Intestinal immunology

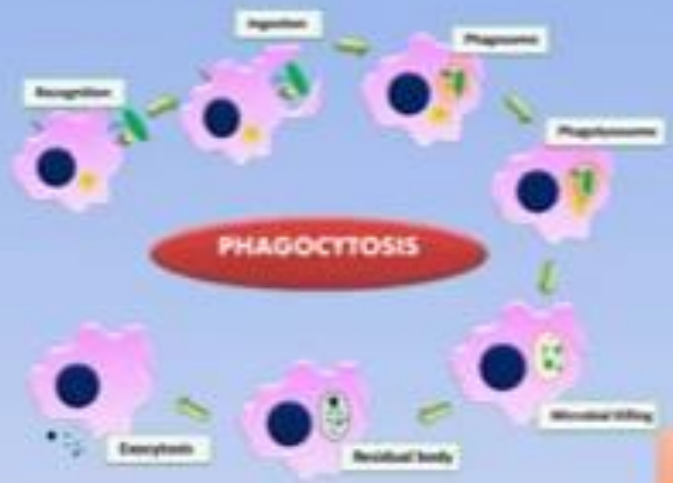
Spier Paediatric Gastroenterology 2019

Basic Immunology 101
A brief refresher

Slides from Frank lecture series on Immunology (Youtube)

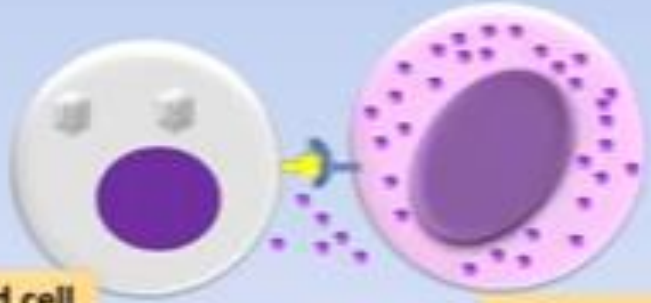
Innate Immunity

inflammation

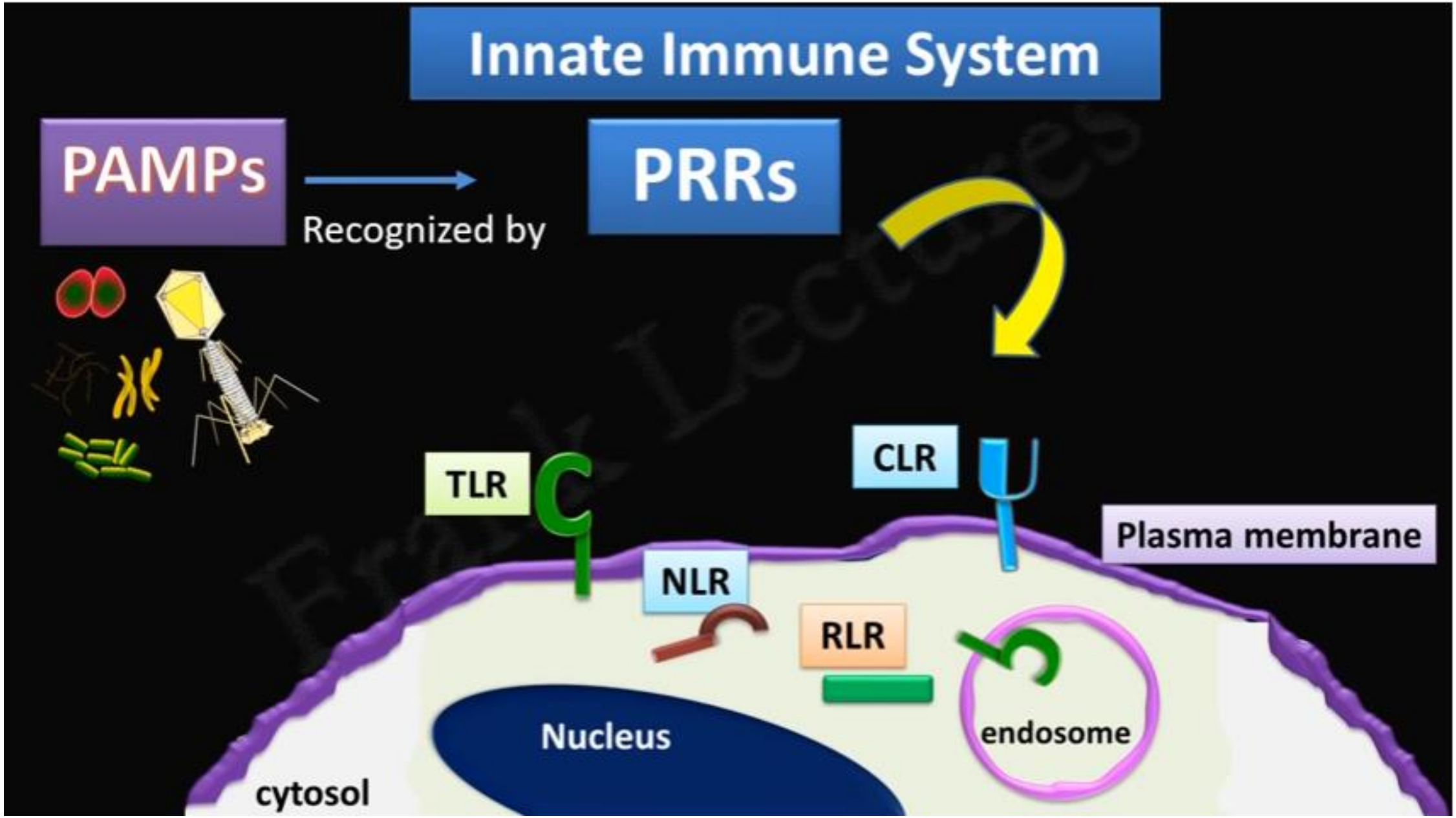


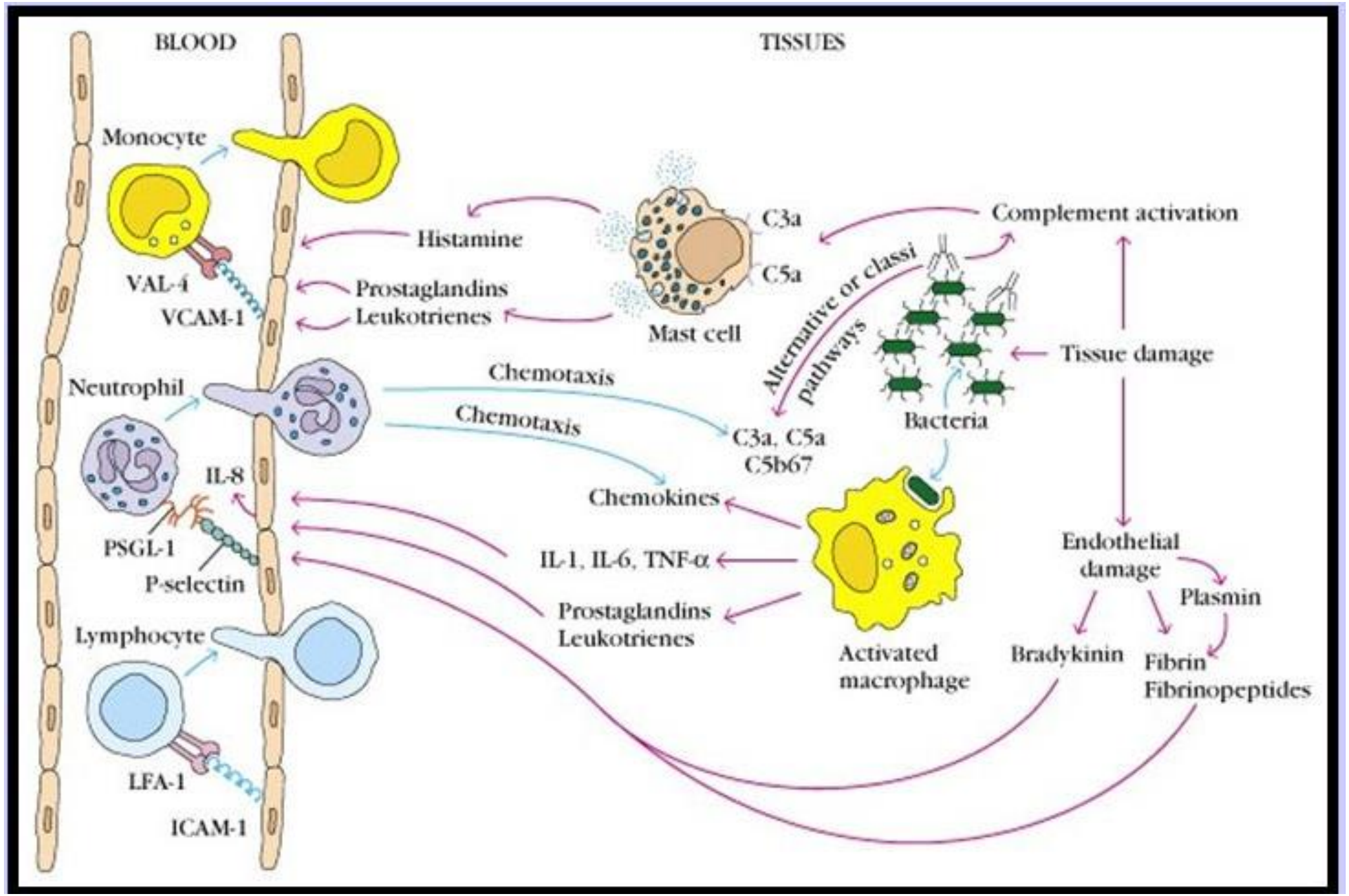
The Complement System

Interferons

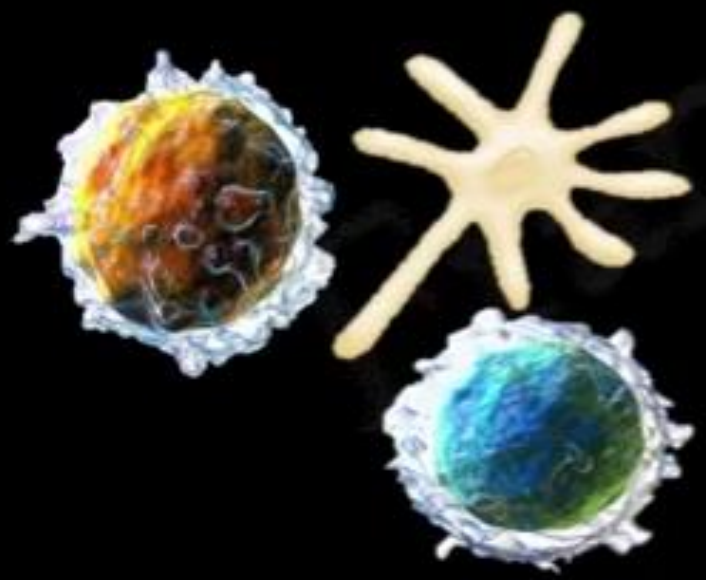


NK Cells


Innate Immune System
PAMPs
Recognized by
PRRs
TLR
CLR
Plasma membrane
NLR
RLR
Nucleus
endosome
cytosol


BLOOD
TISSUES
Monocyte
VAL-4
VCAM-1
Neutrophil
IL-8
PSGL-1
P-selectin
Lymphocyte
LFA-1
ICAM-1
Histamine
Prostaglandins
Leukotrienes
Mast cell
C3a
C5a
Complement activation
Alternative or classi
pathways
Tissue damage
Bacteria
Chemotaxis
Chemotaxis
C3a, C5a
C5b67
Chemokines
IL-1, IL-6, TNF-α
Prostaglandins
Leukotrienes
Activated
macrophage
Endothelial
damage
Plasmin
Bradykinin
Fibrin
Fibrinopeptides

Adaptive Immunity



AQUIRED IMMUNITY

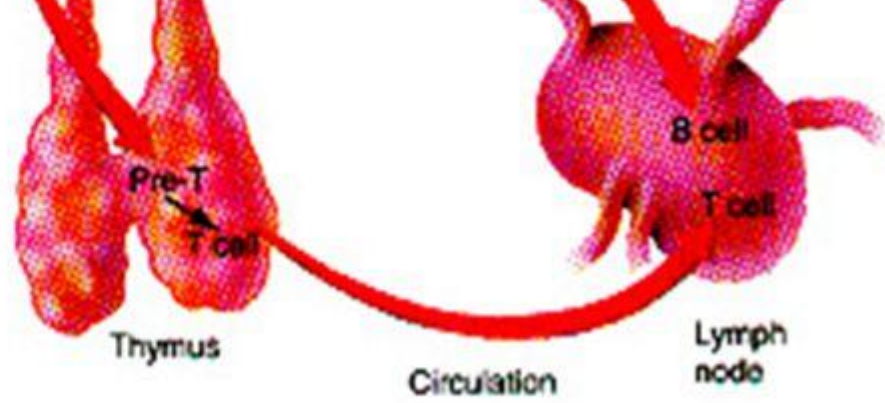
- Adaptive Immunity
- Specific Immunity
- Immunological Memory is Present
- Slower but long-lasting immune response

Major Components are:

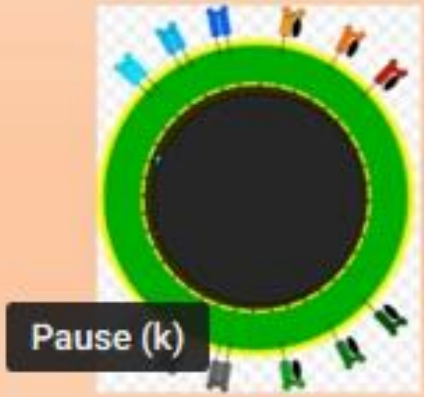
- Antigen Presenting Cells (APCs)
- B- Cells
- T- Cells

immunocompetence occurs in different sites

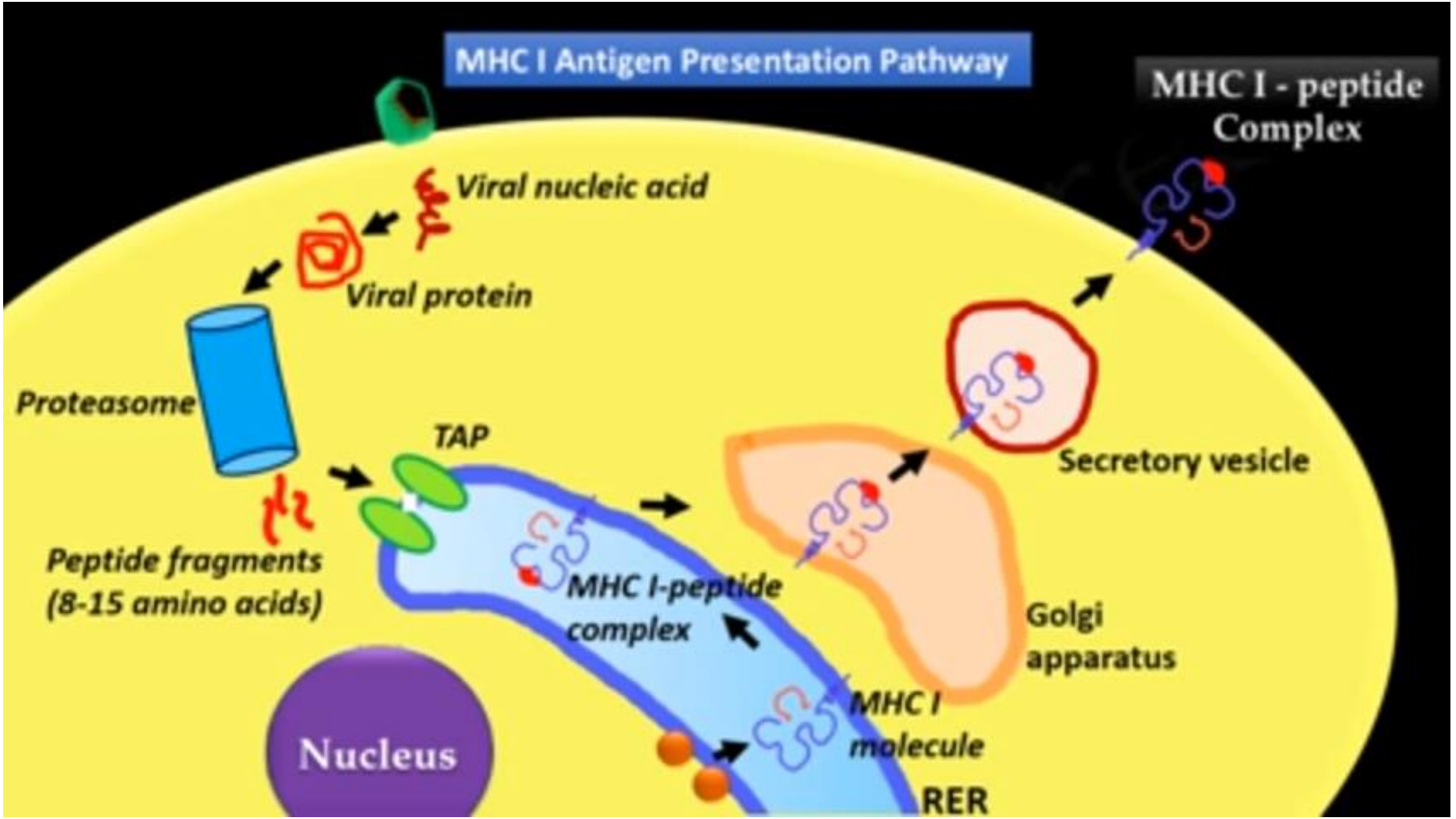
- B cells complete maturation in ***B***one marrow
- Pre-T cells move to ***T***hymus - complete maturation in thymus



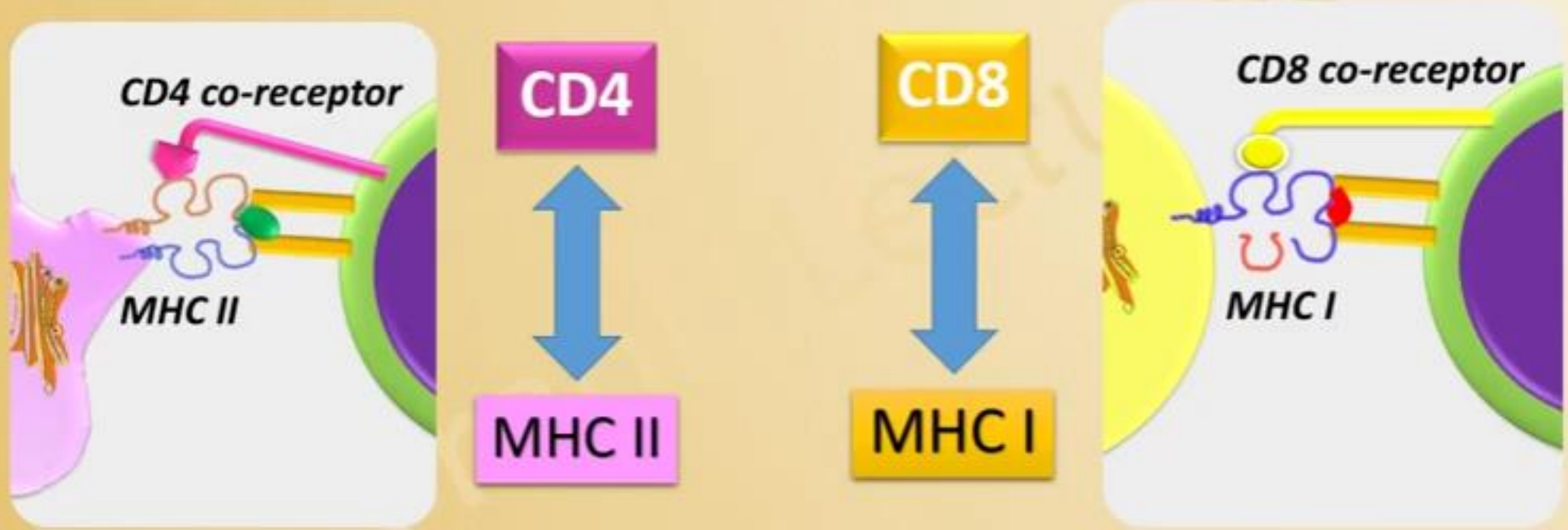
Major Histocompatibility Complex (MHC)

MHC genes	Class I	Class II
MHC molecules	Class I	Class II
	*Expressed on all nucleated cells*	*Expressed on Antigen Presenting Cells*

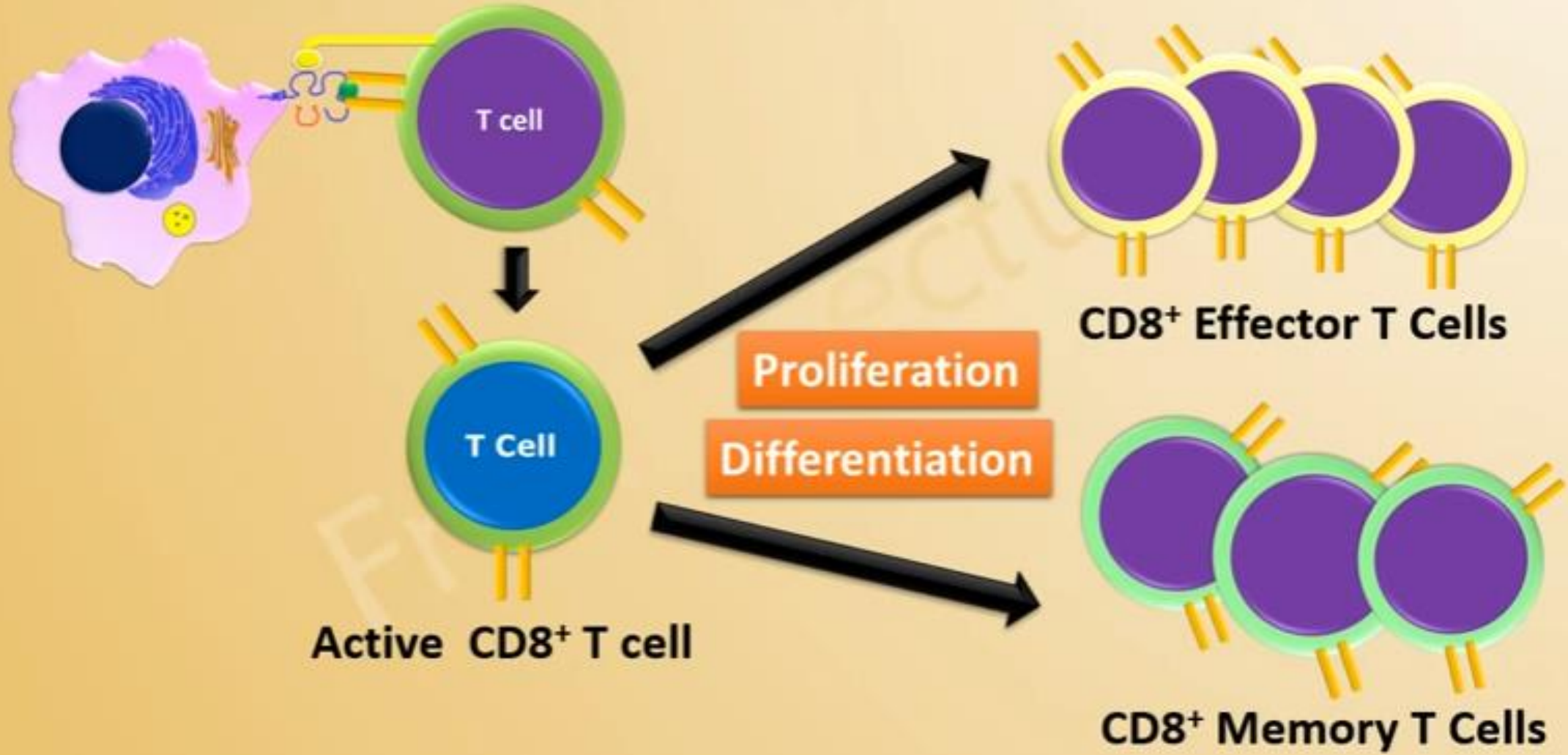
Pause (k)


MHC I Antigen Presentation Pathway
MHC I - peptide Complex
Viral nucleic acid
Viral protein
Proteasome
TAP
Peptide fragments (8-15 amino acids)
MHC I-peptide complex
Secretory vesicle
Golgi apparatus
MHC I molecule
RER
Nucleus

Co-receptors: CD4 and CD8



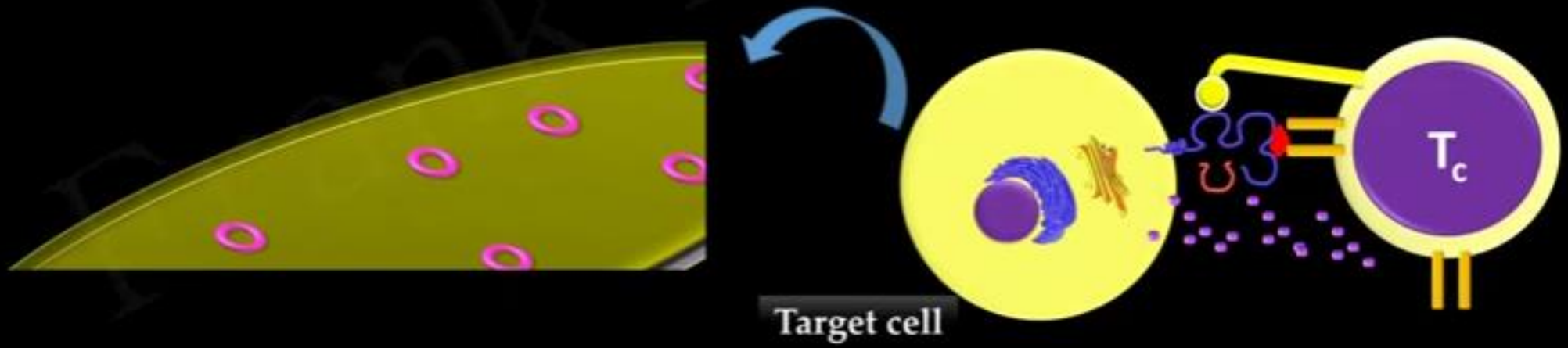
T Cell Activation and Differentiation: CD8⁺ Cells

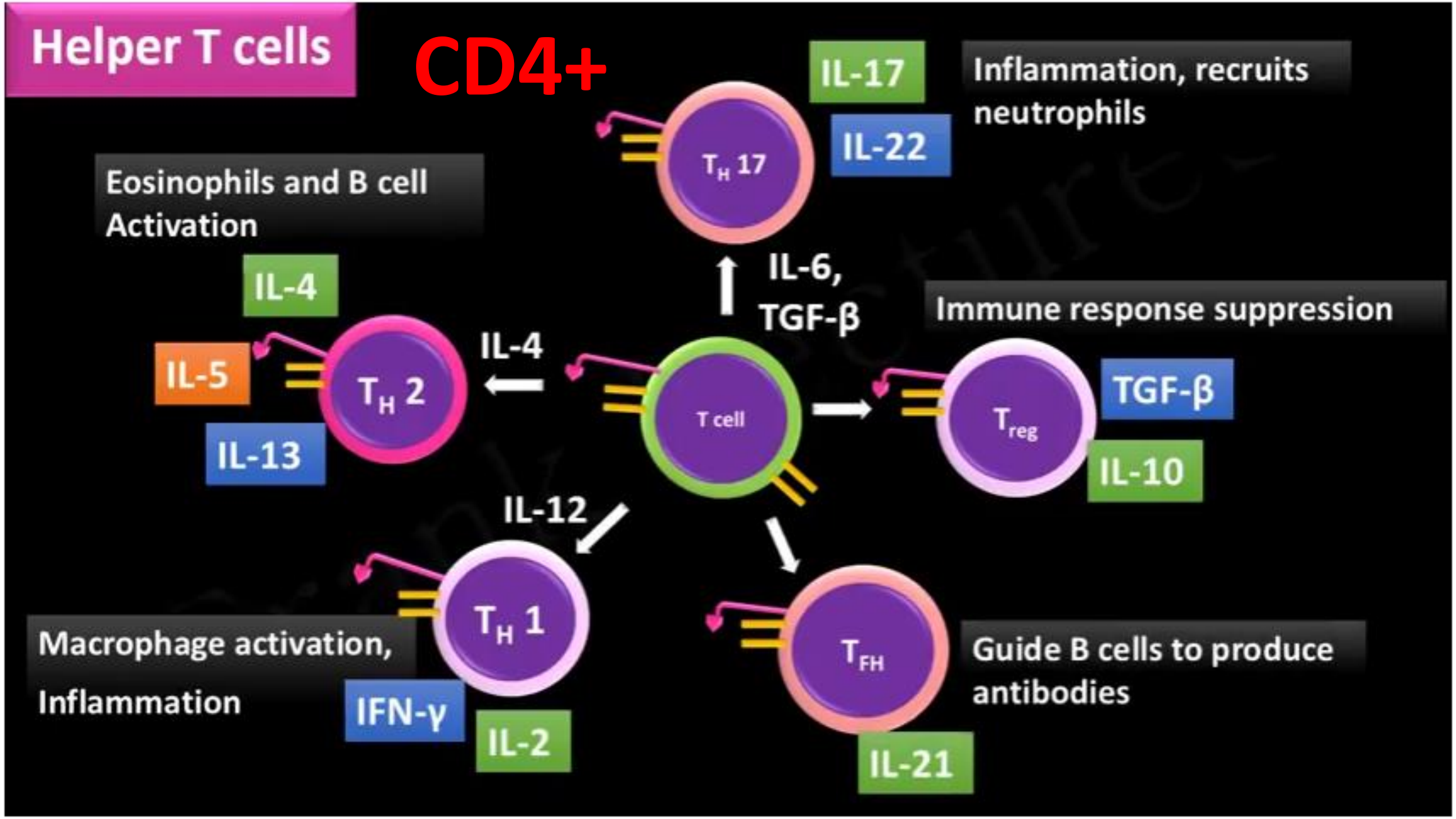


Cytotoxic T cells contains specific cytotoxic granules

CD8+

- Perforin forms pores in the membrane of target cell
- Granzymes cause apoptosis or programmed cell death
- Granulysin has antimicrobial activity




Helper T cells
CD4+
IL-17
IL-22
Inflammation, recruits neutrophils
T_H 17
Eosinophils and B cell Activation
IL-4
IL-5
IL-13
T_H 2
IL-4
IL-6, TGF-β
Immune response suppression
T cell
T_{reg}
TGF-β
IL-10
IL-12
T_H 1
Macrophage activation, Inflammation
IFN-γ
IL-2
T_{FH}
Guide B cells to produce antibodies
IL-21

Intestinal immune system:GALT

Challenges of the Intestinal Mucosa

- Large surface area (300m^2)
- Exposure to:
  - Microbes (10^{12} micro-organisms/g stool)
  - Ingested antigens (30kg food protein/year)
- Digest and absorb food, water & electrolytes
- Single layer epithelium
- Rich blood supply and lymphatic network

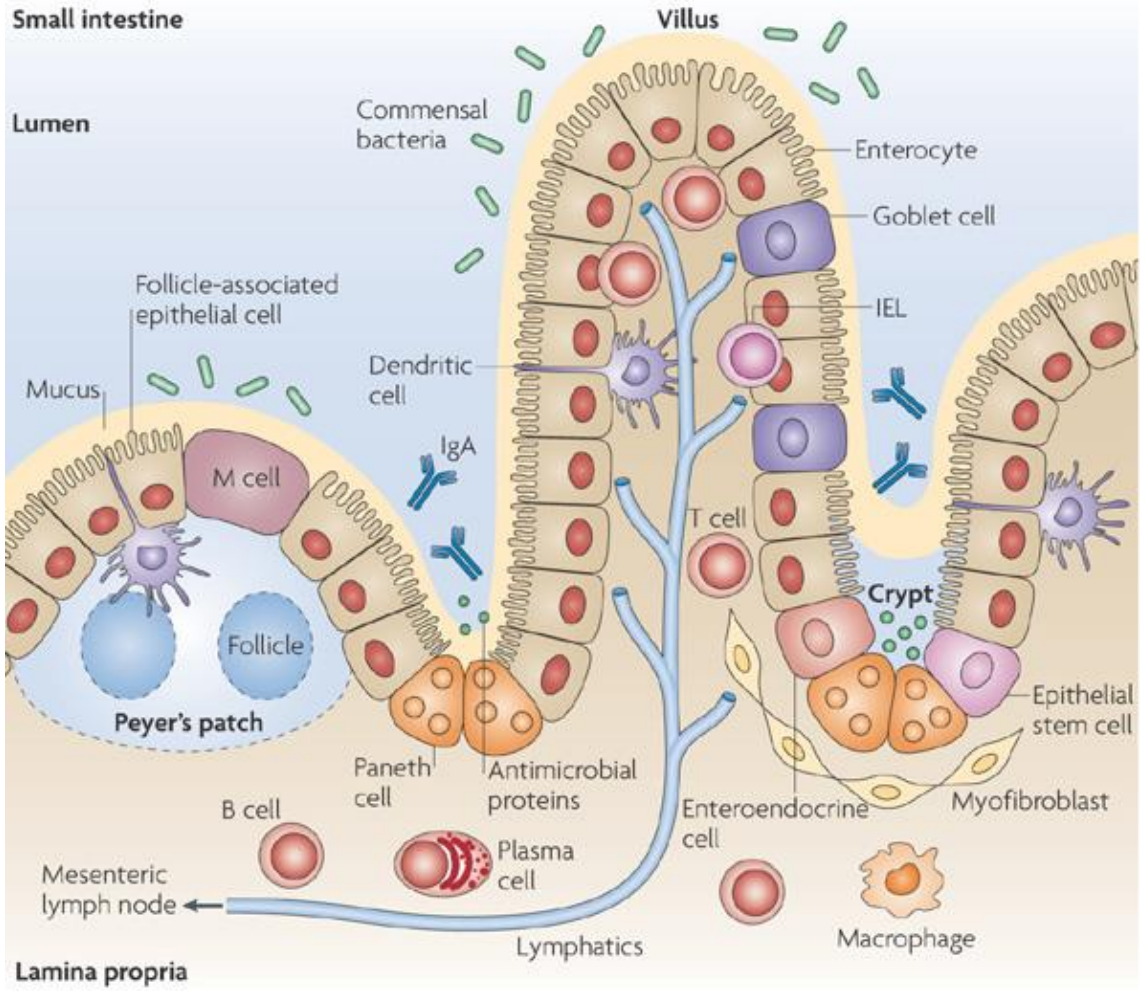
BUT

- Must keep pathogens out
- Avoid excessive immune response to food antigens and microbes

Features of the Intestinal Immune Response at Rest

- Immune suppressed
- Tolerance to food antigens (local & systemic)
- Tolerance to commensal organisms (local, not systemic)

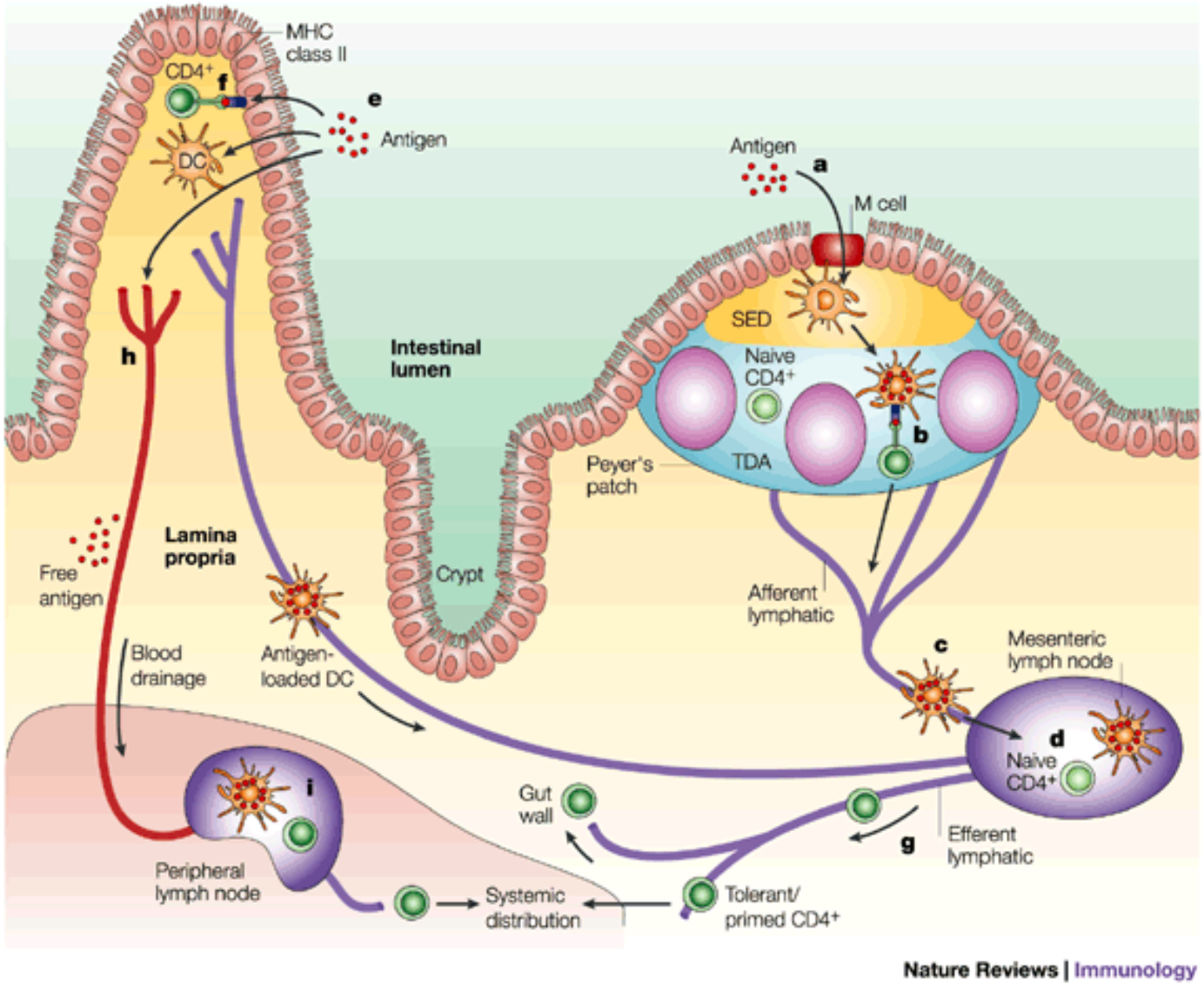
Organisation of the Intestinal Immune System



First Line of Defence

- Microbiome
- Mucus
  - Goblet cells
- IEC and tight junctions
- IgA
- Antimicrobial Substances
  - Paneth cells

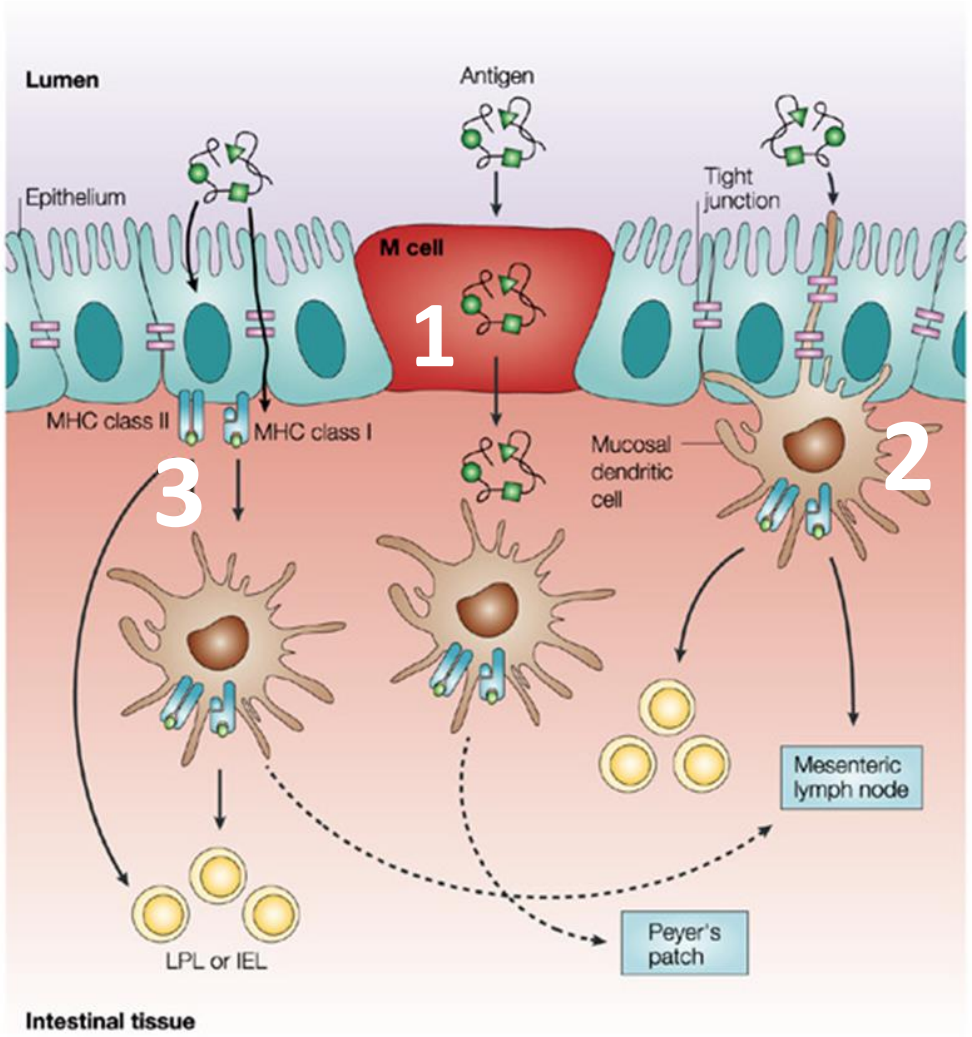
Anatomy of Intestinal Immune System



Nature Reviews Immunology 3, 331-341 (April 2003)

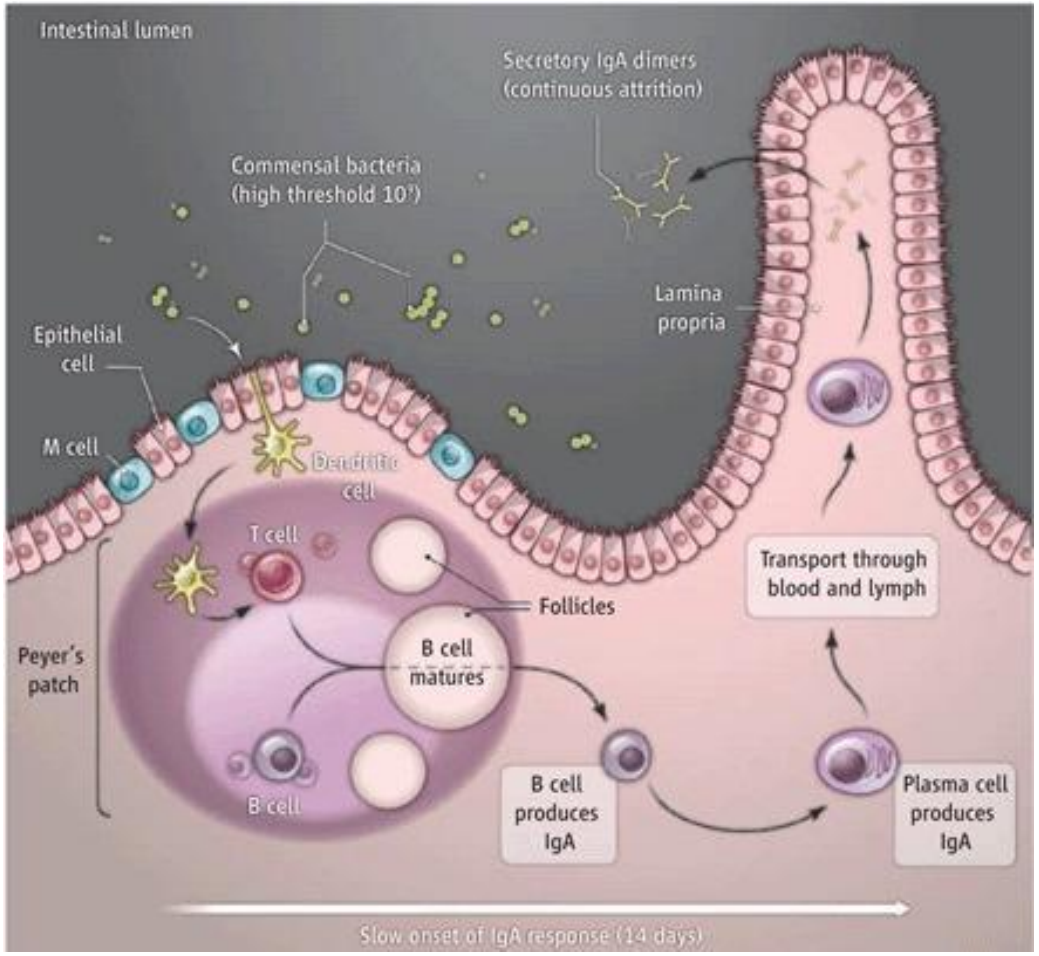
Response to Antigens

Transport across the epithelium to Dendritic Cells



Cheroutre 2004

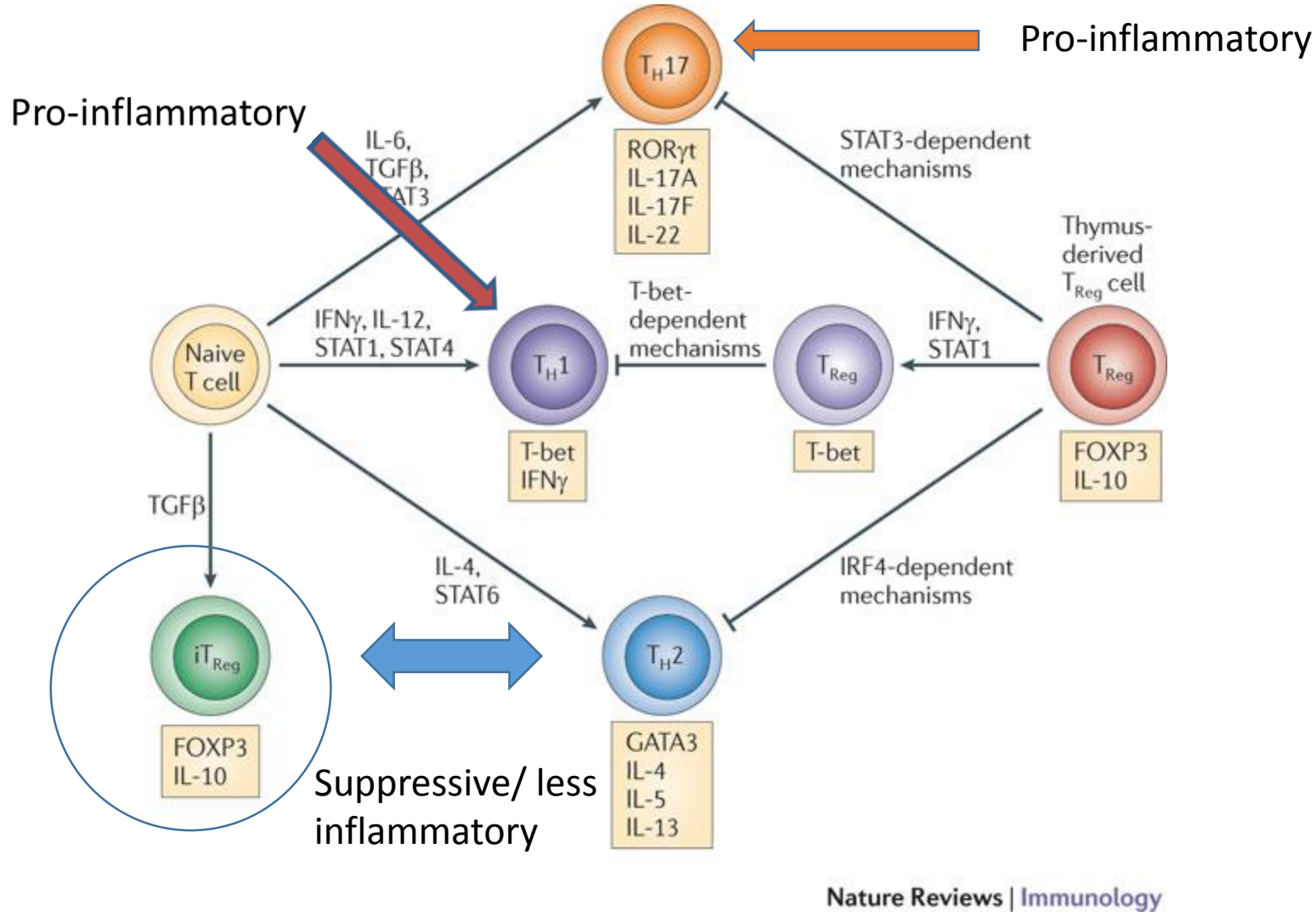
B-cells
Production of secretory IgA



Secretory IgA

- Maintains mucosal barrier
- Less pro-inflammatory than other Ig's
- Protects against infection
- Oral tolerance

T Cells


Pro-inflammatory
Pro-inflammatory
T_H17
RORγt
IL-17A
IL-17F
IL-22
IL-6,
TGFβ,
AT3
STAT3-dependent
mechanisms
Thymus-
derived
T_{Reg} cell
Naive
T cell
IFNγ, IL-12,
STAT1, STAT4
T_H1
T-bet
IFNγ
T-bet-
dependent
mechanisms
T_{Reg}
T-bet
IFNγ,
STAT1
T_{Reg}
FOXP3
IL-10
TGFβ
IL-4,
STAT6
IRF4-dependent
mechanisms
iT_{Reg}
FOXP3
IL-10
T_H2
GATA3
IL-4
IL-5
IL-13
Suppressive/ less
inflammatory
Nature Reviews | Immunology

T Regulatory Cells

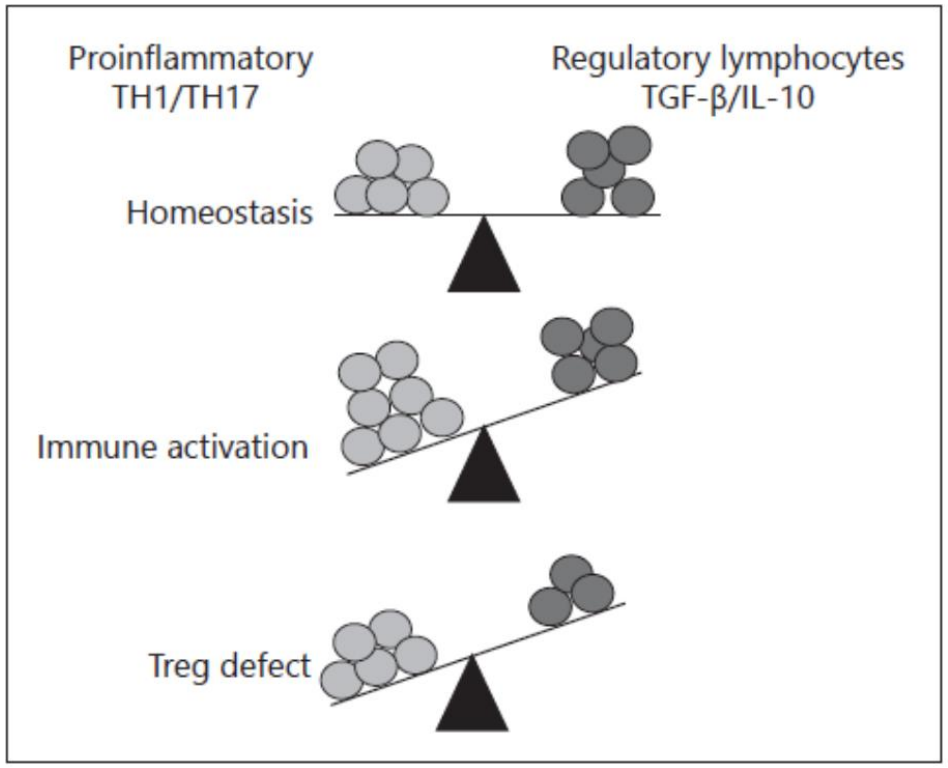
Mechanisms of Action

- Cytokine mediated effects (TGF-β, IL-10, IL-35)
- Direct cytolysis of APC & effector cells
- Metabolic disruption/direct inhibition of DC maturation

Julia Bollrath, Fiona M. Powrie. Seminars in Immunology. 2013

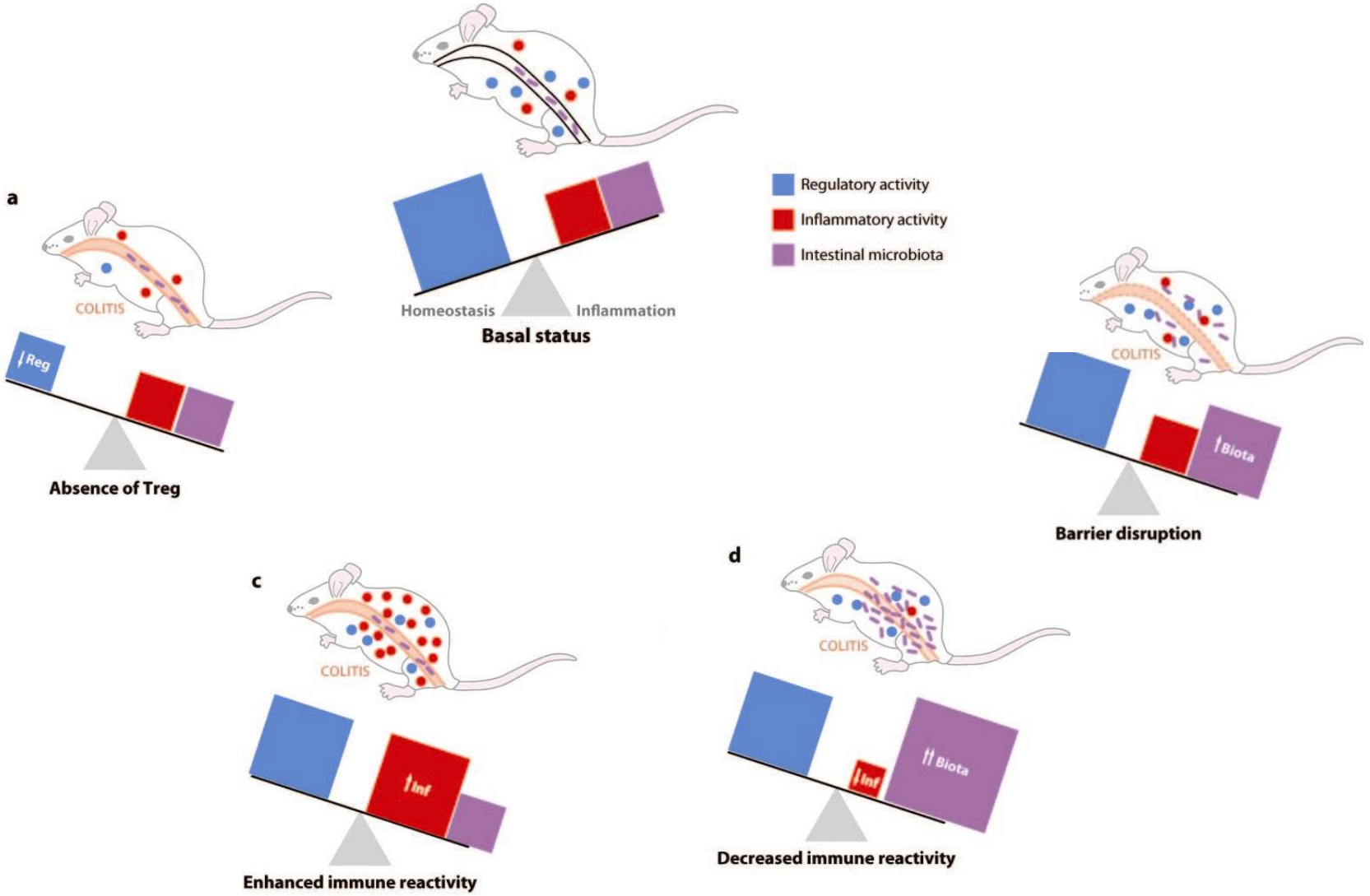
Balance between proinflammatory & tolerant Ag response

- **Pro inflammatory**
  - **Th 1**
  - **Th 17**
- **Tolerant**
  - **Th 2**
  - **TReg**



Ruemelle 2013

Immune Balance in the Intestine



Izcue A, et al. 2009.
Annu. Rev. Immunol. 27:313–38

Oral Tolerance

Specific suppression of cellular/humoral immune response to an Ag by prior administration of the Ag by the oral route

Normal tolerance cannot be established in the absence of a gut flora

Mechanisms of Tolerance

- Epithelium integrity
- sIgA
- Tolerogenic DC’s
- Treg cells
  - TGF beta
  - IL10
- Macrophages – IL10 release

Intestinal diseases

Immunodeficiency or dysregulation

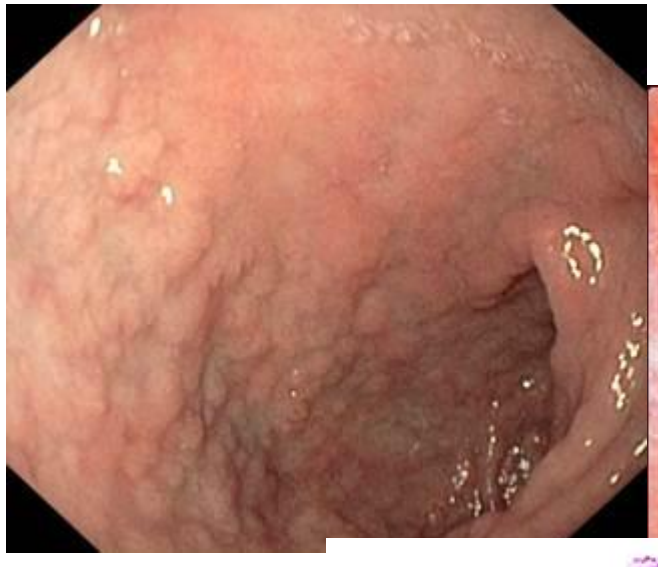
IPEX syndrome

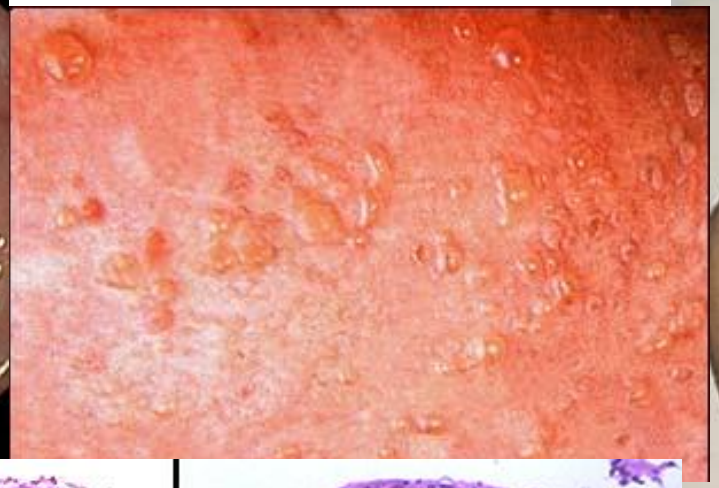
IPEX

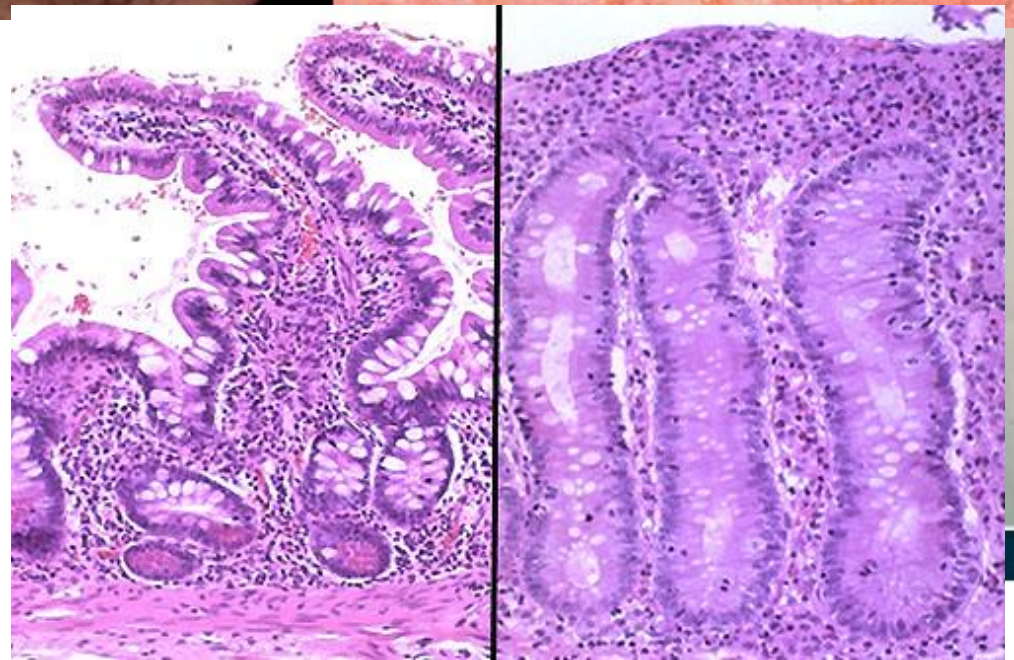
- Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked
- Presents first months of life
- Intractable diarrhoea, FTT, eczema
- Diabetes mellitus, hypothyroidism

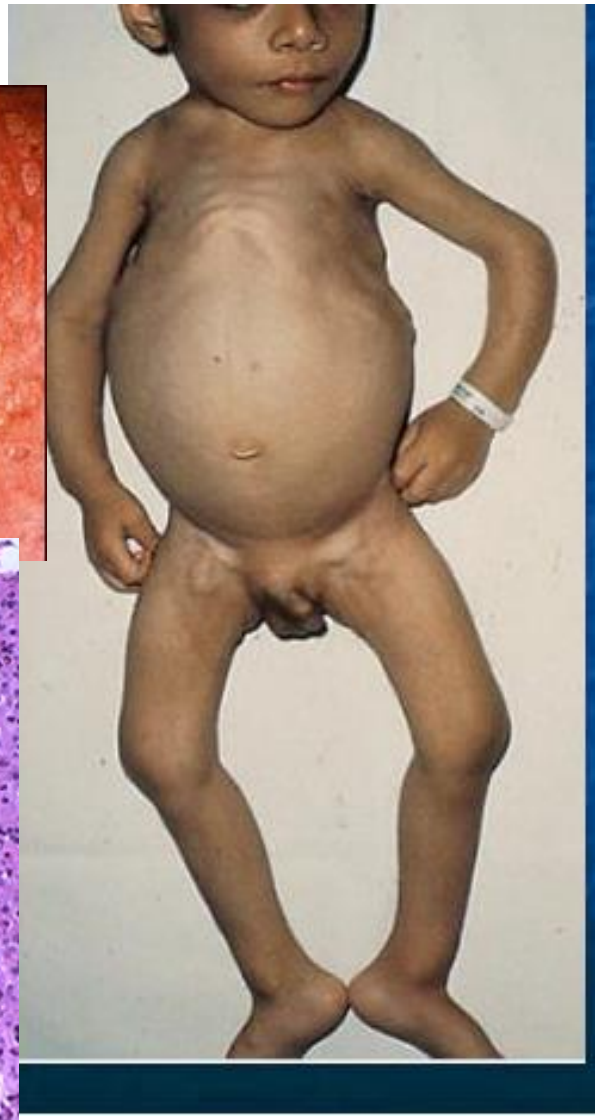
- Mutations in FOXP3 gene

Coeliac Disease





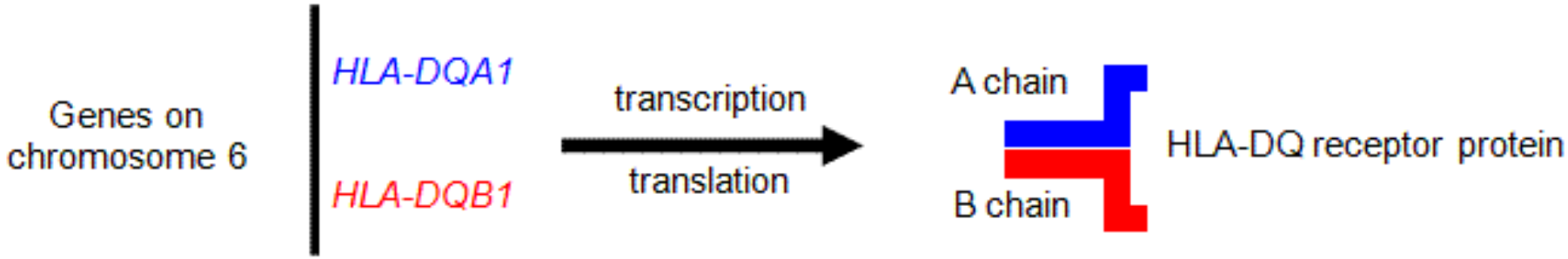




Coeliac disease

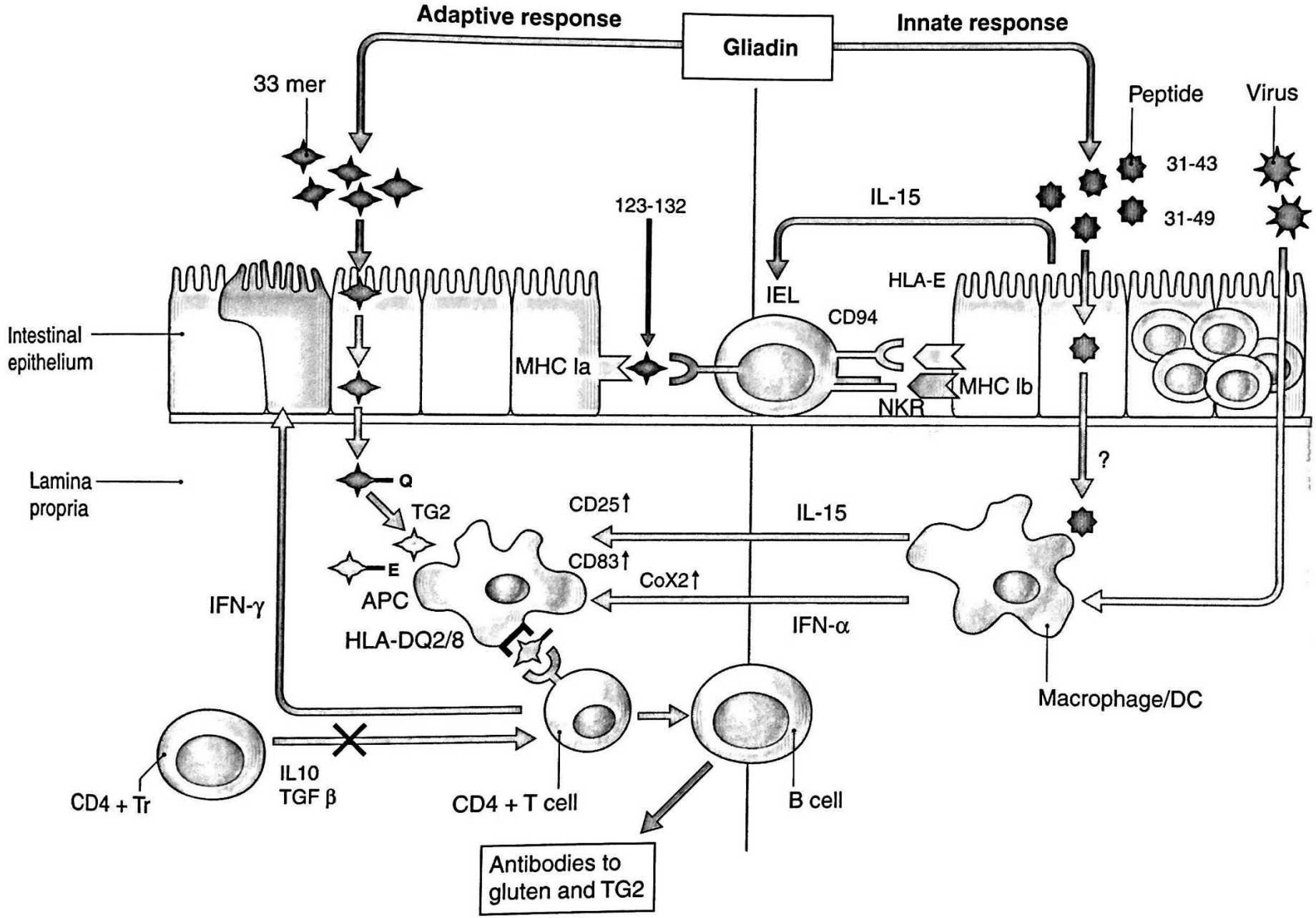
- Immune-mediated systemic disorder elicited by ingestion of wheat protein gliadin

- T-cell mediated, chronic inflammatory disorder with an autoimmune component
- Genetically predisposed - gliadin activates innate and adaptive immune system
- Predominantly TH1



There are a range of possible HLA-DQ protein types, from DQ1 to DQ9, that are located on the surface of cells to act as receptors of antigen molecules.

HLA-DQ2 and HLA-DQ8 bind gluten peptide fragment more strongly and can trigger an immune response more easily

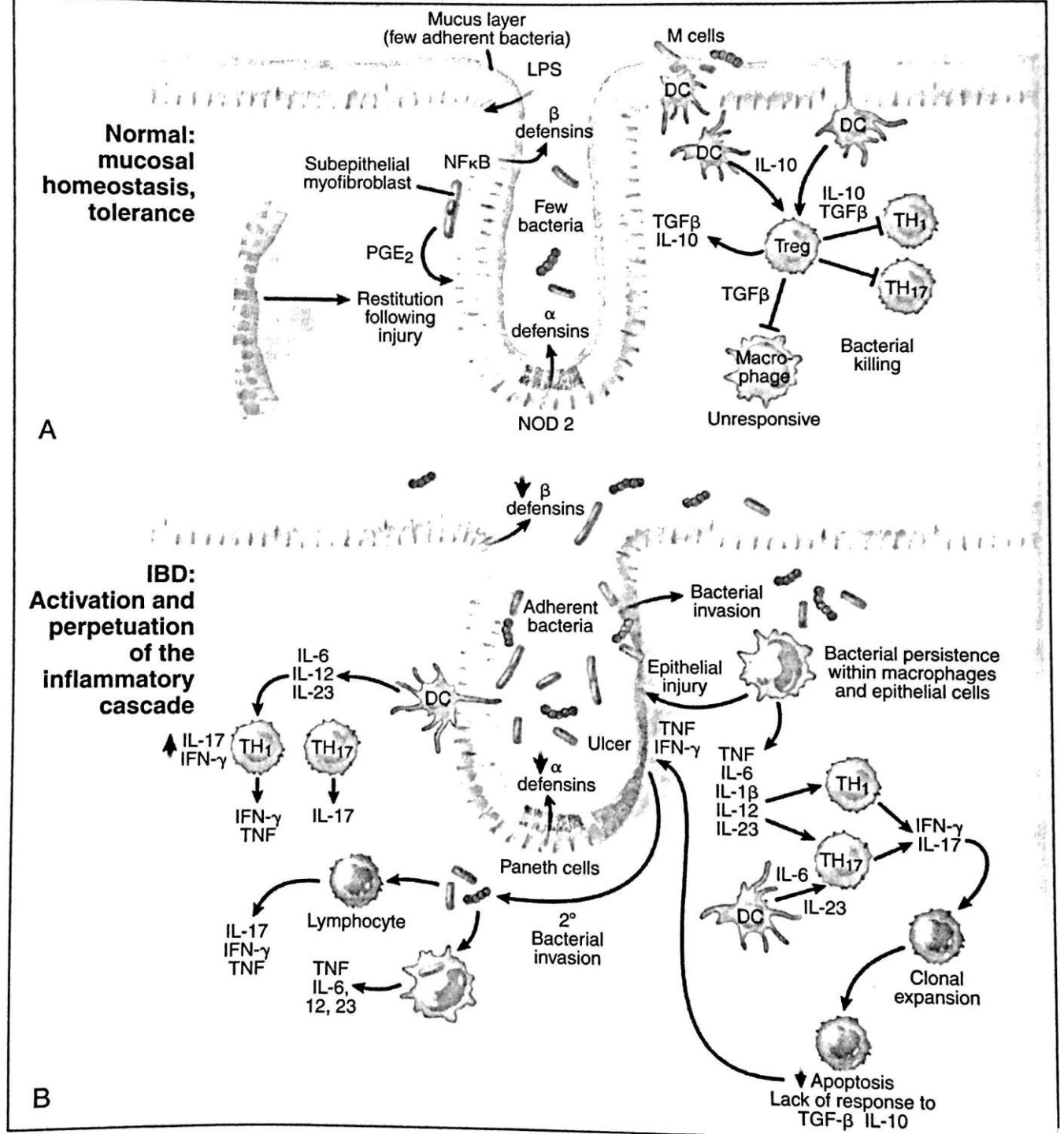

Adaptive response
Gliadin
Innate response
33 mer
Peptide
Virus
31-43
31-49
123-132
IL-15
IEL
HLA-E
CD94
Intestinal epithelium
MHC Ia
MHC Ib
NKR
?
Lamina propria
Q
TG2
CD25↑
IL-15
E
CD83↑
CoX2↑
APC
IFN-γ
IFN-α
HLA-DQ2/8
Macrophage/DC
IL10
TGF β
CD4 + Tr
CD4 + T cell
B cell
Antibodies to gluten and TG2

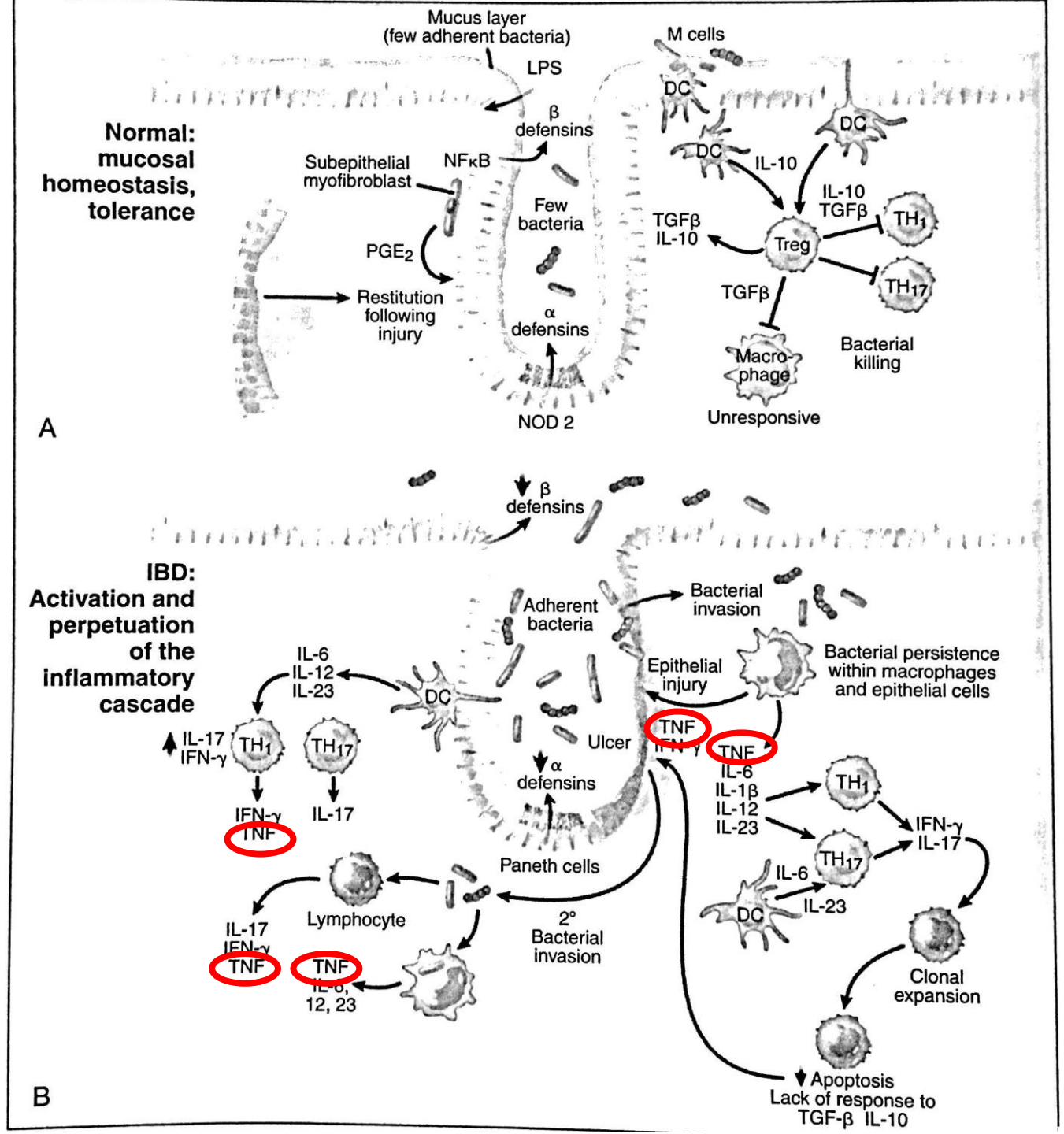
Inflammatory bowel disease

- Dysregulation of the normally controlled immune response to commensal bacteria in a genetically susceptible individual

- Genome-wide association studies: Crohn's disease – alterations in gene coding for **NOD2** – innate immune system
- Mutations in **ATG16L1** – genes involved in degradation of intracellular pathogens, antigen processing, regulation of cell signalling and T-cell homeostasis

- ?altered recognition and processing of bacterial antigens may play a role in disease pathogenesis


Normal: mucosal homeostasis, tolerance
Mucus layer (few adherent bacteria)
LPS
β defensins
Subepithelial myofibroblast
NFκB
Few bacteria
PGE2
Restitution following injury
α defensins
NOD 2
M cells
DC
IL-10
IL-10 TGFβ
TGFβ IL-10
Treg
TH1
TH17
TGFβ
Macro-phage
Bacterial killing
Unresponsive
A
IBD: Activation and perpetuation of the inflammatory cascade
β defensins
Adherent bacteria
Bacterial invasion
Epithelial injury
Bacterial persistence within macrophages and epithelial cells
IL-6
IL-12
IL-23
DC
IL-17 IFN-γ
TH1
TH17
IFN-γ TNF
IL-17
Ulcer
α defensins
Paneth cells
TNF IFN-γ
TNF IL-6 IL-1β IL-12 IL-23
IFN-γ IL-17
IL-6
IL-23
Lymphocyte
IL-17 IFN-γ TNF
2° Bacterial invasion
TNF IL-6, 12, 23
Clonal expansion
Apoptosis
Lack of response to TGF-β IL-10
B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TGFβ IL-10
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IL-6 IL-12 IL-23
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IFN-γ IL-17
IL-6
IL-23
Lymphocyte
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TNF IL-6, 12, 23
2° Bacterial invasion
Clonal expansion
Apoptosis
Lack of response to TGF-β IL-10
B

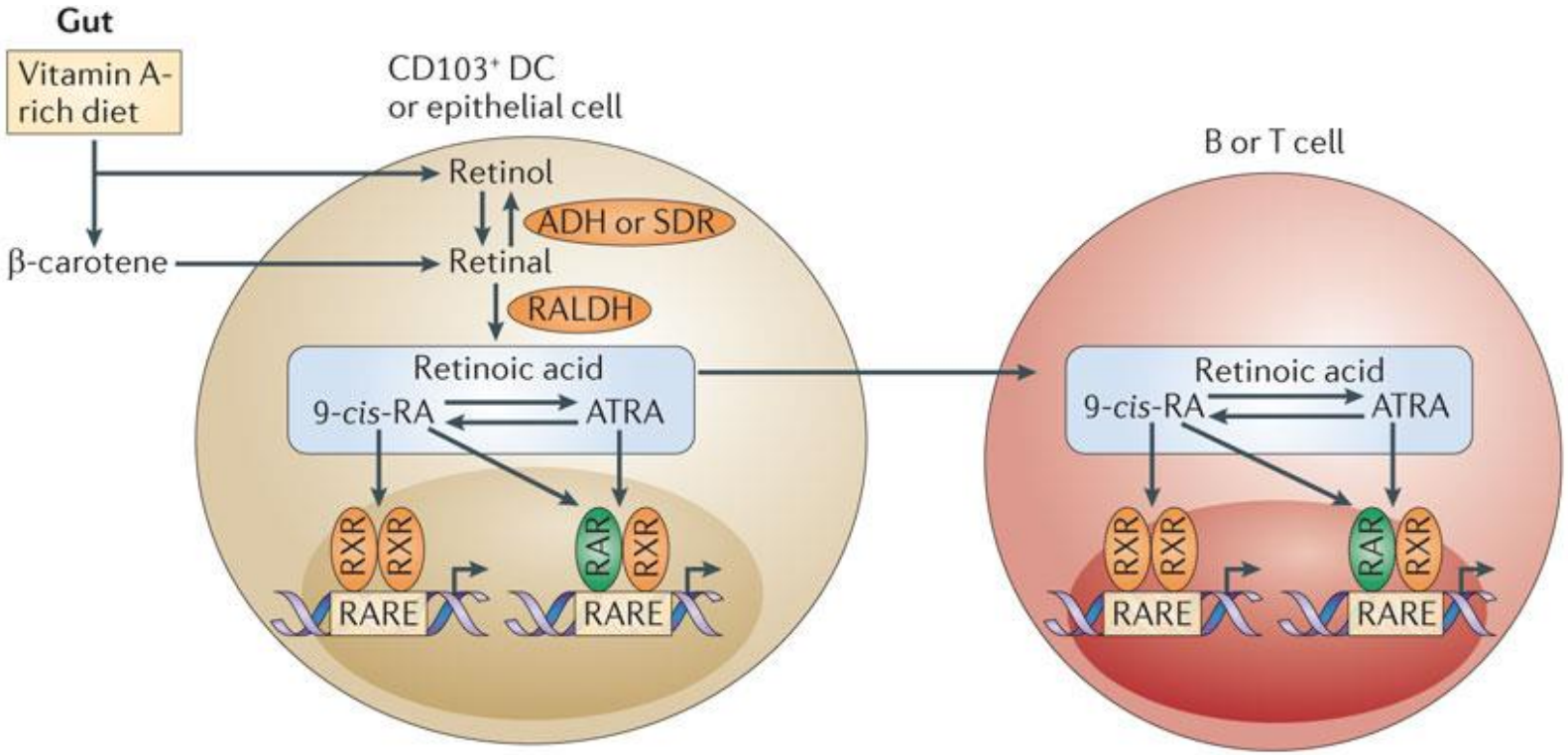
Intestinal immunity and diet

Vitamin A

Vitamin A

- Reduces all cause mortality < 5years
  - Diarrhoeal disease
  - Measles
- Prophylactic supplementation reduces severity of diarrhoea

Vitamin A in the Intestine

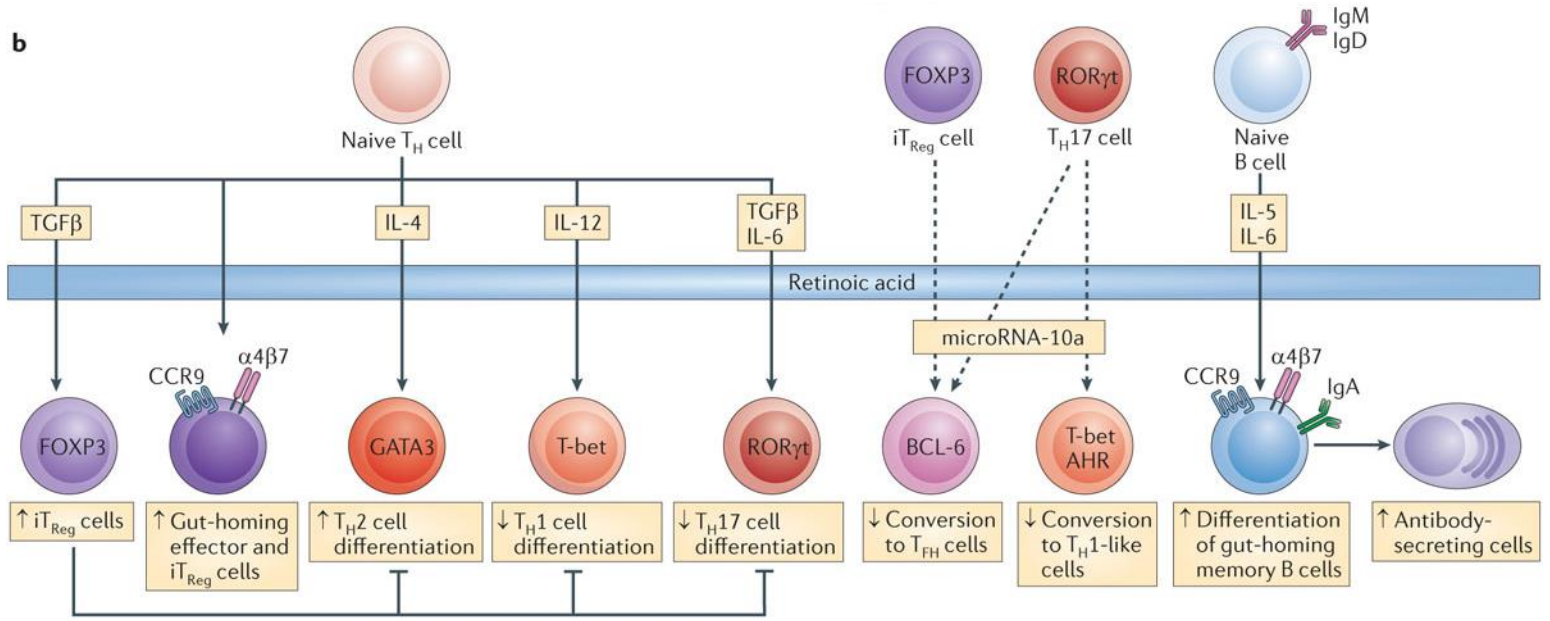


Vitamin A regulates gene expression

Marc Veldhoen and Verena Brucklacher-Waldert,2012

Mucosal Immune Effects of Vitamin A

- *Favours Treg differentiation (together with TGF beta)*
- *CCR9 and α4β7 integrin expression*
- *Promotes Th2 cell differentiation*
- *Opposes Th17 cell differentiation (increases TGF beta; decreased IL6)*



Marc Veldhoen and Verena Brucklacher-Waldert,2012

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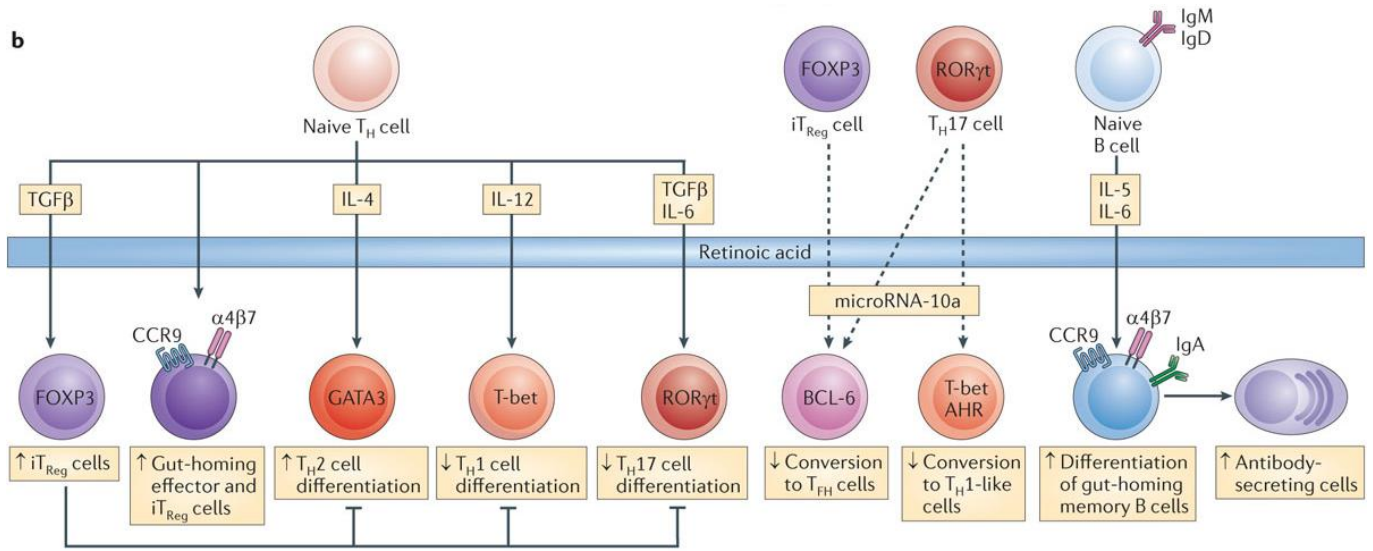
Mucosal Immune Effects of Vitamin A

- *Maintains intestinal epithelial integrity*
- *Regulates mucin gene expression*
- *Normal IgA production*
- *Reduces autoimmunity*



Marc Veldhoen and Verena Brucklacher-Waldert,2012

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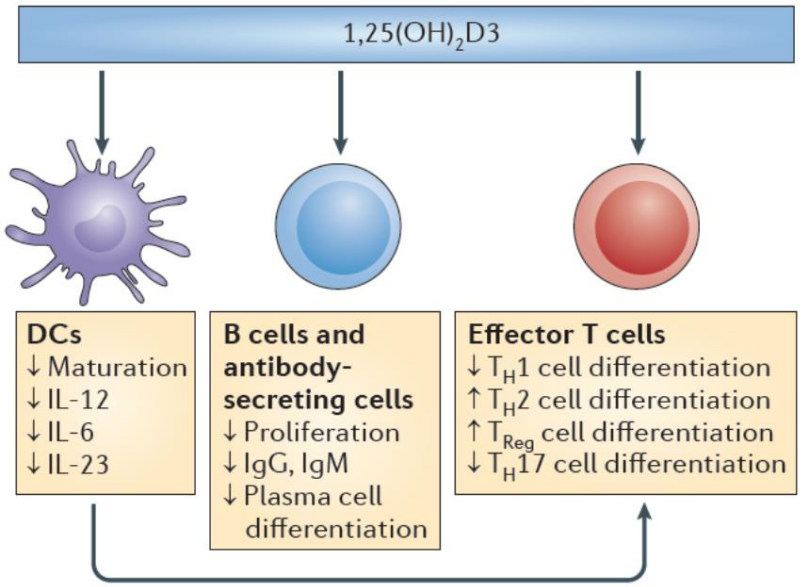
Vitamin D

- ***Control of infection***
- **Cancer**
- **Autoimmune disease**
- **Diabetes**
- **Osteoarthritis**
- **Periodontal disease**

Vitamin D

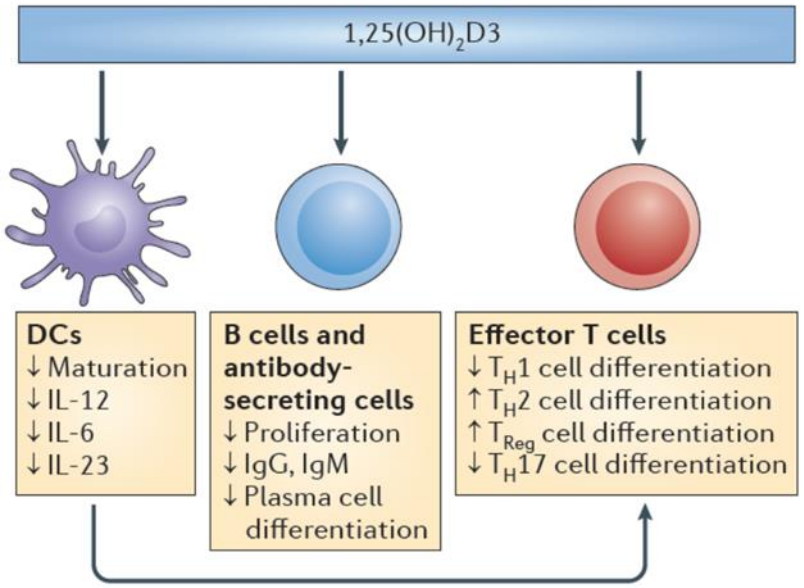
- Inhibits Th1/ enhances Th2
- Treg ↑
- TCR expression (but delays TCR-mediated signalling)
- DC maturation ↓
- Decreases secretion: IL-1, IL-6, IL-8, IL-12, IL-17, IL-23 & TNF-α



Marc Veldhoen and Verena Brucklacher-Waldert,2012

Vitamin D

- ↓Th17 differentiation & homing
- Enhances innate immunity
  - IEL recruitment
  - Stabilises tight junction structures
  - Stimulates expression of NOD2/CARD15/IBD1
  - Paneth cell secretion



Marc Veldhoen and Verena Brucklacher-Waldert,2012

Conclusions

- Intestinal function is closely linked to immune regulation
- Loss of normal immune regulation leads to a number of intestinal diseases
- Oral tolerance is influenced by dietary factors and the intestinal microbiome
- Future research will define interventions for the treatment of the immune mediated diseases.