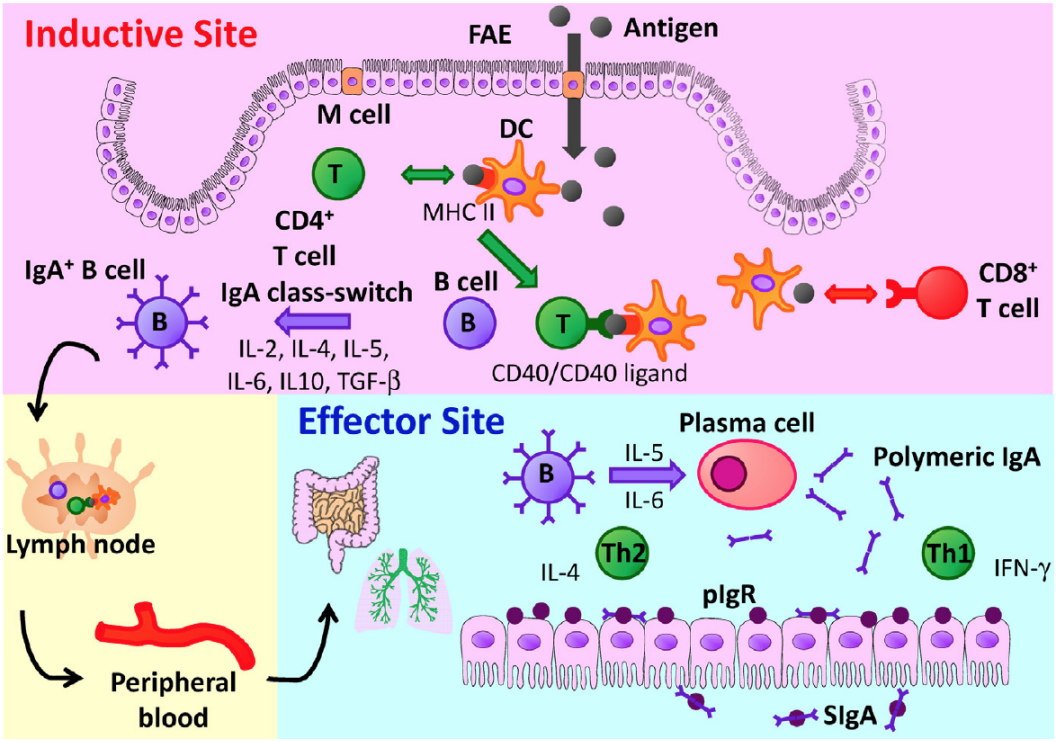
Das mucosale Immunsystem



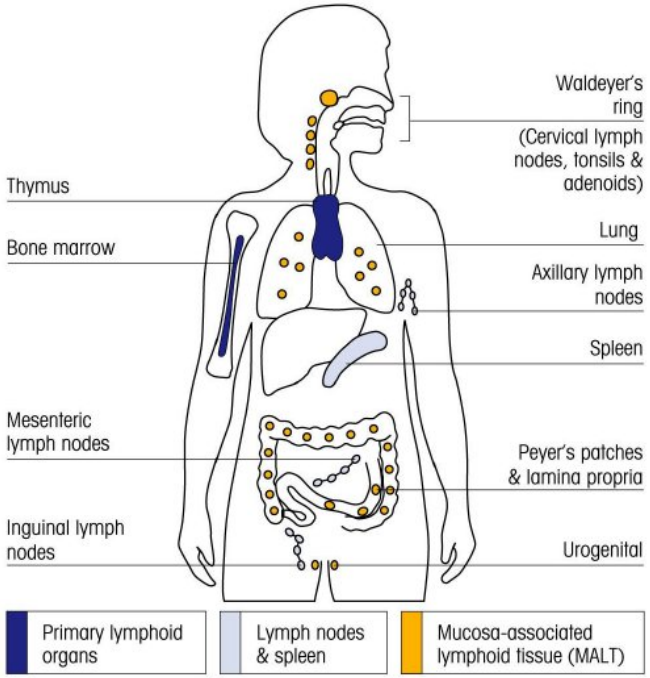
PD Dr. M. Stassen

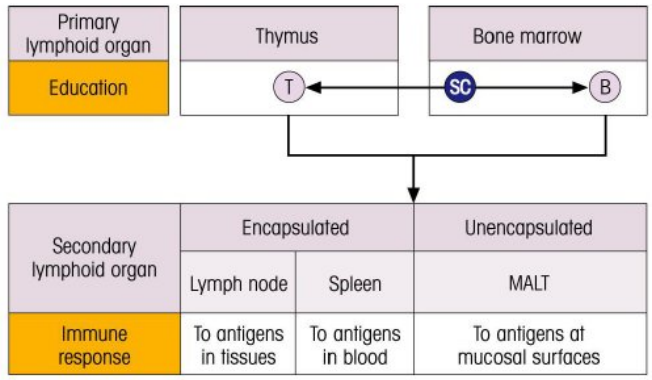
INSTITUTE FOR
IMMUNOLOGY
MAINZ

Inhalte der Vorlesung

- Anatomie des „mucosa-/gut-associated lymphoid tissue“ (MALT/GALT)
- Wichtige zelluläre und lösliche Komponenten des GALT
- Intestinale Alkalische Phosphatase, Transport von IgA, IgM, IgE
- Homing von Lymphocyten im GALT
- Dendritische Zellen und Induktion von Toleranz
- Kommensale Mikroflora und opportunistische Erreger
- Abwehr gastrointestinaler Parasiten und die Rolle von Mastzellen und IgE
- Infektionskrankheiten und mucosale Vakzinierungen am Beispiel Poliomyelitis

MALT / GALT: 400m² Fläche (nur Darm!), 75% aller Lymphocyzen, 3g IgA/Tag





The tonsils and adenoids form a ring of lymphoid tissues, Waldeyer's ring, around the entrance of the gut and airway

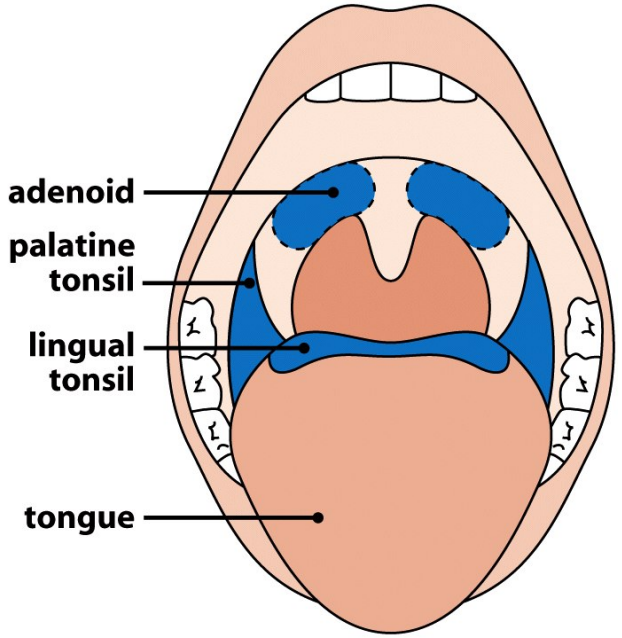


Figure 11-5 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

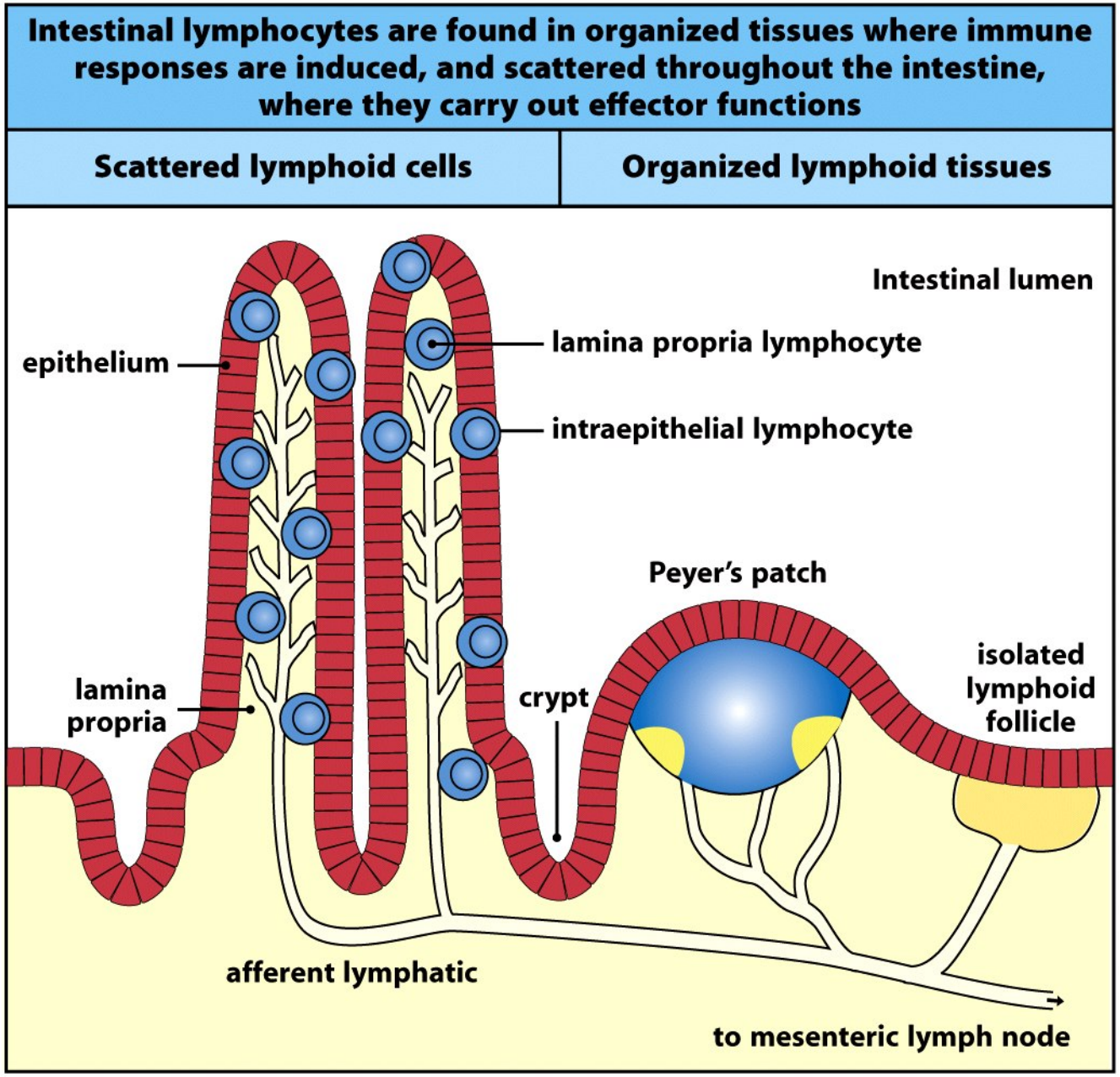
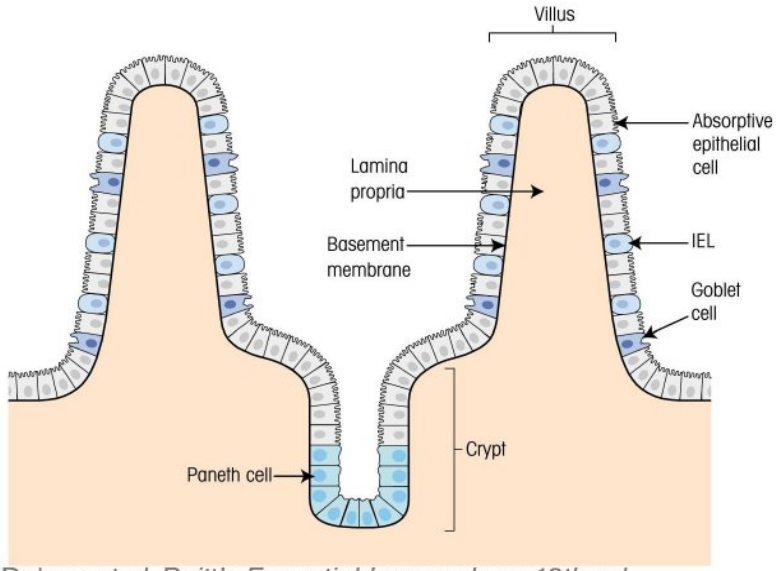


Figure 11-4 Immunobiology, 7ed. (© Garland Science 2008)



Delves *et al. Roitt's Essential Immunology, 12th ed.*
© 2011 Delves *et al.* Published 2011 by Blackwell Publishing Ltd.

Paneth Zellen: Produzieren Lysozym und antimikrobielle Peptide (Defensine, Cathelicidine)

Goblet Zellen: Produzieren Mucine (Glykoproteine, die ein Gel bilden von 50-700µm Dicke)

Intraepitheliale Lymphocyten (IEL):
Hauptsächlich $CD8^+$ (CD8αα) mit γδ TCR, produzieren antimikrobielle Peptide

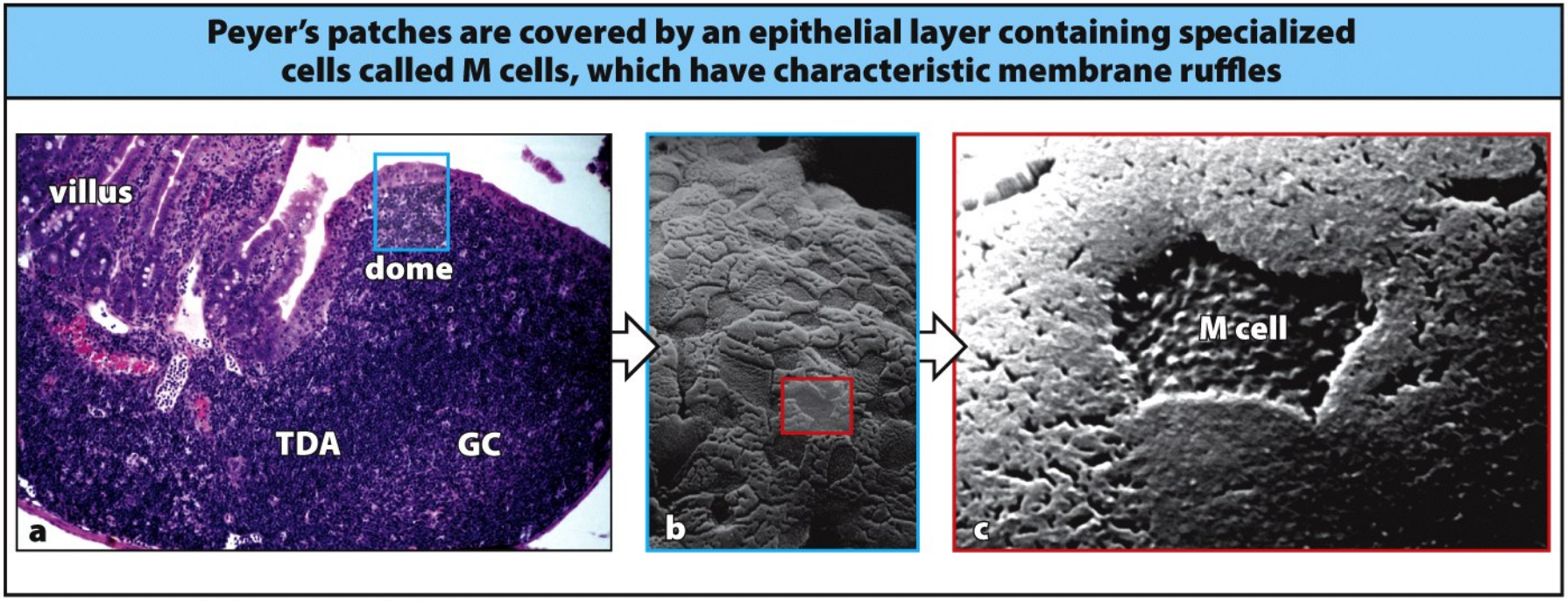
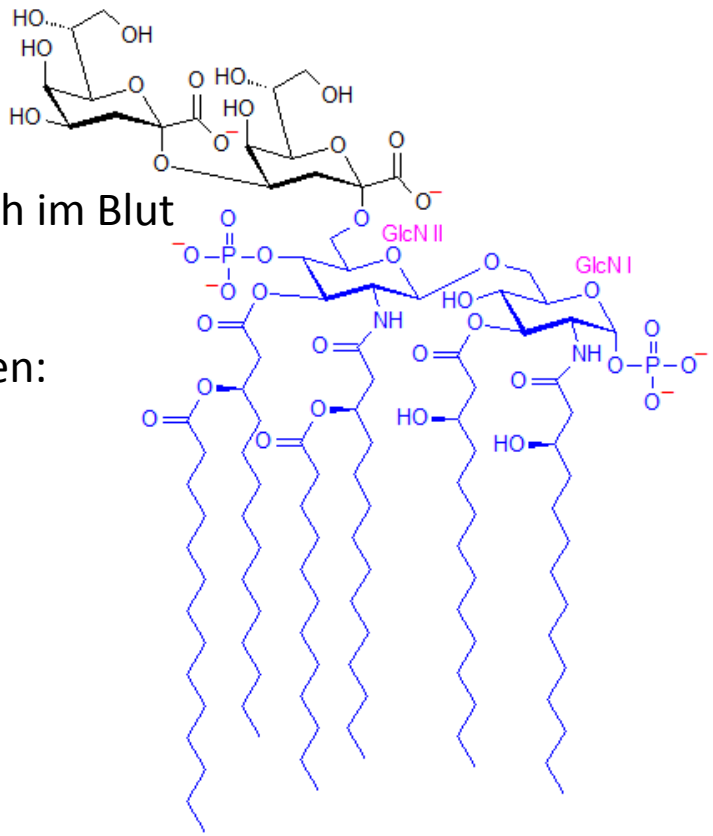


Figure 11-6 Immunobiology, 7ed. (© Garland Science 2008)

Intestinale Alkalische Phosphatase

- Hydrolysiert Phosphatester, pH Optimum 9,7
- Produziert von Enterocyten, v. a. im Duodenum
- Abgabe in Vesikeln, membranständig, kl. Teil löslich im Blut
- Dephosphorylierung proinflammatorischer Liganden:
  LPS, ATP, Flagellin, CpG Dinukleotide



The basic lipopolysaccharide of *E. coli*, incorporating lipid A (blue portion of the structure).

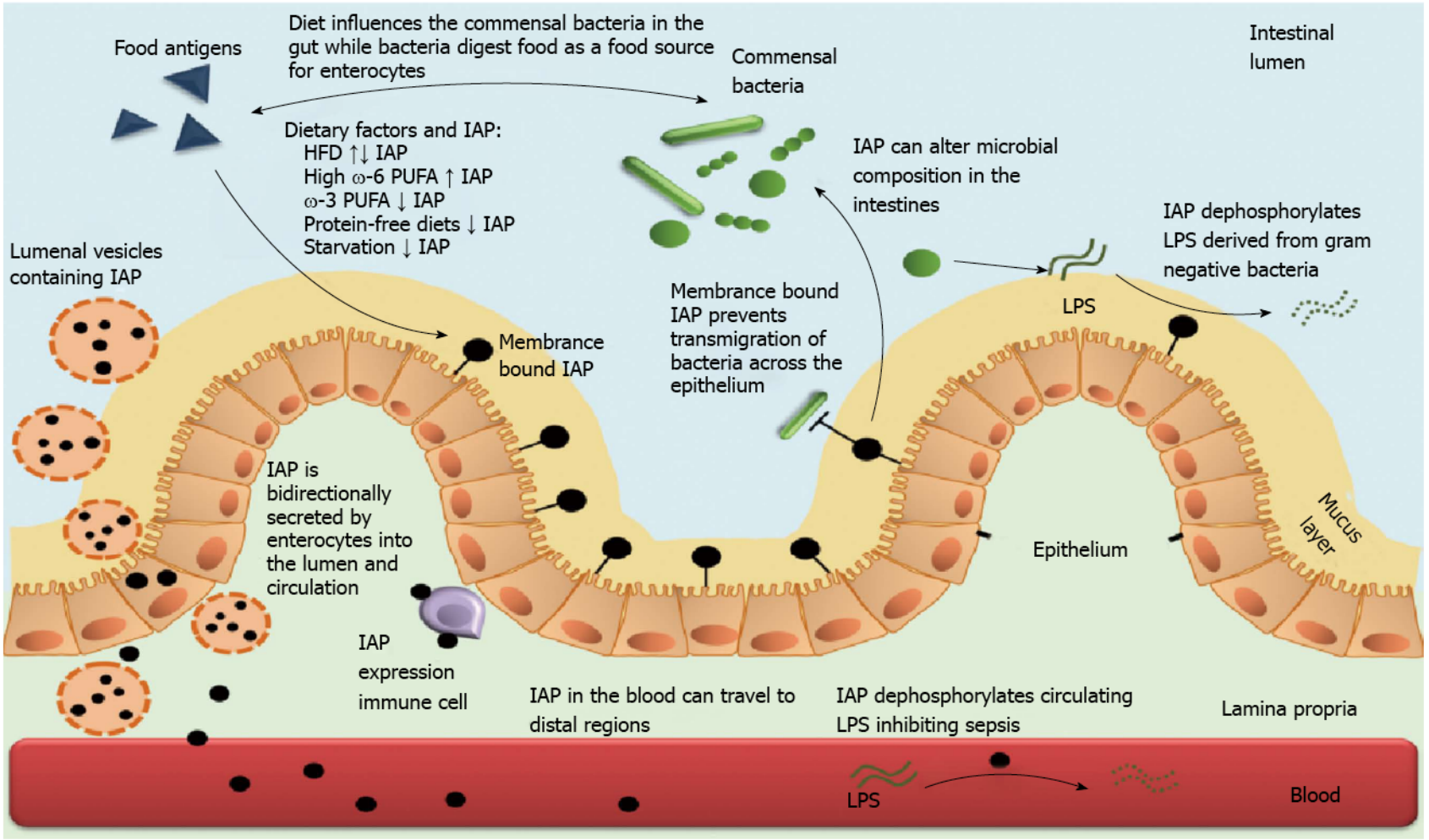


Figure 1 Intestinal alkaline phosphatase regulates gut homeostasis. Intestinal alkaline phosphatase (IAP) secreted by the enterocytes plays a vital role in various physiological functions in and around the intestine. Though mainly membrane-bound, IAP can be found both in the lumen and blood. High concentration of IAP molecules are present in protein-rich lumenal vesicles on the lumenal and apical side of the epithelium. IAP dephosphorylates both lumenal and circulating lipopolysaccharides (LPS) derived from the cell wall of gram negative bacteria effectively eliminating their toxic constituent. Preliminary work from our lab and others have shown IAP expressed on infiltrated immunocytes in the lamina propria. IAP is also crucial in preventing the transmigration of bacteria across the epithelium layer, preventing downstream activation of immunocytes and the subsequent inflammatory responses. Through its complex relationship with food, commensal bacteria and immune cells, IAP plays an essential role in gut homeostasis.

HFD: high fat diet
PUFA: poly unsatturated fatty acids

Estaki et al. *World J Gastroenterol* (2014)

Transport über Epithelgrenzen I

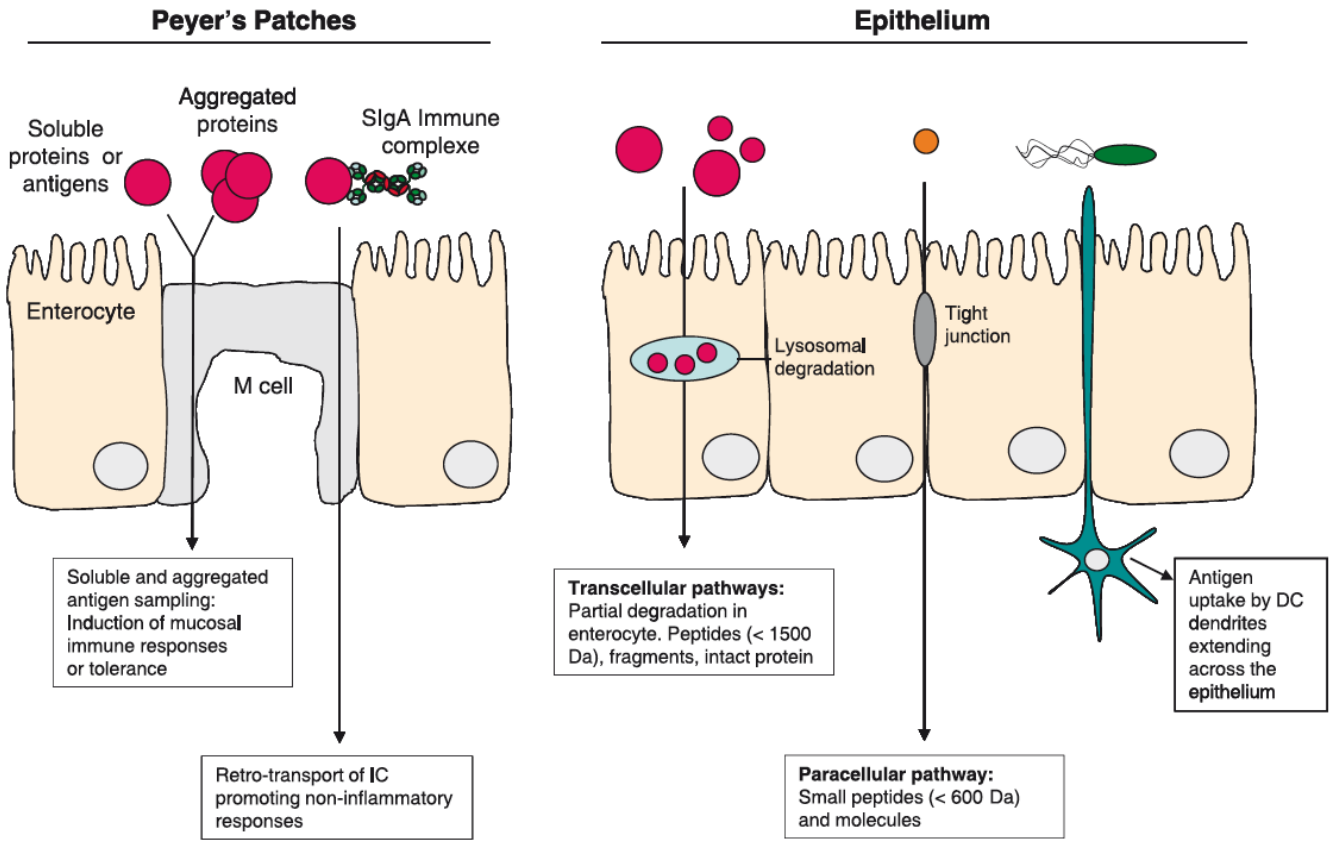


Fig. 1. Differential pathways of antigen sampling in the healthy epithelium. Organization of the gut epithelium makes it an efficient tight barrier with filtering properties against the entry of pathogenic agents and possibly harmful molecules such as toxins and allergens. Microfold (M) cells present on the surface of the follicle-associated epithelium in intestinal Peyer's patches transport particulate antigens and aggregated proteins for presentation by local dendritic cells, resulting in the onset of a tolerogenic type of immune responses under steady-state conditions. Secretory IgA-based immune complexes are similarly taken up by M cells and promote the induction of non-inflammatory cytokines (TGF-β and IL-10), ensuring low reactivity against the transported antigen. Partially degraded proteins and a small proportion of intact proteins are taken up by enterocytes. Degradation along the phago-lysosomal pathway occurs, thus resulting in the loss of potentially allergenic properties. Paracellular selective leakage provides access to ions, amino acids and carbohydrates, which are important in ensuring liquid fluxes and maintenance of transepithelial gradients. Direct intestinal sampling of bacterial antigens by dendritic cells extending their dendrites across the tight epithelium and release of exosome vesicles (not drawn) represent other plausible pathways.

Perrier & Corthesy (2010) Clin Exp Allergy

Transport über Epithelgrenzen II

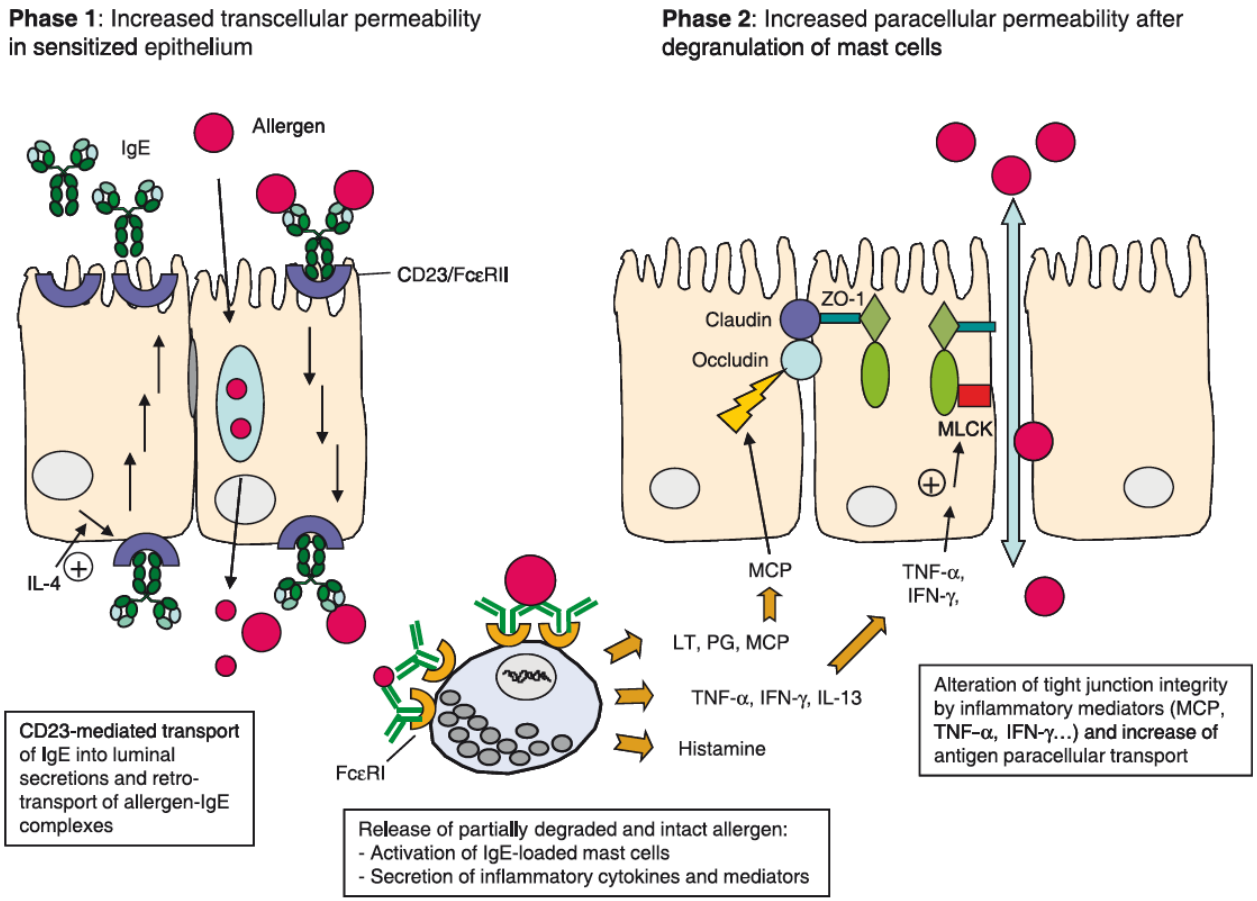
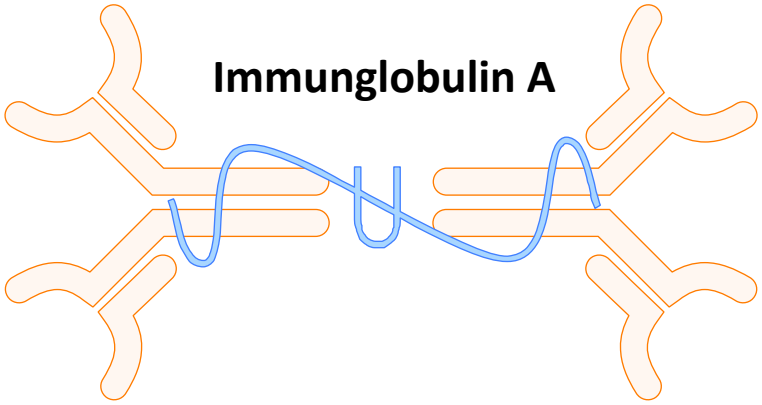


Fig. 2. Mechanism of increased intestinal permeability in the sensitized epithelium. In allergic subjects, mast cells loaded with allergen-specific IgE are present in the lamina propria. Small amounts of intact protein can pass transcellularly and trigger mast cell activation via cross-linking of bound IgE. In addition, elevated IL-4 present in individuals with an atopic background contributes towards up-regulation of the low-affinity IgE receptor (CD23, FcεRII) on the basolateral and apical poles of intestinal epithelial cells. This triggers the secretion of luminal IgE produced by IL-4-induced plasma cells; upon binding of dietary antigens, transepithelial transport back to the lamina propria is initiated, leading to the passage of intact antigen capable of binding and activating mast cells (phase I). Upon degranulation of mast cells, mediators such as cytokines, histamine, leukotrienes (LT), prostaglandins (PG) and proteases (MCP) are released and influence ion secretion and modify paracellular permeability (phase 2). Alteration of the epithelial permeability occurs upon disorganization of the actomyosin ring through activation of myosin light-chain kinase (MLCK) and changes in the architecture of tight junctions resulting from clipping of occludin by MCP. This leads to the entry of greater amounts of undigested allergen through the paracelluar pathway, which further strengthen the intensity of the allergic reaction.

Perrier & Corthesy (2010) Clin Exp Allergy



- Häufigster Isotyp in Säugern
- ¾ der gesamten Ig-Produktion entfällt auf IgA (3-5g/Tag beim Menschen)
- Der größte Teil wird über mucosale Oberflächen sezerniert
- Kommensale Mikrobiota wichtig für IgA Produktion
  (10^{12} Prokaryoten pro ml Darminhalt; 10^{14} total)
  Fast kein IgA in keimfrei („gnotobiotisch“) aufgezogenen Mäusen
- IgA KO Mäuse ohne Phänotyp, wird funktionell durch IgM ersetzt
  (Transport durch polymeren Ig-Rezeptor!)

Die IgA-Pumpe

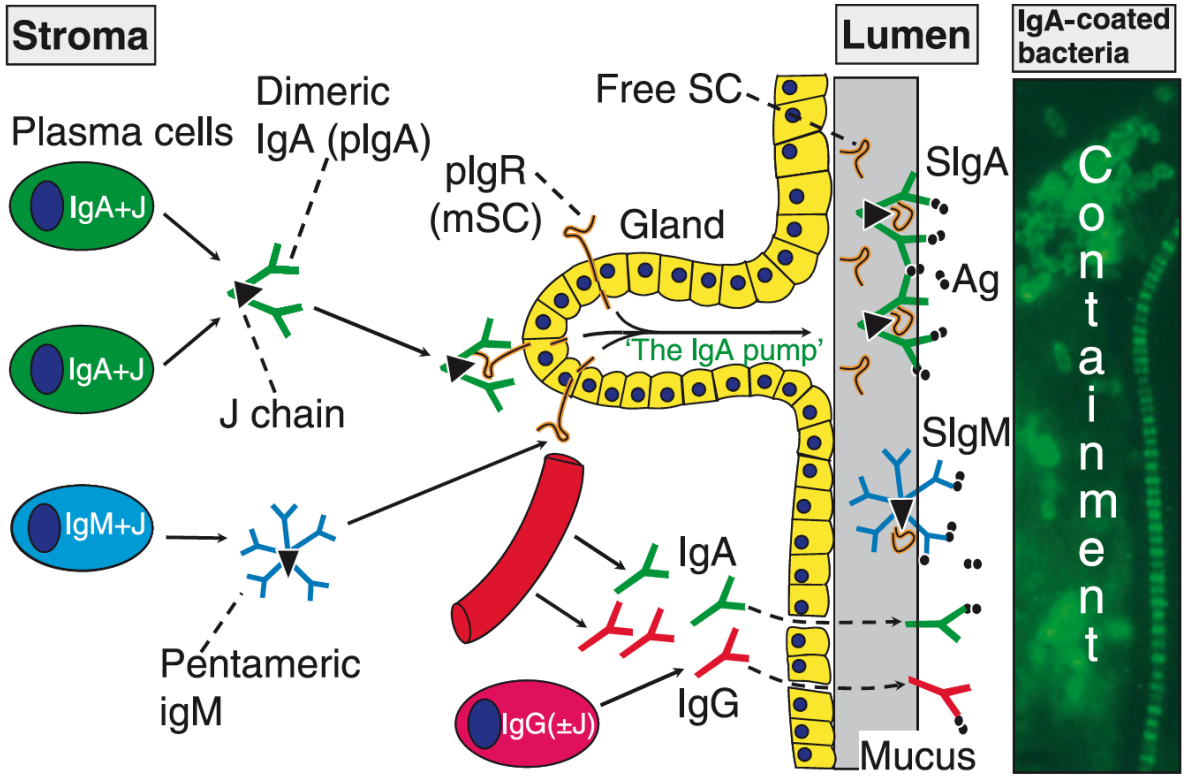


Figure 3 Receptor-mediated export of dimeric IgA and pentameric IgM to provide secretory antibodies (SIgA and SIgM) functioning in immune exclusion of antigen (Ag) at the mucosal surface. Polymeric Ig receptor (pIgR) is expressed basolaterally as membrane secretory component (mSC) on secretory epithelial cells and mediates transcytosis of dimeric IgA and pentameric IgM, which are produced with incorporated J chain (IgA+J and IgM+J) by mucosal plasma cells. Although J chain is often produced by mucosal IgG plasma cells (70–90%), it does not combine with this isotype and is therefore degraded intracellularly as denoted (±J). Locally produced (and serum-derived) IgG is therefore not subject to pIgR-mediated transport, but can be transmitted paracellularly to the lumen together with monomeric IgA as indicated. Free SC (depicted in mucus) is generated when pIgR in its unoccupied state (top basolateral symbol) is cleaved at the apical face of the epithelium like bound SC in SIgA and SIgM. Commensal bacteria in the right-hand panel are coated *in vivo* with SIgA, which aids their containment and thereby promotes host-microbial mutualism.

Brandtzaeg *Scand J Immunol* 2009

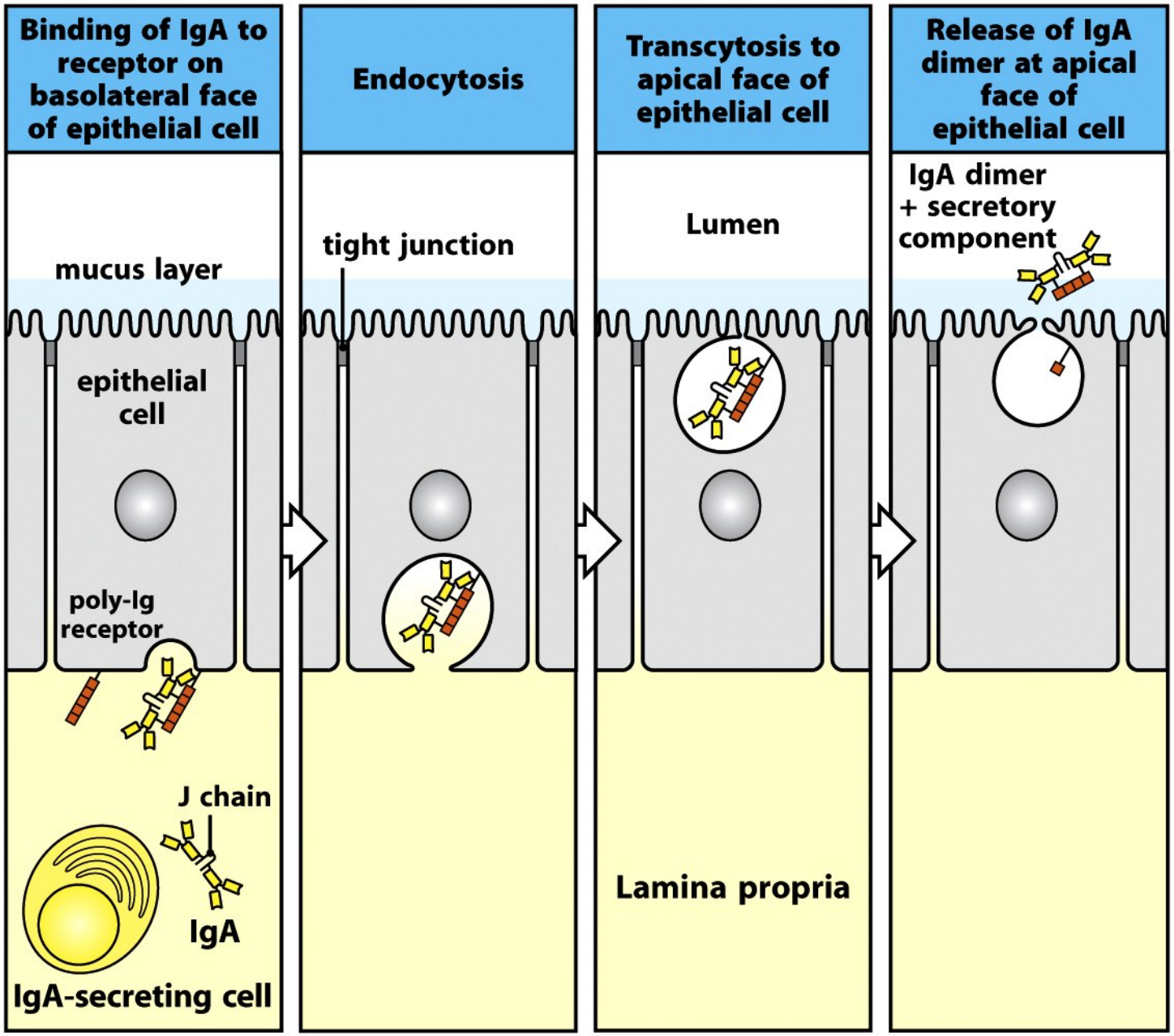
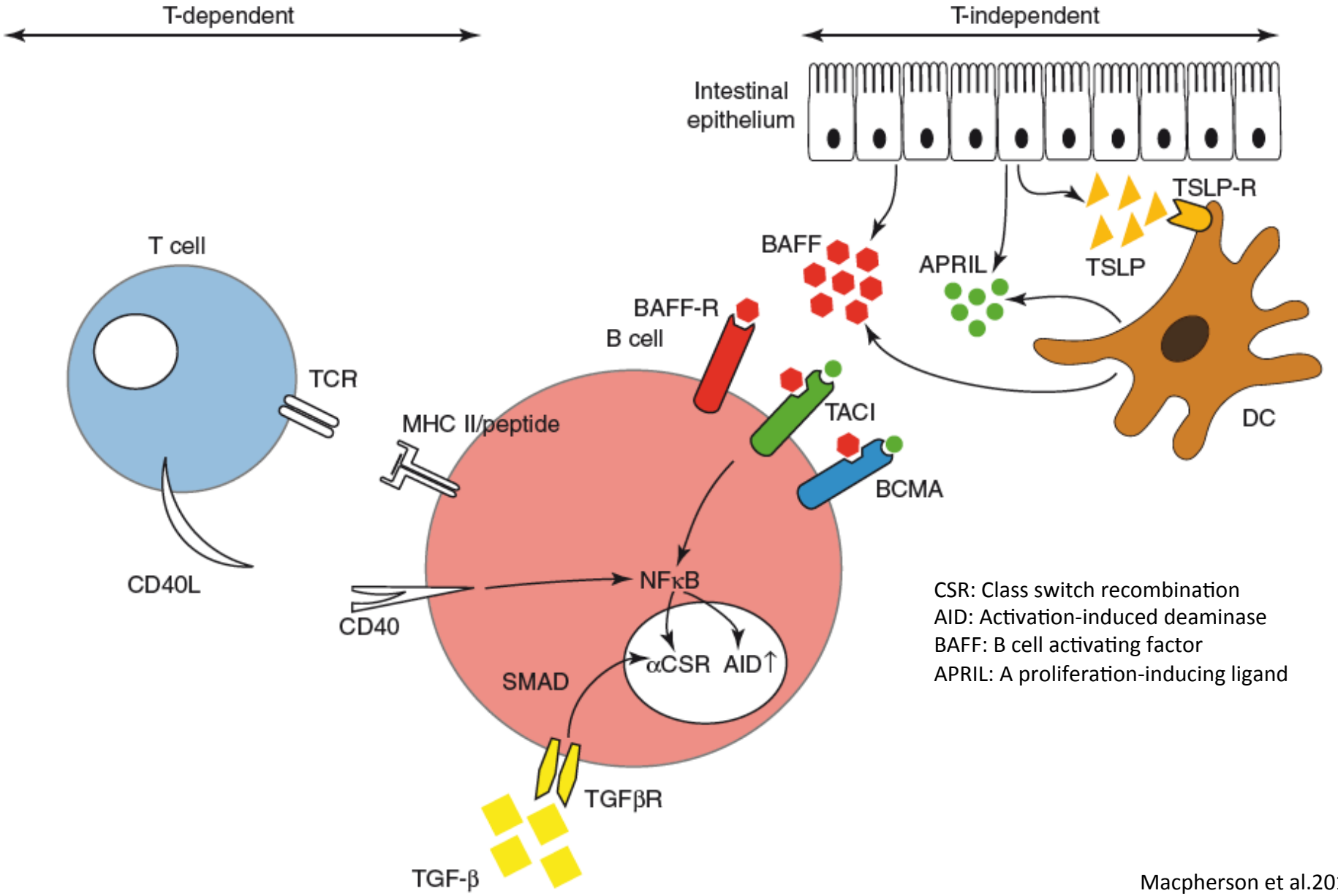


Figure 11-13 Immunobiology, 7ed. (© Garland Science 2008)

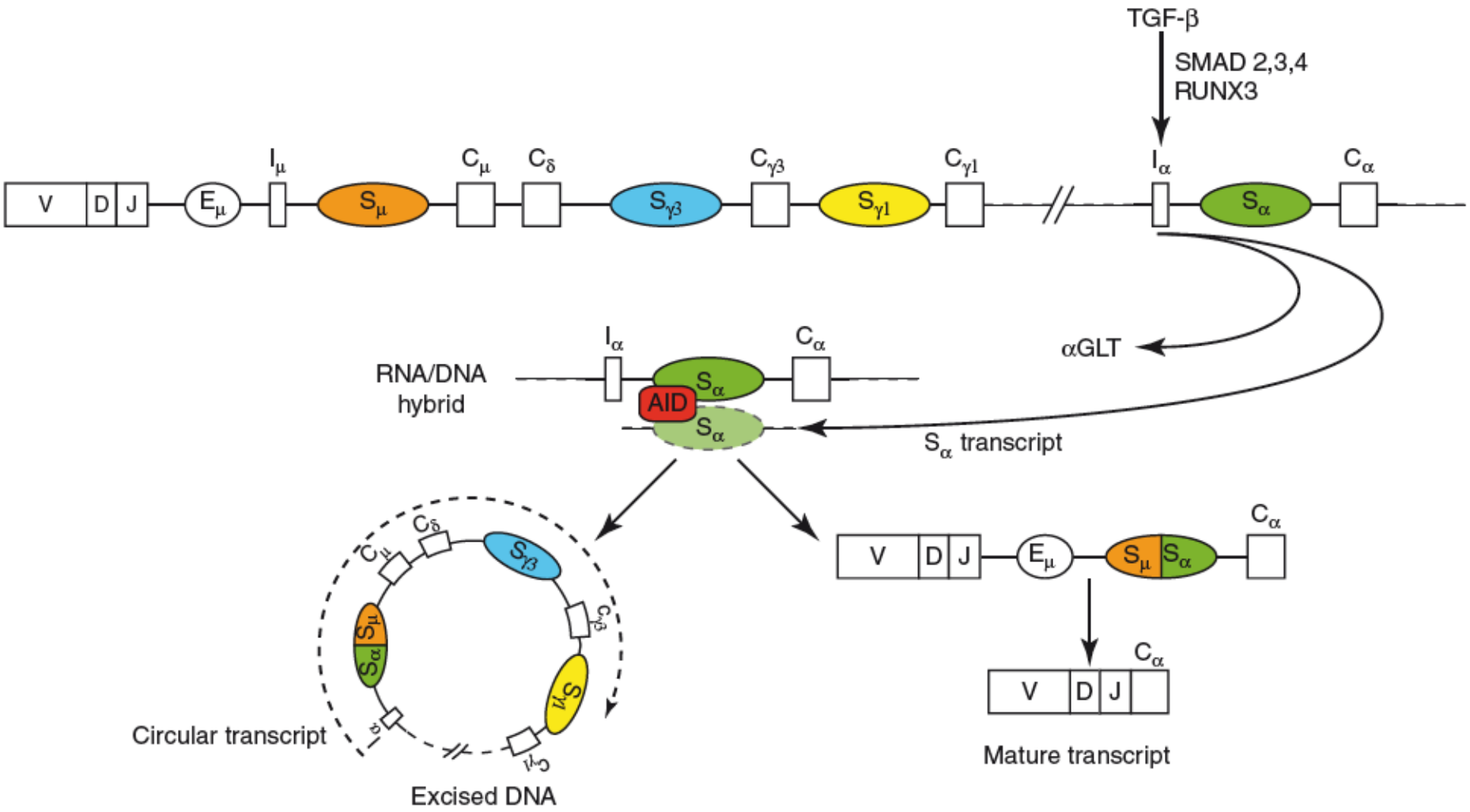
Klassenwechsel zu IgA mit und ohne T-Zell-Hilfe durch NF-κB Aktivierung



CSR: Class switch recombination
AID: Activation-induced deaminase
BAFF: B cell activating factor
APRIL: A proliferation-inducing ligand

Macpherson et al.2012

TRENDS in Immunology


TGF-β
SMAD 2,3,4
RUNX3
V
D
J
E_μ
I_μ
S_μ
C_μ
C_δ
$S_{\gamma 3}$
$C_{\gamma 3}$
$S_{\gamma 1}$
$C_{\gamma 1}$
I_α
S_α
C_α
αGLT
RNA/DNA
hybrid
AID
S_α transcript
Circular transcript
Excised DNA
Mature transcript

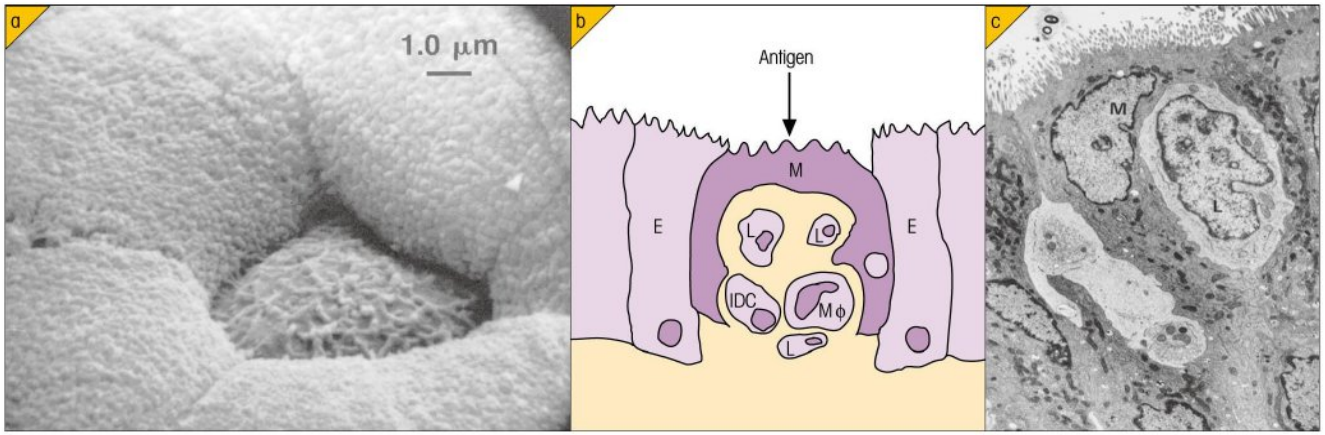


Figure 7.11. M-cell within Peyer's patch epithelium.

(a) Scanning electron micrograph of the surface of the Peyer's patch epithelium. The antigen-sampling M-cell in the center is surrounded by absorptive enterocytes covered by closely packed, regular microvilli. Note the irregular and short microfolds of the M-cell. (Reproduced with permission of the authors and publishers from Kato T. & Owen R.L. (1999) In Ogra R. *et al.* (eds) *Mucosal Immunology,* 2nd edn. Academic Press, San Diego.) (b) After uptake and transcellular transport by the M-cell (M), antigen is processed by macrophages and dendritic cells, which present antigen to T-cells in Peyer's patches and mesenteric lymph nodes. E, enterocyte; IDC, interdigitating dendritic cell; L, lymphocyte; Mφ, macrophage. (c) Electron photomicrograph of an M-cell (M in nucleus) with adjacent lymphocyte (L in nucleus). Note the flanking epithelial cells are both absorptive enterocytes with a typical brush border. (Lead citrate and uranyl acetate, ×1600.) ((b) Based on Sminia T. & Kraal G. (1998) In Delves P.J. & Roitt I.M. (eds) *Encyclopedia of Immunology,* 2nd edn, p. 188. Academic Press, London.)

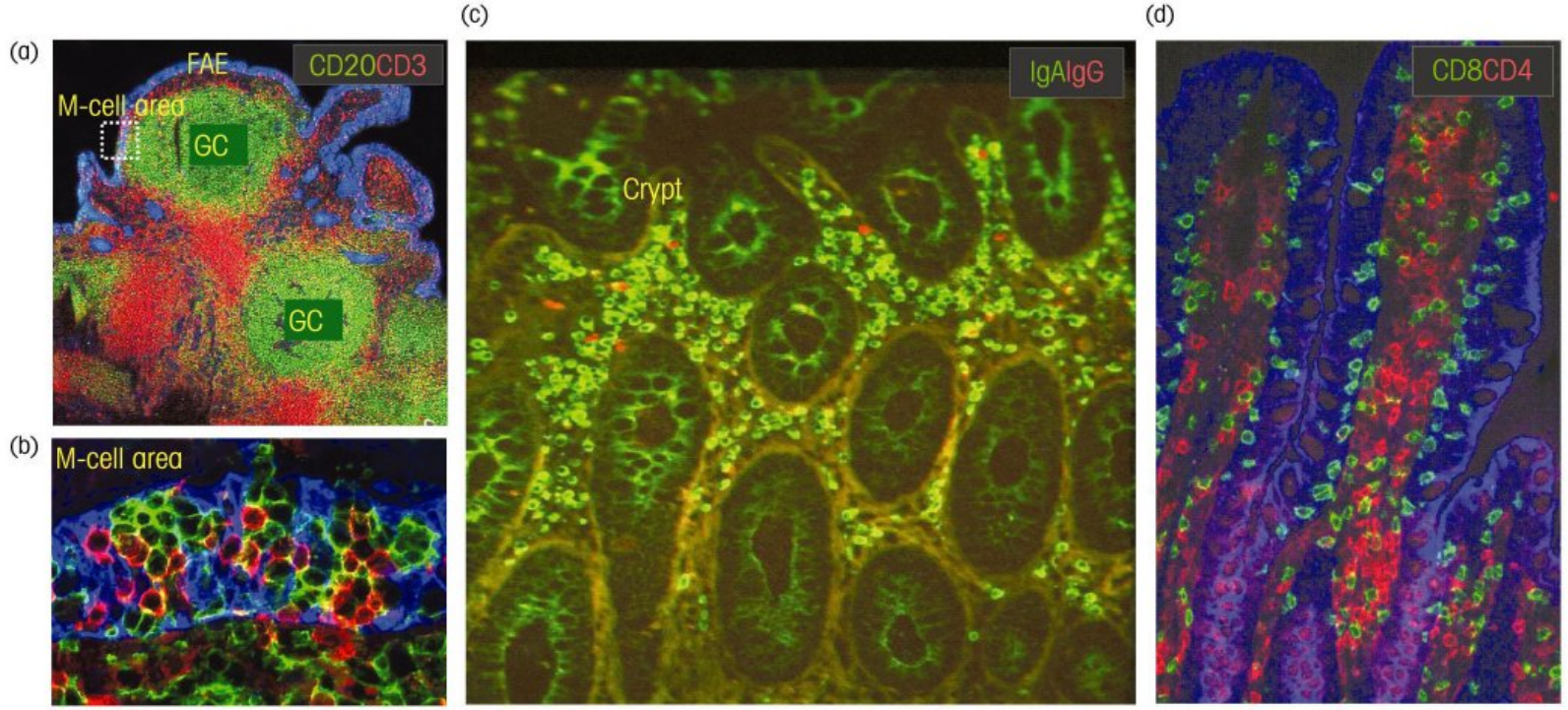


Figure 7.10. Gut-associated immunity.

(a) Immunofluorescence staining indicating the B-cells (with anti-CD20, green), T-cells (with anti-CD3, red) and the follicle-associated epithelium (FAE) (with anti-cytokeratin, blue) in Peyer's patch of human small intestine. GC, germinal center; M-cell, microfold cell. (b) Details from the antigen-sampling microfold-cell (M-cell) area. (c) Staining for IgA (green) and IgG (red) in a section of human large bowel mucosa. Crypt epithelium shows selective transport of IgA. Only a few scattered IgG-producing cells are seen in the lamina propria, together with numerous IgA plasma cells (staining bright green). (d) Staining for CD4 (red) and CD8 (green) T-cells in human duodenal mucosa. The epithelium of the villi is blue (cytokeratin). The weak CD4 expression seen in the background is either macrophages or dendritic cells. (Reproduced from Brandtzaeg P. & Pabst R. (2004) *Trends in Immunology* **25**, 570–577 with permission from the publishers.)

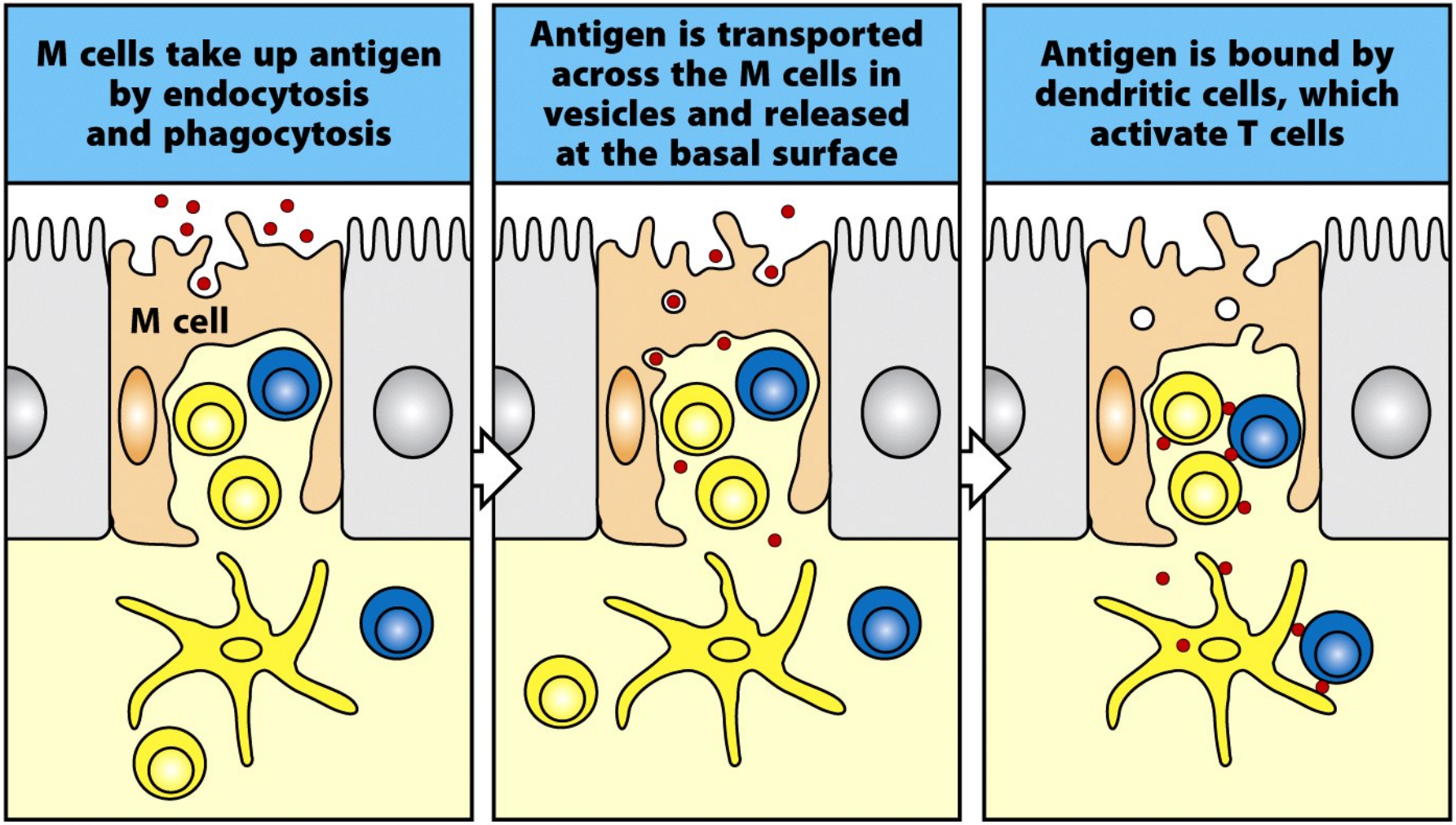
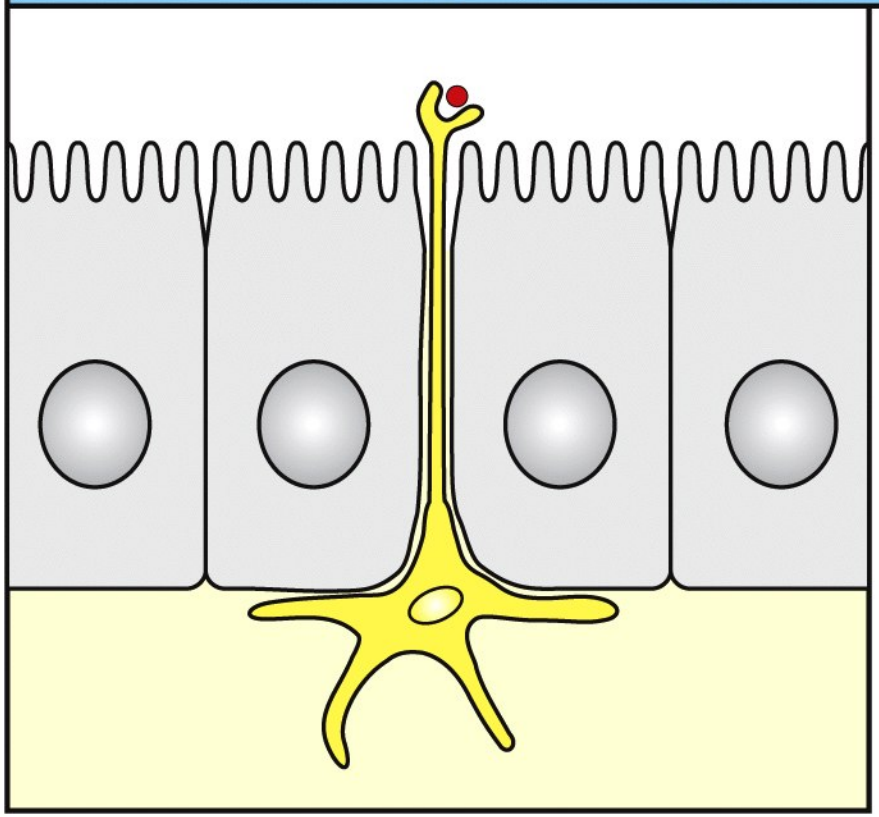


Figure 11-8 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Dendritic cells can extend processes across the epithelial layer to capture antigen from the lumen of the gut



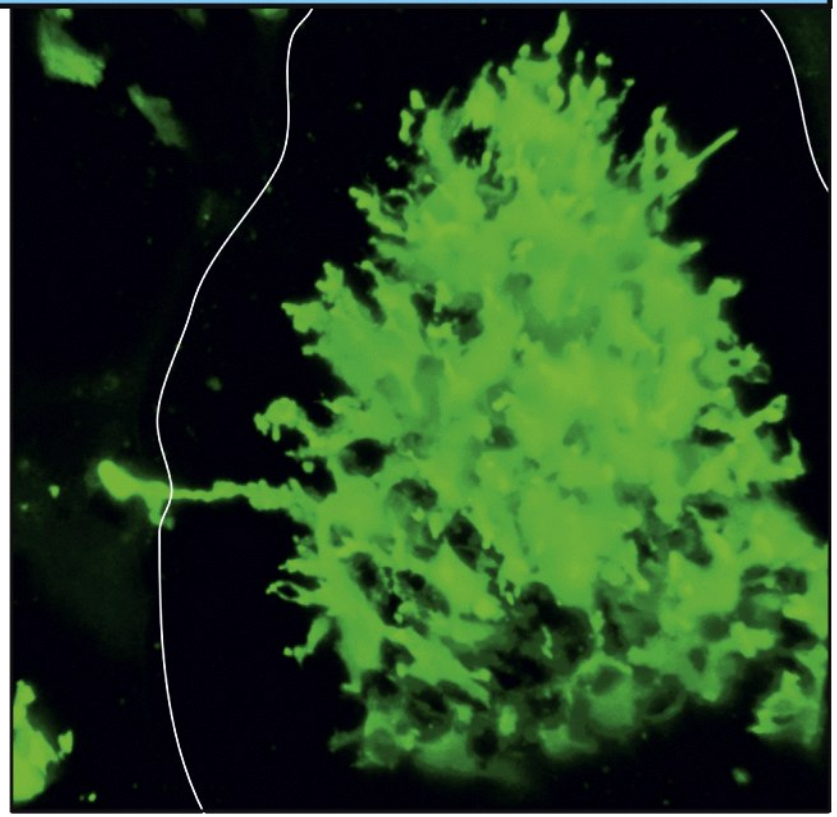


Figure 11-9 Immunobiology, 7ed. (© Garland Science 2008)

Mucosale Dendritische Zellen: Tolerogenes Milieu im „steady state“

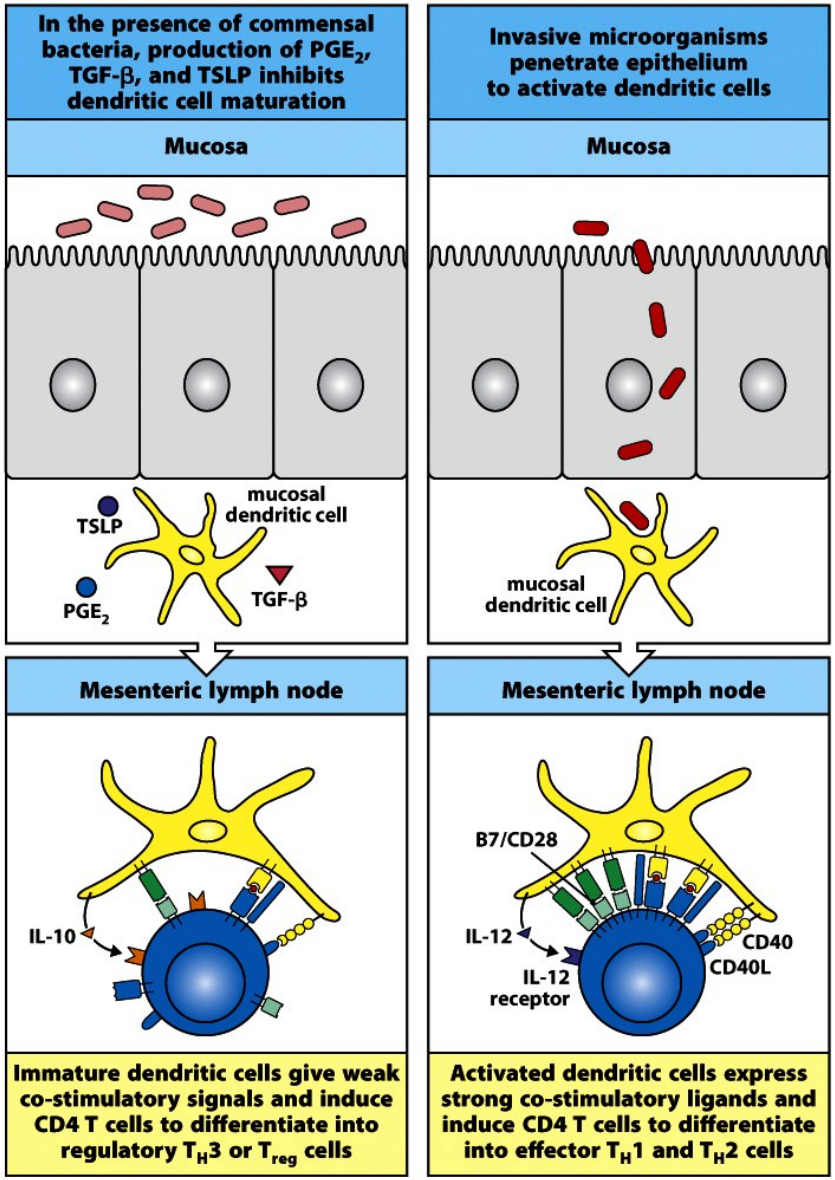


Figure 11-24 Immunobiology, 7ed. (© Garland Science 2008)

Orale Toleranz

Gegen Nahrungsproteine, kommensale Bakterien

Keine zentrale Toleranz, da Antigene nicht im Thymus präsent

Produktion von IgA (TGF-β!)

Keine lokale Reaktion der T-Effektorzellen

Induktion von pTreg durch TGF-β und Retinsäure von speziellen CD103-positiven APC

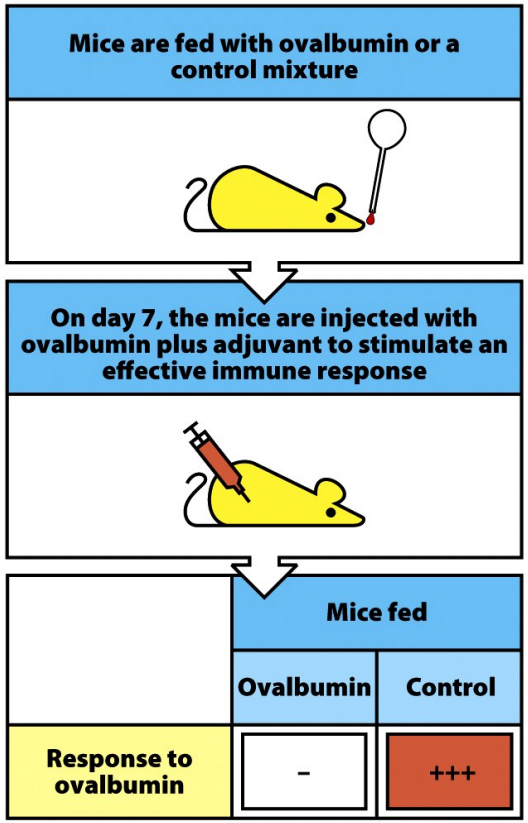
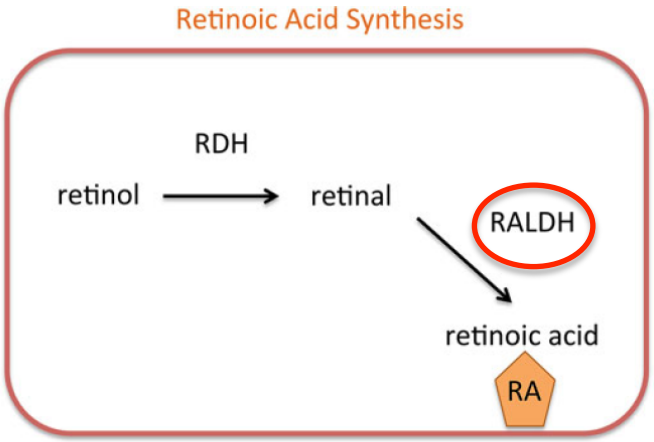
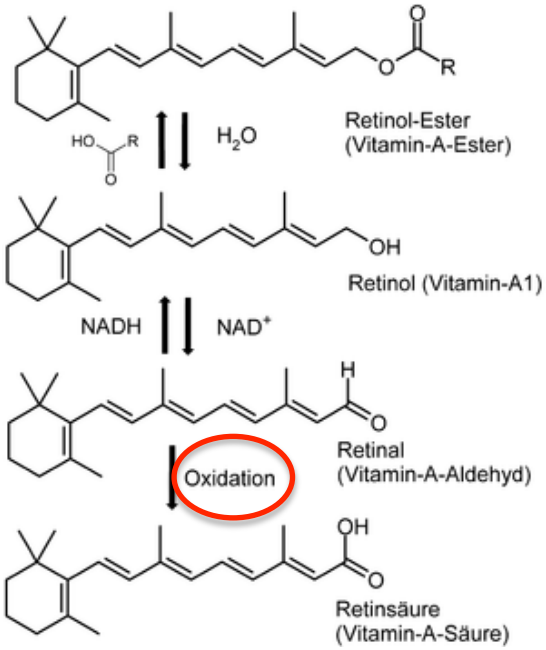


Figure 11-22 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Exkurs: Vitamin A:
Wichtig für die Expression von „Homing“ Molekülen und die Entstehung von pTreg



Retinal-Dehydrogenase



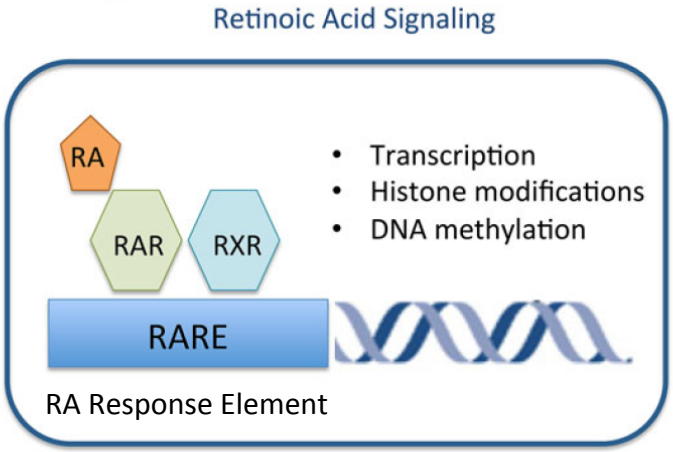


Figure 1. Retinoic acid synthesis and signaling. Retinol is taken up from the blood and oxidized first to retinal by retinol dehydrogenases (RDH) and then to all-trans-retinoic acid (RA) by retinal dehydrogenases (RALDH). Within the immune system, RALDH2 is the predominant isoform expressed by dendritic cells. Retinoic acid receptors (RARs) are nuclear hormone receptors that function as ligand-dependent transcription factors. RARs form heterodimers with retinoid X receptors (RXRs). RA binds to RAR and triggers a conformational change that promotes recruitment of coactivator complexes to initiate transcription and modify the surrounding chromatin via histone modifications and DNA methylation.

Brown & Noelle, *Eur J Immunol* 2015

Orale Toleranz: Spezielle CD103⁺DC-Populationen, nicht Makrophagen, induzieren Treg

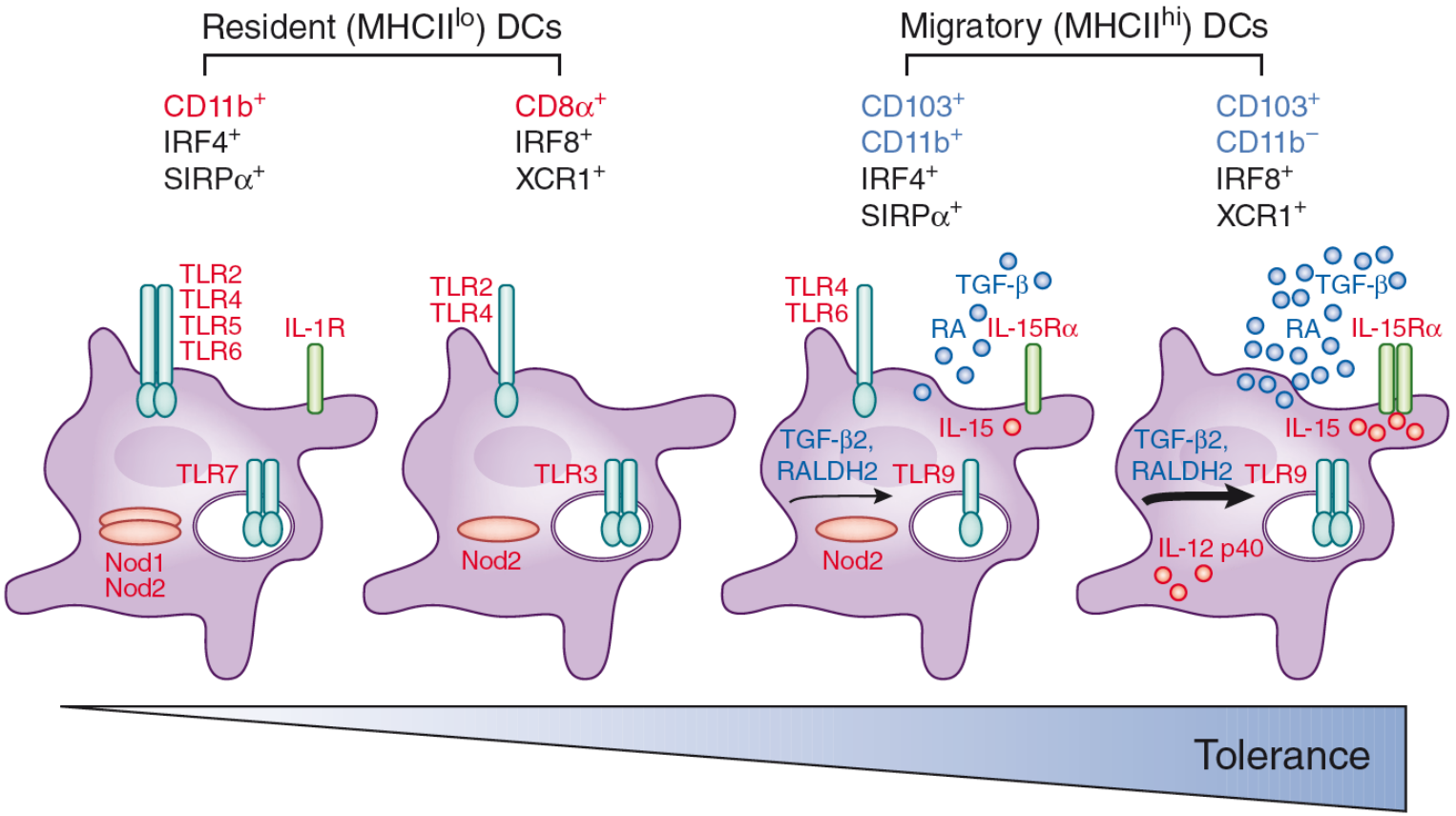
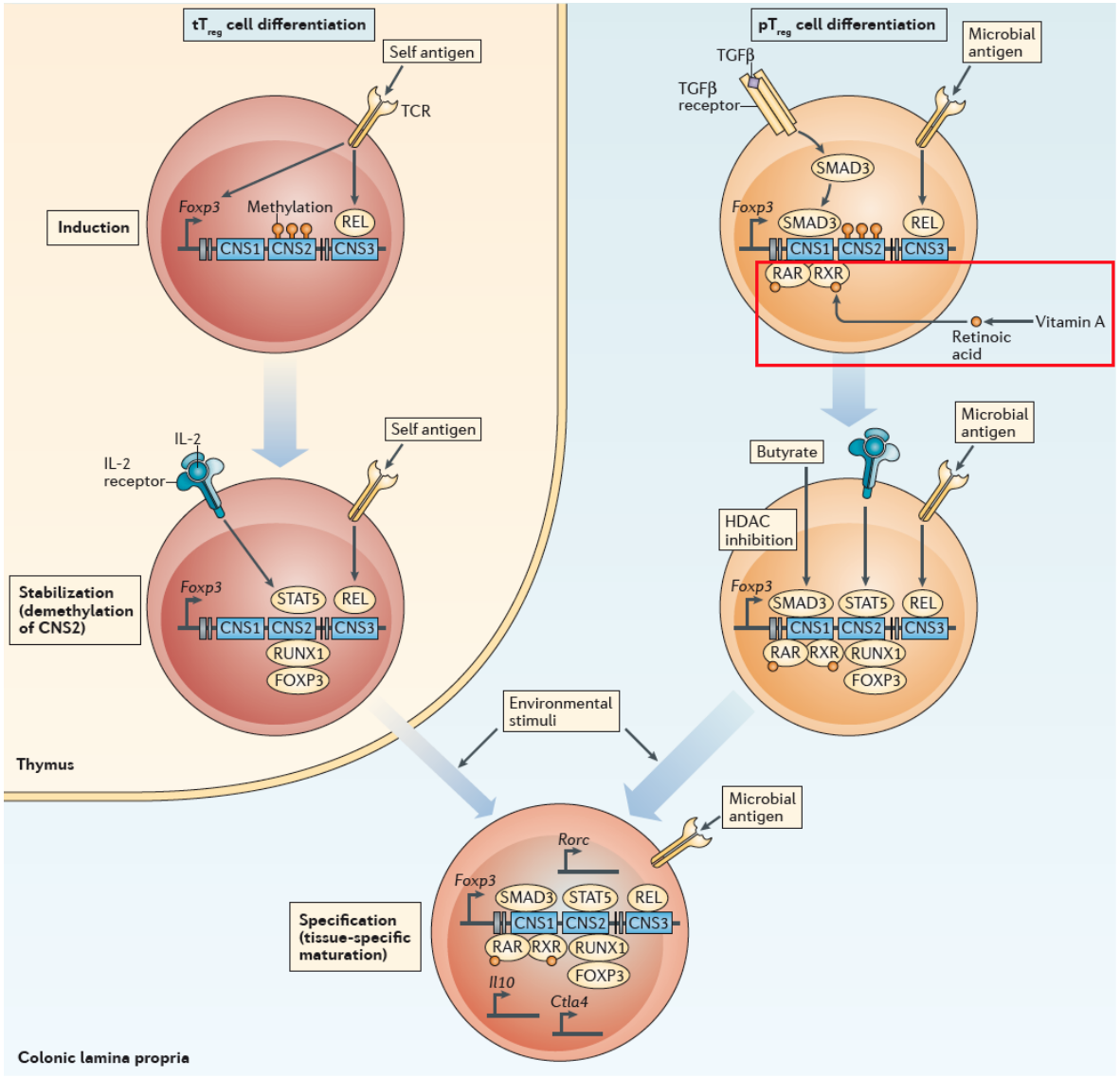


Figure 1 mLN DC subsets in immunotolerance and protective immunity. Individual DC subsets used for gene-expression profiling are categorized by expression of the key transcription factors IRF4 and IRF8 and expression of the chemokine receptor XCR1 and the signal regulator SIRPα. DC subsets have different potential to maintain tolerance through retinoic acid (RA) synthesis and TGF-β secretion. DC subsets have different abilities to induce inflammatory responses on the basis of their individual specific expression of pattern-recognition receptors, cytokine receptors and cytokines.

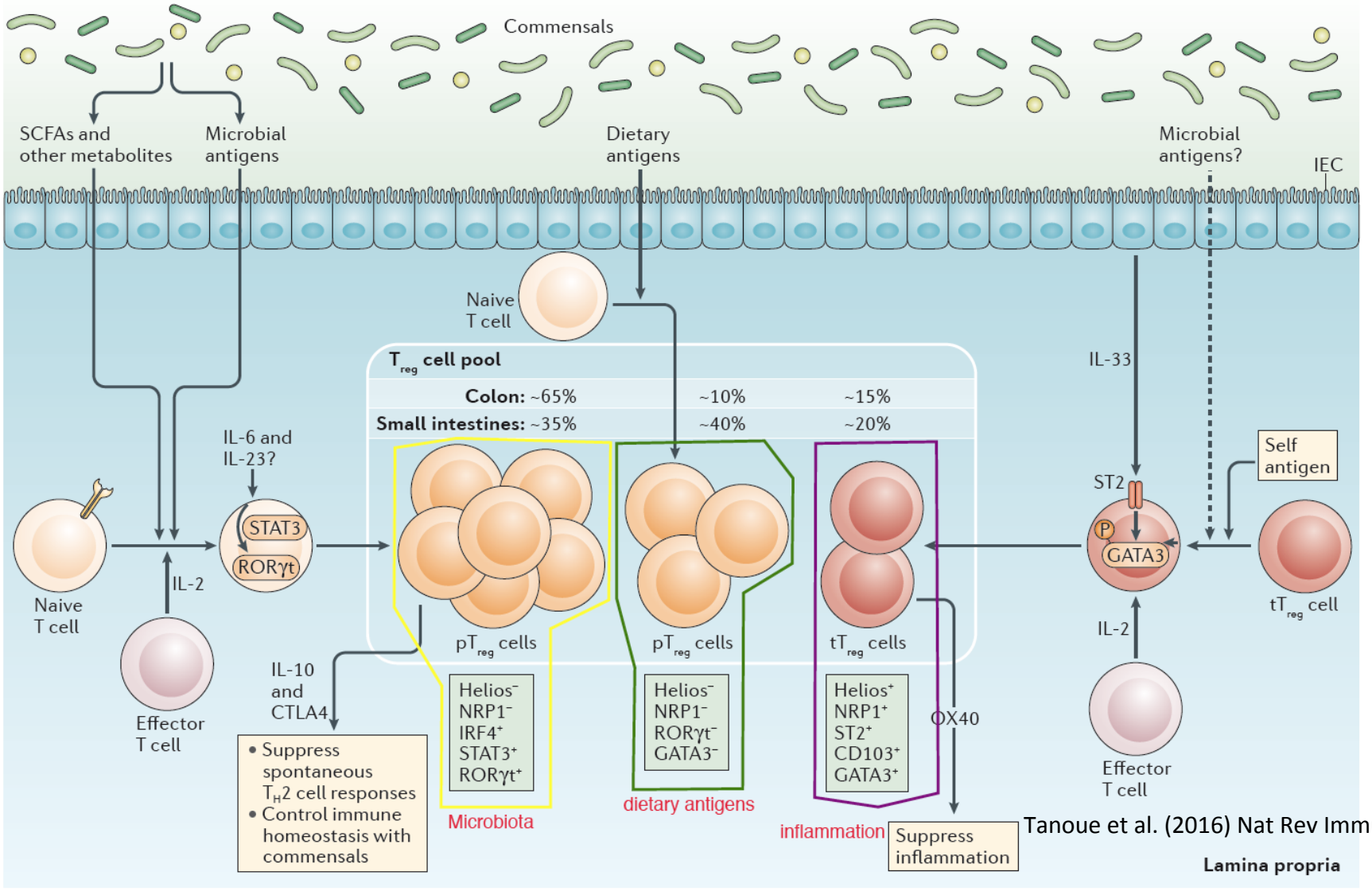
Hinterleitner & Jabri (2016) Nat Immunol

Intestinale FoxP3⁺CD4⁺ Treg exprimieren konstitutiv IL-10 und TGF-β und bestehen aus tTreg (Erkennung von Eigenantigenen) und pTreg (Erkennung von Fremdantigenen)



Tanoue et al. (2016) Nat Rev Immunol

pTreg entwickeln ihre Spezifität in der Peripherie (nicht im Thymus !) und bestehen aus 2 Subpopulationen



Tanoue et al. (2016) Nat Rev Immunol

3 Typen von Treg mit komplementären Funktionen !

Generalisten werden zu Spezialisten: „Gut homing“ durch α4:β7 und αE:β7, CCR10 und CCR9

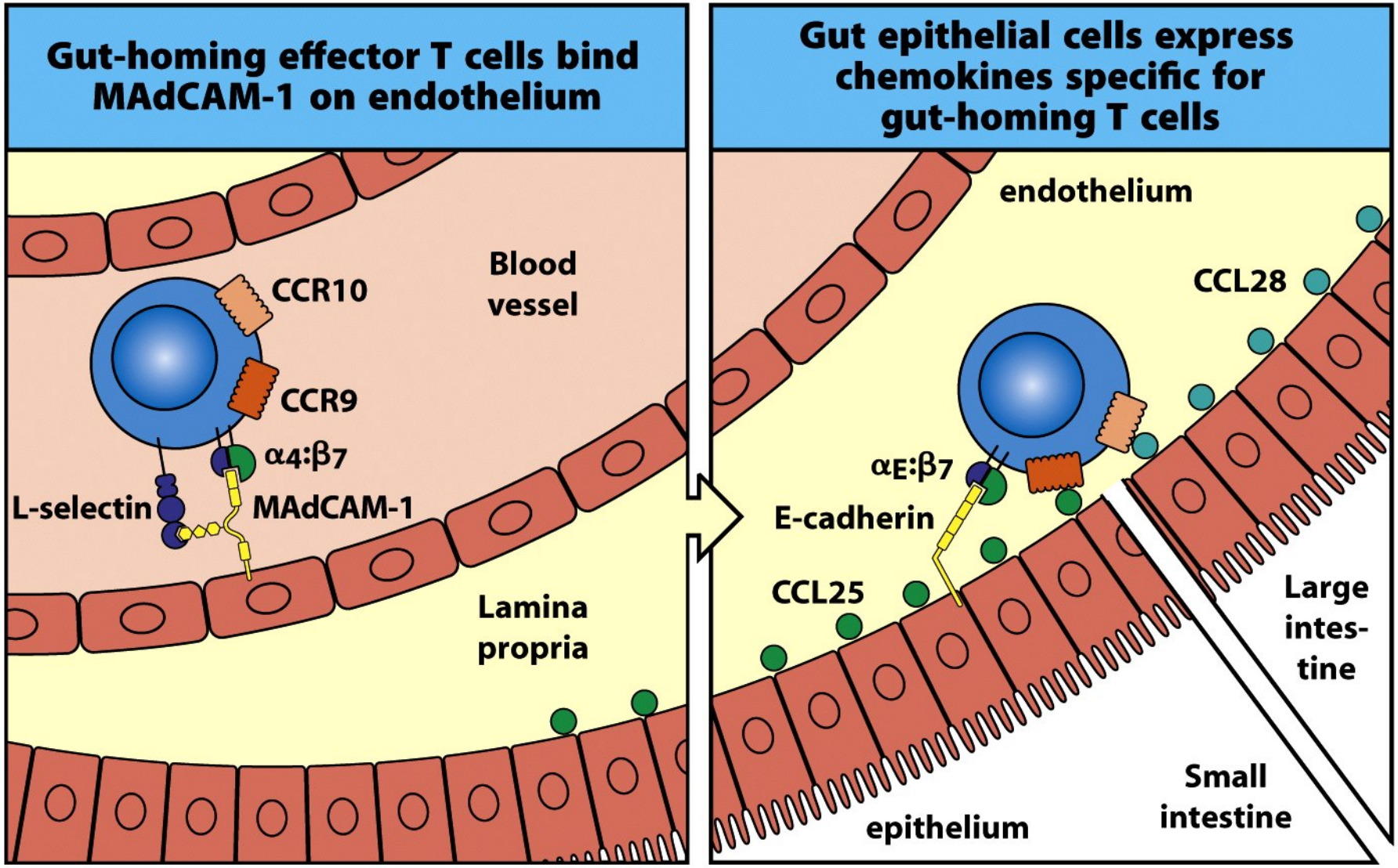


Figure 11-12 Immunobiology, 7ed. (© Garland Science 2008)

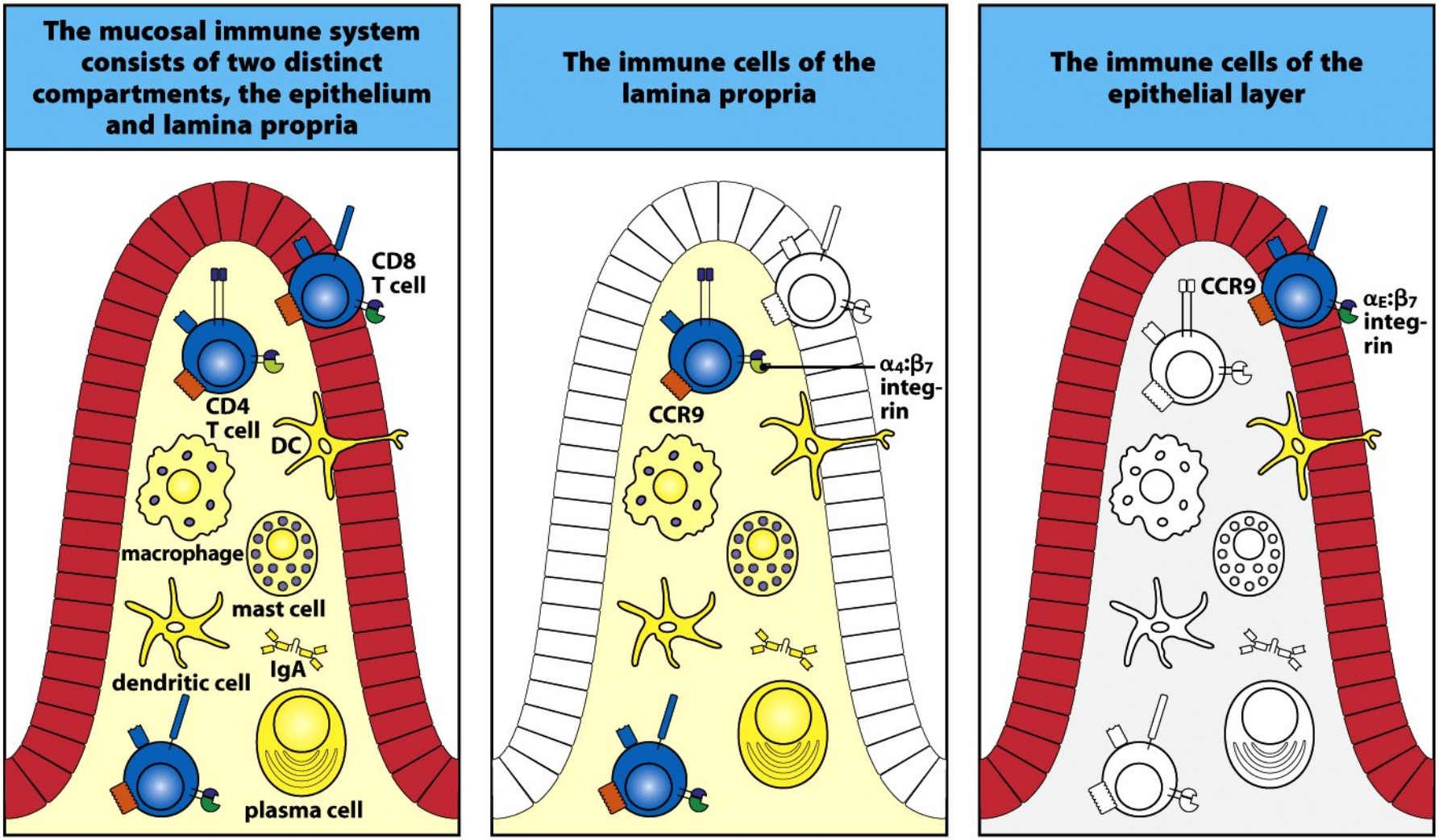
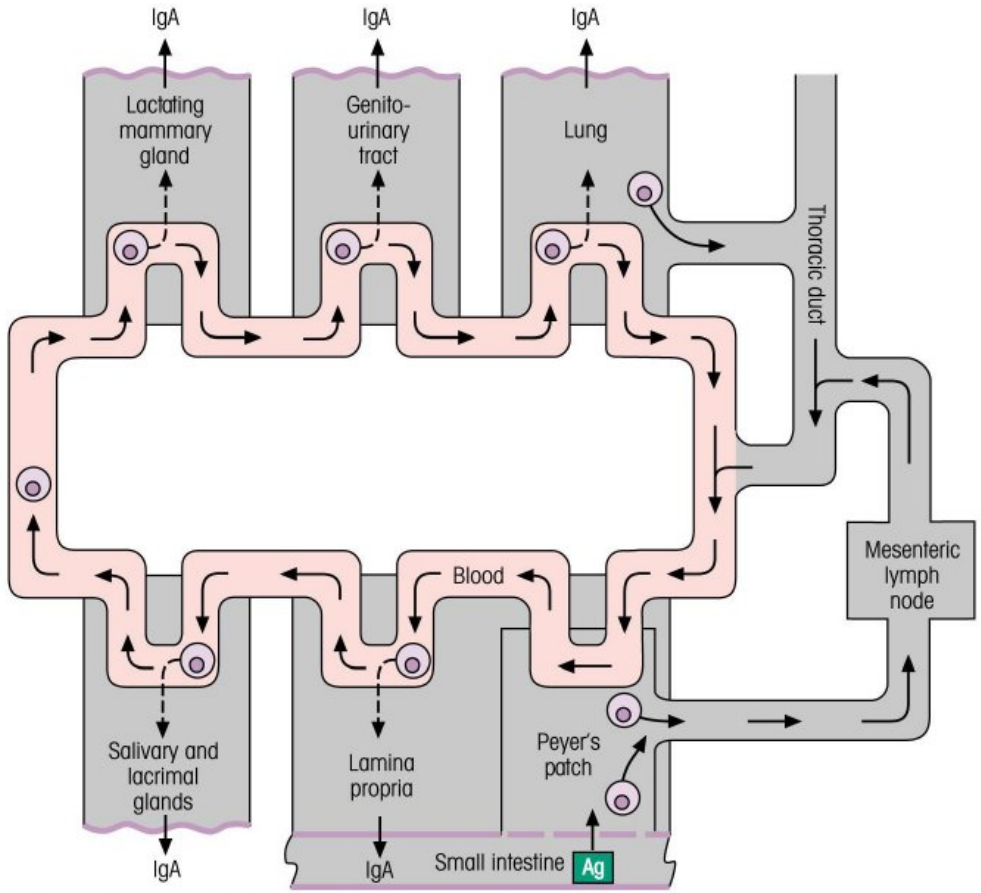


Figure 11-10 Immunobiology, 7ed. (© Garland Science 2008)

Prägung im „GALT“ und Rückkehr der Lymphocyten in das GALT und auch andere mucosale Gewebe: Prinzip des mucosalen Immunsystems



Delves *et al. Roitt's Essential Immunology, 12th ed.*

Selektive Expression des „mucosal vascular addressin“ MAdCAM-1 auf Endothelzellen

Lamina propria | Peyer‘s patch | Peripherer LN

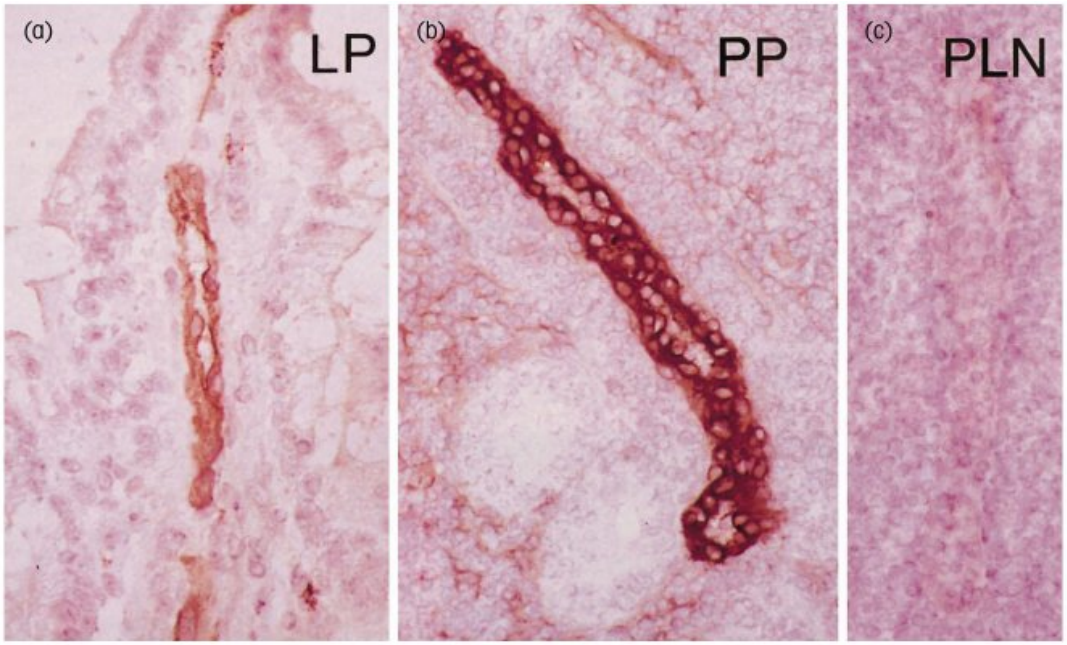


Figure 7.13. Selective expression of the mucosal vascular addressin MAdCAM-1 on endothelium involved in lymphocyte homing to gastrointestinal sites.

Immunohistologic staining reveals the presence of MAdCAM-1 (a) on postcapillary venules in the small intestinal lamina propria (LP) and (b) on high-walled endothelium of the postcapillary venules (HEVs) in Peyer's patches (PP), but its absence from (c) HEV in peripheral lymph nodes (PLN). (Reproduced with permission from Butcher E.C. *et al.* (1999) *Advances in Immunology* **72**, 209.)

Rolle der kommensalen Mikroflora für Entwicklung und Funktion des GALT

In keimfrei aufgezogenen Mäusen:

- Weniger Peyersche Plaques und Lymphfollikel (Stimulation von PRR wichtig für Entwicklung)
- Kaum IgA
- Weniger T-Zellen
- Keine orale Toleranz; Entwicklung von iTreg durch bakterielle Produkte (Butyrat induziert FoxP3)

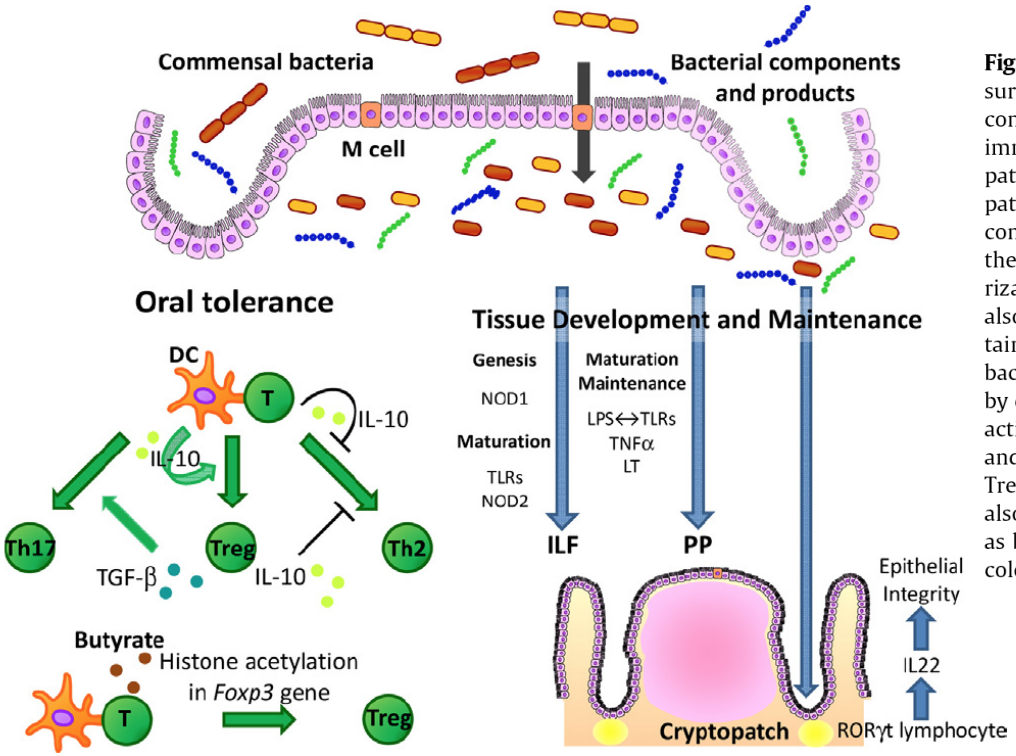


Fig. 3. Critical role of the microbiota in the mucosal immune system. Mucosal surfaces harbor a diverse bacterial community consisting of commensals and their components that is necessary for the development and maintenance of the mucosal immune system. Critical components include the IgA induction and regulation pathway, oral tolerance, and mucosa-associated immune tissues such as Peyer's patches (PPs), cryptopatches, and epithelial cells (ECs). Lipopolysaccharide (LPS) contribute to the development and maintenance of PPs, and peptidoglycan induces the genesis and maturation of ILFs through the NOD1 (nucleotide-binding oligomerization domain containing 1), NOD2 and TLRs (Toll like receptors). Commensals also induce the differentiation to RORγt$^+$ lymphocytes in cryptopatches, that maintain the epithelial integrity via production of IL22. Some antigens from commensal bacteria taken up from the intestinal lumen via M cells are thought to be captured by dendritic cells (DCs) under the follicle-associated epithelium. Subsequent interactions between DCs and T cells induce regulatory T (Treg) cells that produce IL-10 and TGF-β. IL-10 produced by DCs and Treg cells promotes the accumulation of Treg cells and also inhibits their differentiation into Th2 cells. Paradoxically, TGF-β also promotes the accumulation of proinflammatory Th17 cells. Metabolites such as butyrate that are produced by commensals also promote the differentiation of colonic Treg cells via T-cell intrinsic epigenetic upregulation of the *Foxp3* gene.

Lamichhane et al. *Vaccine* 2014

Mikroflora kann aus dem Gleichgewicht geraten

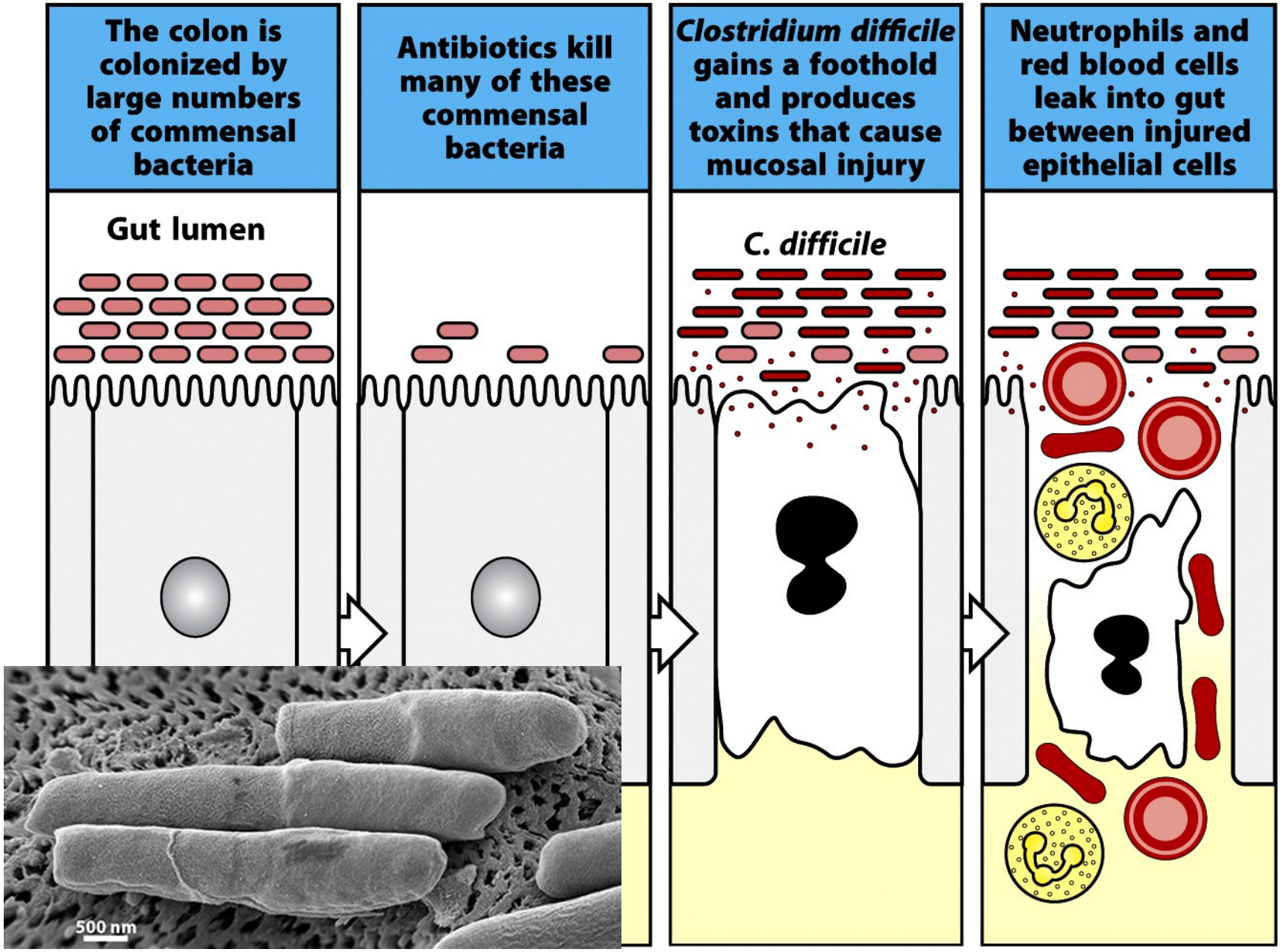
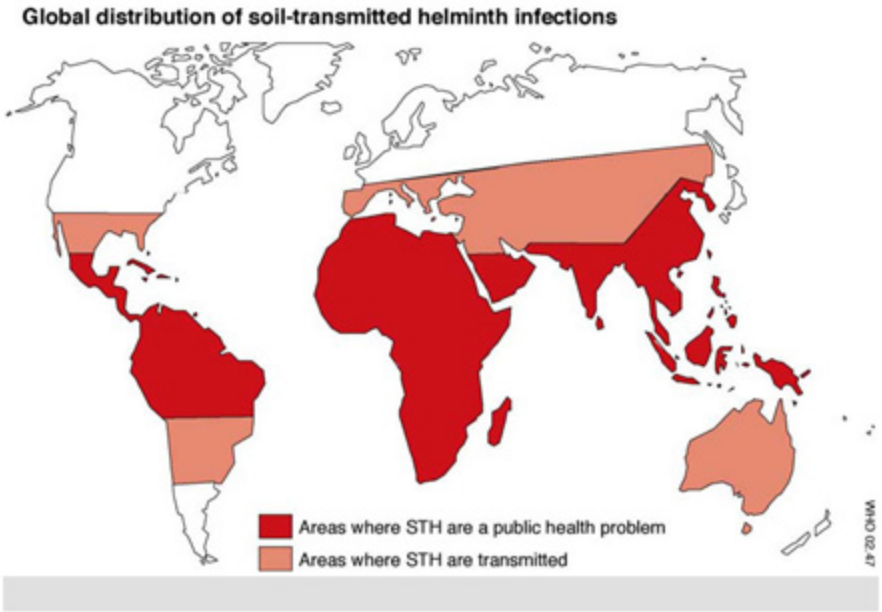


Figure 11-23 Immunobiology, 7ed. (© Garland Science 2008)

Parasitäre Würmer als globales Problem



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Parasitäre Würmer als globales Problem

Schätzungen der WHO für die betroffenen Regionen mit 4,12 Milliarden Einwohnern:

Parasit	**Infizierte in Milliarden (%)**	**% Infizierte mit ernsten gesundheitlichen Einschränkungen**
Ascaris	1,382 (33,5%)	0,3 – 1,5
Trichuris	1,007 (24,4%)	0,5 – 1,1
Ancylostomatidae („Hakenwürmer“)	1,250 (30,34%)	0,9 – 3,7

Cooper et al.(2008) *Allergy* (modifiziert)

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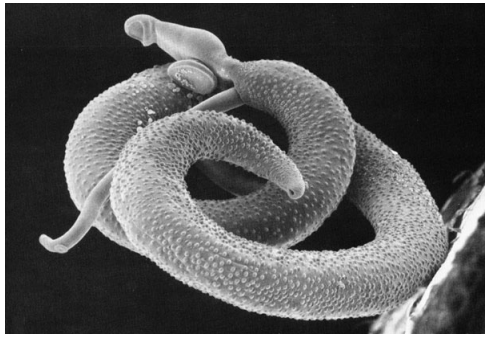
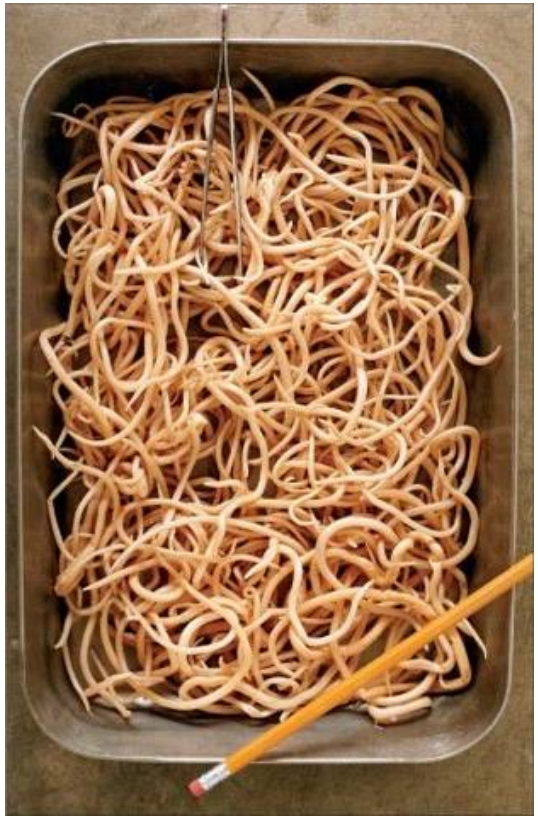
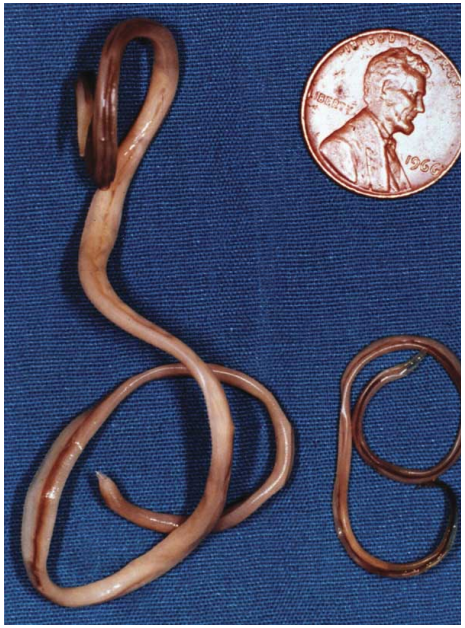
Infektionen mit parasitären Würmern verursachen hohe IgE-Spiegel







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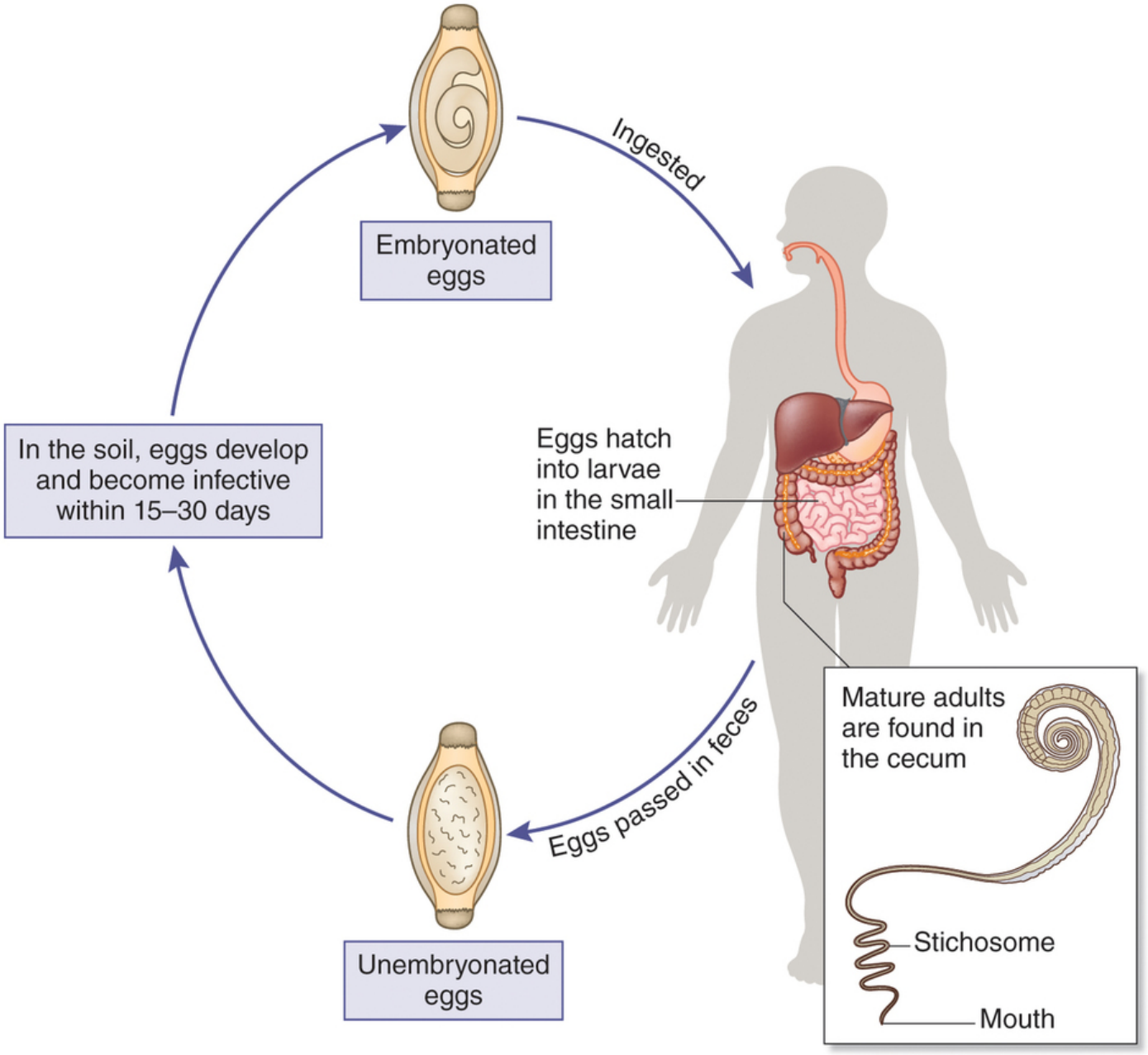
Peitschenwurm (*Trichuris trichiura*): 700 Millionen Infizierte



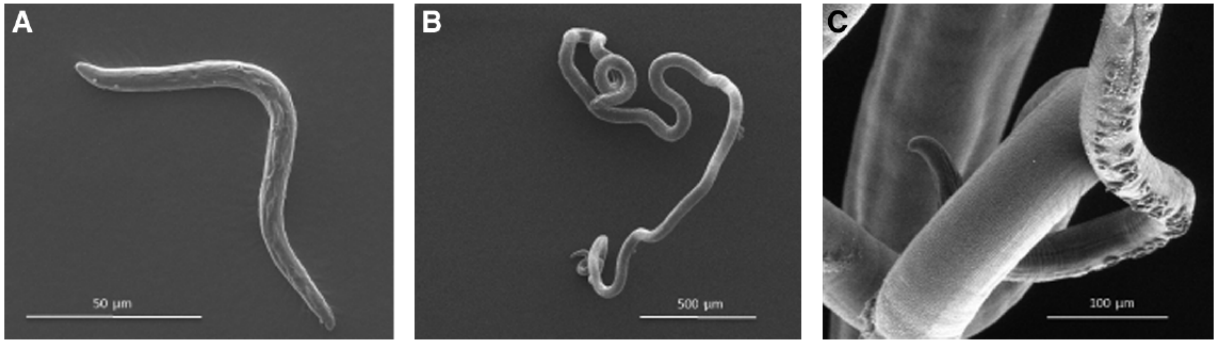
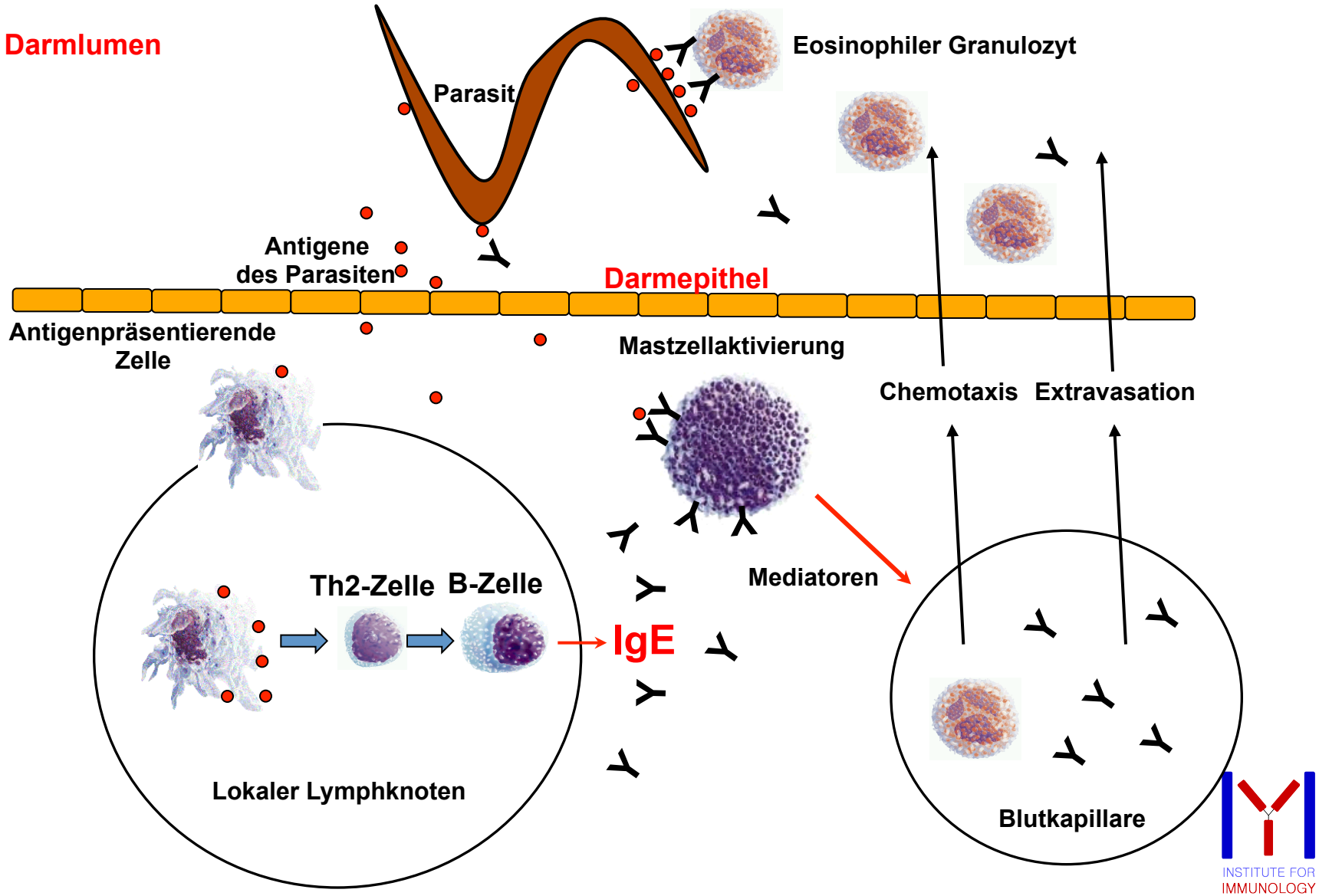


Fig. 1. Scanning electron micrographs of *Trichuris muris*. (A). L1 larvae (days 0–9/11 postinfection), which are found embedded within epithelial cells of the cecum or colon, initially toward the base of the crypts of Lieberkühn. Note lack of slender 'whip-like' anterior end. (B). L3 larvae (days 21- 24-28 postinfection), again lacking a defined slender whip-like anterior morphology. (C). Adult (days 29–32 postinfection onwards). Note slender anterior end (with cuticular cephalic glands of unknown function), which would be embedded within the epithelial cells at the crypt table in the cecum or colon. The large posterior end would extend free into the intestinal lumen to facilitate mating and egg deposition by the female worms. Images taken by U. Rössler and T. Starborg, Faculty of Life Sciences, University of Manchester.

Grencis et al. *Immunological Reviews* 2014

Mögliche Analogie: Allergische Reaktion und Parasitenabwehr



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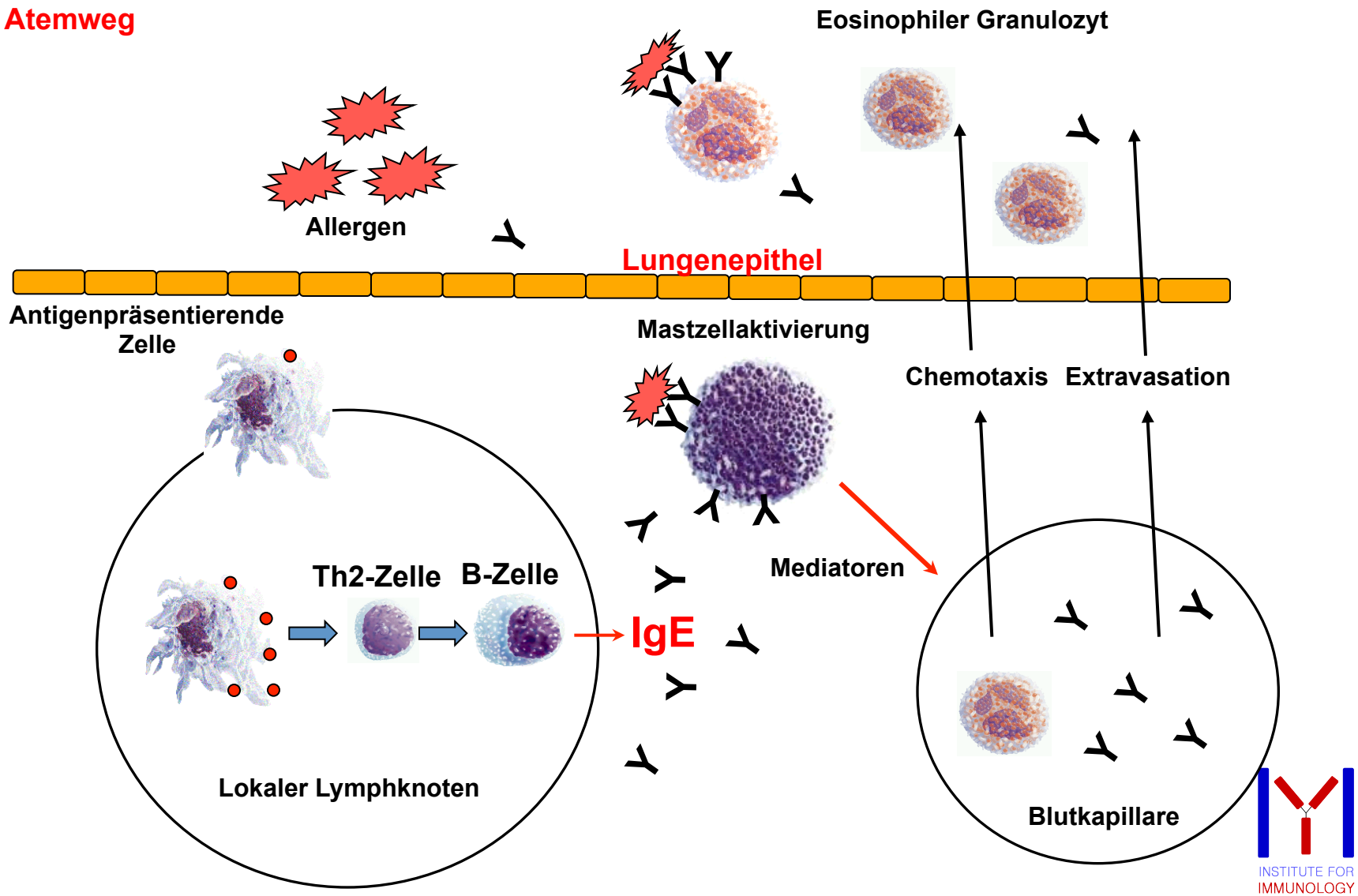
Mögliche Analogie: Allergische Reaktion und Parasitenabwehr



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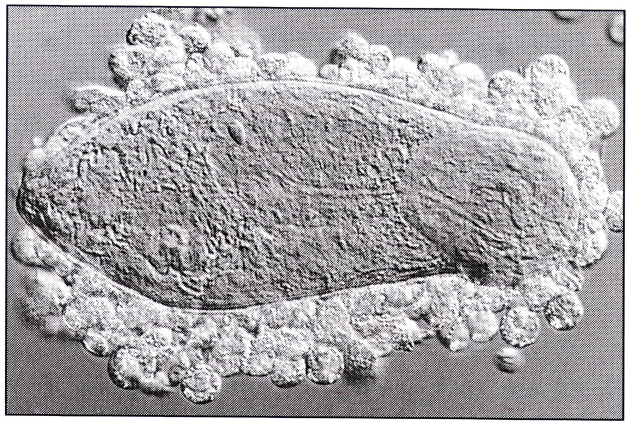
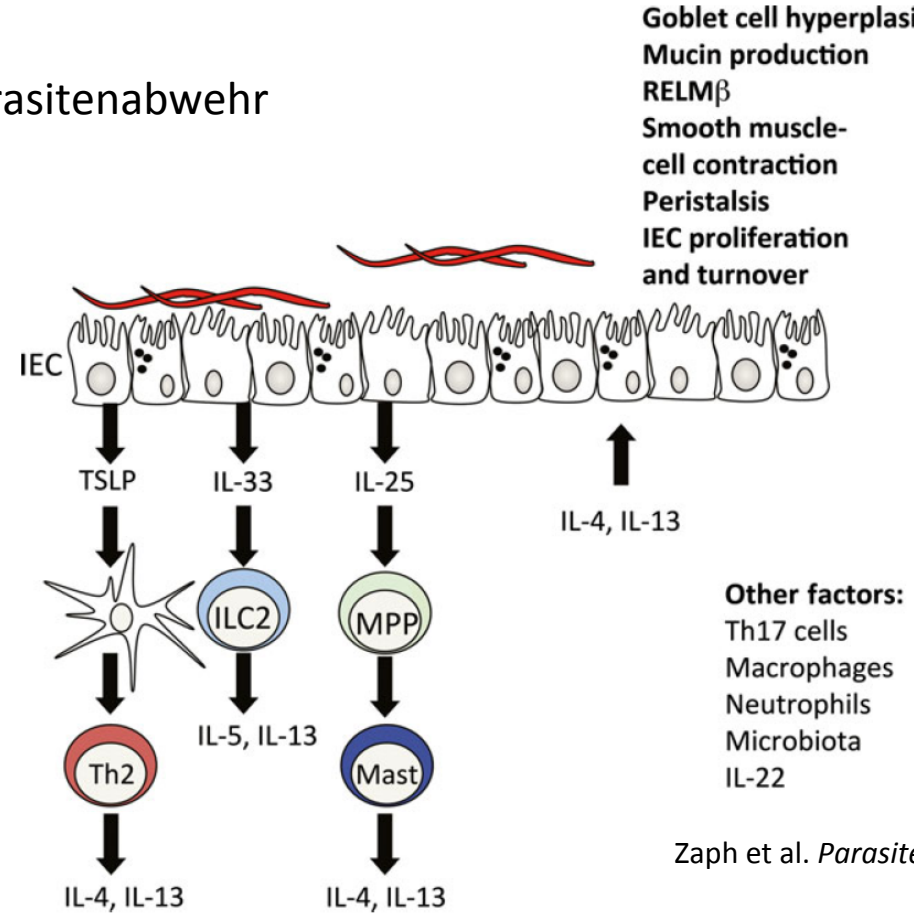
12.12 Eosinophile sezernieren eine Vielzahl hochtoxischer granulärer Proteine und anderer Entzündungsmediatoren.

Produktklasse	Beispiele	biologische Wirkungen
Enzyme	Eosinophilen-Peroxidase	toxisch für die Zielobjekte durch Katalyse von Halogenierungen, löst Histaminausschüttung aus den Mastzellen aus
	Eosinophilen-Kollagenase	Umbau der Bindegewebsmatrix
toxische Proteine	*major basic protein*	toxisch für Parasiten und Säugerzellen löst Histaminausschüttung aus den Mastzellen aus
	kationisches Eosinophilenprotein	toxisch für Parasiten, Neurotoxin
	Eosinophilen-Neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	verstärken die Bildung von Eosinophilen im Knochenmark bewirken die Aktivierung der Eosinophilen
Chemokine	IL-8	fördern die Einwanderung von Leukocyten
Lipidmediatoren	Leukotriene C4, D4, E4	verursachen Kontraktion der glatten Muskulatur erhöhen Gefäßpermeabilität verstärken Schleimsekretion
	plättchenaktivierender Faktor *(platelet-activating factor)*	lockt Leukocyten an verstärkt Produktion von Lipidmediatoren aktiviert neutrophile und eosinophile Zellen sowie Blutplättchen



9.33 Eosinophile attackieren eine *Schistosoma*-Larve in Gegenwart von Serum eines infizierten Patienten. Große Parasiten wie etwa Würmer können nicht von Phagocyten aufgenommen werden. Ist der Wurm aber mit Antikörpern überzogen, besonders mit IgE, können Eosinophile ihn aufgrund einer Bindung an den hochaffinen Fcε-Rezeptor-I angreifen. Ähnliche Attacken auf verschiedene größere Ziele sind auch anderen Zellen mit Fc-Rezeptoren möglich. Diese Zellen setzen dann aus ihren Granula toxische Inhaltsstoffe frei, die direkt auf das Ziel gerichtet sind; dieser Prozess wird als Exocytose bezeichnet. (Foto mit freundlicher Genehmigung von A. Butterworth.)

Th2-lastige Parasitenabwehr



Zaph et al. *Parasite Immunology* 2014

Figure 1 Mechanisms of expulsion of intestinal worms. Although the initial interaction between helminths and the host are poorly defined, infection results in the production of epithelial cell-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25. Resistance to some helminth infections is independent of TSLP. Induction of TSLP regulates dendritic cell (DC) production of IL-12 and promotes basophilia (Baso), both leading to priming of type $CD4^+$ T-cell responses (Th2). IL-33 is normally a nuclear protein that is released upon cellular damage. IL-33 is a potent activator of type 2 innate lymphoid cells (ILCs) that occurs early after helminth infection. IL-25 is induced in response to the microbiota and is increased following helminth infection. IL-25 induces a multipotent progenitor cell (MPP) that can give rise to other innate cell lineages. The result of these pathways is to promote a T_H2 cell response and high levels of IL-4 and IL-13. These cytokines promote worm expulsion by inducing physiological changes in the intestinal epithelium. Some expulsion mechanisms include goblet cell hyperplasia and mucus secretion, increased proliferation and turnover and smooth muscle contractility and peristalsis. In addition, although they are not critical for resistance, other factors such as cells (neutrophils, macrophages and Th17 cells), cytokines (IL-22) and the microbiota are dynamically regulated during infection and most likely play a regulatory role in the development of protective immunity to helminth infection.

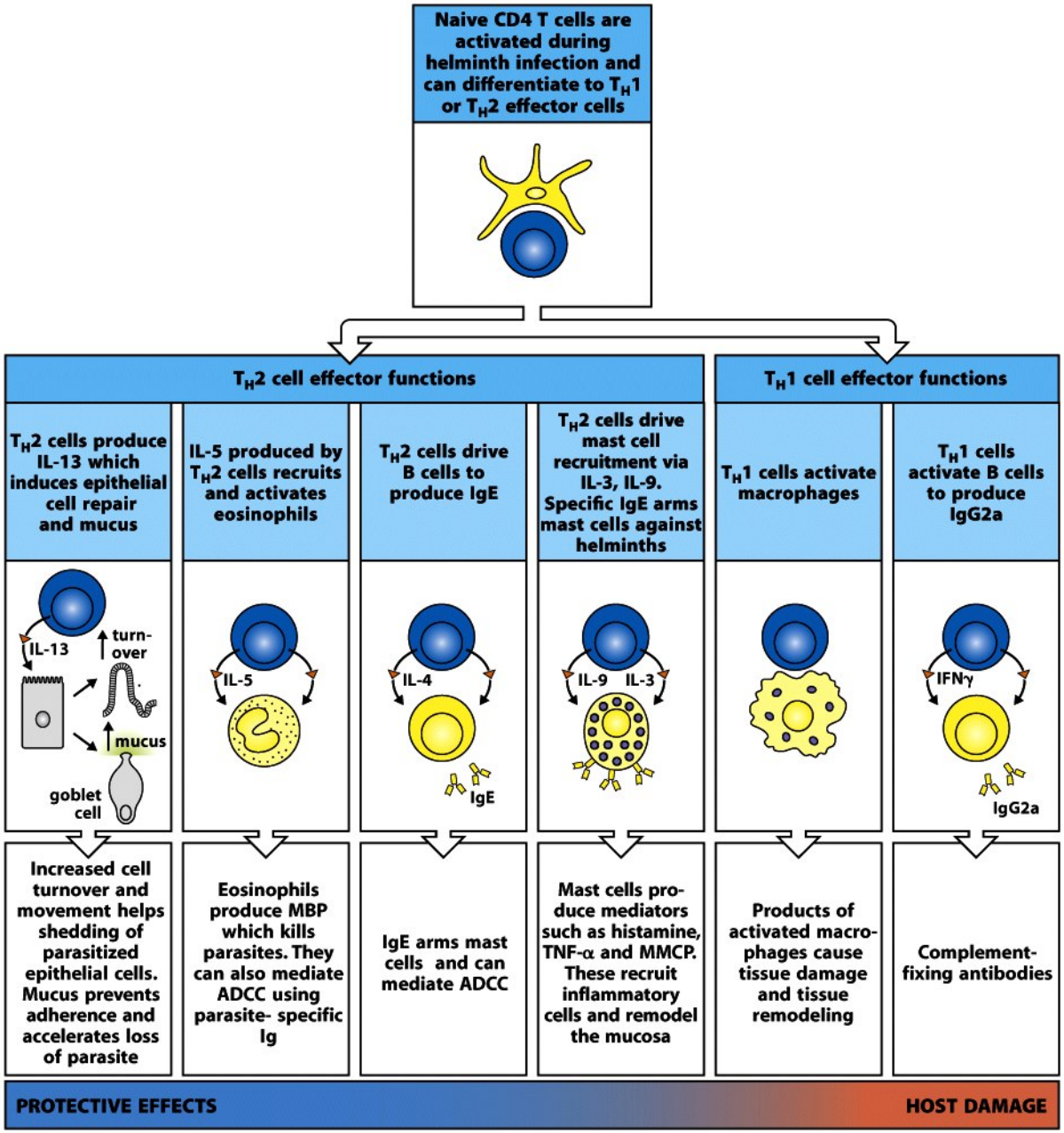


Figure 11-27 Immunobiology, 7ed. (© Garland Science 2008)

Wackelt das Dogma ?

Effekt einer anti-IgE Therapie (Omalizumab) auf die Infektionsanfälligkeit gegenüber Darmparasiten

- **137 Patienten (Brasilien) mit allergischem Asthma oder perennialer Rhinitis**
- **Vor Beginn der Studie parasitenfrei (medikamentöse Behandlung)**
- **Behandlung über 52 Wochen (doppelblinde und Placebo-kontrollierte Studie)**

	Omalizumab (n=68)	Placebo (n=69)
Wurminfektionen	**38 (55,9%)**	**31 (44,9%)**
Protozoeninfektionen (intestinal)	**34 (50%)**	**31 (44,9%)**

Signifikanz des Unterschiedes fraglich (Größe der Stichprobe !)

Kein Einfluß auf den Schweregrad der Infektionen !!!

Cruz et al. (2007) *Clin Exp Allergy*
Cooper et al. (2008) *Allergy* 63:409

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Die Rolle von IgE und Mastzellen in Allergien und Infektionen mit Helminthen

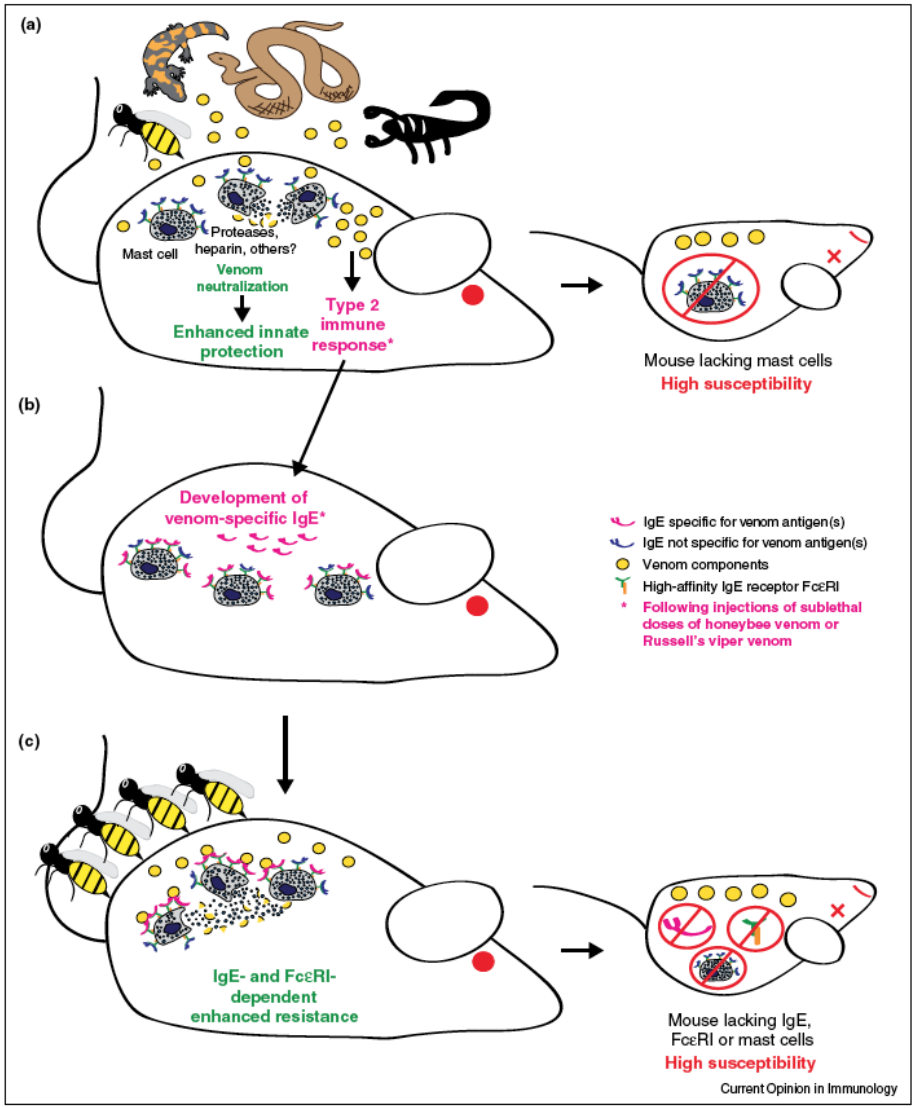
	Typ I Allergie	Parasitäre Infektionen
Abhängig von Mastzellen/IgE	ja	*Trichinella spiralis, Schistosoma mansoni*
Allergen-spezifisches IgE	oft	Selten; enorme Mengen polyklonales IgE
Anaphylaktische Reaktionen	ja	Selten

Infektionen mit Helminthen schützen vor der Entwicklung von Typ I Allergien !

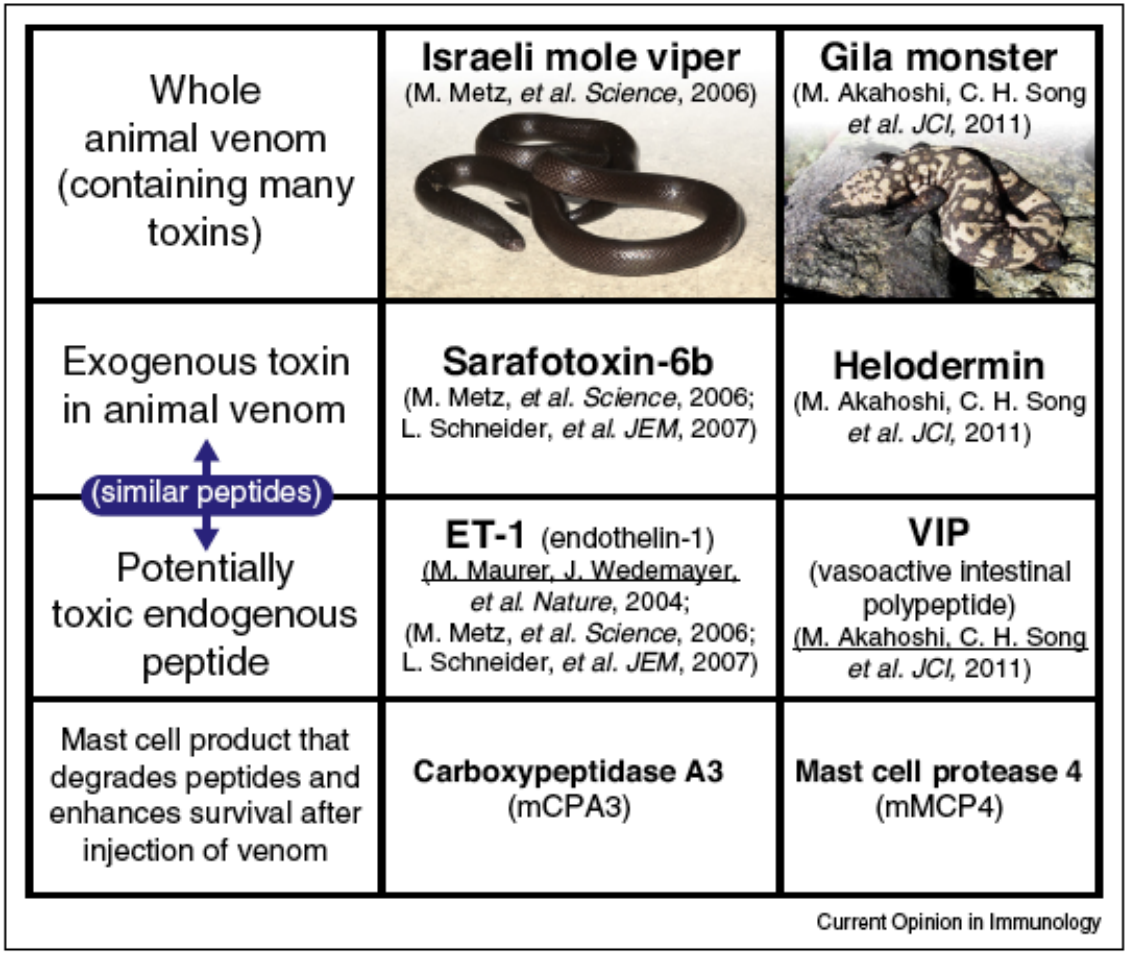
→ „IgE blocking hypothesis“: Absättigung von IgE Rezeptoren mit unspezifischem/polyklonalem IgE

→ Parasiten bewirken Immunsuppression durch Induktion von T regulatorischen Zellen

„Toxin Hypothesis“ (Margie Profet, 1991): Mastzellen schützen vor Umweltgiften



Innate and IgE/FcεRI-dependent activation of mast cells by venom components can enhance resistance to potentially lethal doses of whole venoms. **(a)** MCs can enhance *innate* resistance of mice to the morbidity and mortality induced by the whole venoms of the honeybee, three species of snakes (Israeli mole viper, western diamondback rattlesnake, and southern copperhead), the Gila monster lizard, and two species of scorpions through mechanisms that depend on the release of mediators that can neutralize toxic components of venoms. **(b)** Injection of a sub-lethal dose of honeybee venom (BV) or Russell's viper venom induces an adaptive type 2 immune response in mice that is associated with development of IgE antibodies that can increase the resistance of mice to a potentially lethal dose of the same venom. **(c)** The protective effect of the type 2 immune response against BV is mediated by IgE antibodies, FcεRI and mast cells.



Mast cells can enhance resistance to both high levels of endogenous peptides (helping to restore homeostasis) and structurally similar peptides in reptile venoms. Mouse MC cytoplasmic granules contain proteases such as carboxypeptidase A3 (mCPA3) and mast cell protease 4 (mMCP4) that, upon secretion by activated mast cells, can degrade certain endogenous peptides, such as endothelin-1 (ET-1) and vasoactive intestinal polypeptide (VIP), respectively, as well as structurally similar peptides contained in the venoms of poisonous reptiles, such as sarafotoxin 6b in the venom of the Israeli mole viper (*Atractaspis engaddensis*) and helodermin in the venom of the Gila monster (*Heloderma suspectum*). The ability of mast cells to be activated to degranulate by components of venoms such as these, which can act at the same receptors which recognize the corresponding structurally similar endogenous peptides, permits mast cells to release proteases that can reduce the toxicity of these peptides and which thereby help to enhance the survival of mice injected with the whole venoms of these reptiles, that contain many toxins in addition to sarafotoxin 6b and helodermin. This mechanism may also permit mast cells to restore homeostasis in settings associated with markedly increased levels of the endogenous peptides. This is a modified version of Fig. 4 in the review: Rouse-Whipple Award Lecture: The mast cell-IgE paradox: From homeostasis to anaphylaxis, by Stephen J. Galli, reproduced with the permission of the publisher.

Infektionskrankheiten: 500m² Schleimhautoberfläche versus 2m² Haut
Schleimhäute als wichtigste Eintrittspforte für Erreger

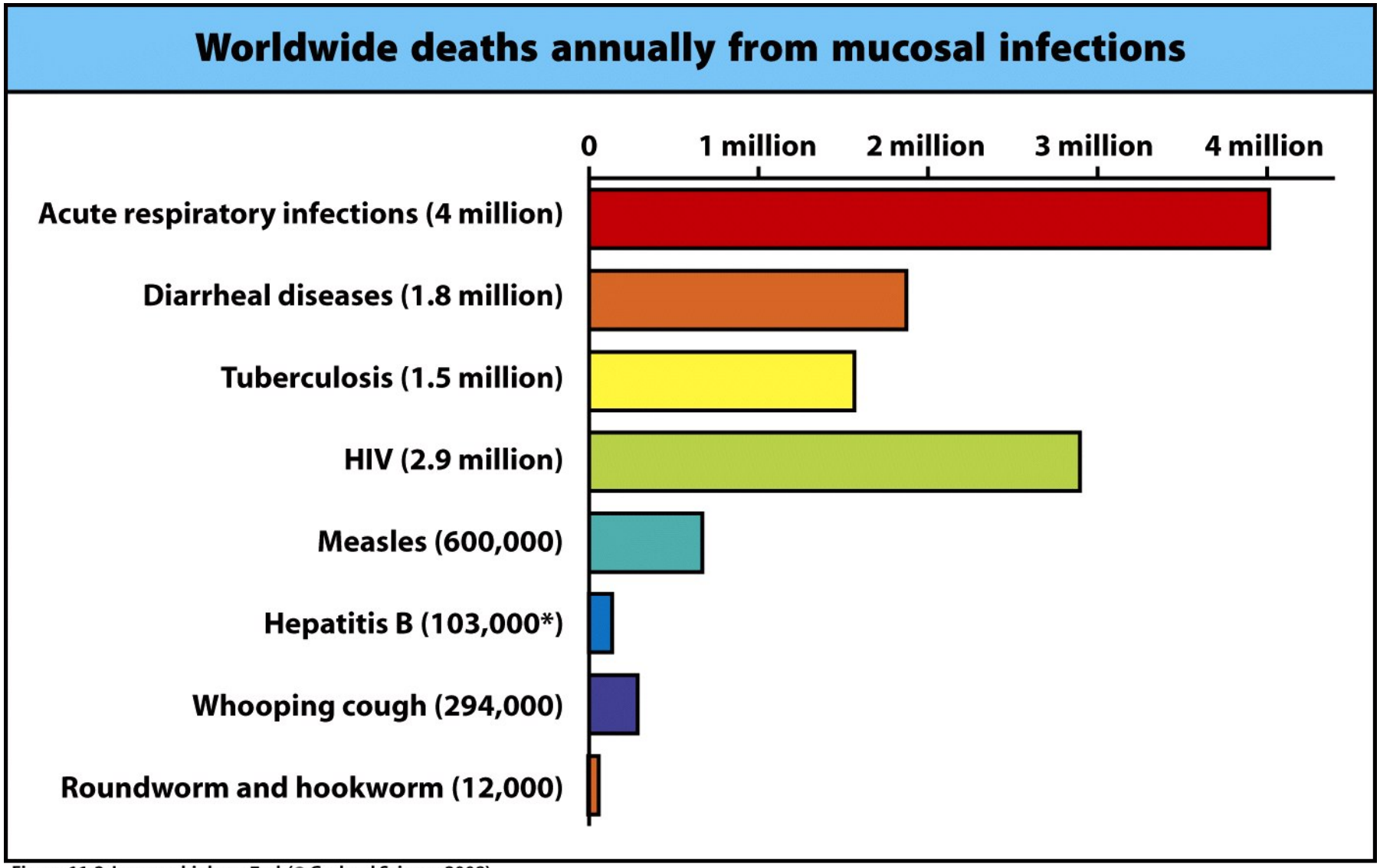


Figure 11-2 Immunobiology, 7ed. (© Garland Science 2008)

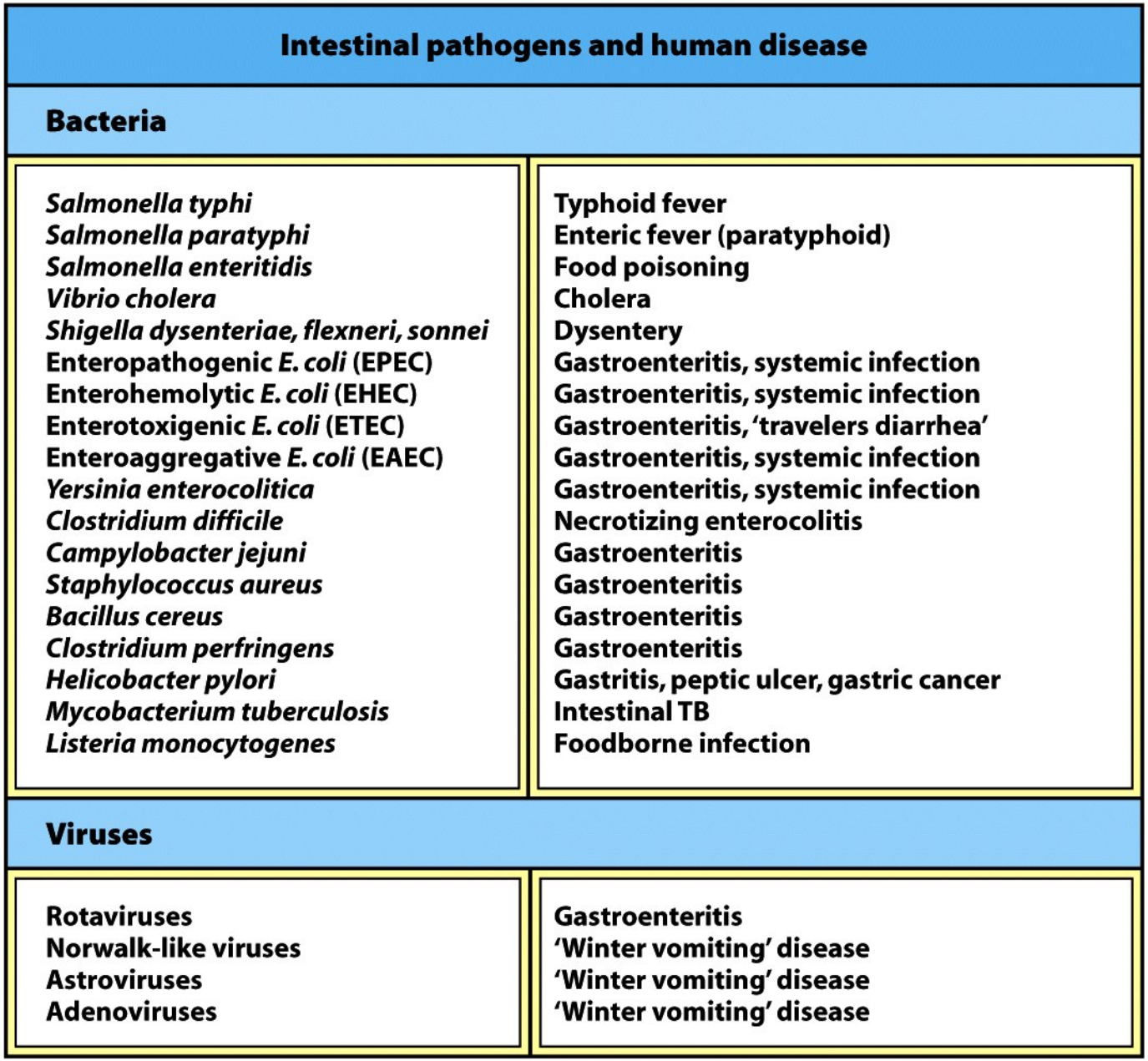
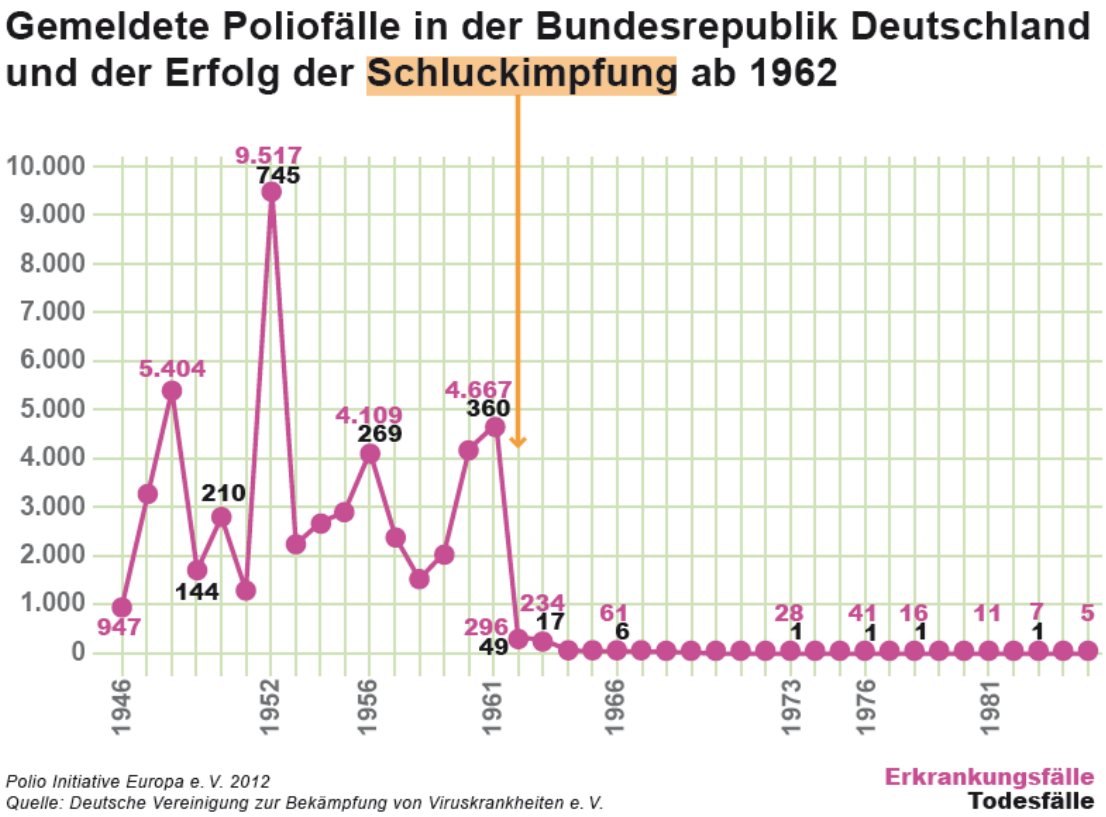


Figure 11-18 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Intestinal pathogens and human disease	
Parasites	
Protozoa	
Giardia lamblia	Gastroenteritis
Blastocystis hominis	Gastroenteritis (esp. in immunocompromised hosts)
Toxoplasma gondii	Gastroenteritis, systemic disease (esp. in immunocompromised hosts)
Cryptosporidium parvum	Gastroenteritis (esp. in immunocompromised hosts)
Entamoeba histolytica	Amebic dysentery + liver abscesses
Microsporidium species	Diarrheal disease
Helminths	
Ascaris lumbricoides	Roundworm infection of small intestine
Necator americanus	Hookworm infection of small intestine
Strongyloides species	Roundworm infection of small intestine
Enterobius species	Pinworm infection of large intestine
Trichinella spiralis	Trichinosis
Trichuris trichiura	Whipworm infection of large intestine
Taenia species	Tapeworm infections
Schistosoma species	Schistosomiasis: enteritis, mesenteric vein infection

Figure 11-18 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

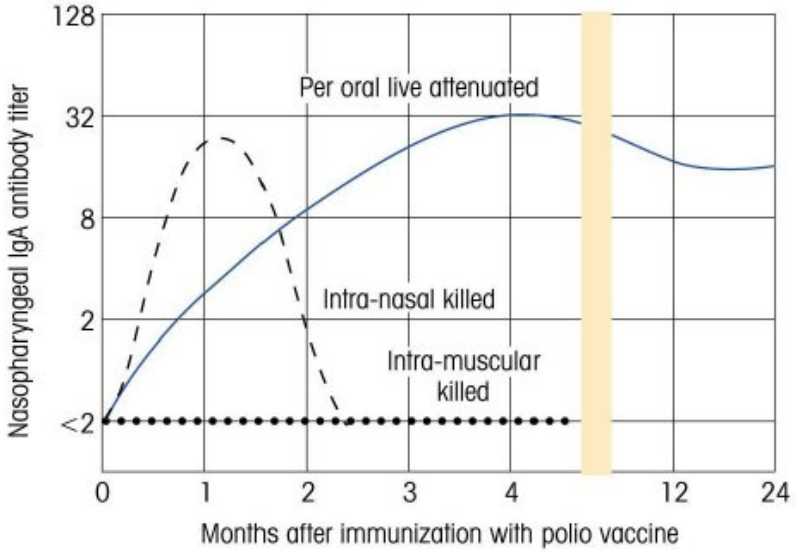
Das Poliovirus und die unheilbare Poliomyelitis (spinale Kinderlähmung)



Orale Vakzinierungen

Herkömmliche Impfungen (*i.m., s.c*) induzieren nur schwache bis keine mucosale Immunität (spez. Homing !)
Immunisierungen über Schleimhäute wünschenswert
Aber: Starke Toleranzmechanismen, Durchbrechung mit Adjuvantien schwierig

Oraler Polioimpfstoff (Sabin 1961): Attenuiertes Virus als Lebendimpfstoff („stille Feiung“)



Durch Sabin-Impfstoff in D 1-3 Tote/Jahr (vermutlich) durch Revertanten, daher ab 1998 Verwendung eines (weniger wirksamen) Todimpfstoffes, der injiziert wird

Orale Vakzinierungen gegen: Cholera, Rotavirus, Salmonella typhimurium, Influenza (nasal)