# Basic Immunology course

## Cells of the Immune system

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# Functions of the immune system

- Remove cancerous cells
- Remove infections and toxins
- Immune surveillance

Thus malfunction of the immune system leads to infections, cancers or autoimmune disease

# Types of immune cells and where they come from

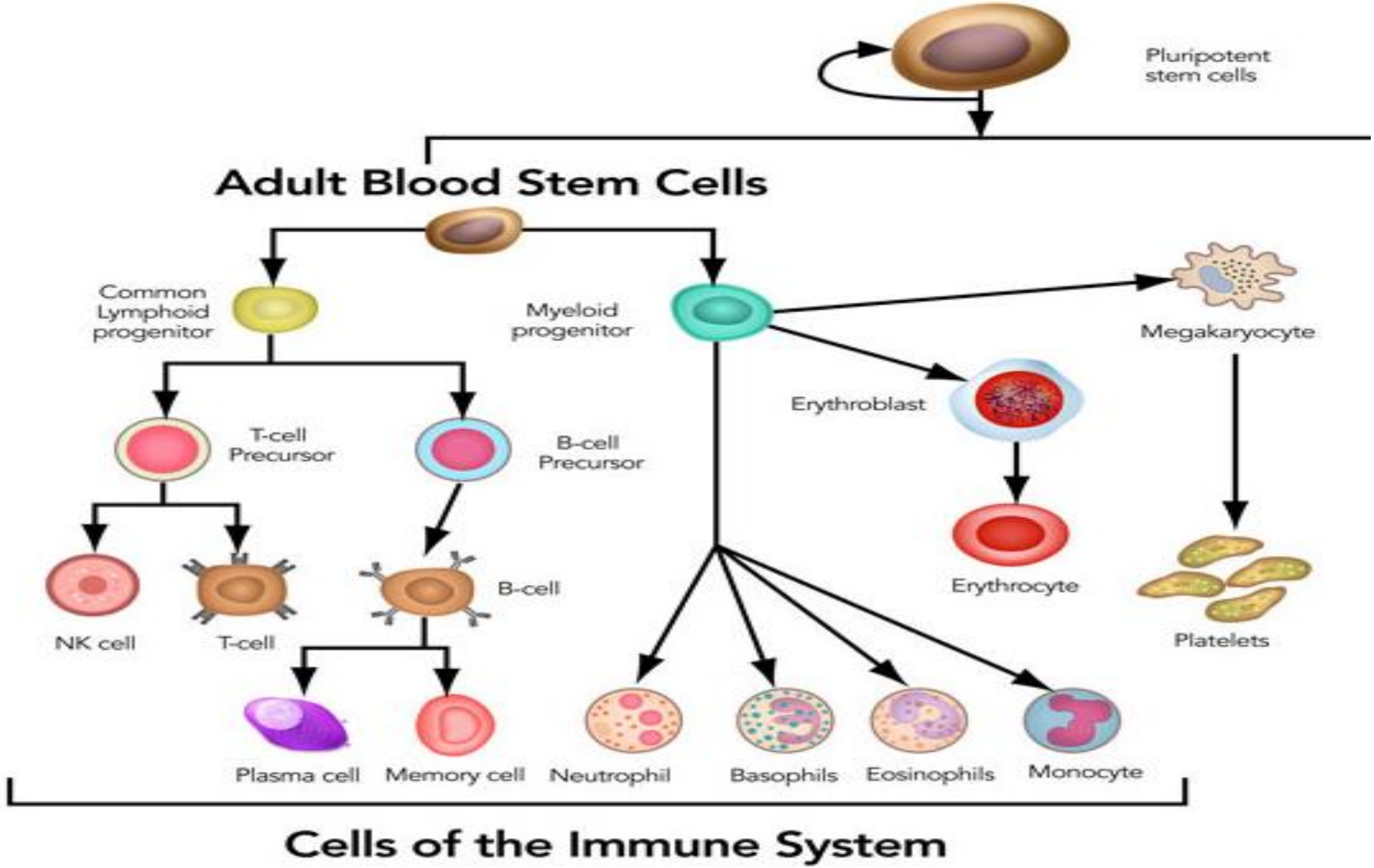
- Multipotent hemopoietic stem cells from bone marrow give rise to lymphoid and myeloid progenitors
- Liver gives rise to complement proteins
- Primary and secondary lymphoid organs where maturation of lymphocytes happen
- Lymphatic vessels where dendritic cells carrying antigen and activated T cells circulate
- Epithelial barriers

# Myeloid progenitors

- Give rise to granulocytes (eosinophils, neutrophils, basophils)
- Give rise to RBCs
- Mast cell precursor
- Pro monocyte – which give rise to monocytes and myeloid dendritic cells
- Thrombocytes

# Lymphoid progenitors

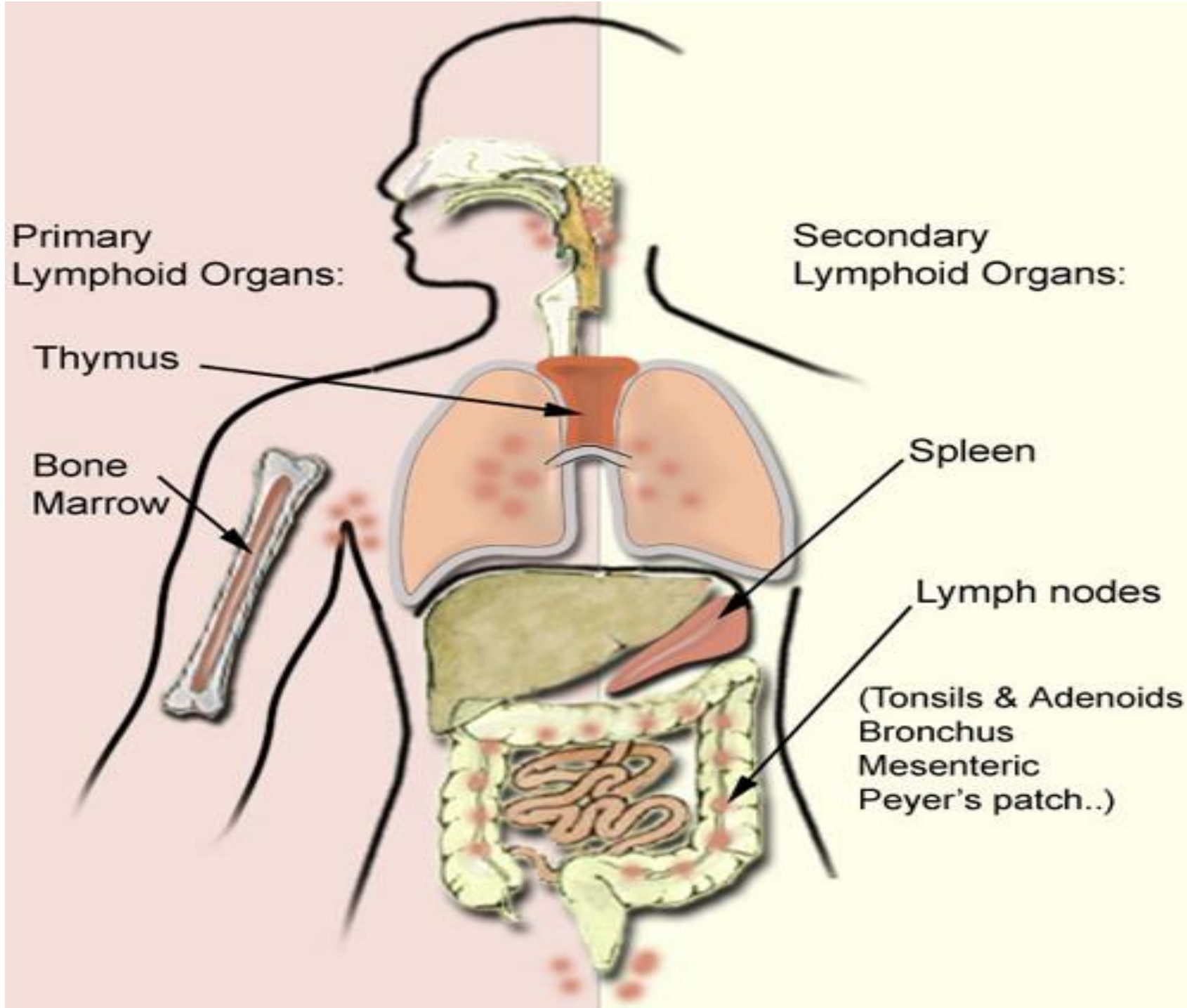
- Give rise to B cells, T cells and NK cells
- B cells mature in bone marrow where they gain central tolerance
- Lymphoid precursors which goes to the thymus gives rise to T cells, both CD4 and CD8 naïve T cells
- In the thymus they gain central tolerance and hence T cells are said to mature in thymus
- Lymphoid precursors also give rise Plasmacytoid dendritic cells (PDC) cells and some form of NK cells




Cells of the Immune System

# Lymphoid organs

- Primary lymphoid organs are the bone marrow and thymus
- Secondary lymphoid organs are lymph nodes, spleen and Peyer’s patches
- Afferent and efferent lymphatics
- In afferent lymphatics activated dendritic cells and antigens reach the lymph nodes where they activate T cells and B cells
- In efferent lymphatics activated T cells migrates towards tissue after leaving the lymph nodes


Primary
Lymphoid Organs:
Thymus
Bone
Marrow
Secondary
Lymphoid Organs:
Spleen
Lymph nodes
(Tonsils & Adenoids
Bronchus
Mesenteric
Peyer's patch..)

# Epithelium

- Epithelial barriers are the skin and mucosa
- Mucosal immune system is called as mucosal associated lymphoid tissue (MALT)
- It consists of GI, respiratory, urogenital, eye and ear mucous membranes
- Epithelium also lines peritoneal, pleural and pericardial cavities
- Epithelium lining the blood vessels is called as endothelium

# Functions of Epithelium

- Protective
- Secretory
- Sensory
- Absorption

- Largest epithelium in terms of surface area is GI which is also the least sterile and it is here where the immune system is most active (75% of lymphocytes are concentrated here)

# Gut associated lymphoid tissue (GALT)

- GALT consists of tonsils, adenoids, oesophagus, Peyer's patches, appendix
- Its role is not just remove infections such as viral, fungal and bacterial but also induce peripheral tolerance
- 2 types of peripheral tolerance : oral and bystander suppression
- Oral tolerance is dose dependent (higher the dose higher is the tolerance). It happens through Treg formation and TGF beta
- Bystander suppression – If tolerance develops orally then it also develops through other routes such as IV, IM, topical etc.

# Layers and defences of GALT

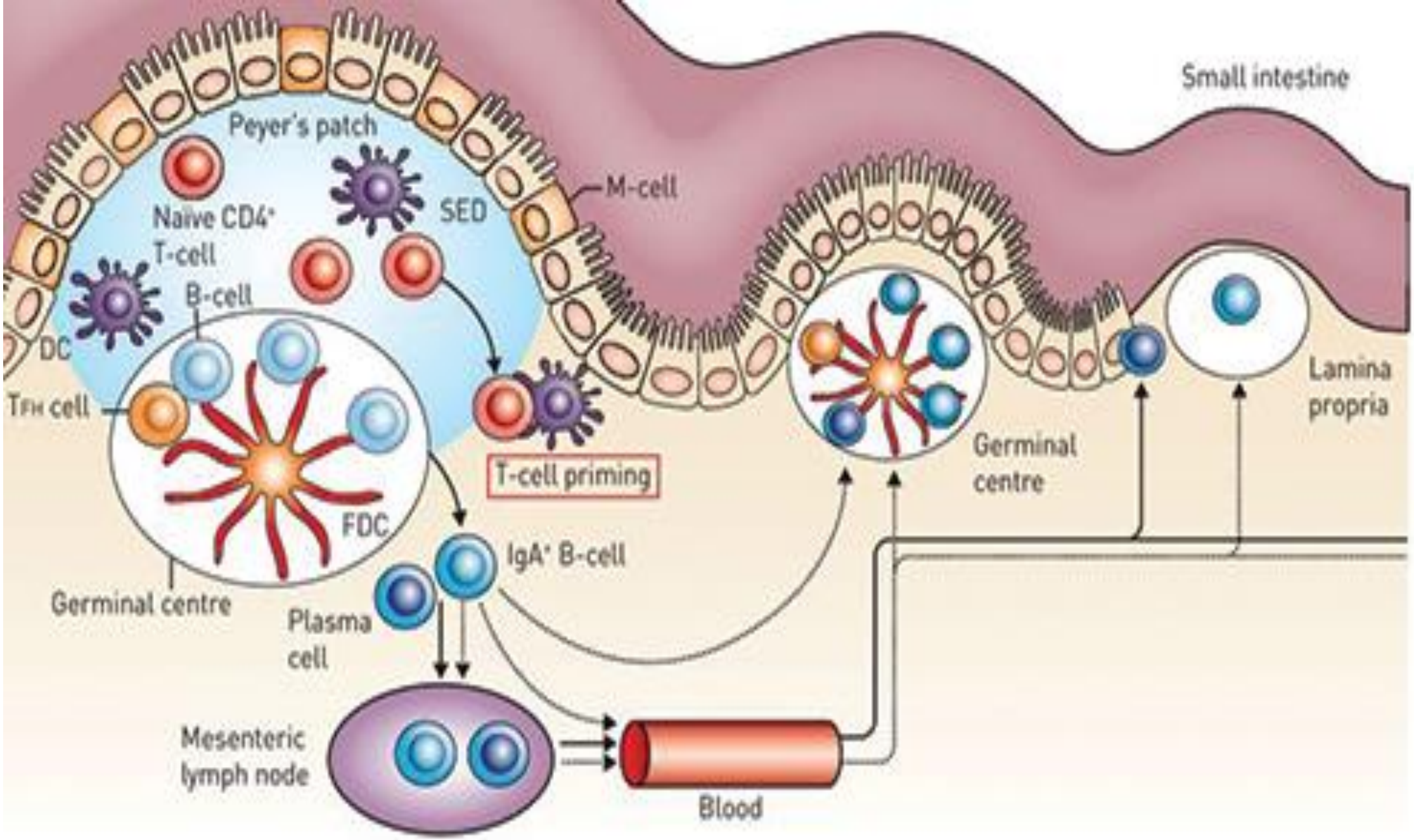
- Mucous
- Epithelium and tight junctions (paracellular and transcellular)
- Intestinal epithelial cells (TLR, NOD etc) trigger cytokines either creating tolerance via IL-10 or inflammation via IL-1
- Paneth cells secrets anti microbial peptides (AMP) such as alpha and beta defences and cathelicidins
- Lamina propria – present beneath the epithelial cells, has inflammatory and dendritic cells (dendritic cells project into lumen)

# Layers and defences of GALT

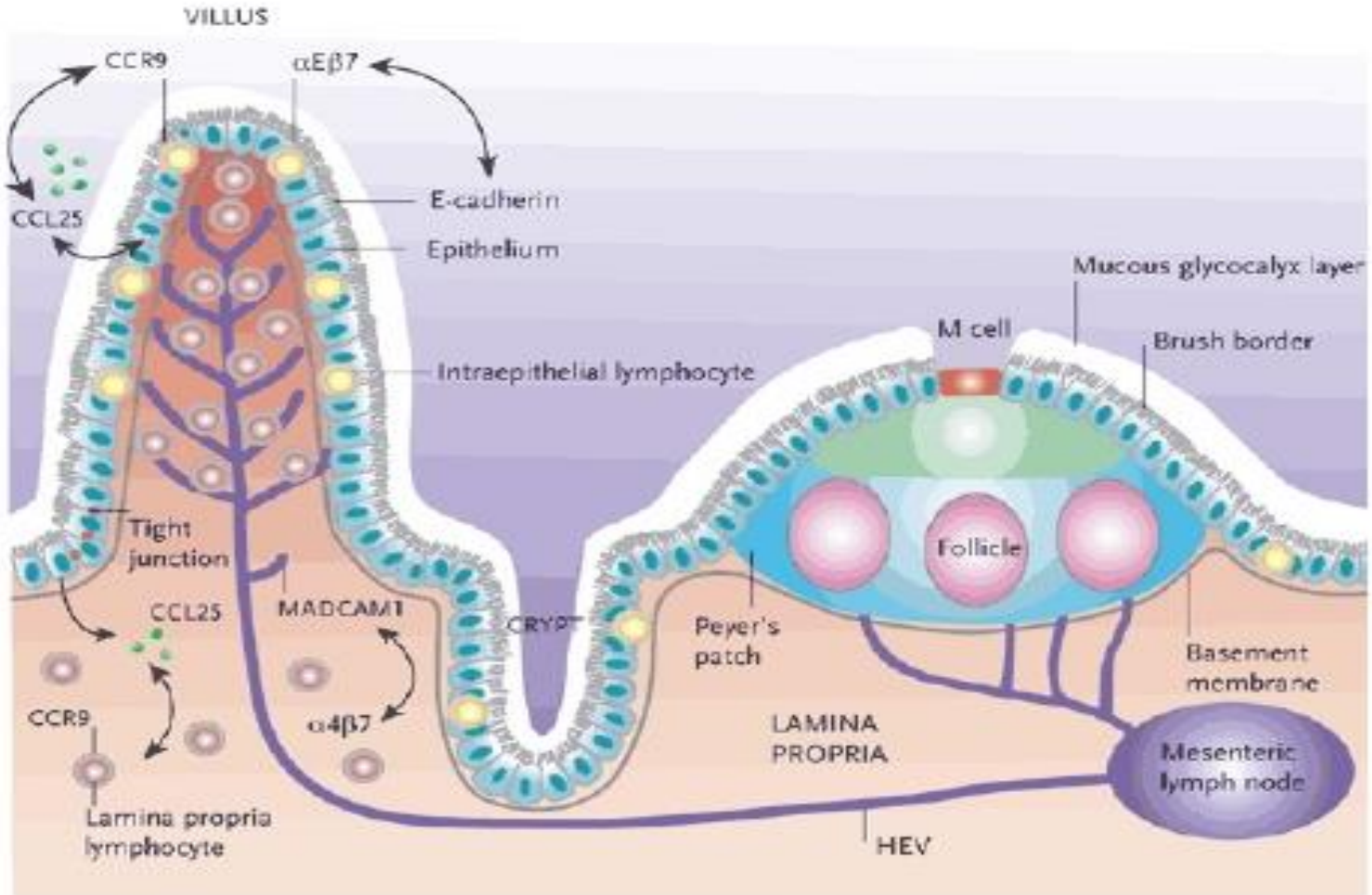
- Peyer's patches – has Microfold (M cells) which are present between epithelial cells and has no mucous covering them, their function is to send antigens to the dendritic cells below them. These dendritic cells then carry antigen to the Peyer's patch where they meet naïve T cells/ B cells and can activate them.
- Intra epithelial lymphocytes – they are cytotoxic CD8 T cells and are present between epithelial cells. Their function is to kill infected or damaged epithelial cells.

# Adaptive immune response of GALT

- Dendritic cells travel to both Peyer's patches and mesenteric lymph nodes where they expose antigen to the naïve T cells.
- When antigen is bacteria which is a commensal (doesn't damage host) or self antigen, the dendritic cells express a lot of IL-10 and TGF beta which then induces formation of Tregs.
- If antigen is bacteria that causes damage there is IL-1 expression which induces TH1, TH17 cell response and inflammation.
- Dendritic cells convert Vit A into retinoic acid which enhances induction of Treg cells along with IL-10 and TGF beta. It also induces expression of the homing receptor α4β7 which is an integrin which drives CD4 T cells towards the intestine where it binds to the receptor on the epithelium called MADCAM. Citral from lemongrass stops conversion of vit A to retinoic acid for α4β7 expression and hence reduces homing of T cells into gut.


Small intestine
Peyer's patch
M-cell
Naive CD4+
T-cell
SED
B-cell
DC
TFH cell
T-cell priming
FDC
Germinal centre
IgA+ B-cell
Plasma cell
Germinal centre
Lamina propria
Mesenteric lymph node
Blood

# Lymphocyte circulation in GALT



# Adaptive immune response of GALT

- Vit A induces B cells to secrete IgA which binds to antigens and removes them and helps in mucosal defence.
- IgA is inhibited by cortisol, cortisol is inhibited by phosphatidyl serine.
- Elevated cortisol suppress IgA and triggers intestinal inflammation.

# Role of IL-22

- IL-22 expression is increased in order to increase epithelial proliferation and thereby create strong barrier. Useful in initial inflammatory response.
- However, too much of IL-22 (persistent inflammation) reduces the differentiation of the intestinal epithelial stem cells and hence organoids such as Paneth cells, M cells, neuroendocrine cells reduce and absorption defects start.
- On skin the increased expression of Il-22 in the gut is seen as lichenification and skin thickness.
- Our medication Skookum balances IL-22 and reduces thick skin and lichenification.

# Immune system map

- Innate and adaptive
- Innate deals with all infections in the same way, it is non specific
- Consists of mainly neutrophils, complement and macrophage response
- Adaptive consists of cell mediated and humoral responses
- Cell mediated are T helper cells CD4 and CD8 cytotoxic responses
- Humoral responses are mediated through B cells which release antibodies

# Cytokines and interleukins

- These are secreted proteins and signal molecules
- They regulate cell growth, differentiation and motility
- Some like IL10 are anti inflammatory and some like IL1 are inflammatory
- Cytokines are broader in definition and include chemokines, interferons, interleukins while interleukins are just messenger cells between immune cells
- Cytokines/interleukins are secreted by immune and non immune cells

# DAMPS and PAMPS

- These are structures that innate immune system receptors can recognize to initiate inflammation and repair process.
- These damage producing agents are either PAMPS (pathogen associated molecular peptides) or DAMPS (damage associated molecular peptides).
- E.g. of PAMPS can be structures of gram-negative and gram-positive bacteria, viruses, fungi or any infectious agents. E.g. of DAMPS can be any nuclear or cytosolic proteins which are released from cells following tissue injury.
- They do this via binding to the receptors on the surface and within the cells called PRR's (pattern recognition receptors).
- There are three types of PRR's based on location; those present on the cell membrane, those present in the cytosol, those present in endosomes.