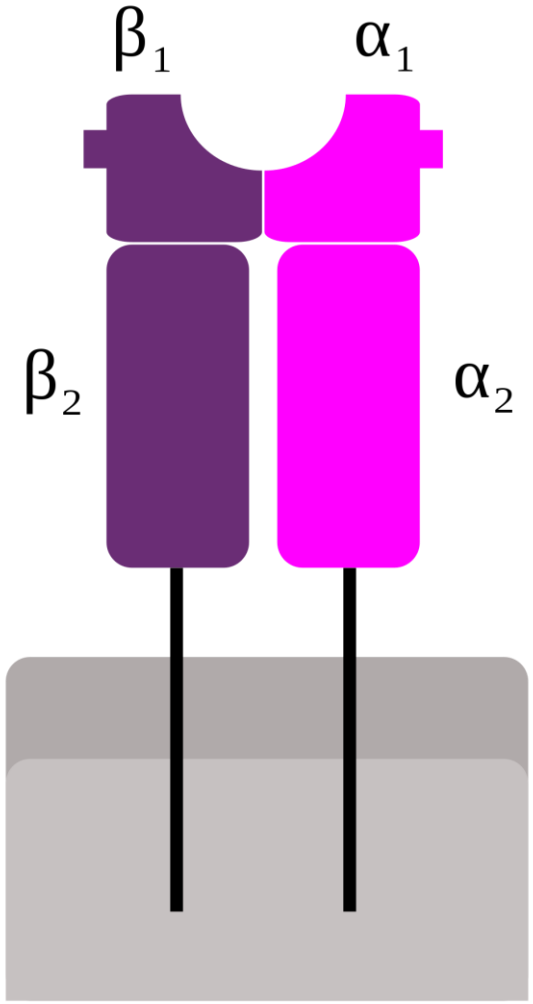
- Surface proteins that distinguish one's cells as «self», i.e. self-markers
- MHC Class I proteins expressed on all nucleated cells
- MHC Class II proteins, only expressed on specialized cells.

The immune system is tolerant to the self

Human Leukocyte Antigen (HLA)

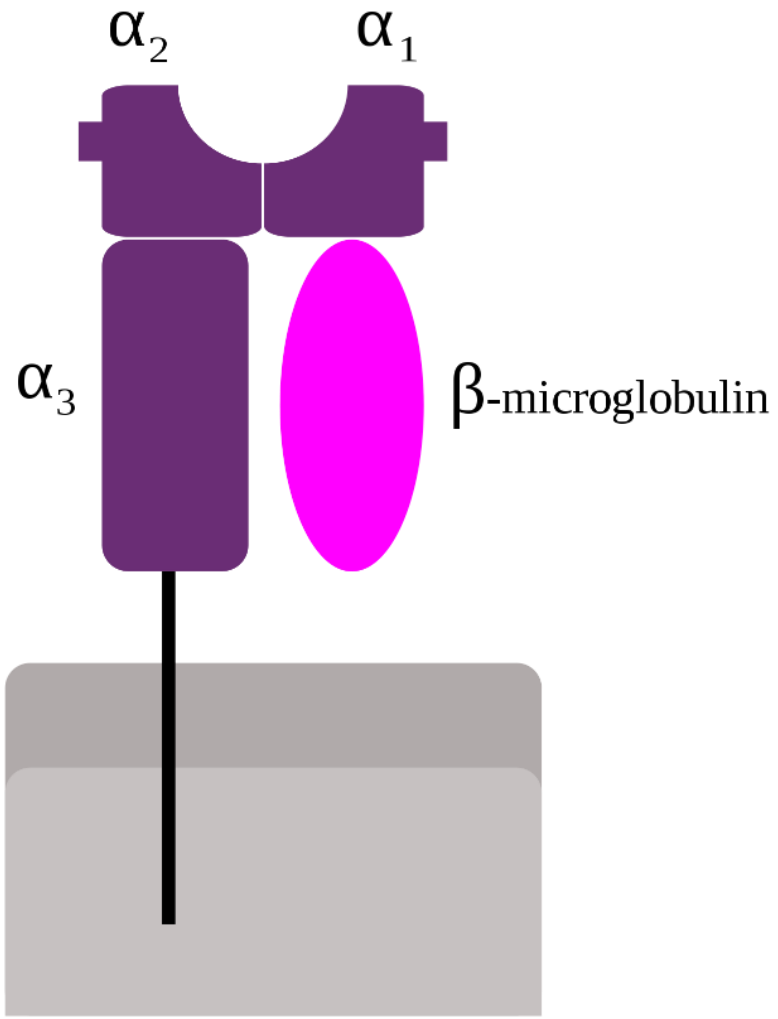


Class I

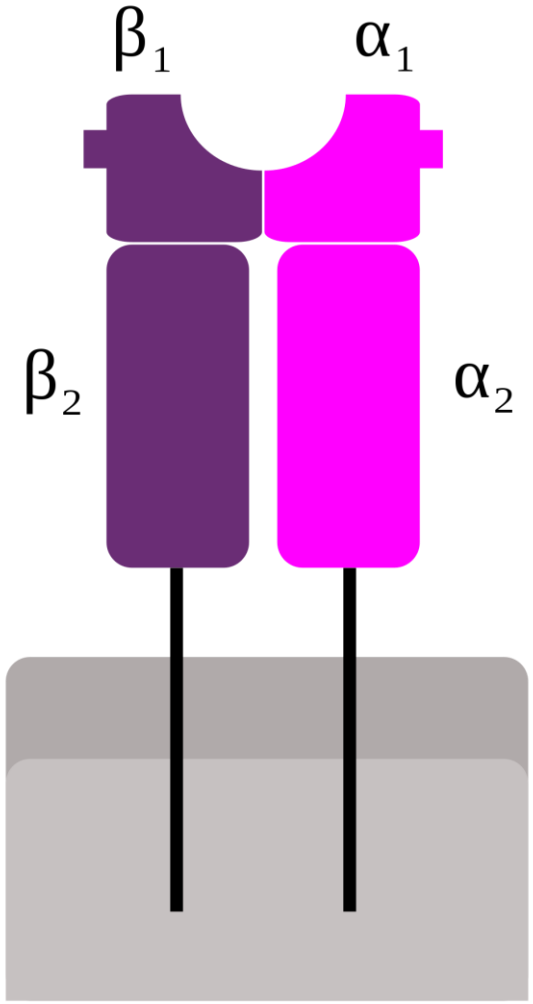


Class II

Human Leukocyte Antigen (HLA)

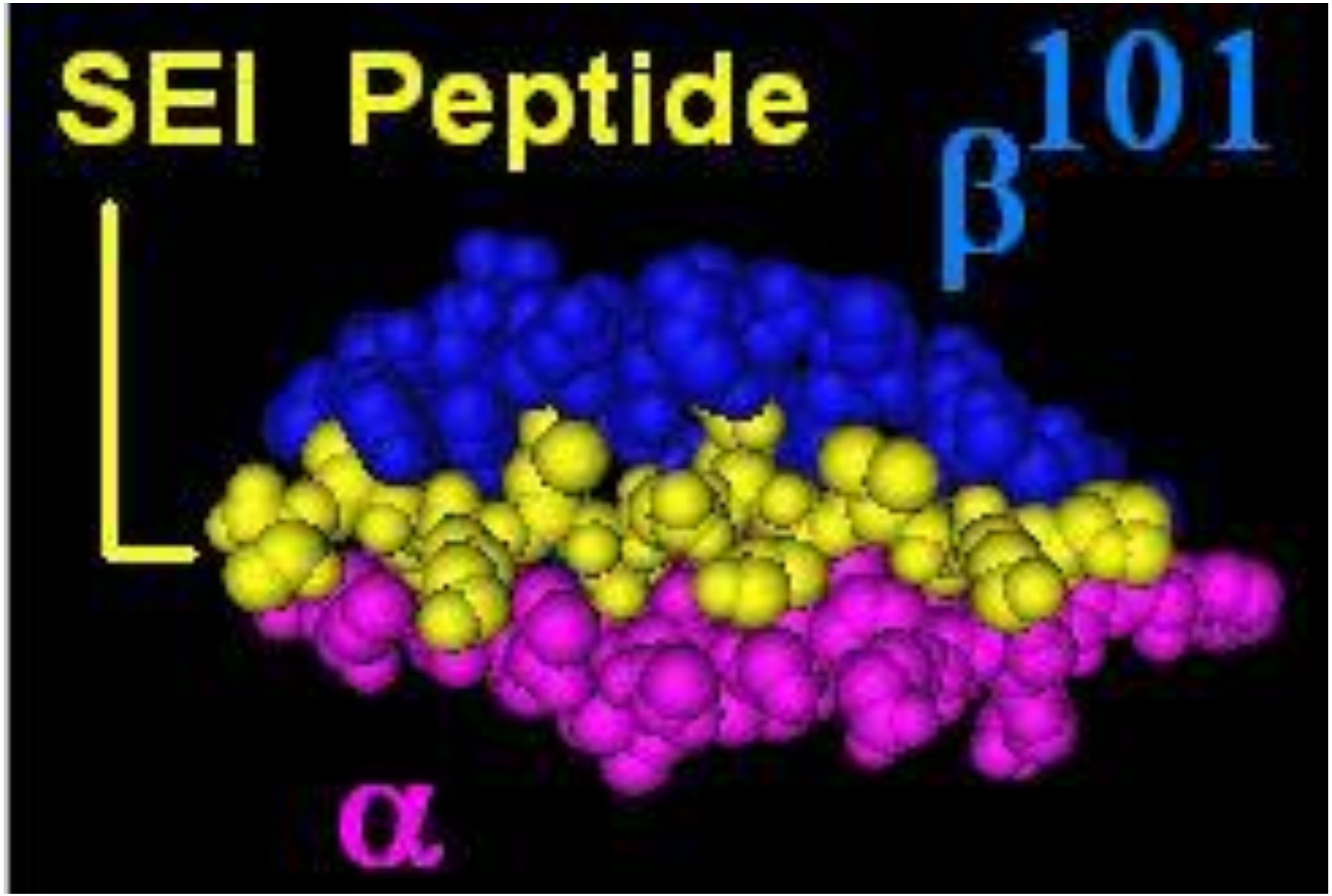


Class I



Class II

Human Leukocyte Antigen (HLA)



HLA molecule allele frequency

HLA class I

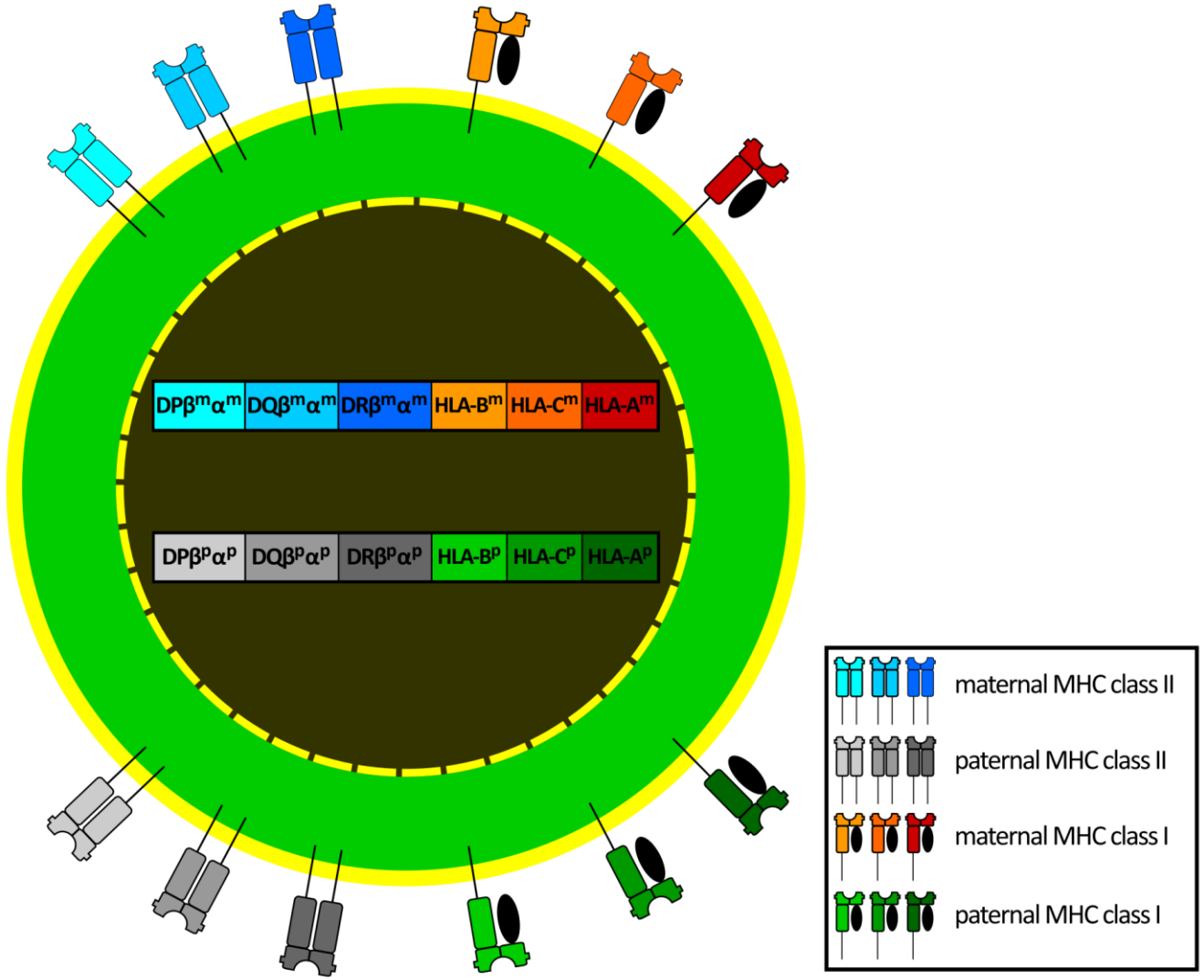
locus	#[13][14]
Major Antigens	
HLA A	4,340
HLA B	5,212
HLA C	3,930
Minor Antigens	
HLA E	27
HLA F	31
HLA G	61

HLA class II

HLA locus	-A1 #[14]	-B1 #[14]	-B3 to -B5[1] #[14]	Theor. possible combinations
DM-	7	13		91
DO-	12	13		156
DP-	67	1,014		16,036
DQ-	95	1,257		34,528
DR-	7	2,593	312	11,431

[1]DRB3, DRB4, DRB5 have variable presence in humans

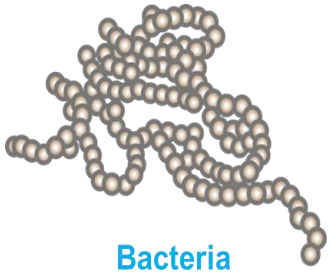
Codominant expression of the HLA molecules

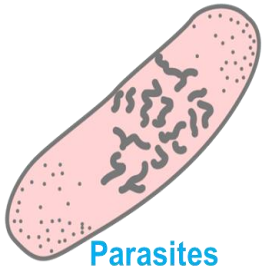


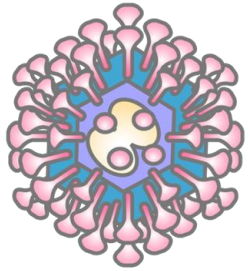
The immune system protects from: pathogens, abnormal host cells and toxins.

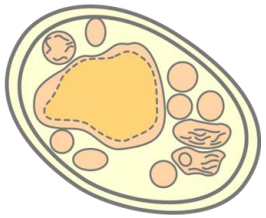
Antigen = **anti**body **gen**erating

- Substances able to stimulate a cellular and/or humoral immune response (proteins, peptides or polysaccharides)


Bacteria


Parasites


Viruses


Fungi

The role of the immune system is to keep Antigen (Ag) $= constant$