Chemocezione e microbioma intestinale

Significato funzionale della chemocezione intestinale

- Modulare l'attività motoria e la secrezione intestinale per consentire:
- Assorbimento nutrienti
- Allontanamento tossici (vomito diarrea comportamenti di avversione per il cibo)

- Le cellule enteroendocrine trasducono i segnali luminali attivando target locali o sistemici, sia mediante la stimolazione di fibre nervose che il rilascio di fattori solubili

- Modulano: MOBILITA'

  FLUSSO SANGUIGNO

  SECREZIONE DI ACQUA ED ELETTROLITI

Cellule enteroendocrine

- Costituiscono circa l'1% delle cellule intestinali
- Hanno un turn-over molto veloce (4-6 gg)
- Se ne conoscono diverse popolazioni:

G cells: gastrina

P e X cells: gelina

D cells: somatostatina

I cells: CCK

Cellule enterocromaffini: serotonina

K cells: GIP

L cells: GLPs e PYYY

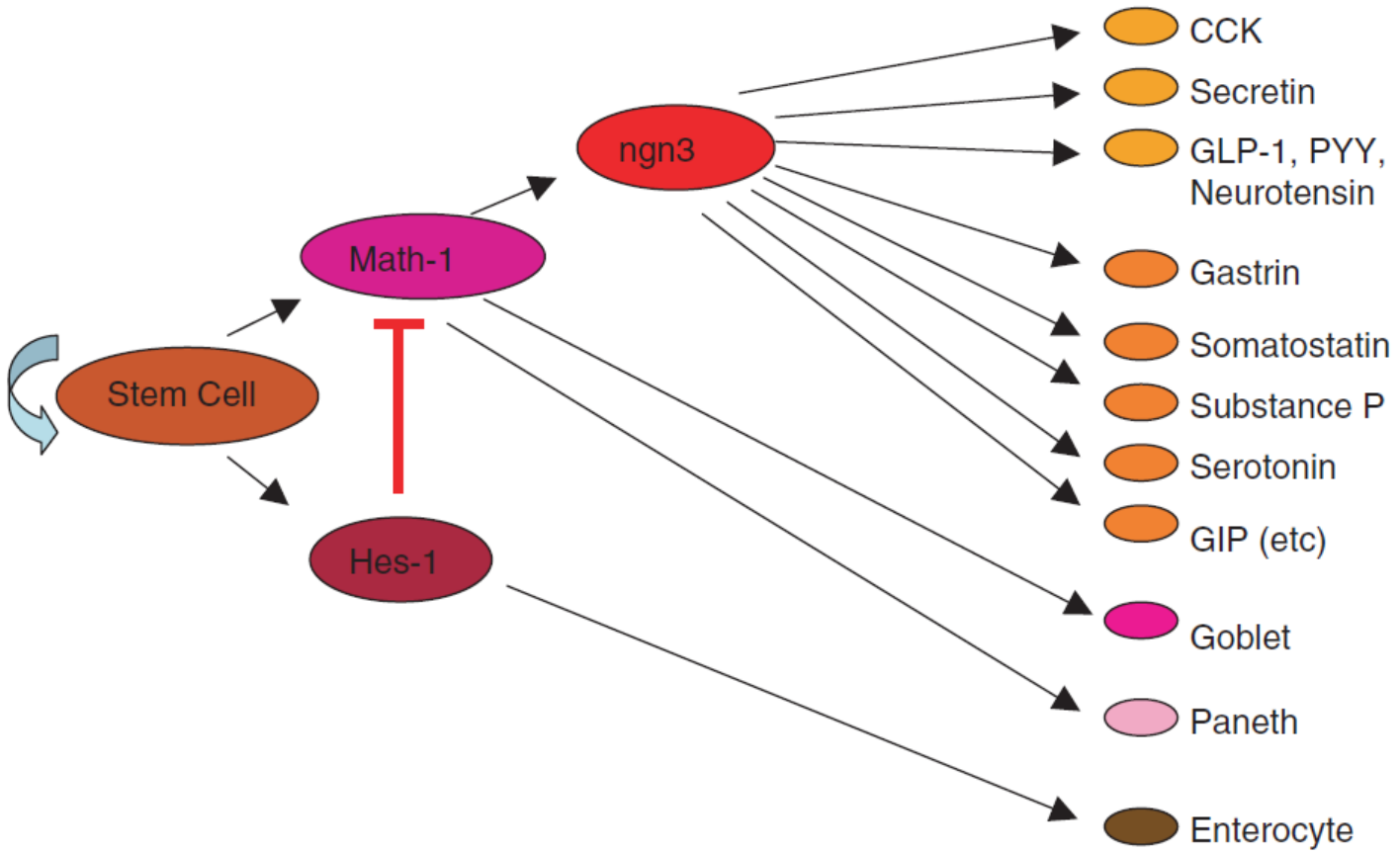


Figure 1. Intestinal stem cell pathways for terminal differentiation into absorptive enterocytes and secretory (EEC, Goblet and Paneth) cell lineages.

- Si distinguono open eclosed cells: a seconda che arrivino o no al lume intestinale.

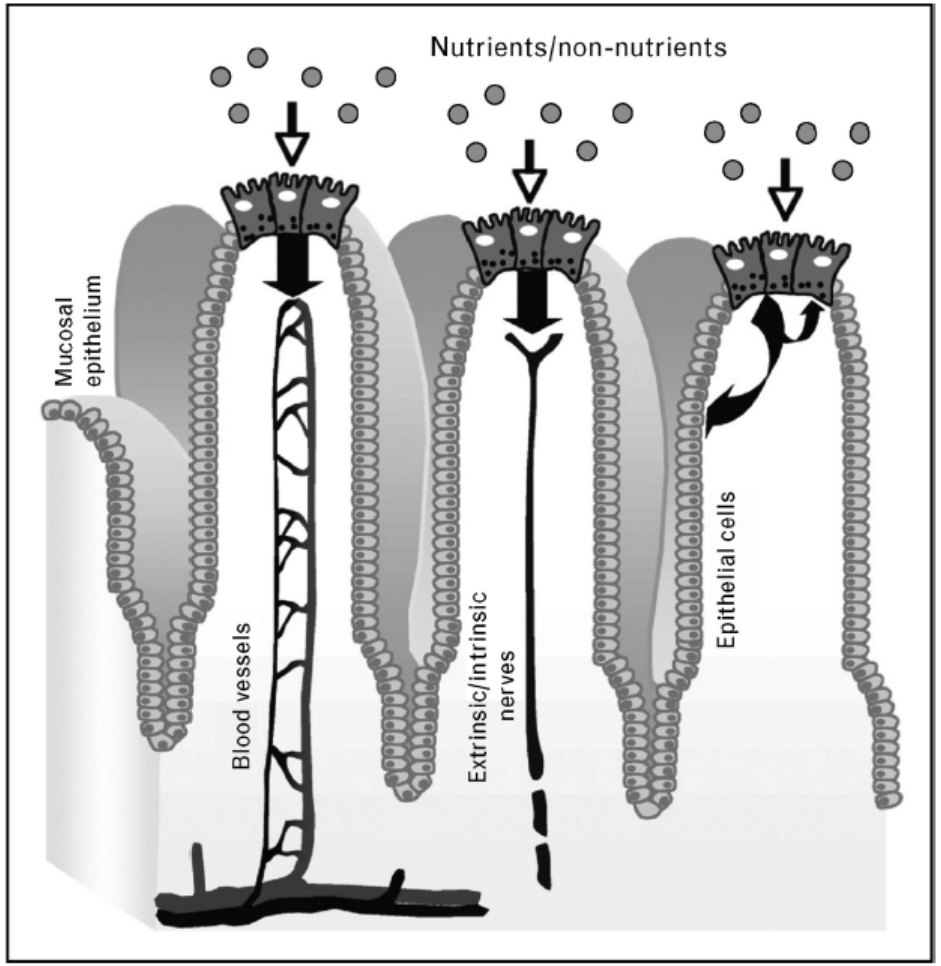


Figure 1. Possible pathways involved in nutrient sensing by enteroendocrine cells
Putative sites of chemosensing are localized on the cell surface. When the luminal content (nutrients and non-nutrients) comes in contact with enteroendocrine cells, it induces release of hormones that enter blood vessels or signaling molecules that activate extrinsic or intrinsic afferent neurons thereby sending neuronal messages to the central nervous system and to enteric neurons. Released molecules can also act directly on adjacent cells, including other enteroendocrine cells and other types of epithelial cells like brush cells

esempio

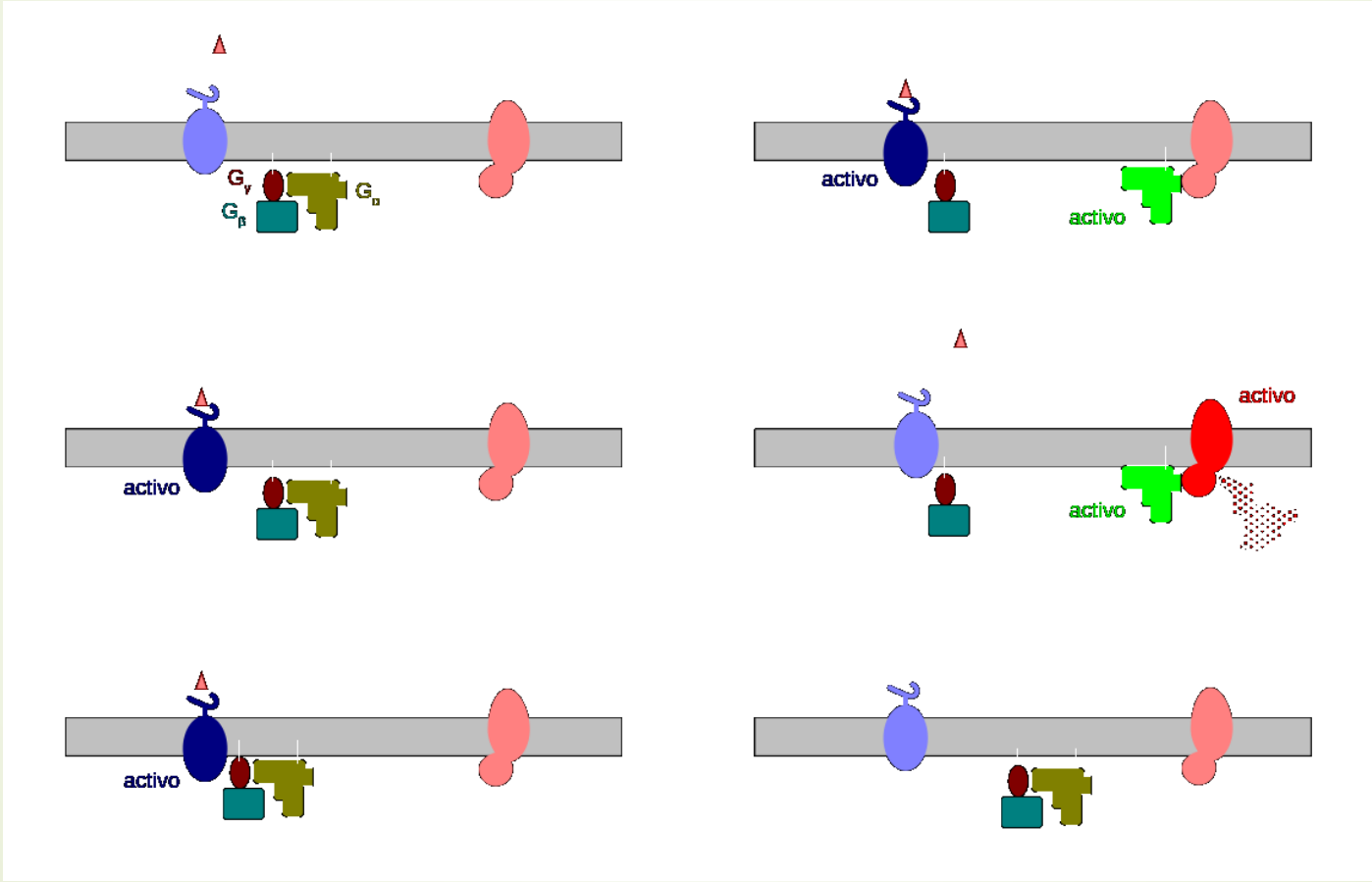
- Presenza di aa e Ca^{2+} nel lume
- G cells (open cells) liberano Gastrina
- La gastrina, per via sistemica induce le cellule enterocromaffini a secernere Istamia
- L'Istamina stimola la secrezione acida da parte delle cellule parietali

Implicazioni in patologie del tratto GI:

- PYY
- GLP1
- GIP

Sono implicati in eziopatogenesi di patologie quali obesità e diabete di tipo 2.

Trasduzione del segnale: recettori GCPR



Trasduzione del segnale

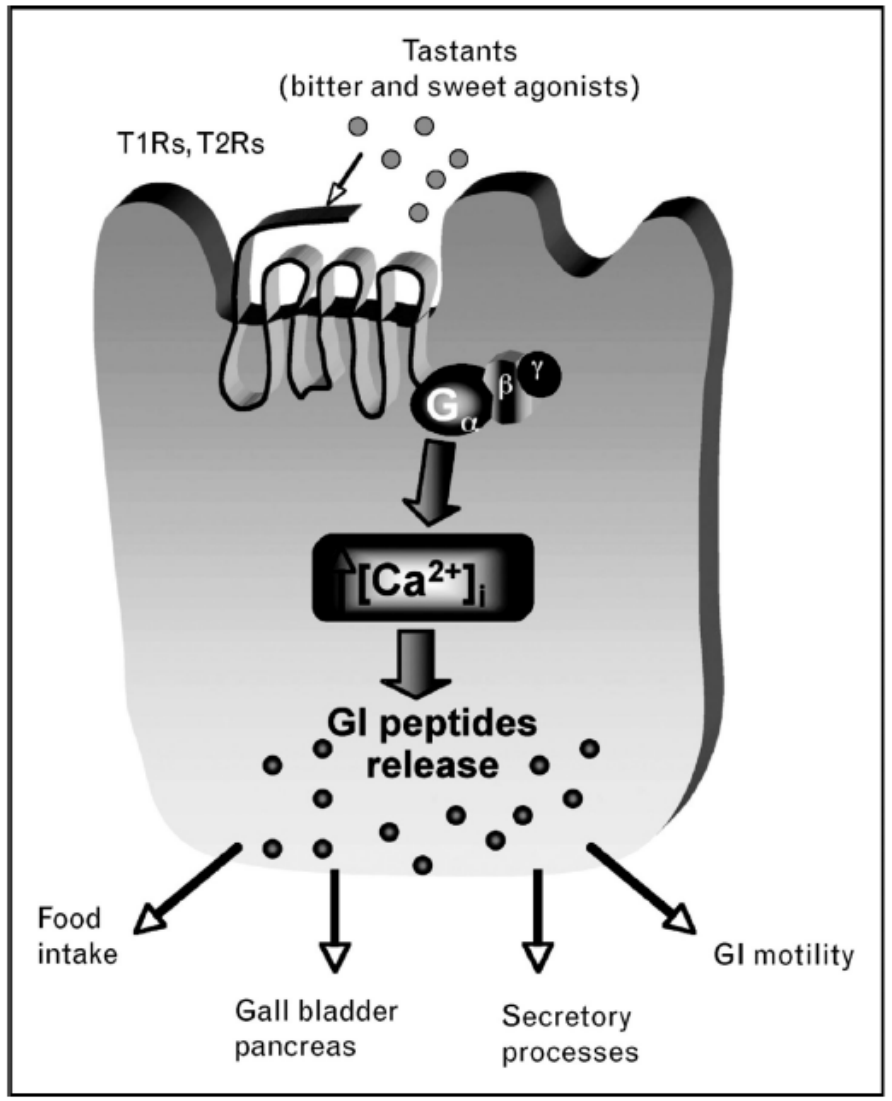


Figure 2. Postulated mechanism involving sweet (T1R) and bitter (T2R) taste receptors on enteroendocrine cells

Taste receptors couple to G proteins upon activation to induce intracellular Ca^{2+} increase resulting in release of peptides, which regulate a variety of gastrointestinal functions, including action on organs associated with the gut like the gallbladder and pancreas, via neuronal or humoral pathways to induce digestion and absorption or protection from harmful substances. Released peptides can also control food intake through the gut–brain axis.

Gut microbiota

- Ha un influenza su: maturazione del sistema immunitario
  digestione degli alimenti
  metabolismo dei farmaci
  detossificazione
  produzione di vitamine
  prevenzione dell'adesione batterica

- Il feto è sterile, la colonizzazione inizia con il passaggio nel canale del parto, con l'allattamento e continua per tutta la vita.
- Il microbiota intestinale è influenzato da:

- Dieta
- Terapie (es. antibiotici)
- Microorganismi ambientali

E dipende anche da:

- Sesso
- Età
- Origine geografica

- L'intestino umano ospita un enorme numero e varietà di microrganismi, comprendente almeno 10^{14} batteri appartenenti a 1.000 specie. La dimensione del genoma di questo organo microbico, collettivamente chiamato microbioma, supera la dimensione del genoma nucleare umano da due ordini di grandezza

- La concentrazione batterica aumenta progressivamente lungo l'intestino tenue da 10^4 nel digiuno a 10^7 colonie unità per grammo di contenuto luminale alla fine dell'ileo, con prevalenza di aerobi gram-negativi e alcuni anaerobi obbligati. Nel colon, il numero di batteri raggiunge circa 10^{12} unità formanti colonie per grammo, con una predominanza di anaerobi. E 'stato stimato che il 60% della massa fecale sia rappresentato da batteri.

Table 1. Animals, experimental design, and analytical methods used in selected studies aimed at characterizing the canine GI microbiome

Reference	Sample type	Type of dog	Age of dog	Breed	Sex	BCS	Method
Garcia-Mazcorro *et al.* (2012)	Gastric and duodenal biopsies	Research dogs (*n*=8)	0.75 years	Mixed breeds	Four females, four males	–	qPCR, FISH, V1–V3 region 16S rRNA gene pyrosequencing
Garcia-Mazcorro *et al.* (2011)	Fecal	Privately owned dogs (*n*=12)	0.7–10.2 years	Ten different breeds	Five females, seven males	4–8 (9 point scale)	V1–V3 region 16S rRNA gene pyrosequencing
Handl *et al.* (2011)	Fecal	Privately owned dogs (*n*=12)	0.7–10.2 years	Ten different breeds	Five females, seven males	4–8 (9 point scale)	V1–V3 region 16S rRNA gene pyrosequencing
Swanson *et al.* (2011)	Fecal	Research dogs (*n*=6)	1.7 years	Two mongrels, four hound-crosses	Females	No obese dogs	Whole genome pyrosequencing
Middelbos *et al.* (2010)	Fecal	Research dogs (*n*=6)	1.7 years	Two mongrels, four hound-crosses	Females	No obese dogs	V3 region 16S rRNA gene pyrosequencing
Jia *et al.* (2010)	Fecal	Research dogs (*n*=8)	4–13 years	Beagles	–		FISH hybridization
Suchodolski *et al.* (2009)	Jejunal mucosa	Research dogs (*n*=5)	2 years	–	–	3–4 (5-point scale)	16S rRNA gene sequencing
Xenoulis *et al.* (2008)	Duodenal biopsies	Privately owned dogs (*n*=9)	2.7–6 years	Three greyhounds, six beagles	Six females, three males	–	16S rRNA gene pyrosequencing
Suchodolski *et al.* (2008)	Duodenum, jejunum, ileum, and colon	Research dogs (*n*=6)	3.6–7 years	Hound dogs	Three males, three females	–	V1–V3 region 16S rRNA gene pyrosequencing

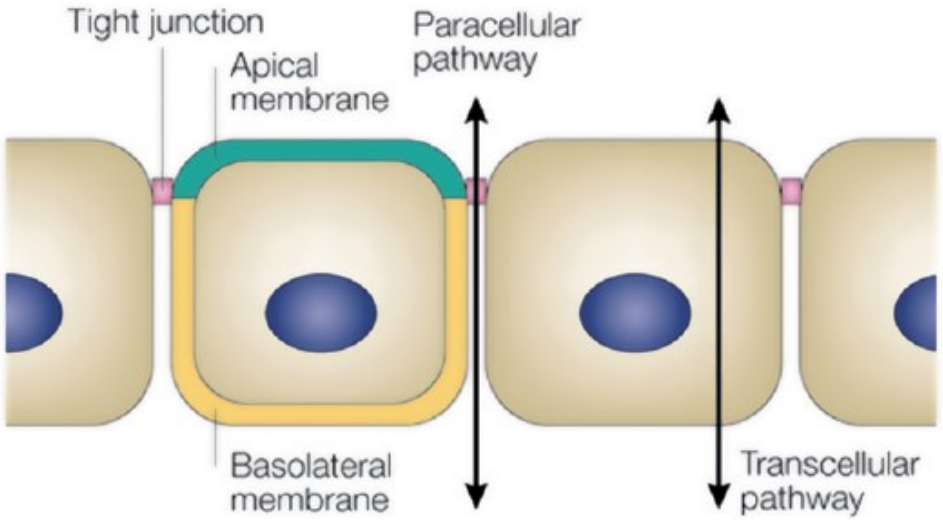
Table 2. Bacterial phyla (expressed as percentage of sequences) in fecal and mucosal samples of select canine GI microbiome studies

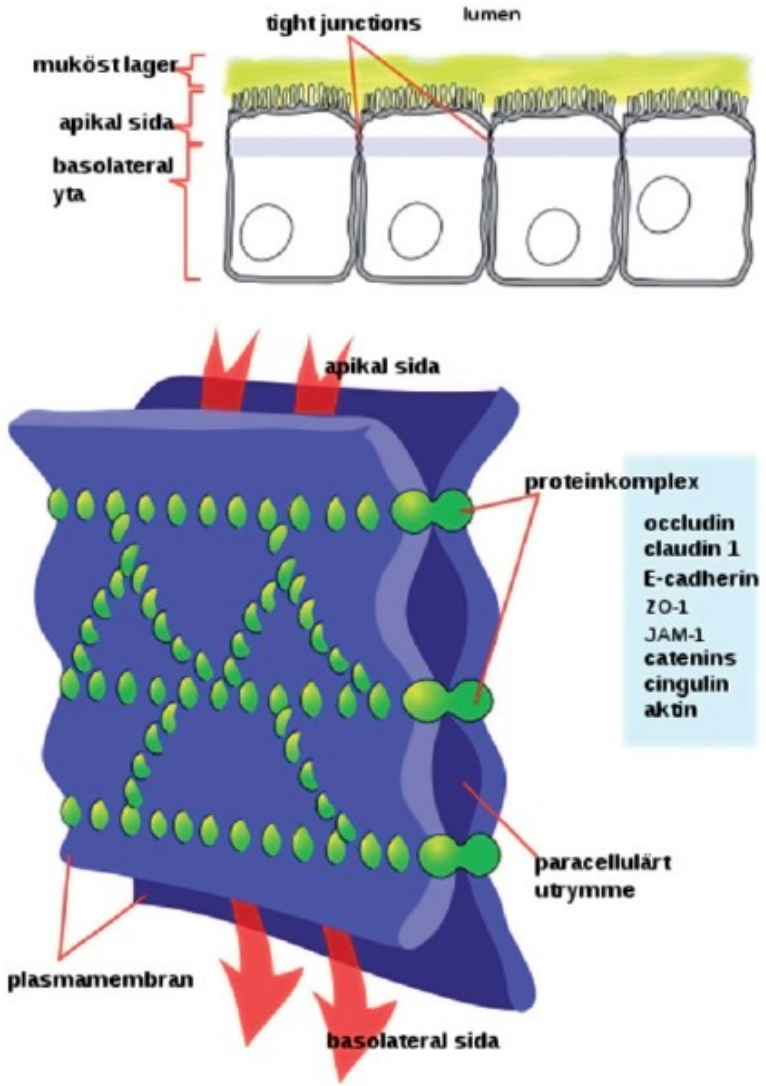
Reference	Sample type	Method	Actinobacteria	Bacteroidetes	Firmicutes	Fusobacteria	Proteobacteria
Garcia-Mazcorro *et al.* (2011)	Fecal	V1–V3 region 16S rRNA gene pyrosequencing	0.9–2.0	0.1–1.1	97.5	0.1–0.8	0.1
Handl *et al.* (2011)	Fecal	V1–V3 region 16S rRNA gene pyrosequencing	1.8	2.2	95	0.3	–
Swanson *et al.* (2011)	Fecal	Whole genome pyrosequencing	1	37–38	31–35	7–9	13–15
Middelbos *et al.* (2010)	Fecal	V3 region 16S rRNA gene pyrosequencing	0.8–1.4	32–34	15–28	24–40	5–6
Suchodolski *et al.* (2009)	Jejunal mucosa samples	16S rRNA gene pyrosequencing	11.2	6.2	15	5.4	46.7
Xenoulis *et al.* (2008)	Duodenal biopsies	16S rRNA gene sequencing	1.0	11.2	46.4	3.6	26.6
Suchodolski *et al.* (2008)	Duodenum, jejunum, ileum and colon contents	V1–V3 region 16S rRNA gene pyrosequencing	–	12.4	47.7	16.6	23.3

Table 3. Most abundant bacterial families and genera in fecal and mucosal samples of select canine GI microbiome studies

Reference	Sample type	Method	Most abundant families	Most abundant genera
Handl *et al.* (2011)	Fecal	V1–V3 region 16S rRNA gene pyrosequencing	Ruminococcaceae, Clostridiaceae, Lachnospiracea, and Erysipelotrichaceae	*Clostridium, Ruminococcus, Dorea, Roseburia, Clostridium* clusters XIVa and cluster XI,
Swanson *et al.* (2011)	Fecal	Whole genome pyrosequencing		–
Middelbos *et al.* (2010)	Fecal	V3 region 16S rRNA gene pyrosequencing		–
Suchodolski *et al.* (2009)	Jejunal mucosa samples	16S rRNA gene pyrosequencing	Moraxellaceae, Spirochaetaceae, Corynebacteriaceae, Clostridiaceae, Enterobacteriaceae, and Fusobacteriaceae	–
Xenoulis *et al.* (2008)	Duodenal biopsies	16S rRNA gene pyrosequencing	Clostridiaceae, Carnobacteriaceae, Turicibacteriaceae, Pasterellaceae, Helicobacteriaceae, Porphyromonadaceae, and Spirochaetaceae	–
Suchodolski *et al.* (2008)	Duodenum, jejunum, ileum and colon contents	V1–V3 region 16S rRNA gene sequencing	–	*Fusobacterium, Lactobacillus, Streptococcus, Clostridium, Escherichia*, and *Klebsiella*

–, Data not provided.


Tight junction
Apical membrane
Paracellular pathway
Basolateral membrane
Transcellular pathway


tight junctions
lumen
mukös lager
apikal sida
basolateral yta
apikal sida
proteinkomplex
occludin
claudin 1
E-cadherin
ZO-1
JAM-1
catenins
cingulin
aktin
paracellulärt utrymme
plasmamembran
basolateral sida

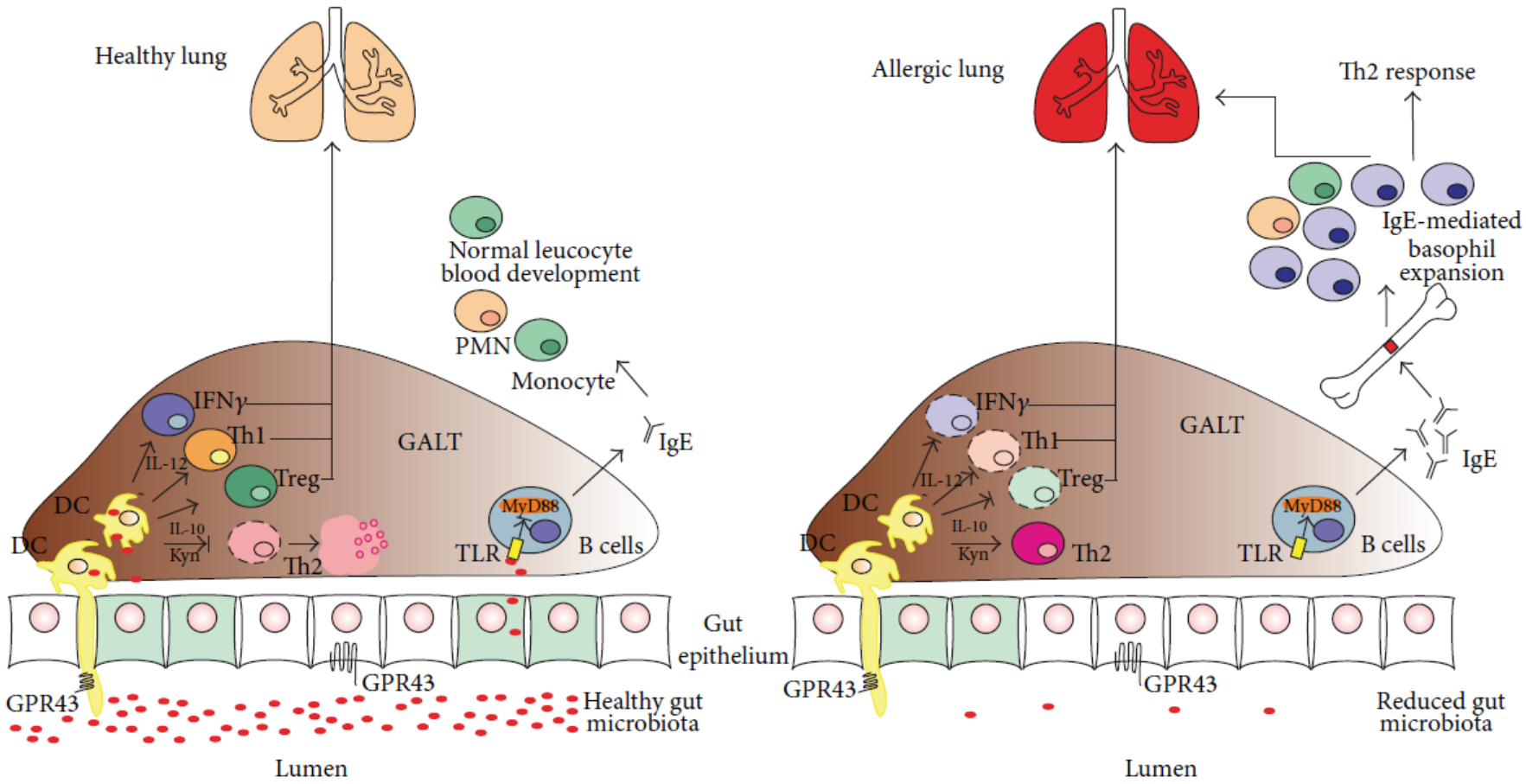


FIGURE 1: Schematic representation of the pulmonary allergic response induced by gastrointestinal (GI) immune cells and two microbiota-related conditions (a healthy gut microbiota and a reduced gut microbiota following antibiotic treatment). Microbes in the intestines are sampled by Toll-like receptors (TLRs) on DCs either directly in the lumen or in the gut-associated lymphoid tissue (GALT). In the healthy gut microbiota, polymorphonuclear development (PMN) is normal and DCs become regulatory DCs (DCr) that promote development of Tregs and/or Th1 cells and natural killer (NK) cells. These NK cells inhibit Th2 inflammation. Antibiotic treatment kills a large proportion of healthy microbiota, leading to a reduced gut microbiota and an inflammatory environment without DCs, Th1 cells or NK cells. In this environment, an unhealthy microbiota elevates serum immunoglobulin E (IgE) levels, increases circulating basophil populations, and exacerbates basophil-mediated Th2 responses (adapted from Forsythe [110]).

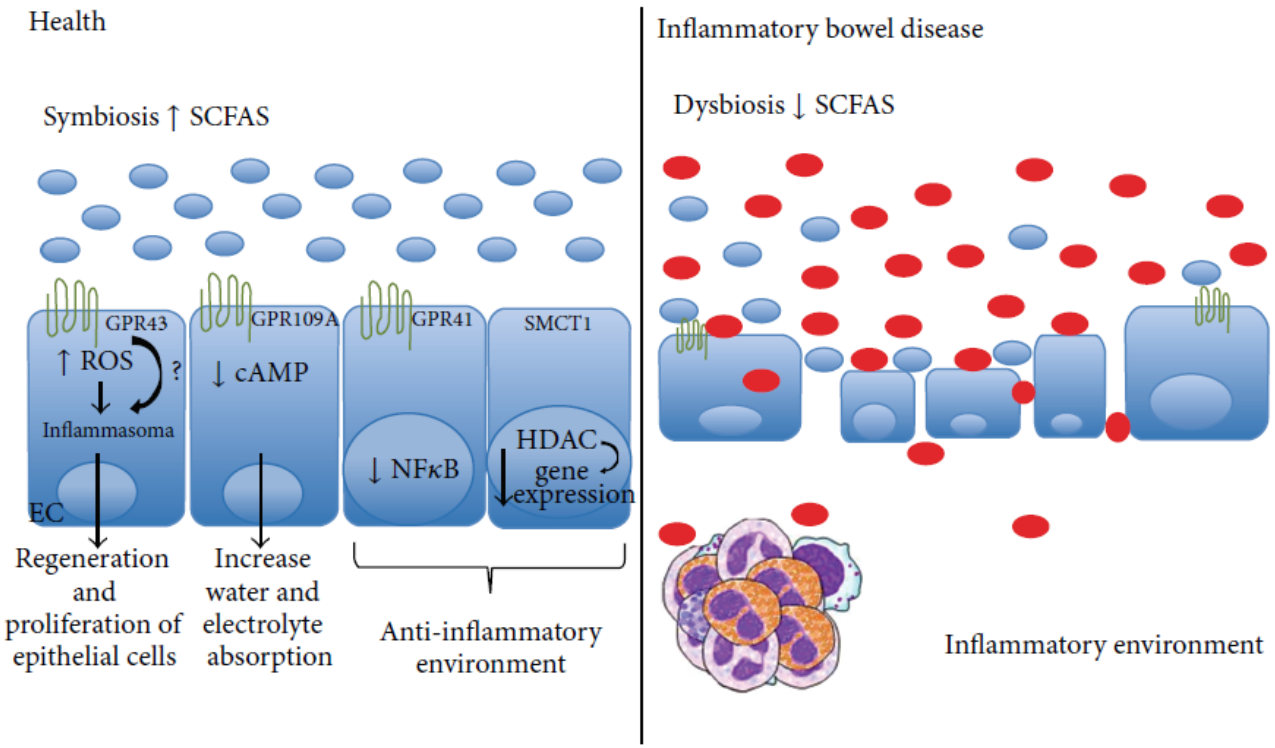


FIGURE 2: Schematic representation of a complex mucosal immune system composed of epithelial and hematopoietic cells that are able to react to pathogenic insults. Development of IBD occurs mainly when epithelial cells are damaged and/or the intestinal microbiota composition is not healthy.

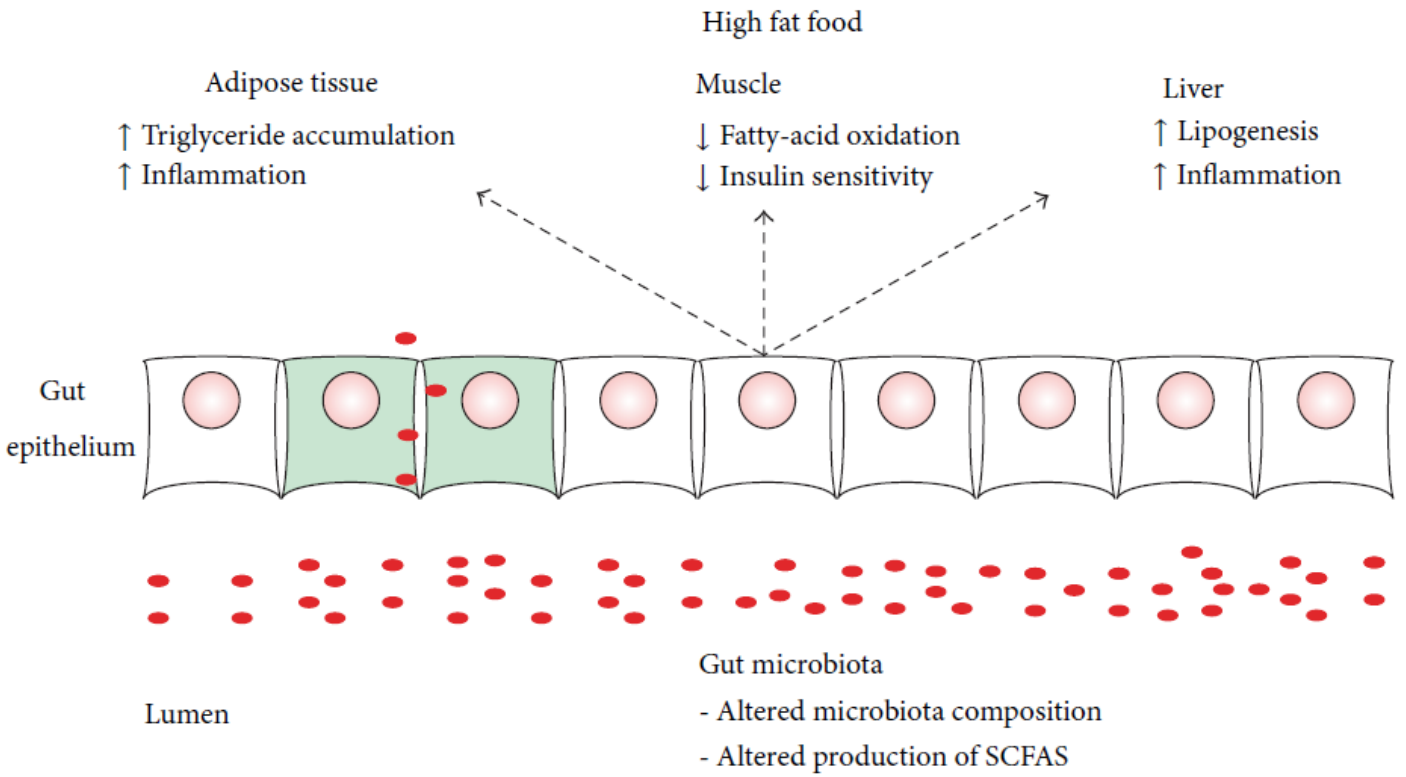


FIGURE 3: Effects of a high-fat diet. The altered microbial community of obese animals and humans promotes adiposity and decreased levels of short chain fatty acids and influences metabolic processes such as storage and metabolism of lipids in adipose tissue, muscle, and liver.

Figure 4. Alteration of intestinal permeability after change in gut microbiota of obese individuals. LPS: lipopolysaccharide; TLR: Toll-like Receptor; ZO-1: zonula occludens.