Introduction

- Overwhelming majority of initial antigen encounters occur at mucosal surfaces
- Surface bathed by a heterogeneous population of microorganisms
- Confronted by a large number of antigenic stimuli which must be deciphered for pathologic potential
- For the majority, a response characterized by either ignorance or active suppression is appropriate
- For a few, a robust immune response is in order

Introduction (II)

- Gut associated lymphoid tissue (GALT) is characterized by a regulated state of physiologic inflammation

- GALT is poised for, but actively restrained from, full action and noteable for a tendency to suppress responses, called oral tolerance

- Certain microorganisms and food antigens elicit vigorous immune responses

- The rules which govern these immunologic decisisons are beginning to be clear and are important to the development of vaccines and the treatment of inflammatory bowel disease

MUCOSAL BARRIER FUNCTION

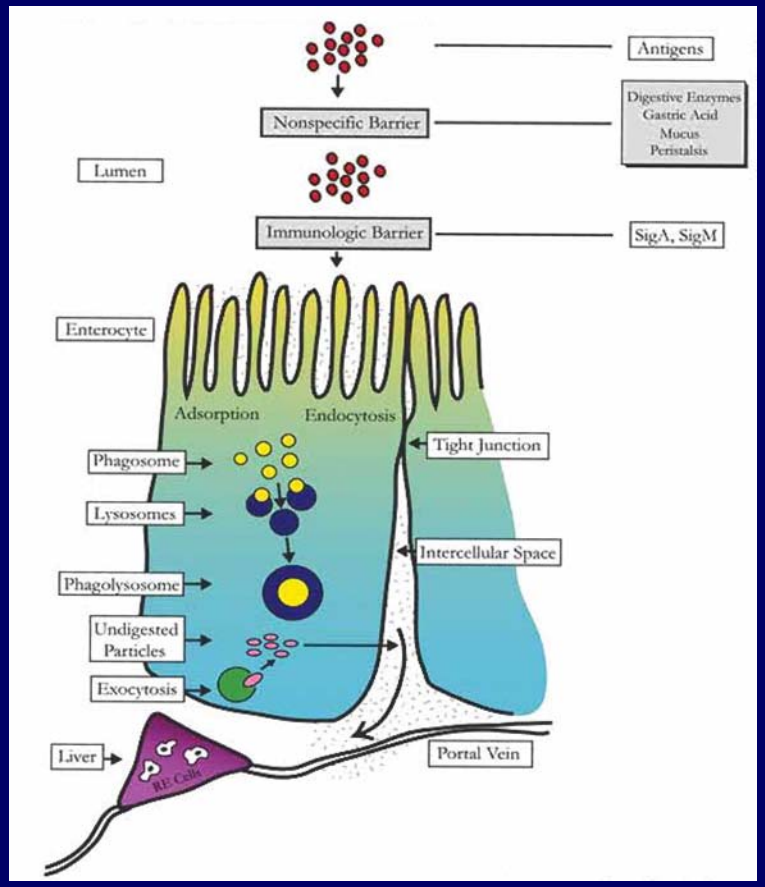
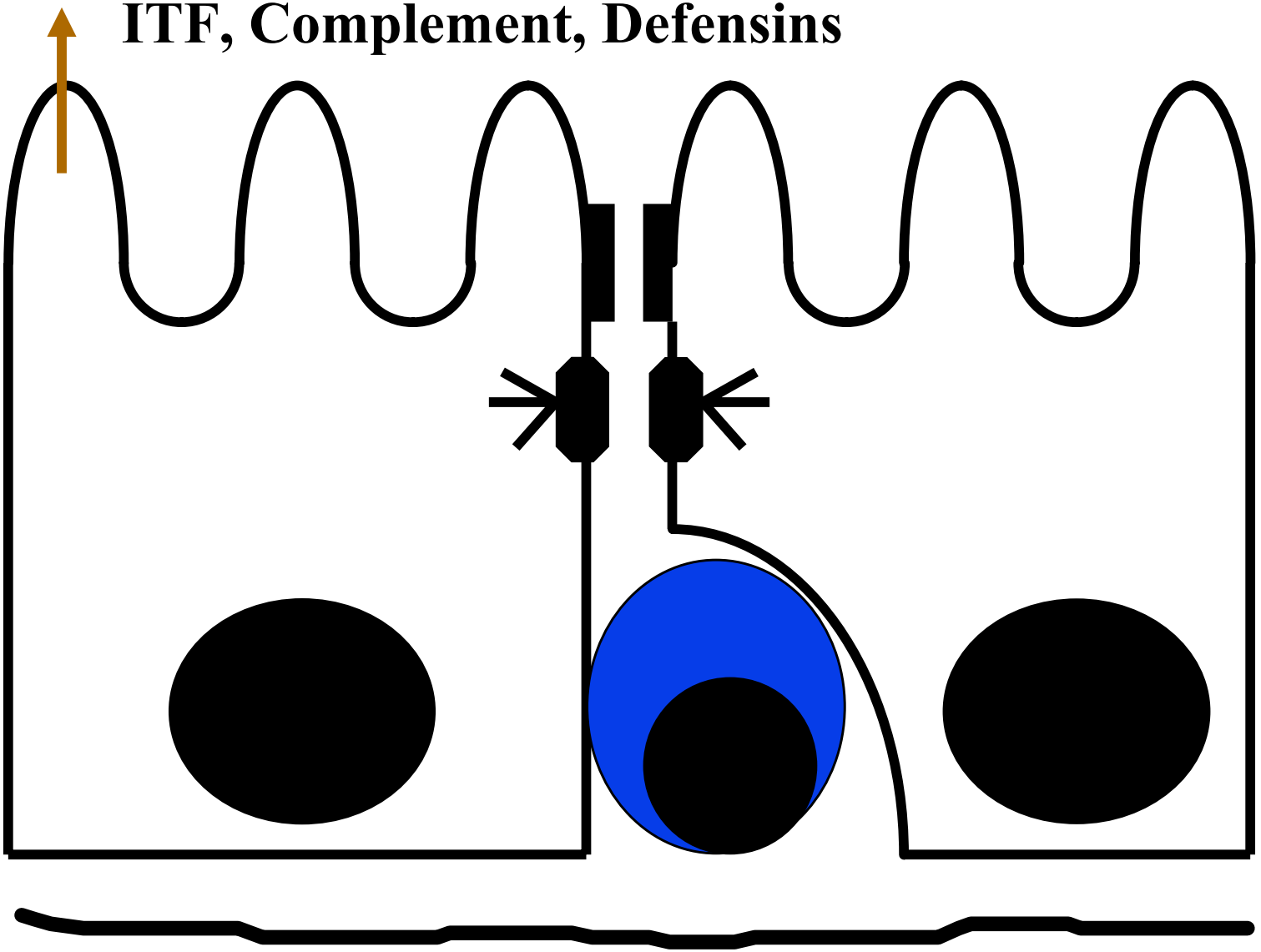


Illustration by MIT OCW.

Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

INNATE HUMORAL FACTORS

Lactoferrin, Lysozyme, Peroxidase,
ITF, Complement, Defensins



TLR Ligands and their Receptors

Figure removed due to copyright reasons. Please see:

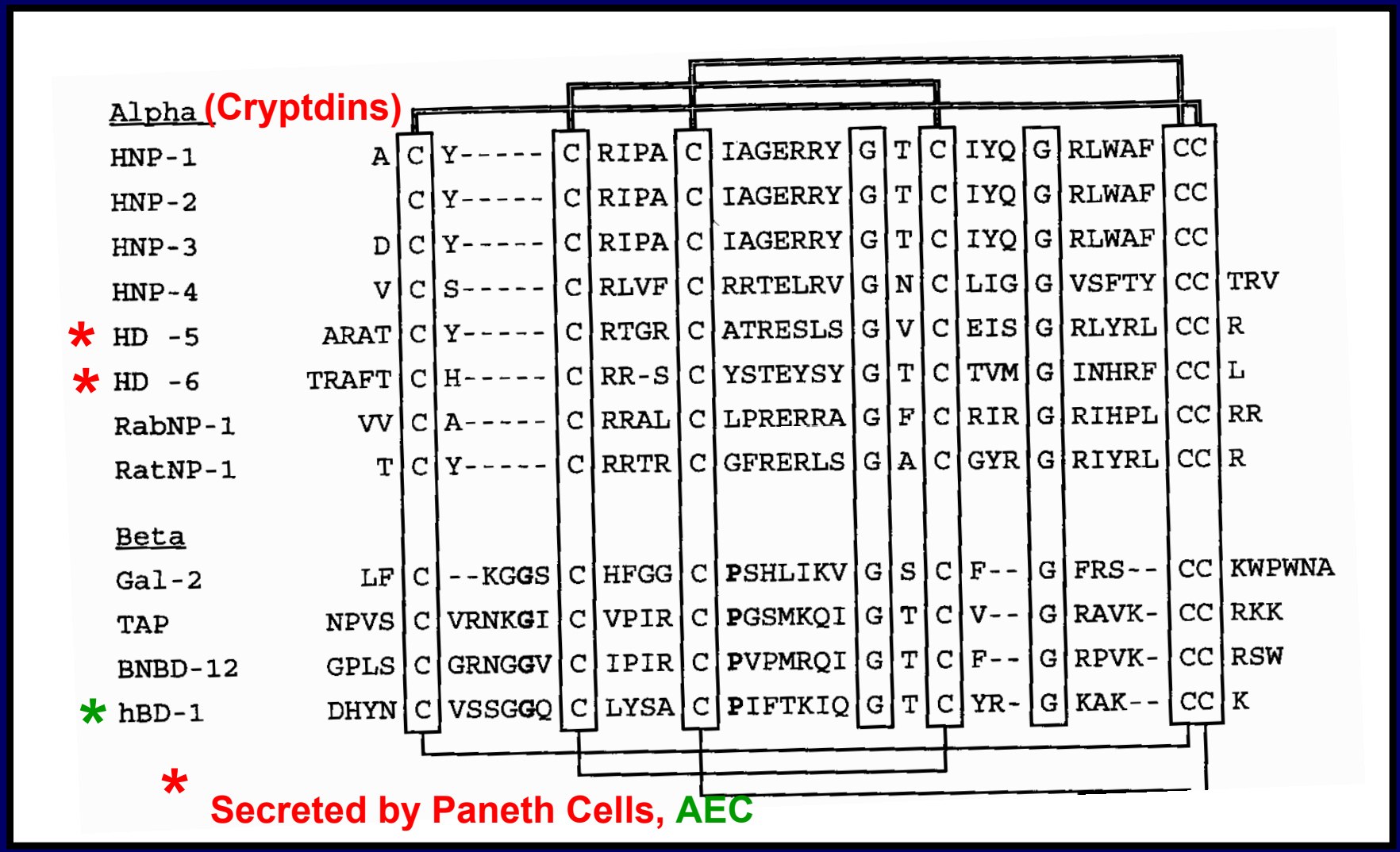
Figure 1 in Akira, Shizuo. "Mammalian Toll-like receptors." *Curr Opin Immunol* 15 (2003): 6.

Commensal Bacteria Regulate Mucosal Gene Expression

Figure removed due to copyright reasons. Please see:

Figure 1 and Figure 2 in Hooper, Lora V., et al. "Molecular Analysis of Commensal Host-Microbial Relationships in the Intestine." *Science* 291 (2001): 881-84.

INNATE HUMORAL FACTORS: DEFENSINS



Luminal Factors:

Specific Extrinsic or Immunologic Barriers

Secretory Immunoglobulins

Isotype Distribution of Ig Production By Mucosal Plasma Cells

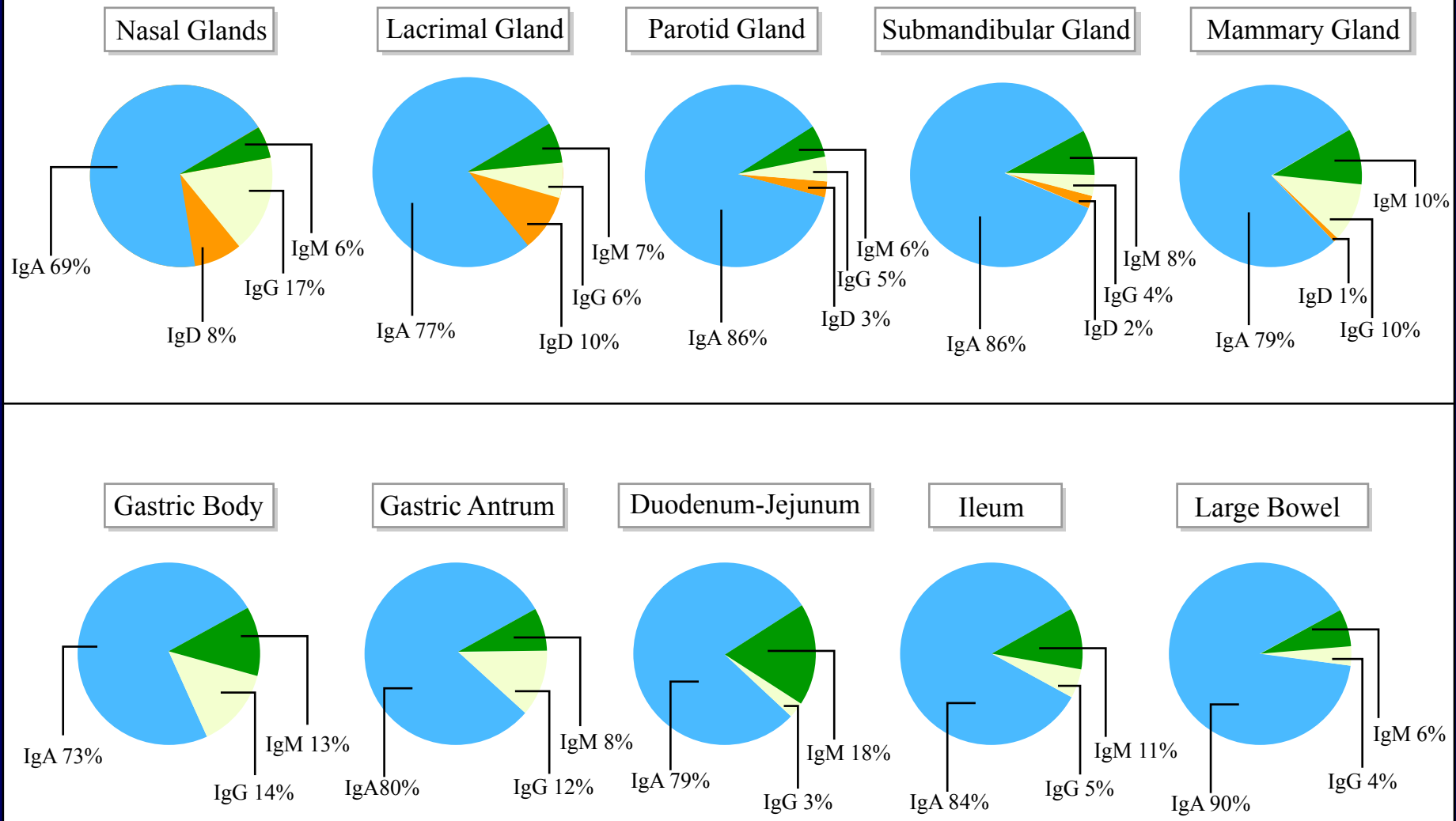


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (I999): 45-87.

Levels (μg/ml) of Immunoglobulins in Human Secretions

Fluid	*IgA*	*IgG*	*IgM*
Nasal Secretions	70-846	8-304	0
Broncho-alveolar fluid	3	13	0.1
Milk	470-1632	40-168	50-340
Duodenal fluid	313	104	207
Colonic fluid	162 μg/min	34 μg/min	17 μg/min

Ogra, Pearay L., et al, eds. *Mucosal Immunology*. San Diego, CA: Academic Press, 1999. ISBN: 0125247257.

IgA2 is Enriched in Mucosal Secretions Relative to Peripheral Blood

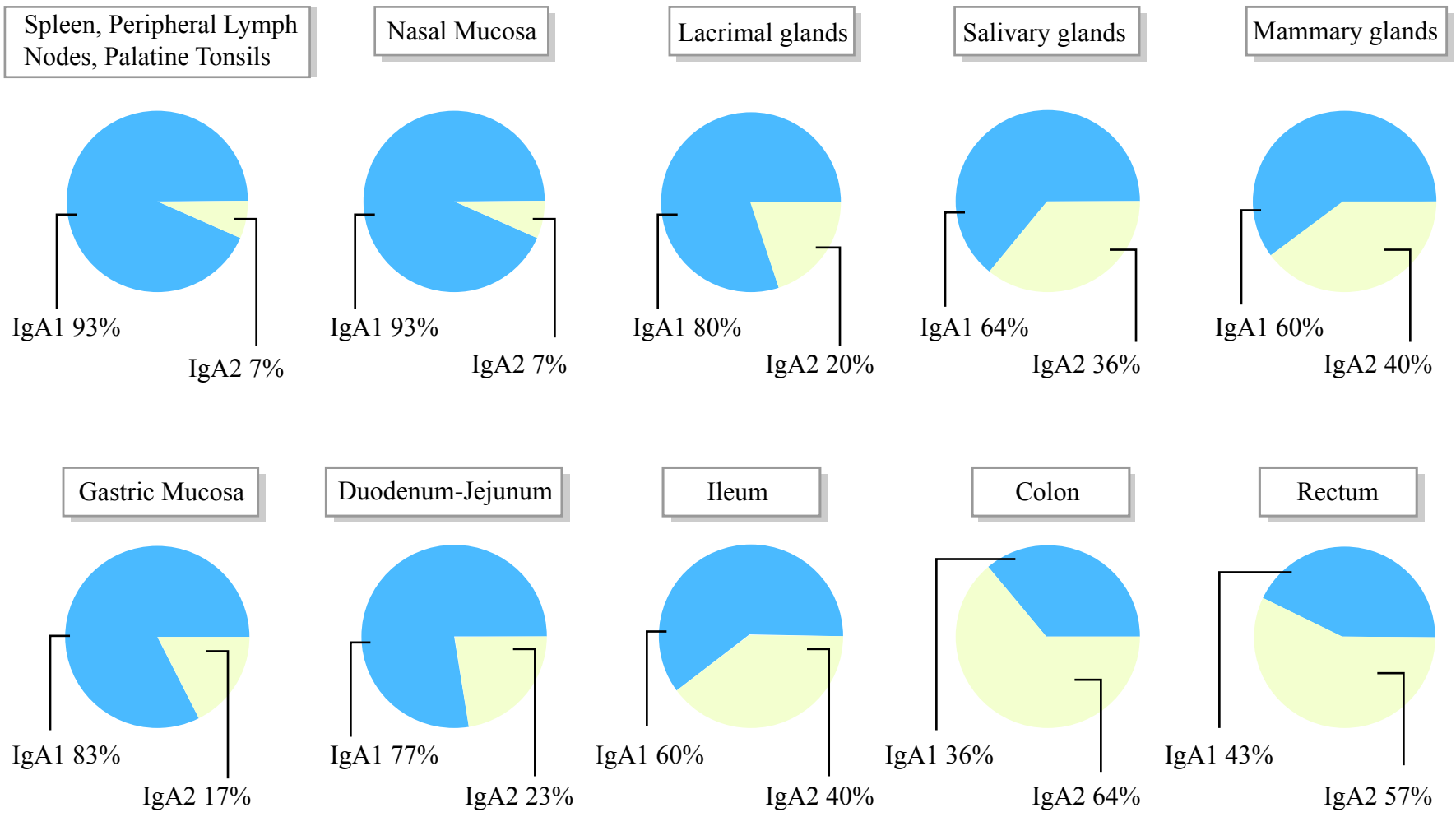


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

T Cell Independent IgA Secretion in the Intestine

(IgA-secreting cells, no. per 10^5 lymphocytes)

Mouse strain	Housing conditions	Intestinal lamina propria
C57BL/6	SPF	11,600 ± 1,500
$TCR^{\beta-/-\delta-/-}$	SPF	3,900 ± 1,600
C57BL/6 *nu/nu*	SPF	2,800 ± 1,700
$CD4^{-/-}$	Conventional	9,100 ± 930
$TNFR\text{-}1^{-/-}$	SPF	9,500 ± 540
aly/aly	SPF	<1
$LT\alpha^{-/-}$	Conventional	<10
C57BL/6	Germ-free	1,600 ± 860

Enrichment of dimeric (d)IgA in Mucosal Secretions Relative to Serum Which contains monomeric IgA

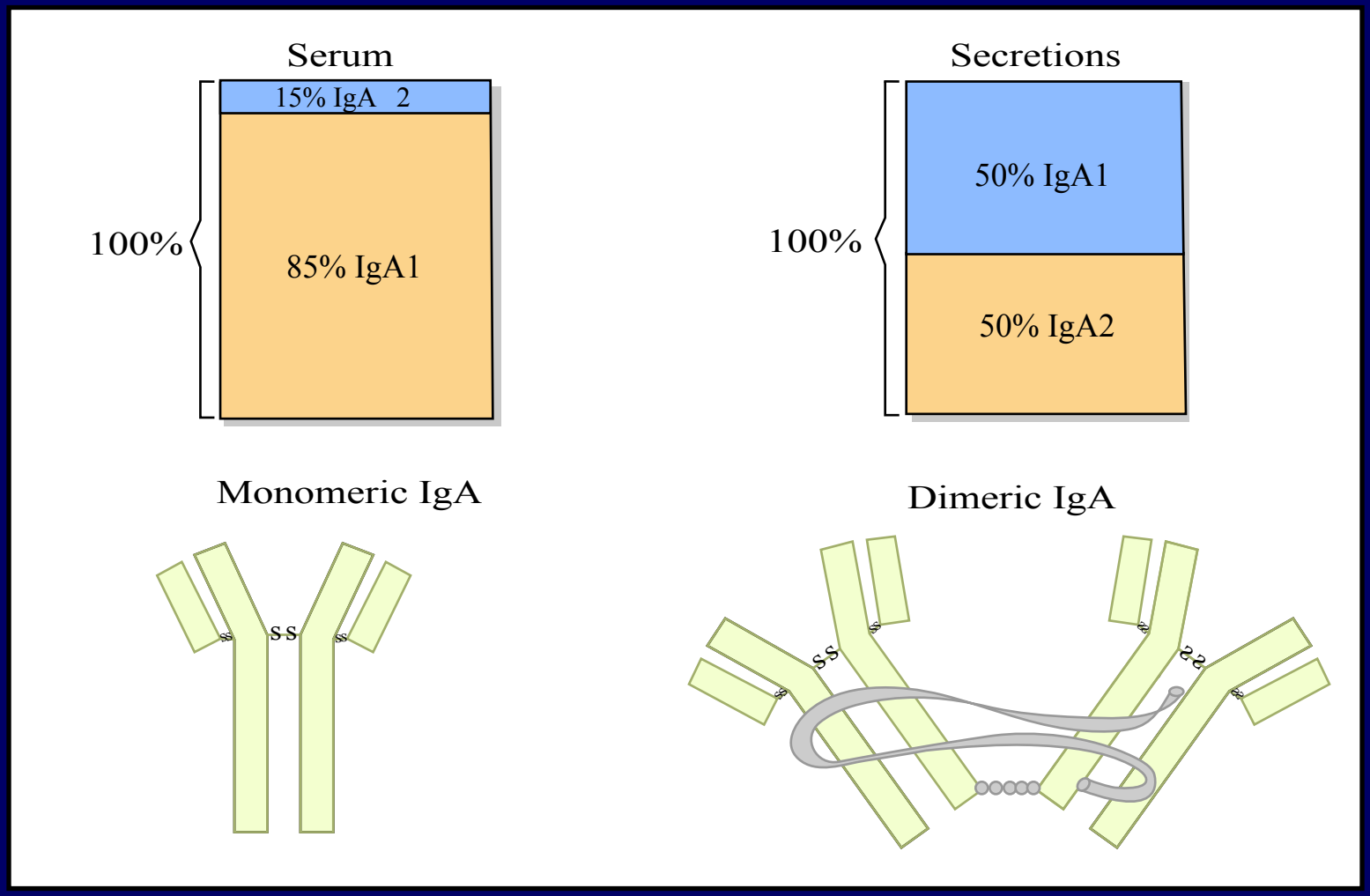


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

Secretory dIgA is formed by Association With J Chain and proteolytic fragment of pIgR or SC

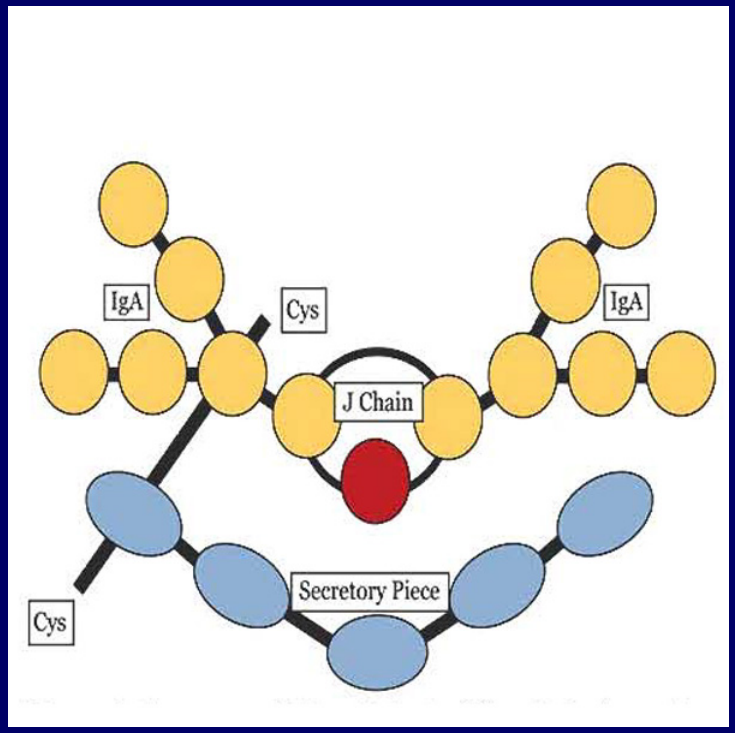


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

STRUCTURE OF POLYMERIC Ig RECEPTOR (pIgR)

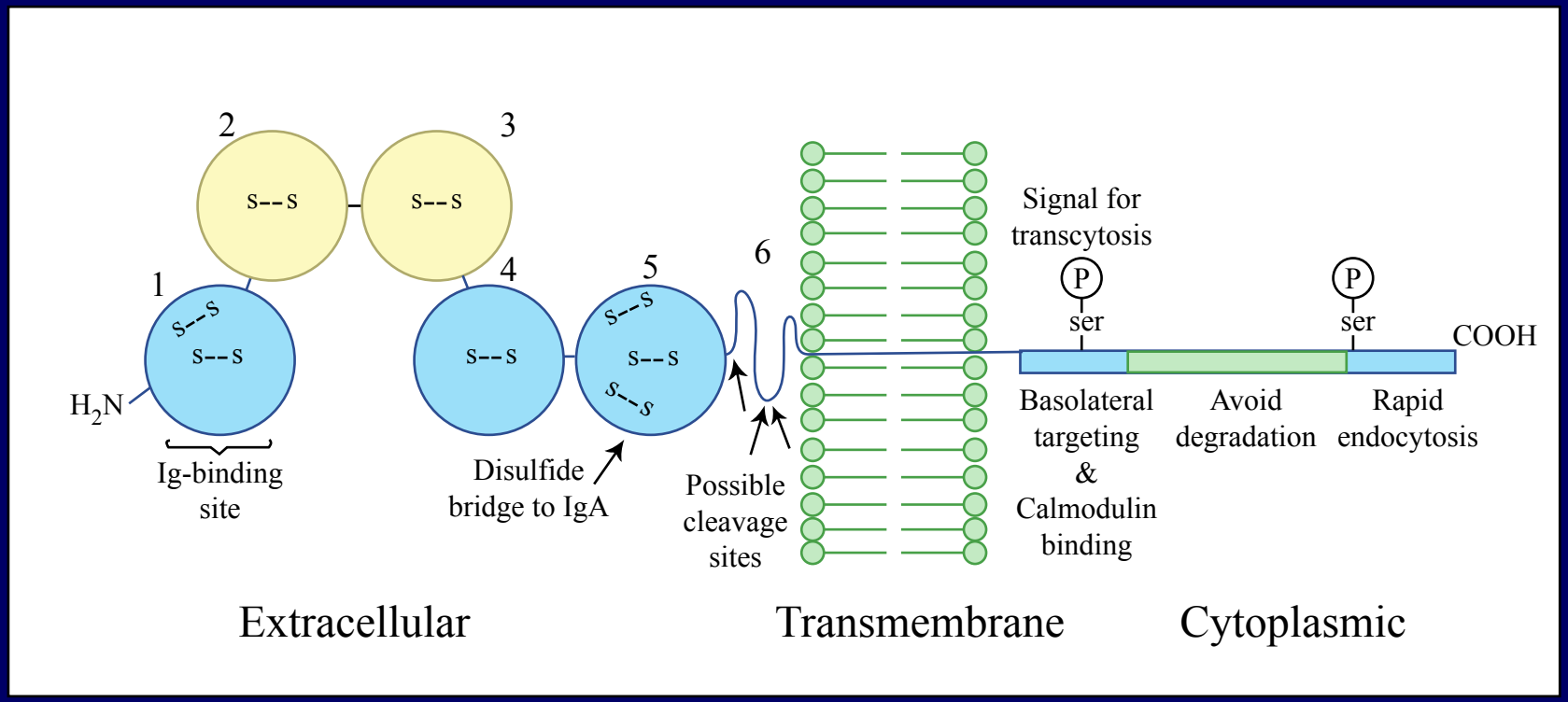


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

Intracellular Transport of pIgA via pIgR

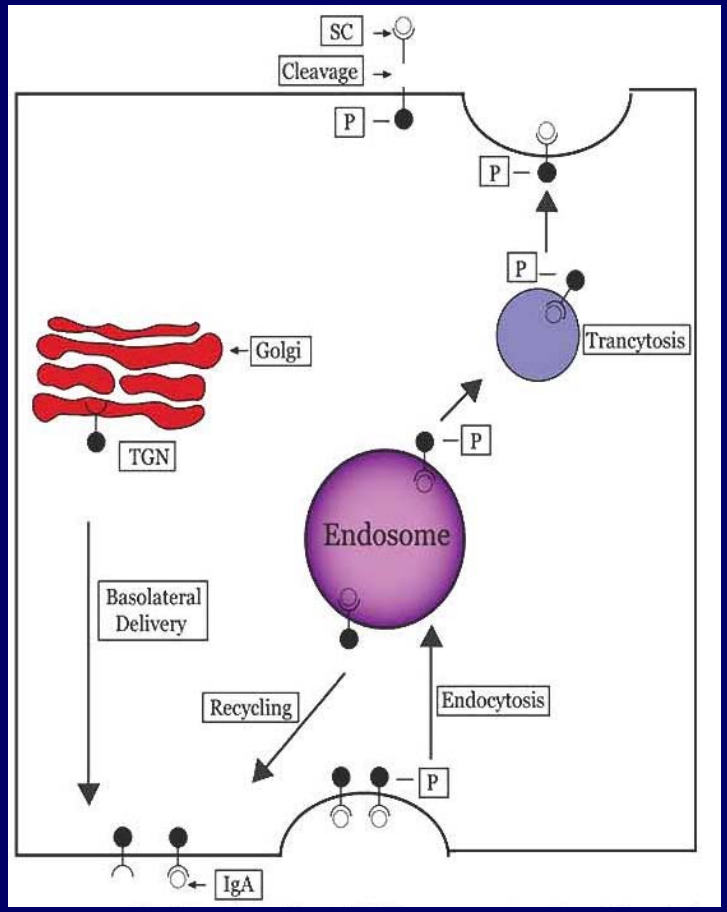


Illustration by MIT OCW. Adapted from illustrations by Per Brandtzaeg at Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) University of Oslo. See Brandtzaeg, P., et al. *Immunol. Rev*. 171 (l999): 45-87.

Quantification of IgA Production In Mucosal Secretions

IgA is a Component of Bile via Expression of pIgR in hepatocytes (rat) or bile duct epithelium (human)

Image removed due to copyright reasons.

IgA has complex effects in Mucosal Tissues Through interaction with Fcα-receptors

Image removed due to copyright reasons.

The Neonatal Fc Receptor for IgG, FcRn

- **MHC I-like structure/β_2m associated**

- **Closed cleft/no defined role in antigen presentation**

- **Binds overlapping region of IgG as Protein A**

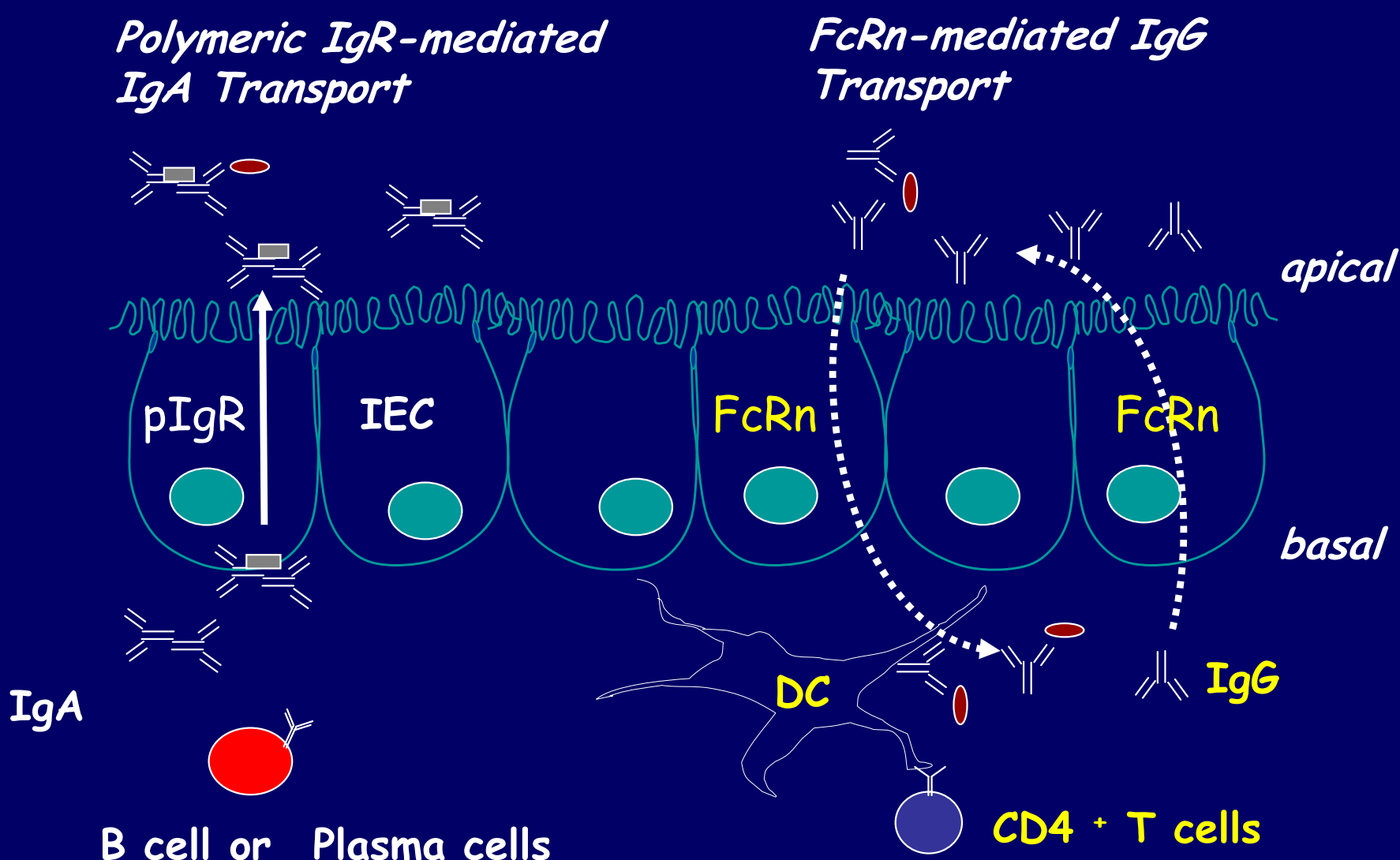
- **Binds IgG with a 2:1 stoichiometry**

- **Binds IgG at pH 6.0 (K_d = 10 nM) but negligibly at physiologic pH 7.4**

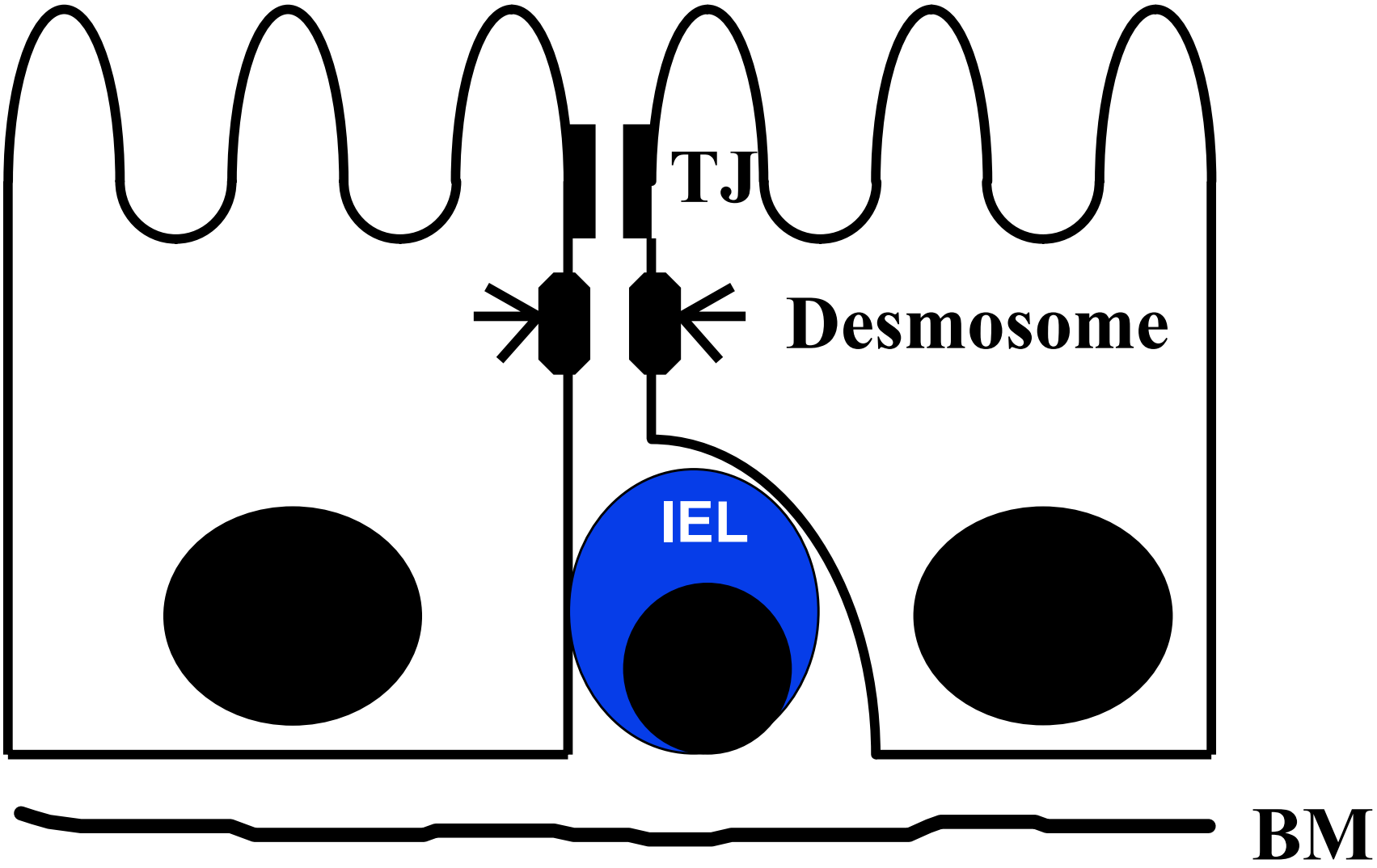
Figure removed due to copyright reasons. Please see:

Burmeister, W. P., et al. "Crystal structure at 2.2 A resolution of the MHC-related neonatal Fc receptor." *Nature* 372 (1994): 336-43.

FcRn Plays a Role in the Uptake of Lumenal Antigens



Intrinsic Barrier Function of Epithelium



Association of Dendritic Cells with Mucosal Epithelium

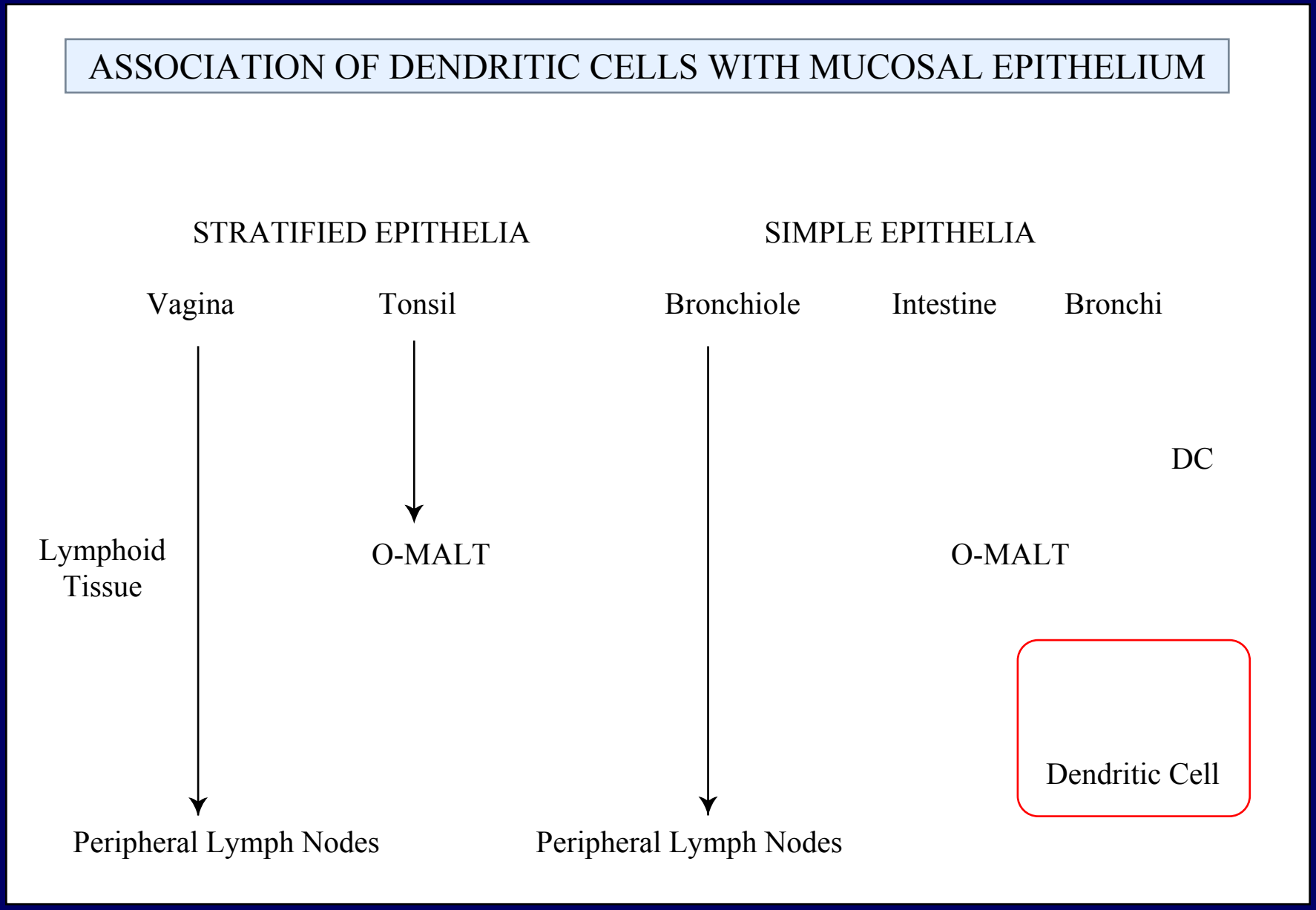
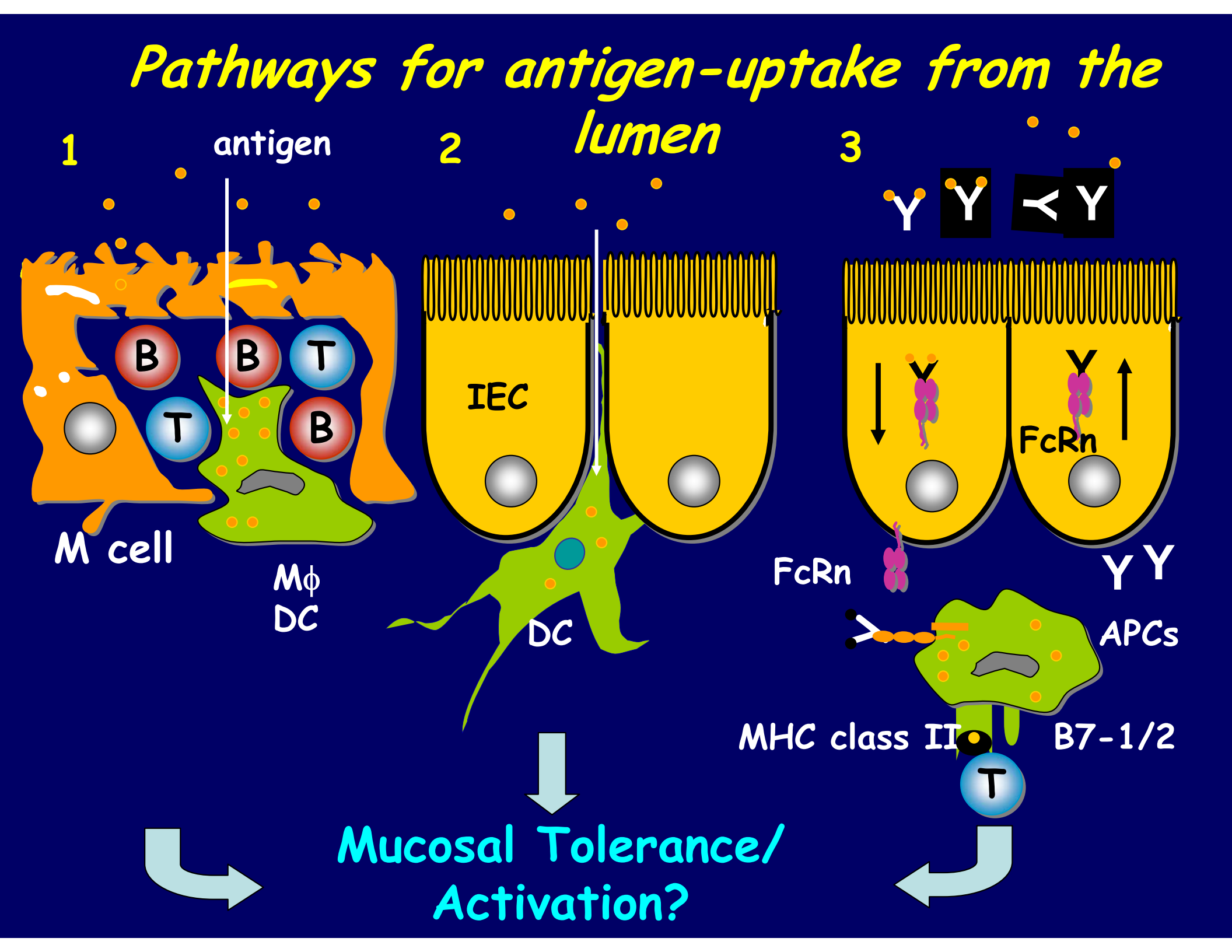


Figure by MIT OCW.


Pathways for antigen-uptake from the lumen
1
antigen
2
3
B
B
T
T
B
M cell
Mϕ
DC
IEC
DC
FcRn
FcRn
APCs
MHC class II
B7-1/2
T
Mucosal Tolerance/
Activation?

Subtypes of Epithelial Cells in Intestinal Mucosa

Image removed due to copyright reasons.

M (MICROVILLOUS FOLD) CELLS

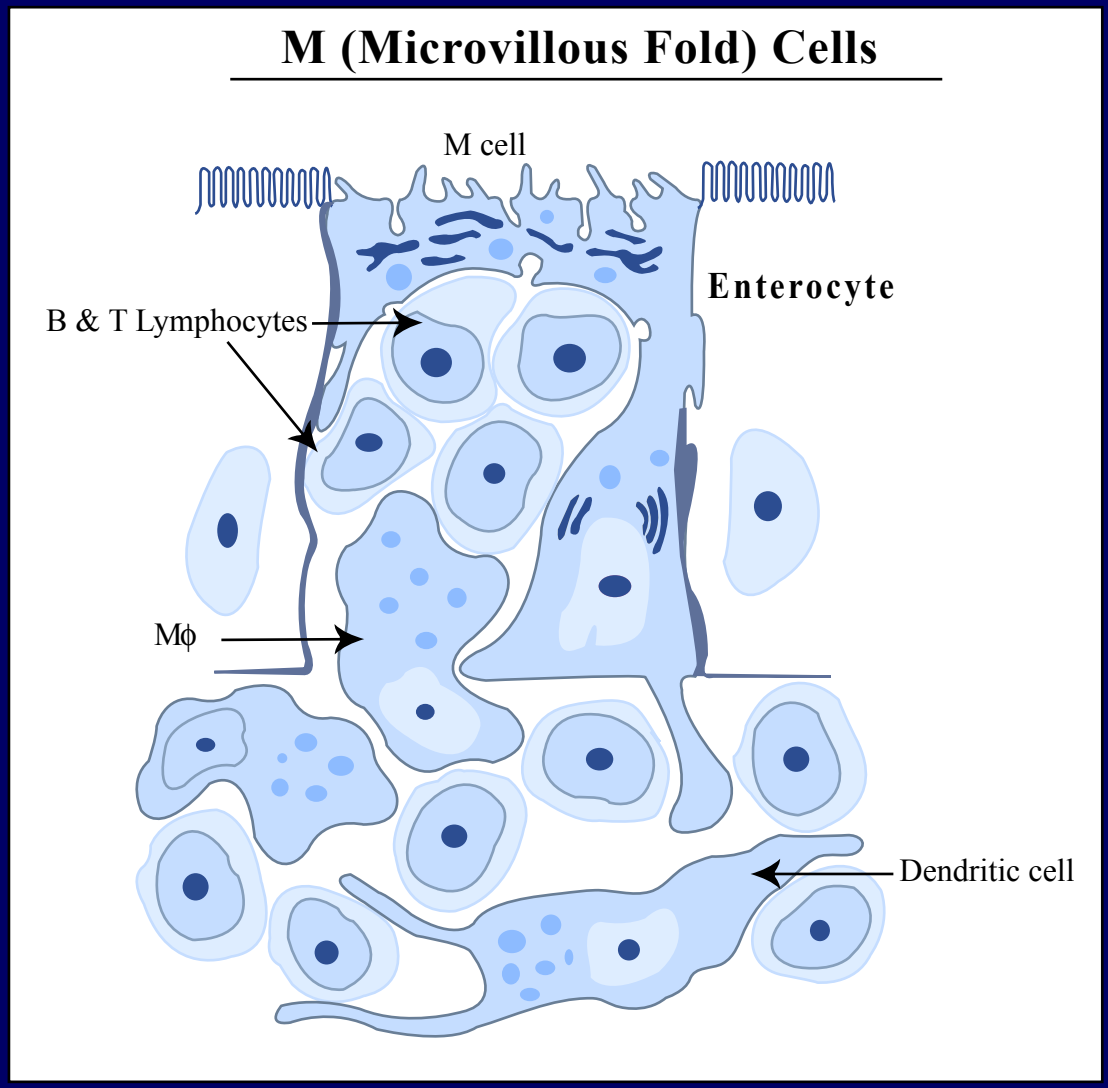
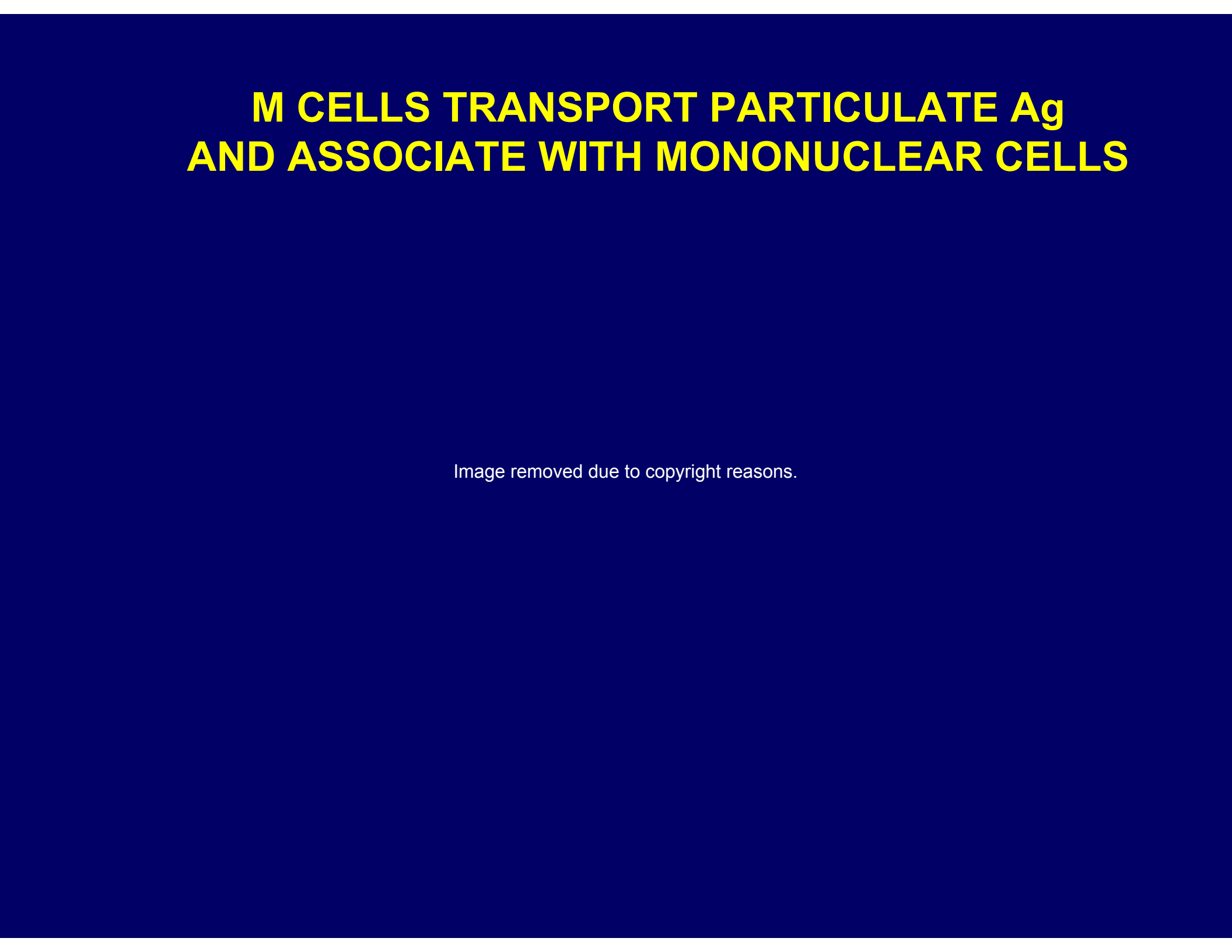


Image by MIT OCW.

M CELLS TRANSPORT PARTICULATE Ag AND ASSOCIATE WITH MONONUCLEAR CELLS



Absorptive epithelial cells take up Ag by Receptor And non-Receptor mediated mechansims sorting Ag to either a degradative or absorptive fate

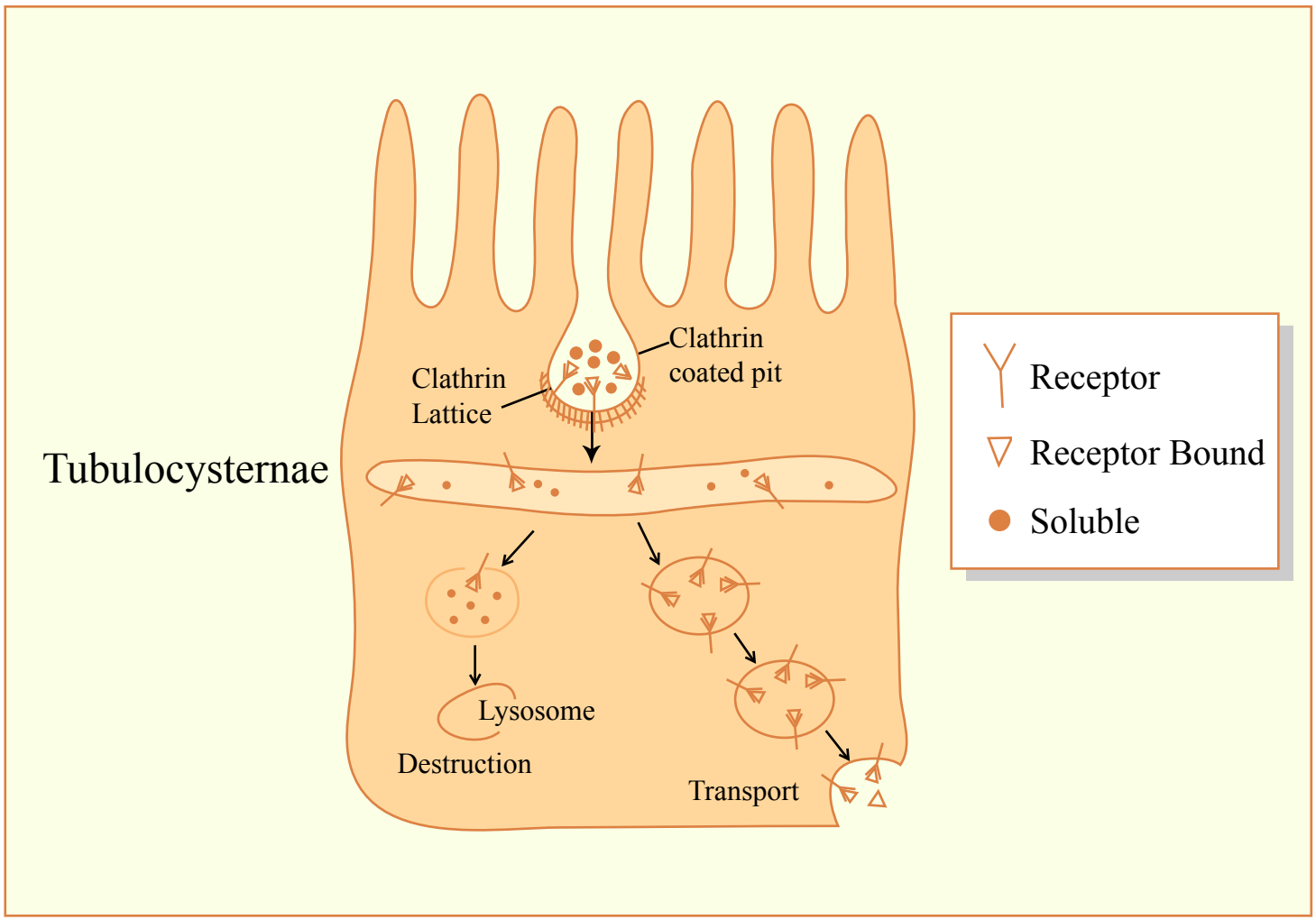
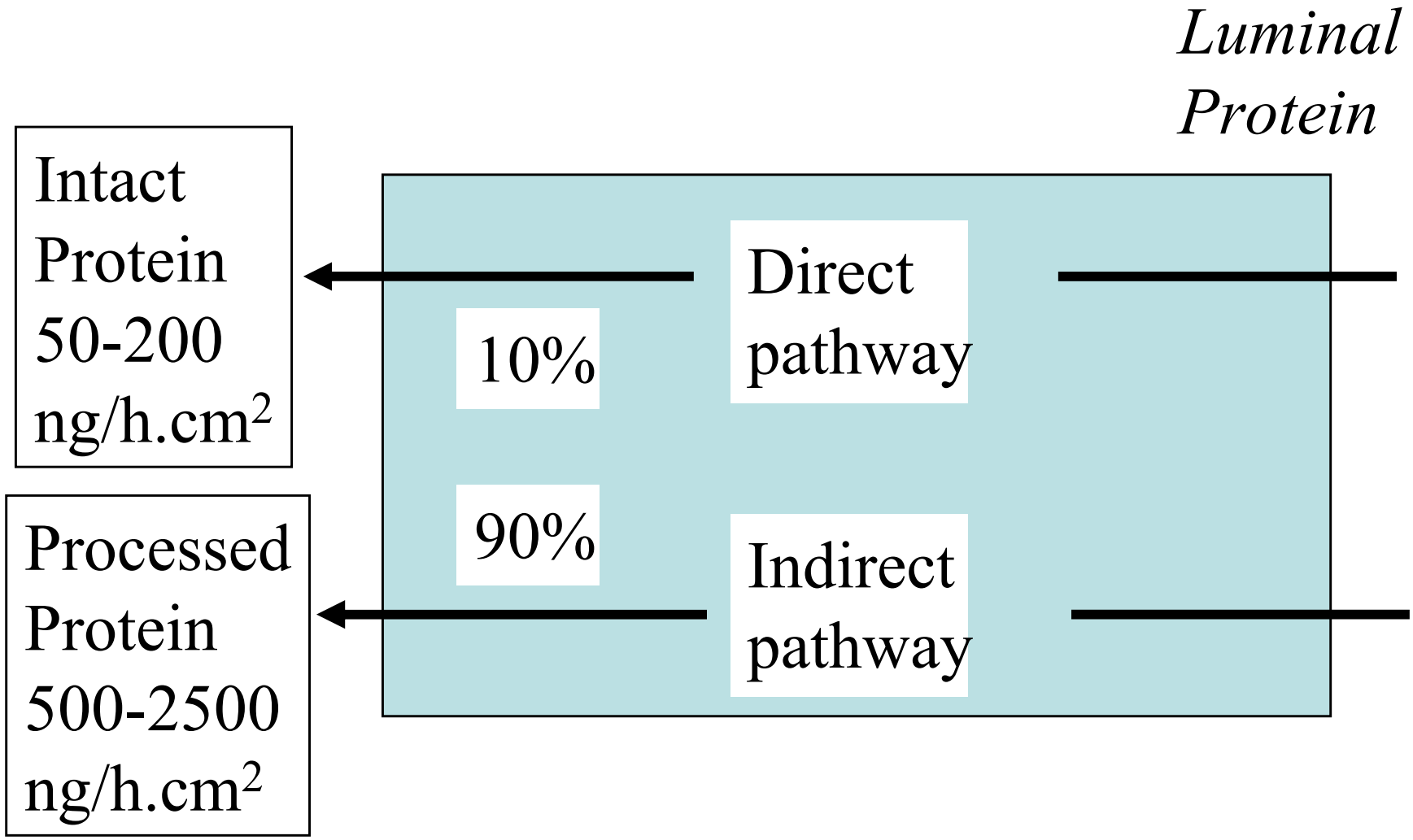


Image by MIT OCW.

Epithelial Transport of Macromolecules



adapted from Martine Heymann

Absorbed antigens may enter an antigen presenting pathway such as that associated with MHC class II

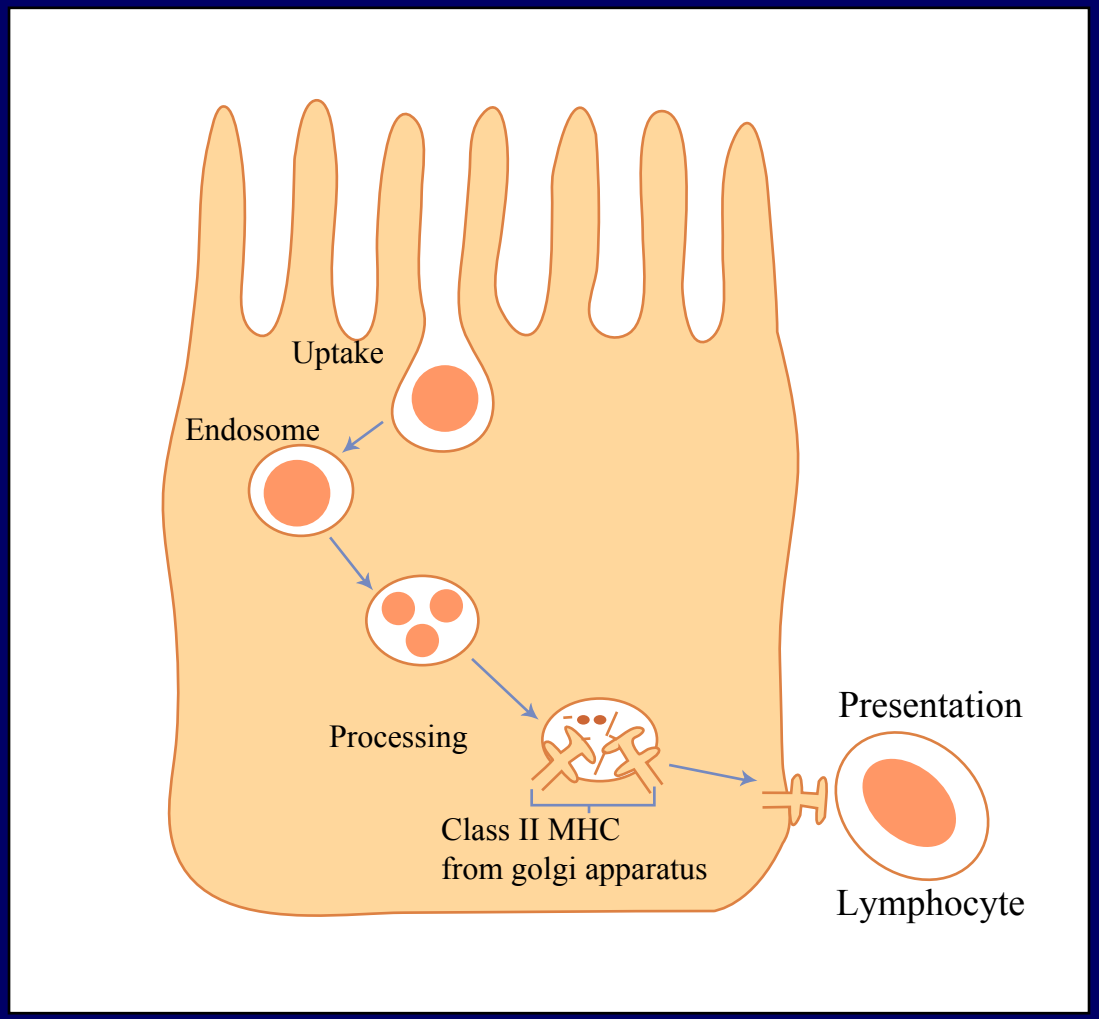


Image by MIT OCW.

THE IEC AS AN APC

- Ability to acquire and/or transport antigen
- Ability to process and/or present antigen
- Ability to provide costimulatory and/or regulatory second signals to T cells

Molecules expressed by IECs possibly associated with antigen presentation

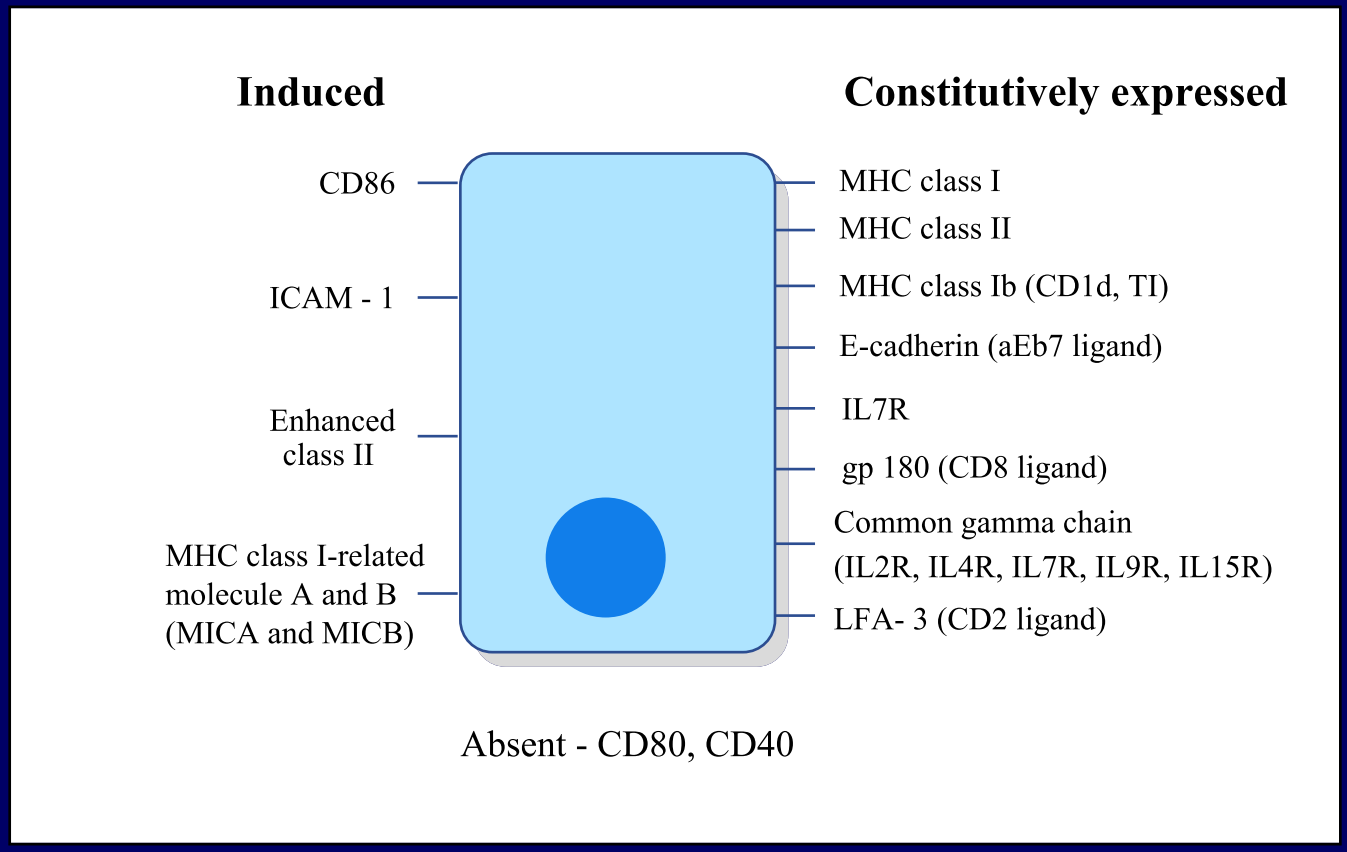
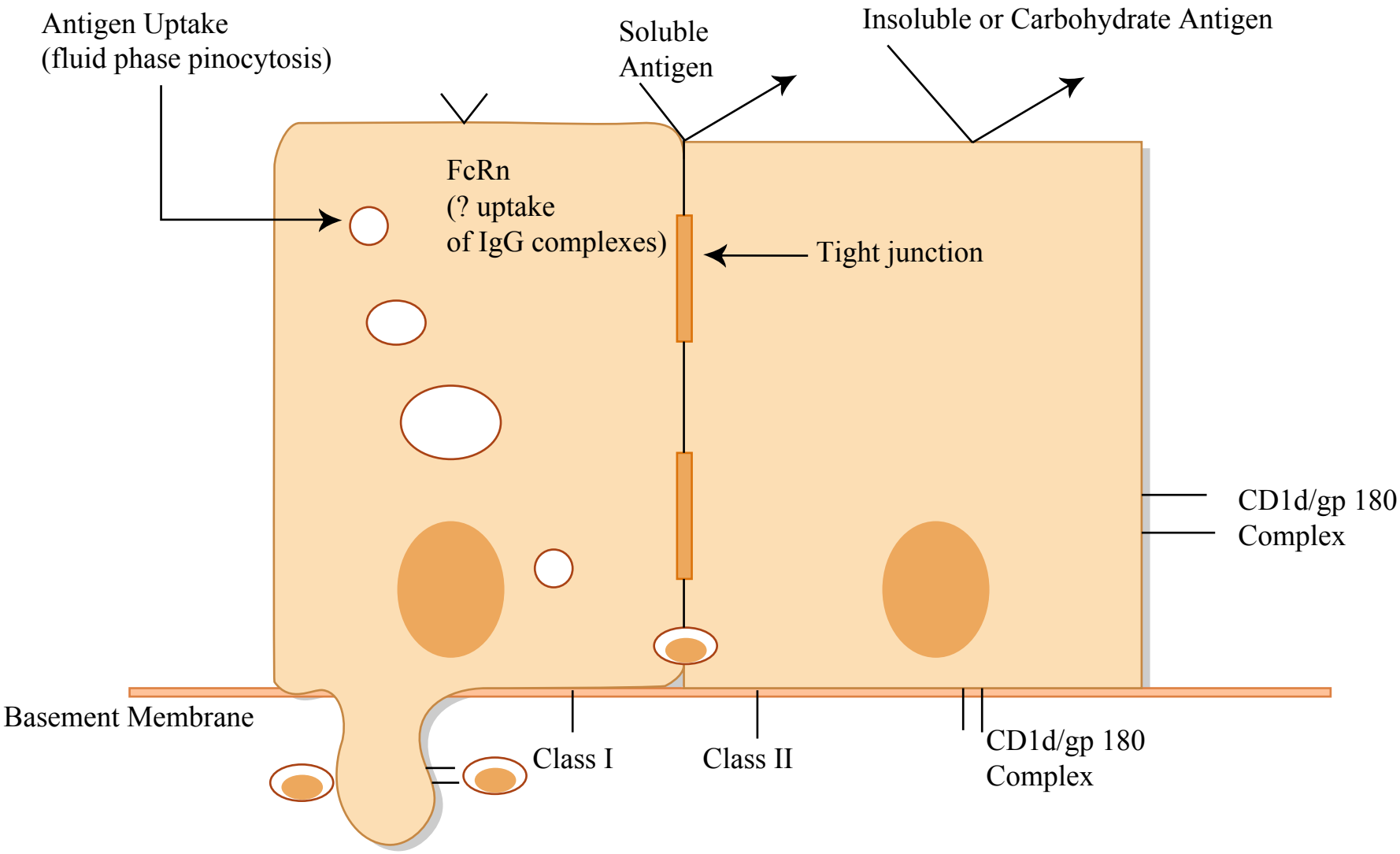


Image by MIT OCW.

Antigen Presentation by Absorptive Epithelial Cell



IEC projection through the basement membrane expressing class Ib, class I, or class II MHC

AEC secrete and respond to a wide variety of cytokines and chemokines

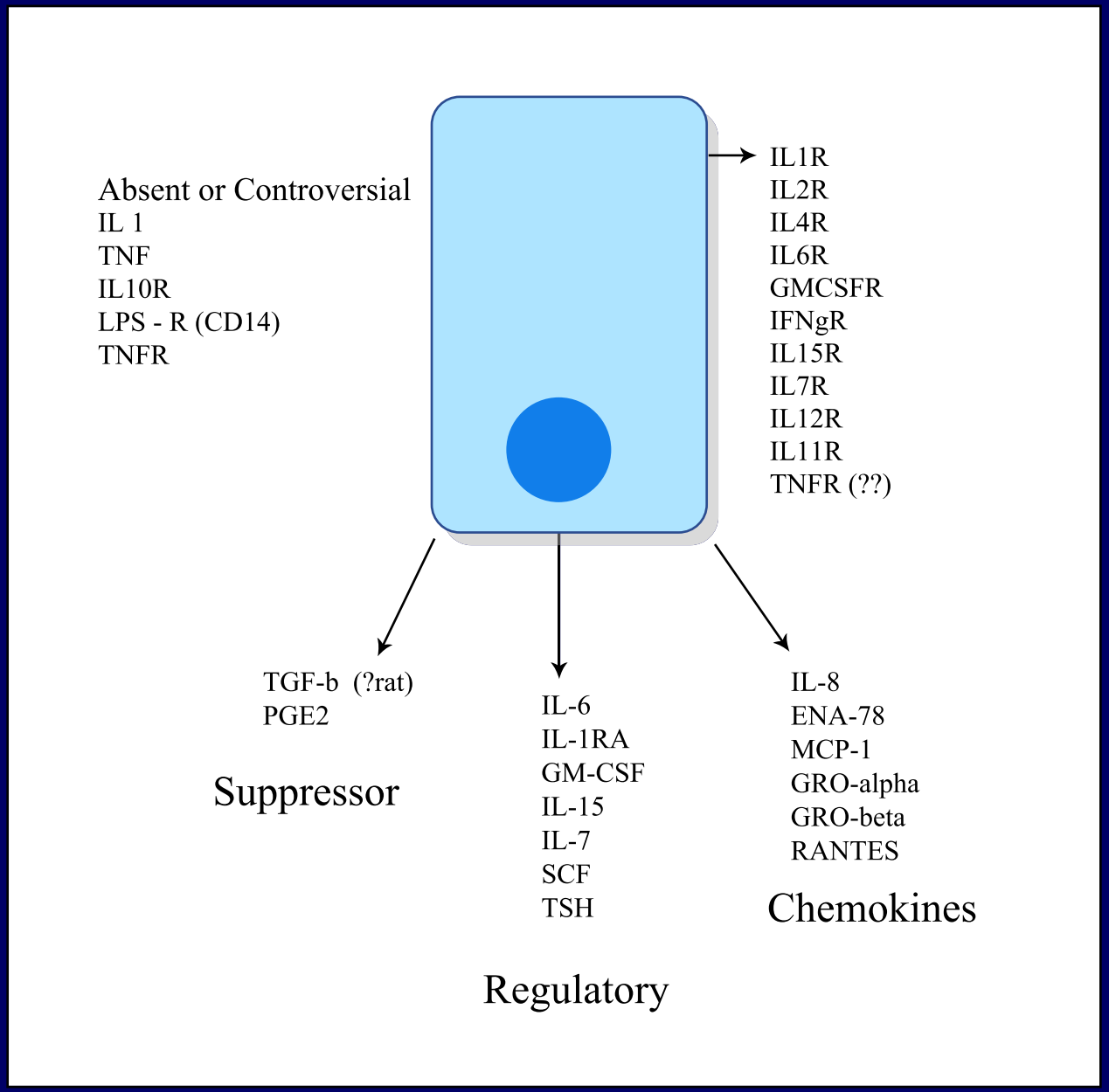


Image by MIT OCW.

AEC Respond to cytokines and inflammatory mediators With increased chloride and mucus secretion and paracellular Permeability resulting in diarrhea clinically

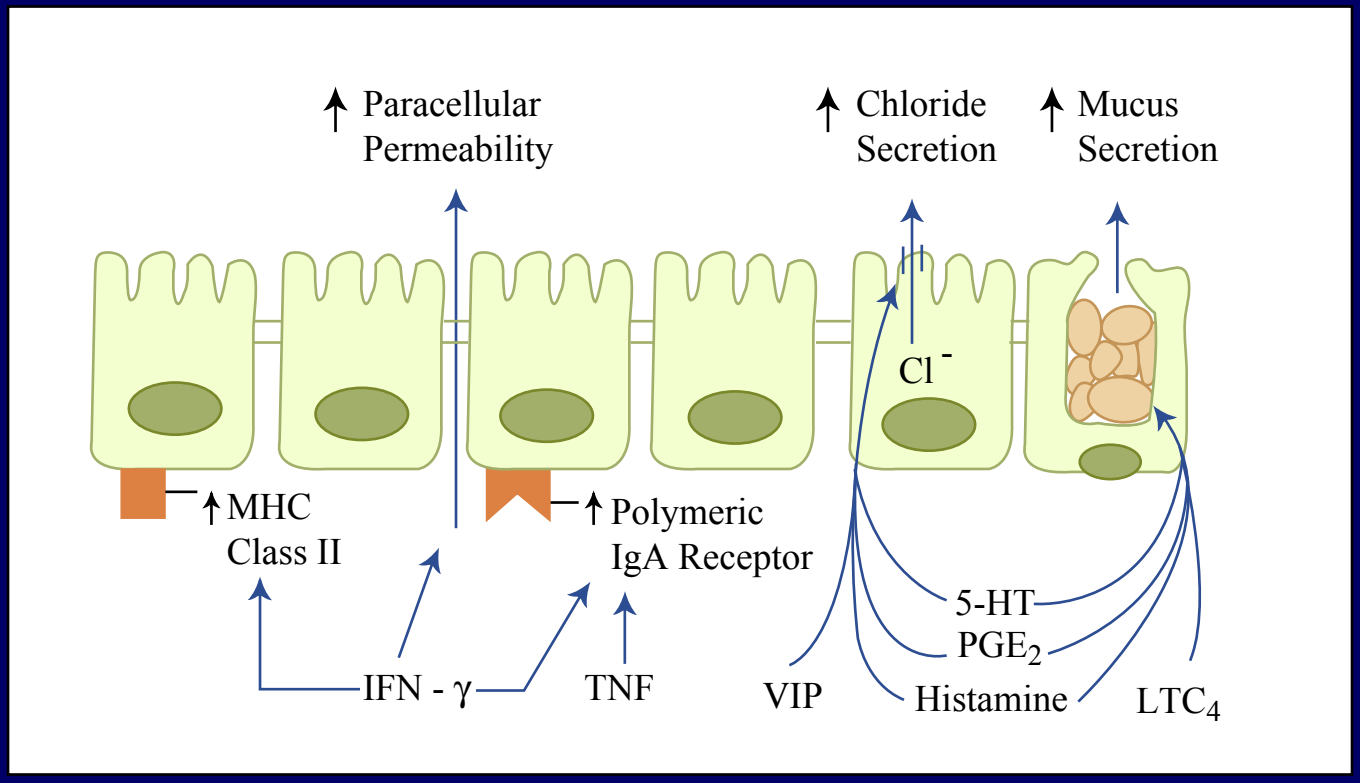
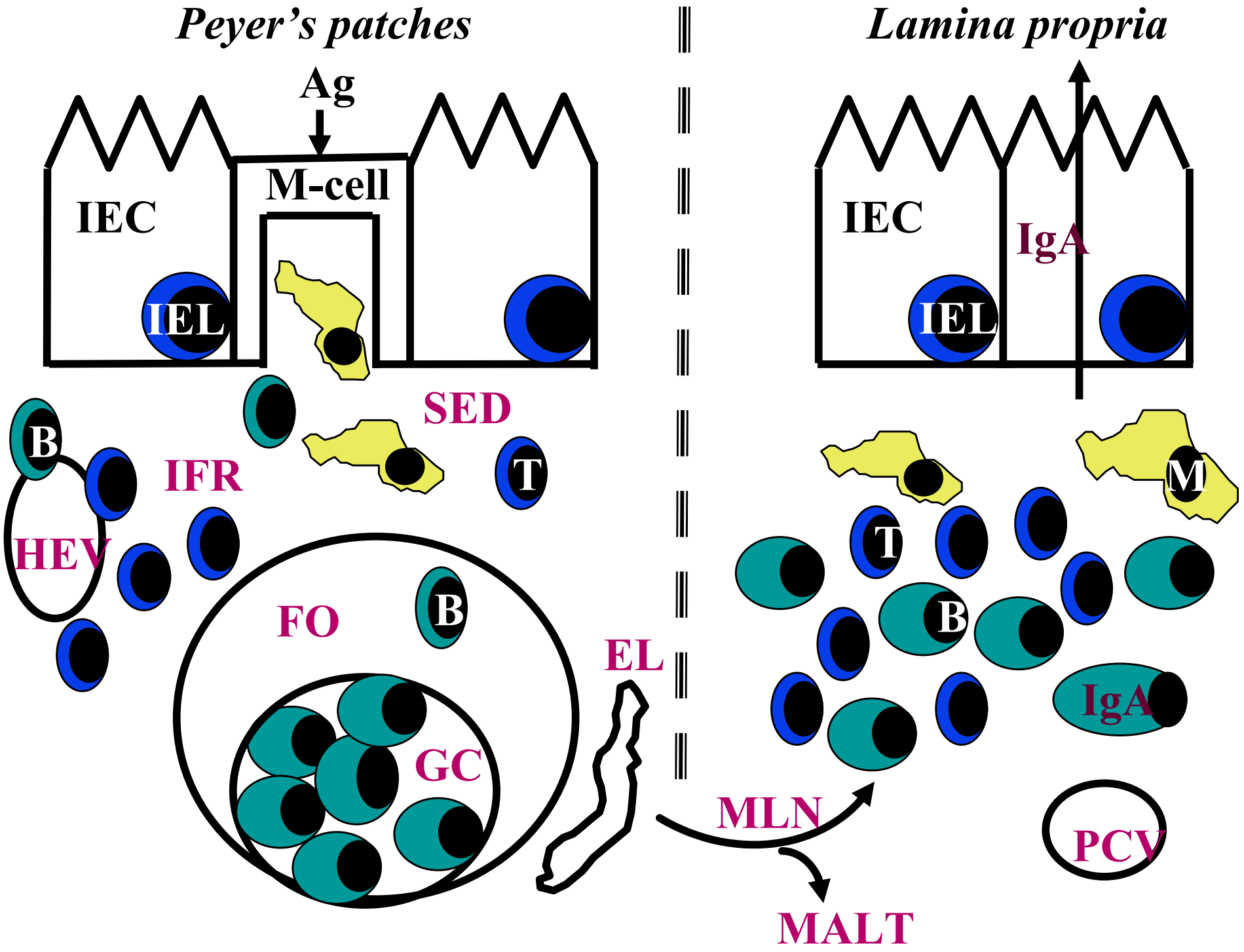
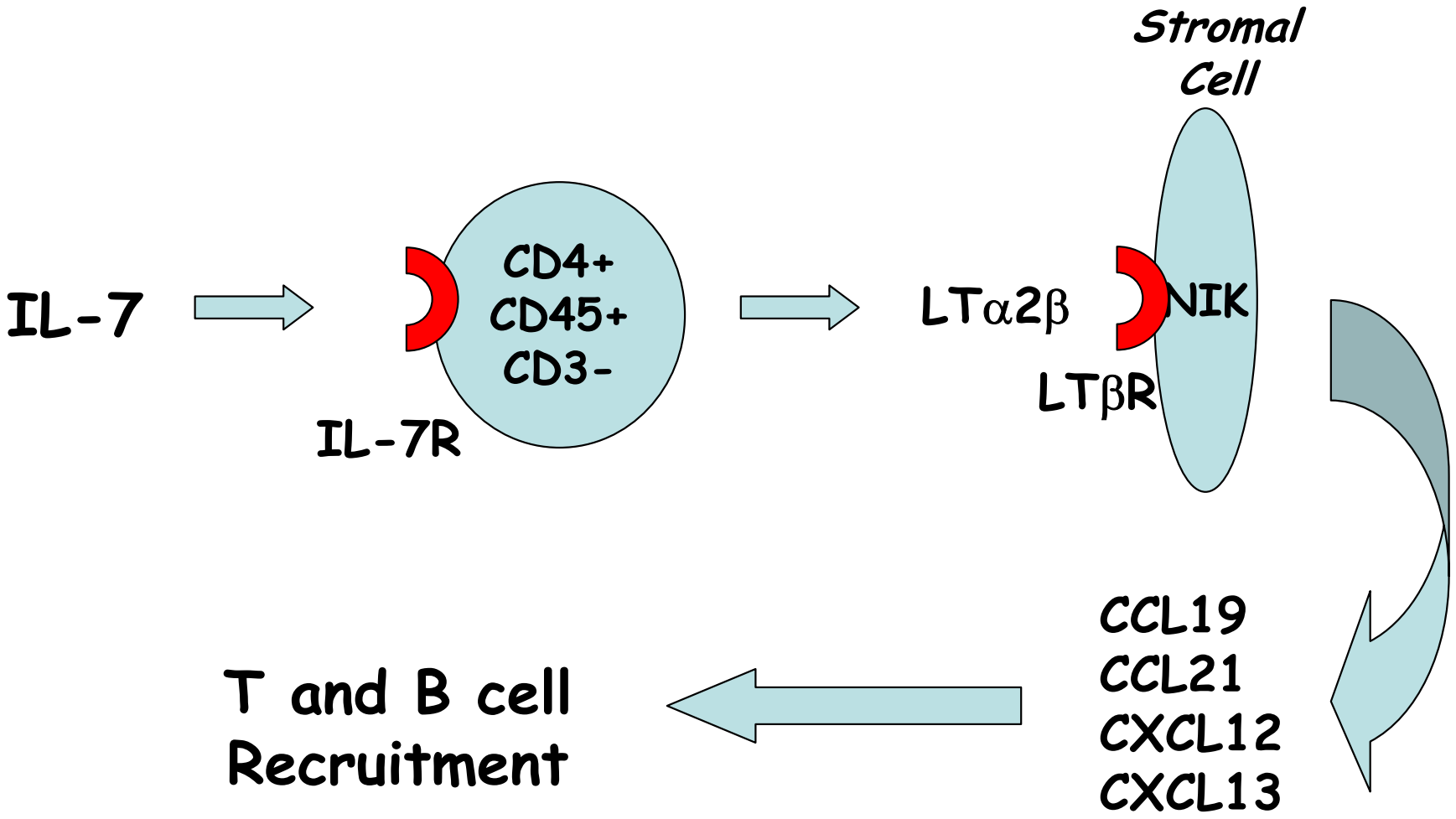


Figure by MIT OCW. After Yamada, *Atlas of Gastroenterology*, 2003.


Peyer's patches
Lamina propria
Ag
M-cell
IEC
IEL
IEC
IgA
IEL
SED
B
IFR
T
HEV
FO
B
EL
T
M
B
IgA
GC
MLN
PCV
MALT

Peyer's Patch Development



Concept of the Common MALT

Image removed due to copyright reasons.

Heirarchal Linkage of MALT Component Tissues

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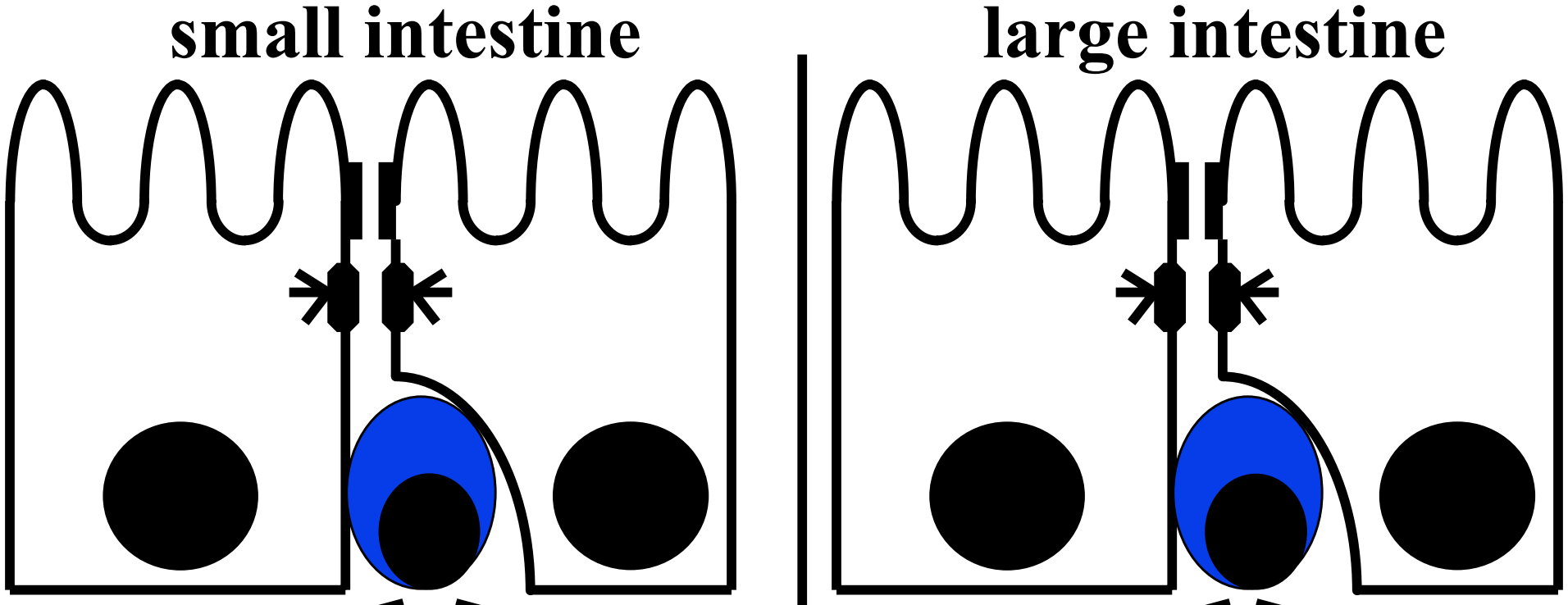
Molecular interactions during lymphocyte trafficking

Lymphocytes		Endothelial Cells		Contact → Rolling (Activation) → Arrest → Diapedesis
Io α4β1 L-selectin^{++} Io α4β7 LFA-1^{++}	Naive B or T cells	Peyer's patch	MAdCAM CHO MAdCAM-1 ICAM's	L-selectin, α4β7, LFA-1
α4β7^{hi} α4β1^{Io} L-selectin$^{\pm}$	Gut homing blasts or memory cells	Lamina propria (or PP)	MAdCAM-1 ICAM's?	α4β7, LFA-1?
Io α4β1 L-selectin^{++} Io α4β7 LFA-1^{++}	Naive B or T cells	Peripheral lymph node	PNAd ??VAP1 ICAM's	L-selectin, ??, LFA-1
α4β1^{++} CLA^{++} β7− LFA-1^{++} L-selectin^{+}	Skin homing memory cells	Skin	E-selectin VCAM-1 ICAM's	CLA, α4β1, LFA-1

Figure by MIT OCW. After Kiyono, *Essentials of Mucosal Immunology*.

Intraepithelial Lymphocyte



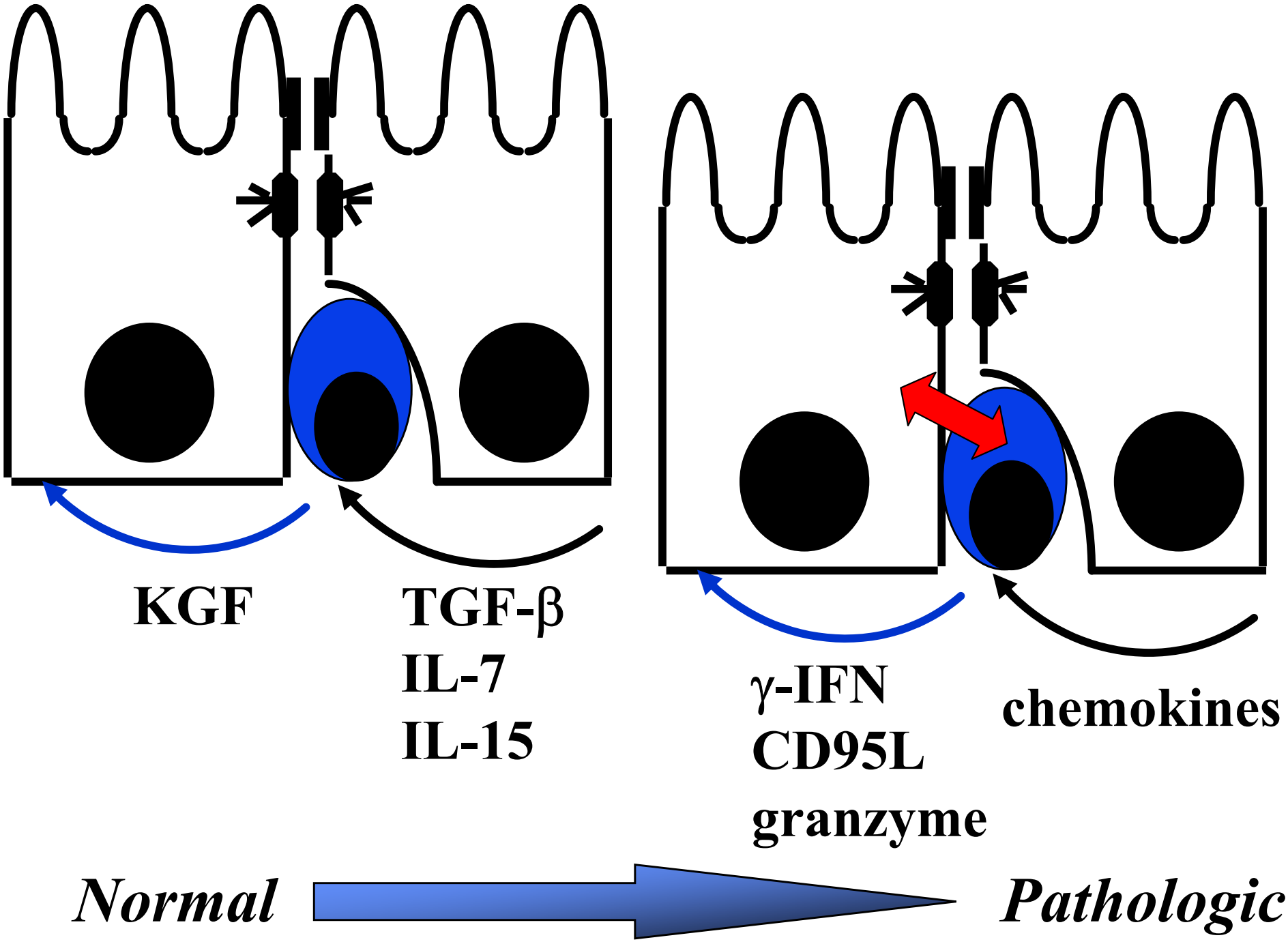
TCRαβ+ CD8+
45RO+ αEβ7+
CD69+ CD25-
CD28- CD101+
BY-55+

1/3 CD8+
1/3 CD4+
1/3 CD4-CD8-

TCRγδ < TCRγδ

Potential Functions of iIELs

	Mouse	*Human*
Oral Tolerance	TCR$\gamma\delta$	????
Cytotoxicity	TCR$\alpha\beta$	TCR$\alpha\beta$ & $\gamma\delta$
Regulation of B cell immunoglobulin production	TCR$\gamma\delta$	????
Anti-microbial immunity	TCR$\alpha\beta$	????


KGF
TGF-β
IL-7
IL-15
γ-IFN
CD95L
granzyme
chemokines
Normal
Pathologic

Mast Cells: Stimuli and Mediators

Stimuli

Allergen-IgE

T cell factor
(antigen specific)

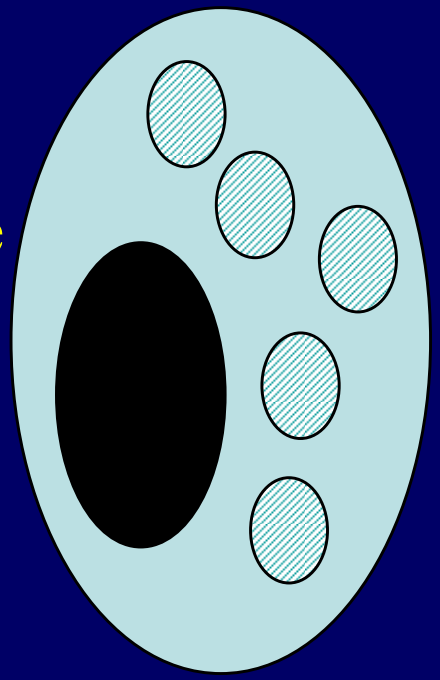
Polypeptide histamine releasing factors

Neuropeptides

Cytokines (e.g. SCF, IL-8)

Complement anaphylatoxins

Cationic agents



Mediators

PREFORMED/STORED

Histamine

Proteoglycans

Proteinases

Chemotactic factors

NEWLY SYNTHESIZED

PGD2,LTC4

PAF, NO

CYTOKINES

IL3,4,5,8,10,13,

TGF-β,TNF-α

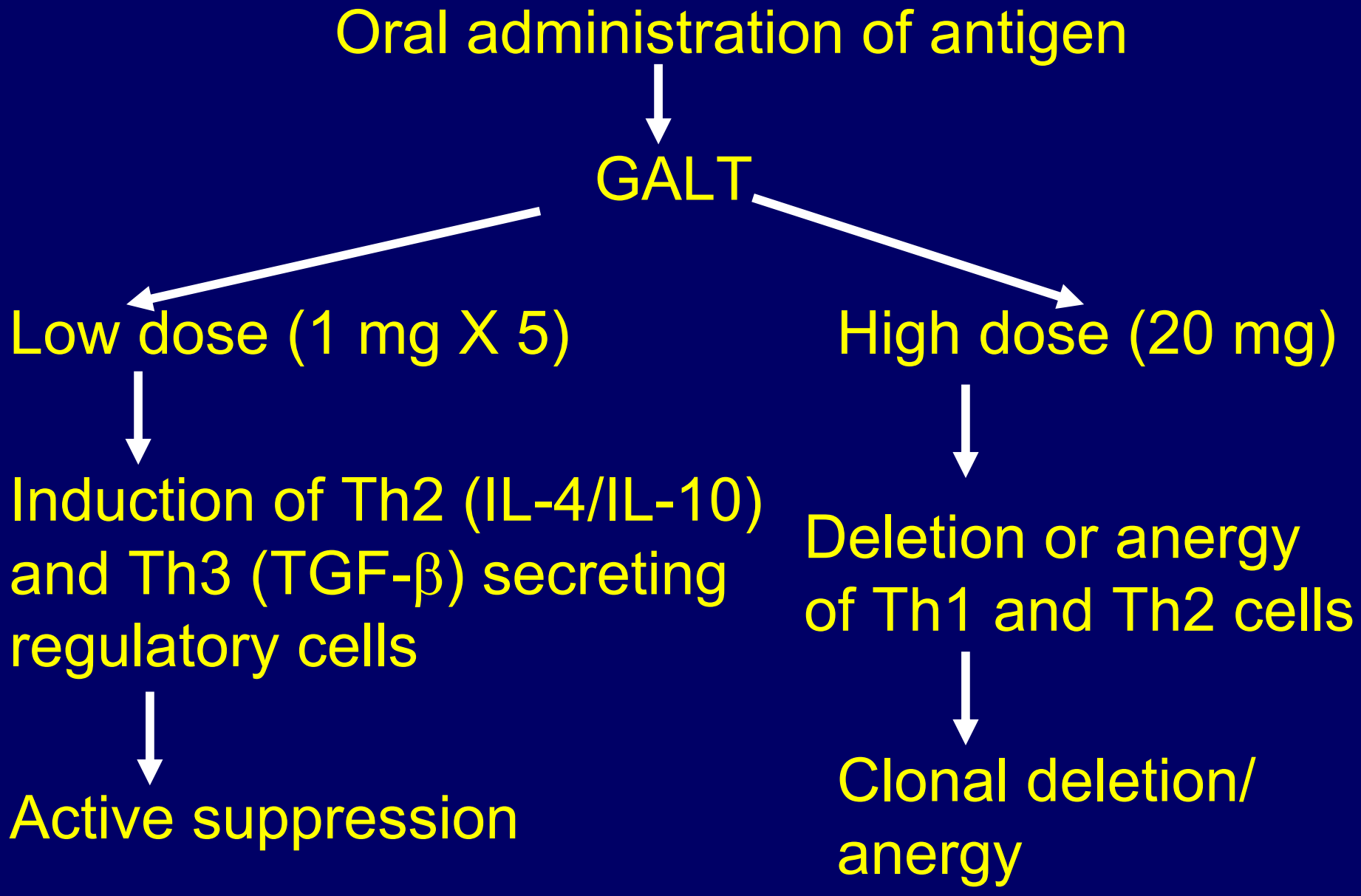
Concept of Oral Tolerance

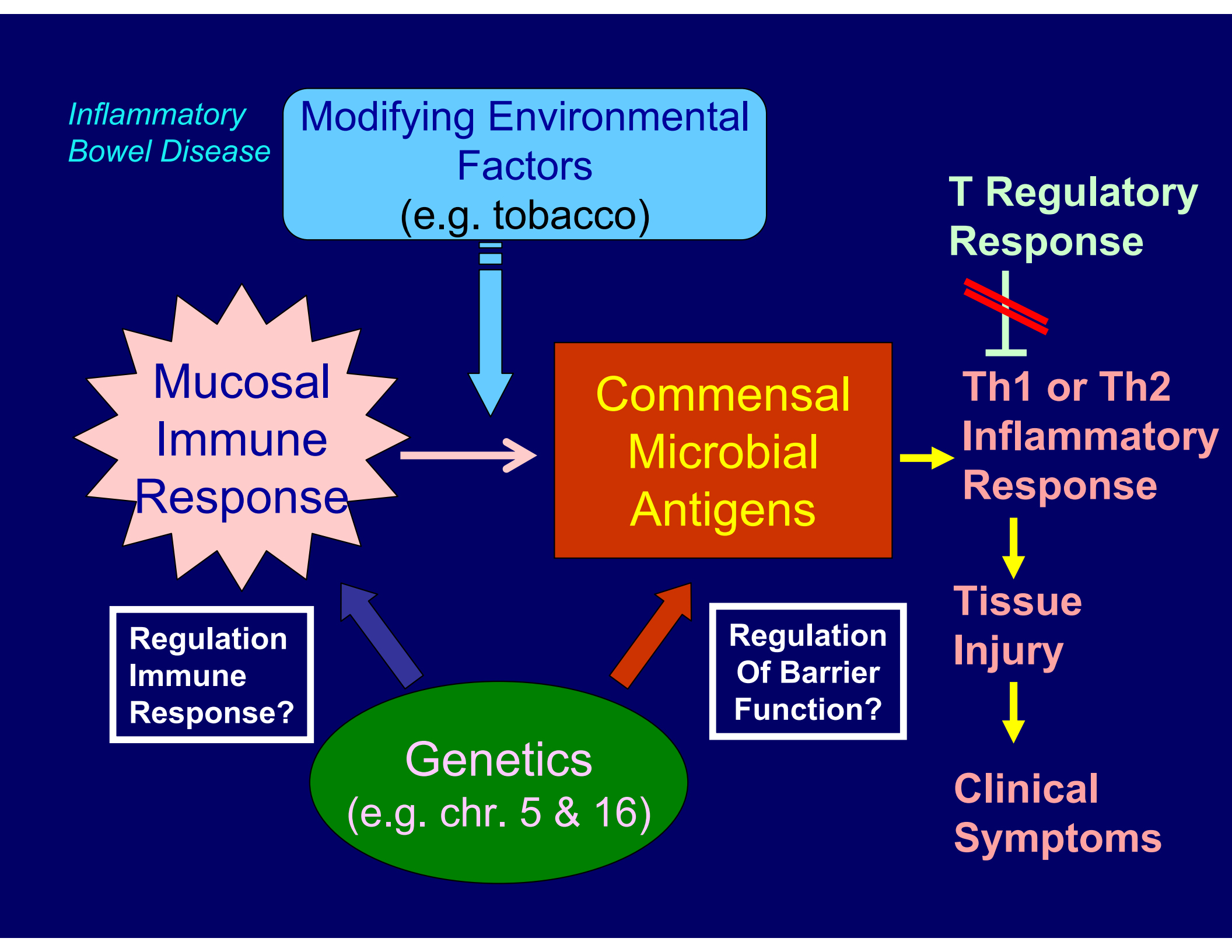
No oral feeding → Immunize subcutaneous → T cells from regional lymph nodes respond

Feed oral antigen → Immunize subcutaneous → 1. T cells from regional lymph nodes do not respond.
2. Specific IgA is measurable in gut.

from Challacombe and Tomasi, J Exp Med, 1980

Mechanisms of Oral Tolerance




Inflammatory Bowel Disease
Modifying Environmental Factors (e.g. tobacco)
T Regulatory Response
Mucosal Immune Response
Commensal Microbial Antigens
Th1 or Th2 Inflammatory Response
Tissue Injury
Clinical Symptoms
Regulation Immune Response?
Regulation Of Barrier Function?
Genetics (e.g. chr. 5 & 16)

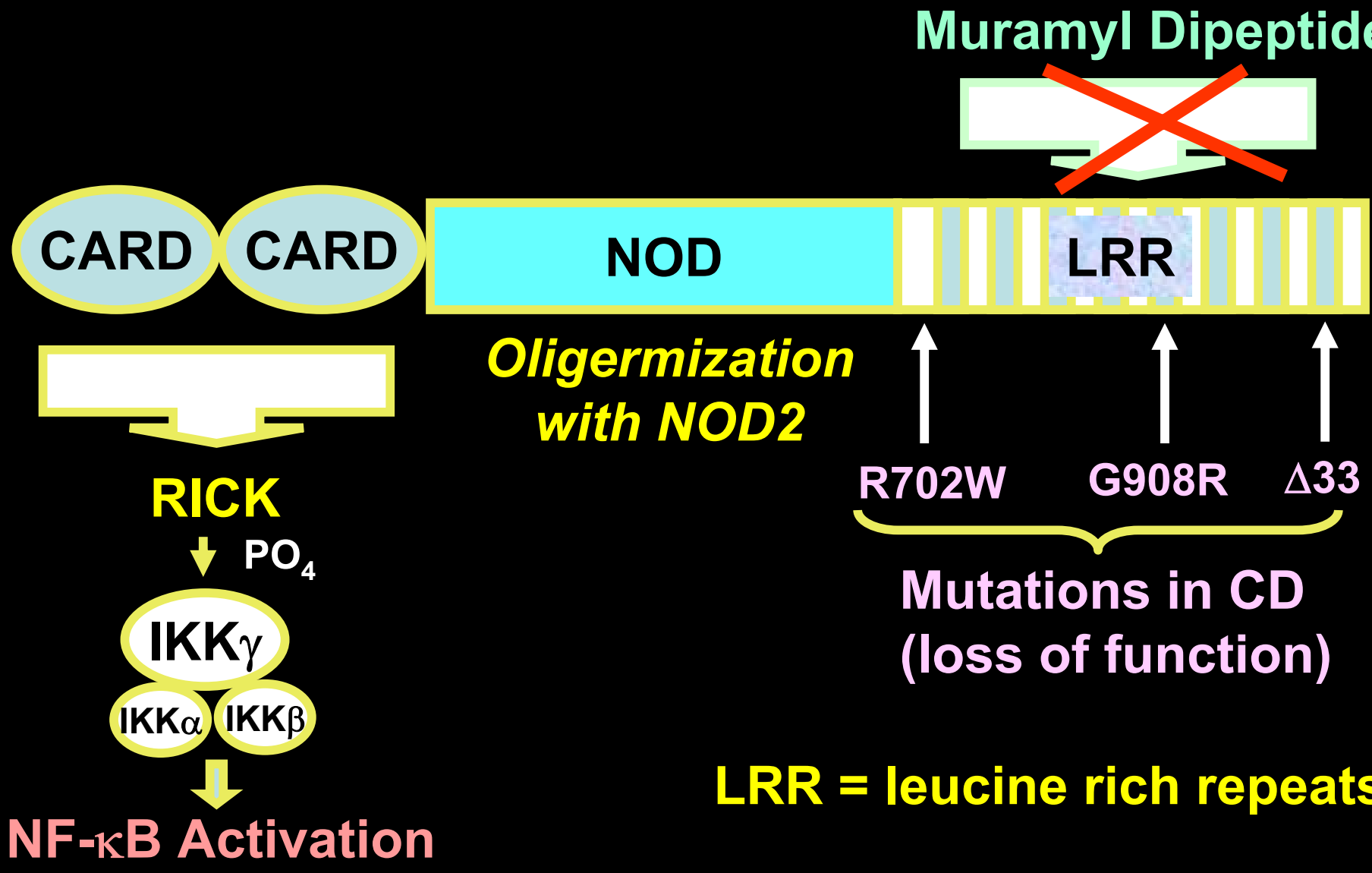
Summary of IBD Susceptibility Loci

Locus	*Chromosomal Region*	*Comments*	*Variation identified*
IBD1	16q12	CD-specific CARD 15	YES
IBD2	12p	Possibly UC specific	No
IBD3	6p	IBD HLA region	Potential HLA alleles
IBD4	14q11-12	Possibly CD specific	No
IBD5	5q31	OCTN§	YES
IBD6	19p13	IBD	No
IBD7	1p36	IBD	No
IBD8	10q30	Scaffold protein	YES

§ OCTN: organic cation transporter

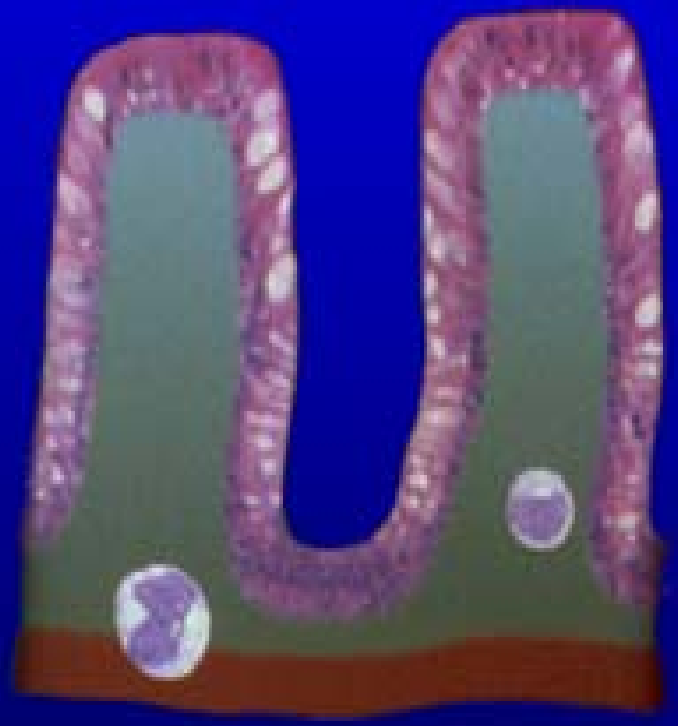
adapted from Rioux J 2003

IBD-1: Nucleotide binding oligermization Domain (NOD)2 or CARD15: Intracellular Bacterial Sensor



Luminal Bacteria Stimulate Colitis

Germ Free Housing → Addition of Bacteria



Mice

IL-2 $^{-/-}$

IL-10 $^{-/-}$

CD45RB^{hi} →

SCID

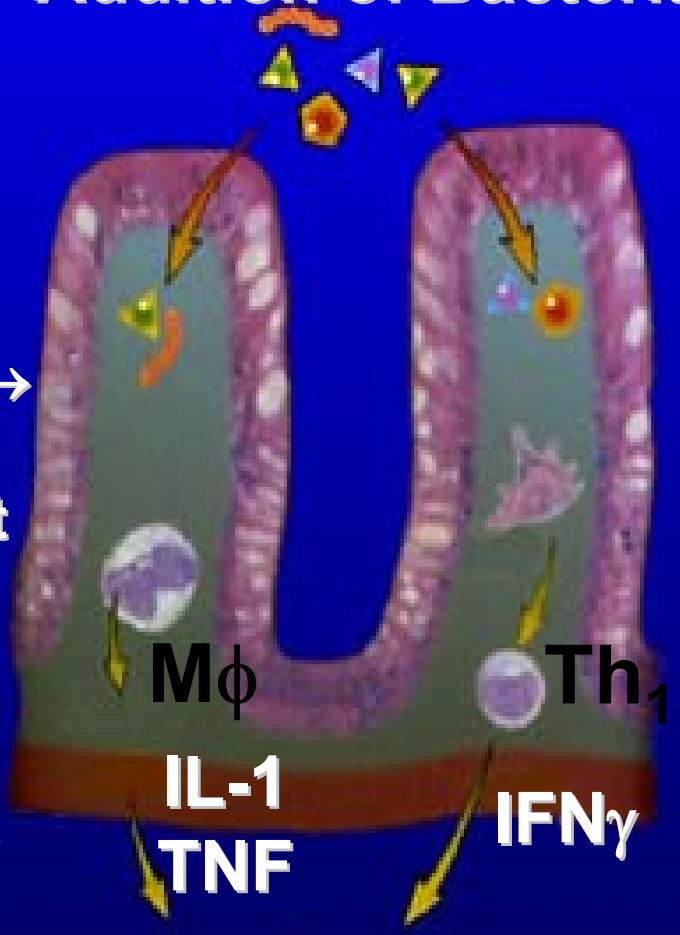
SAMP1-Yit

TCRα $^{-/-}$

Rats

HLA-B27

Transgenic



No immune activation → **Severe Colitis**

No Colitis

Crohn's Disease

Image removed due to copyright reasons.

Ileocolitis
Transmural
Granulomas

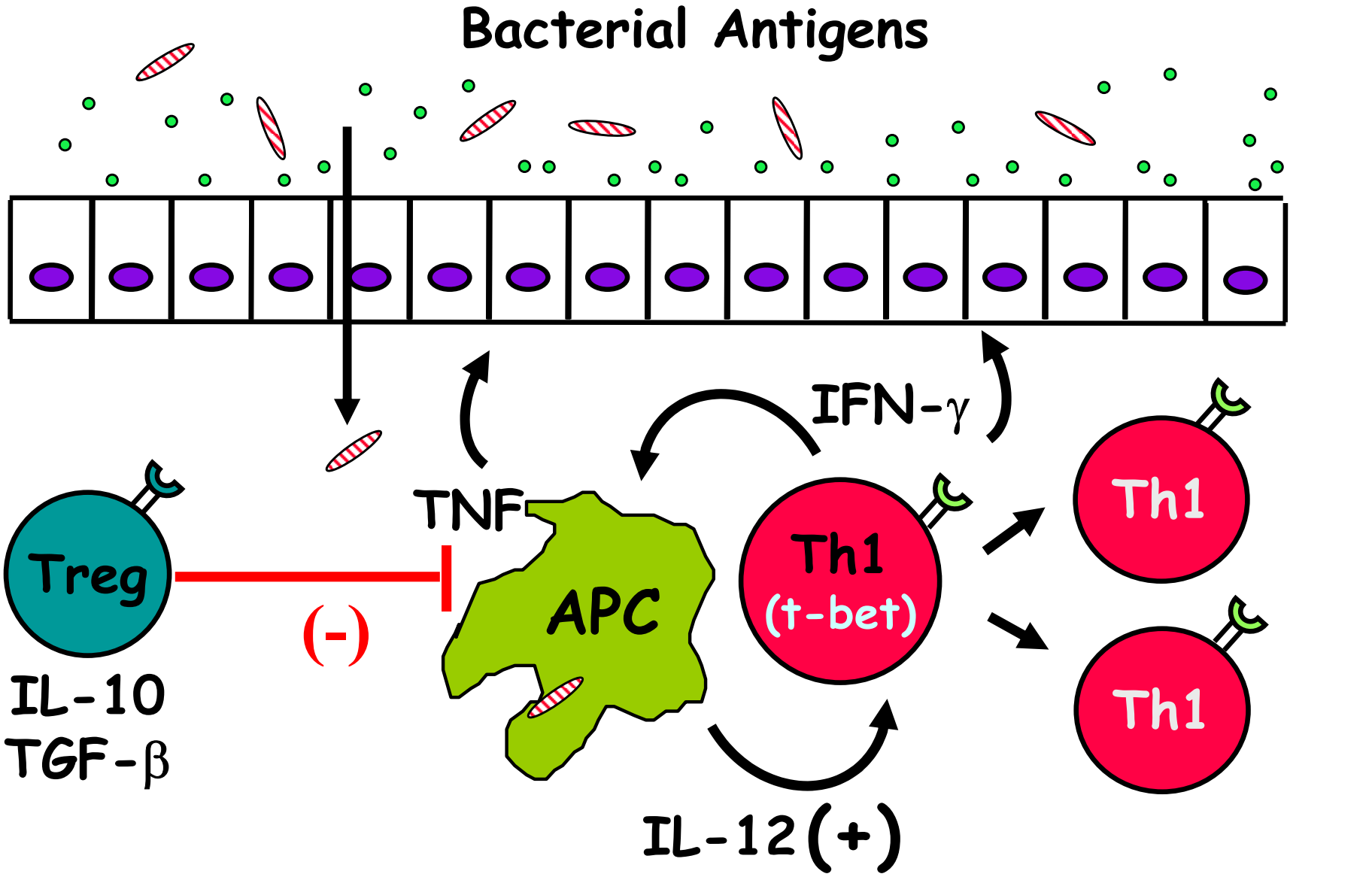
Th1 Inflammation:
IL-12, IFN-γ, TNF-α

Ulcerative Colitis

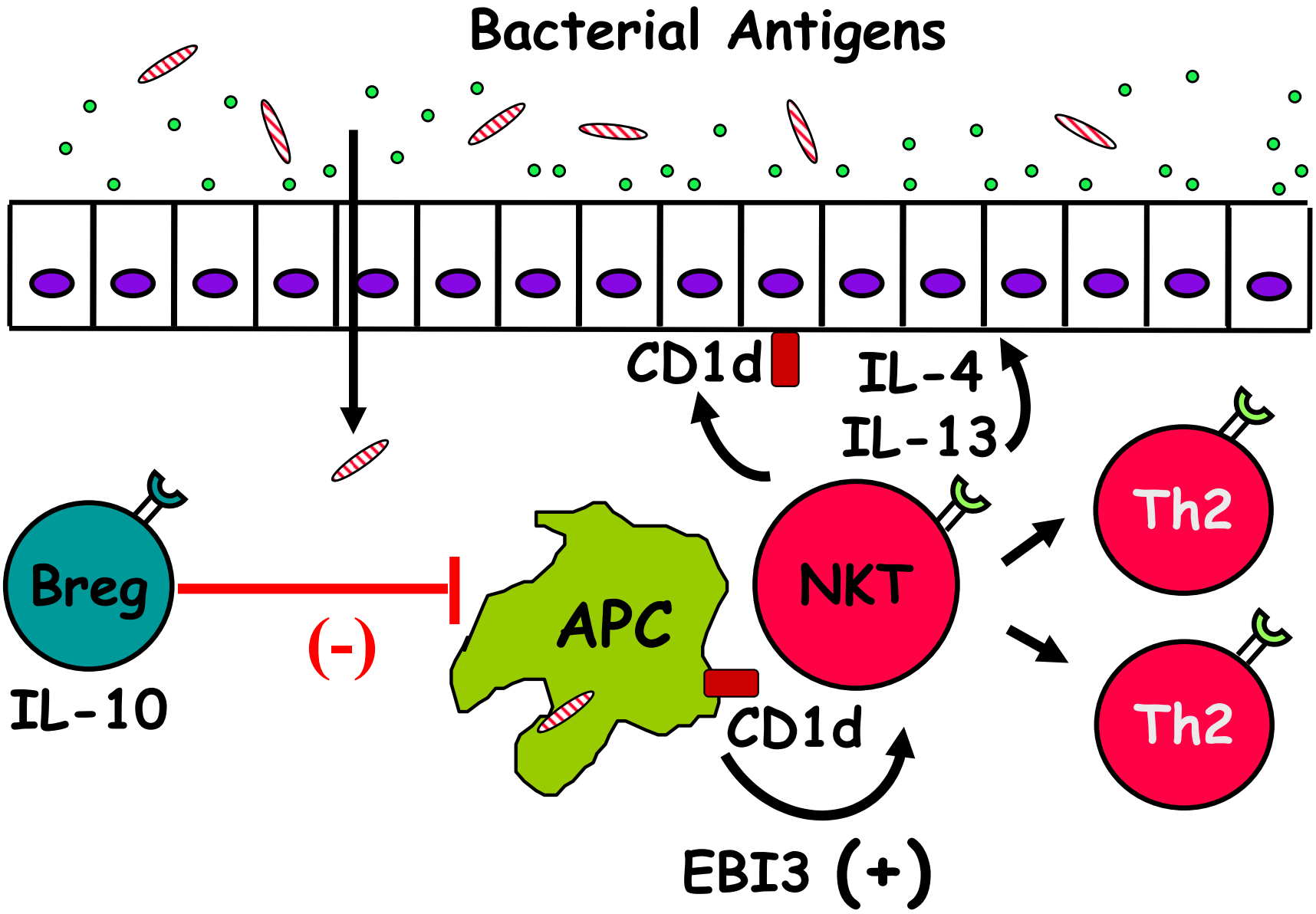
Image removed due to copyright reasons.

Colitis
Superficial
Crypt Abscesses/Ulceration

Th2-like Inflammation:
EBI3, IL-5, IL-13, IL-6



Neurath et al, JEM 2002
Blumberg et al, Ann Rev Immunol 2002



Mizoguchi et al, Immunity 2001
Heller et al, Immunity 2001

Nieuwenhuis et al, PNAS 2002
Van de Waal et al, Gastroenterology 2003

Celiac Disease

Figure removed due to copyright reasons. Please see:
Figure 3 in Green, Peter, and Bana Jabri. "Coeliac disease." *Lancet* 362 (2003): 383-391.

Figure removed due to copyright reasons. Please see:

Figure 4 in Green, Peter, and Bana Jabri. "Coeliac disease." *Lancet* 362 (2003): 383-391.