

The Gut – Brain Axis

Dr. Malay Dave

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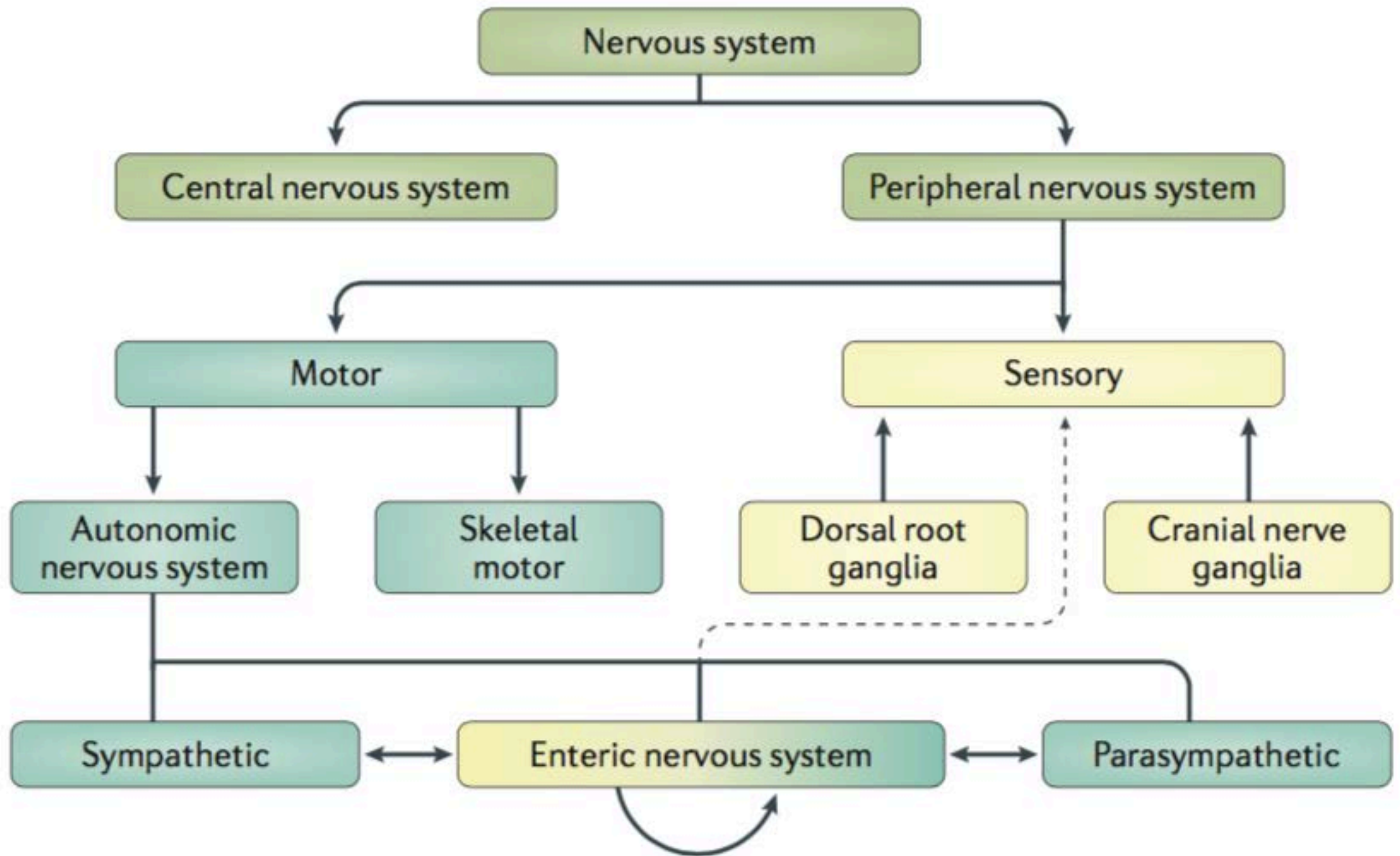
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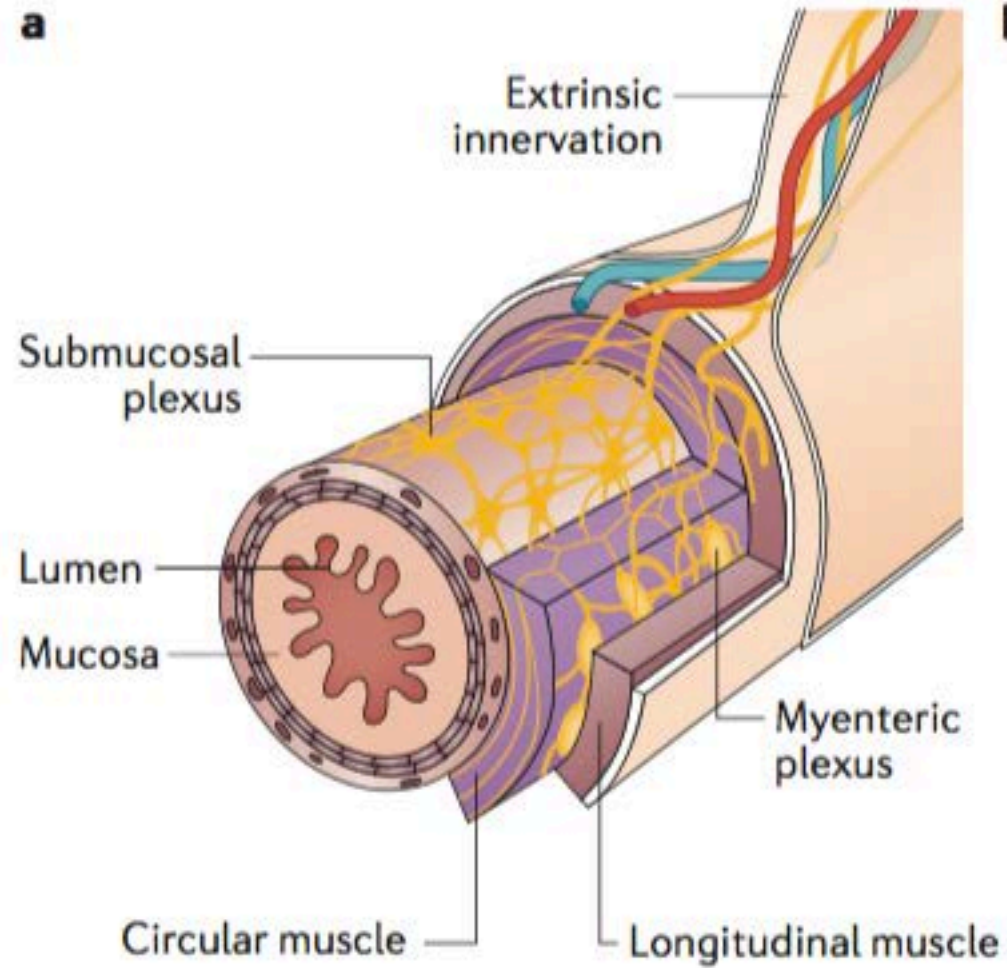
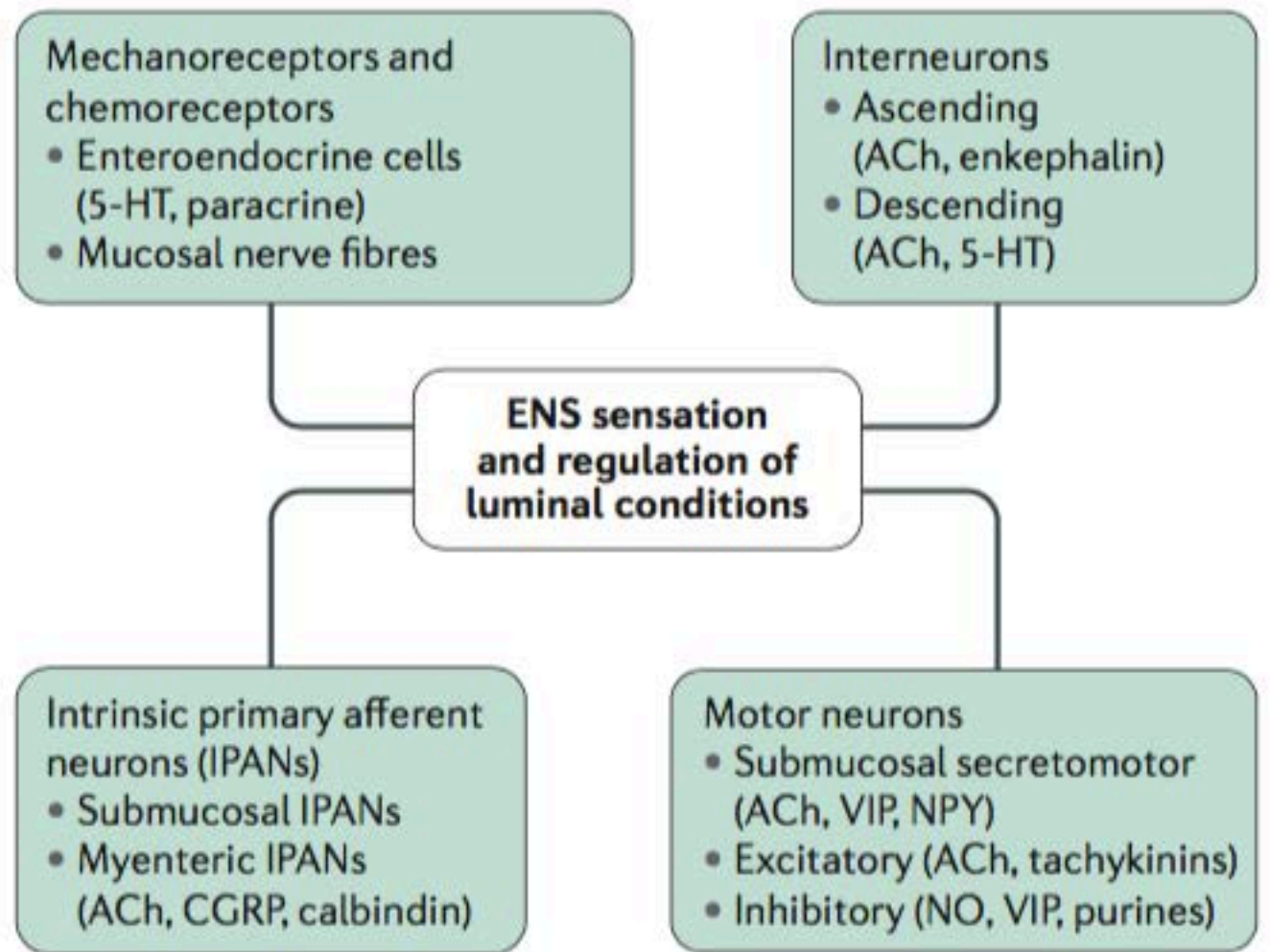
1. The ENS

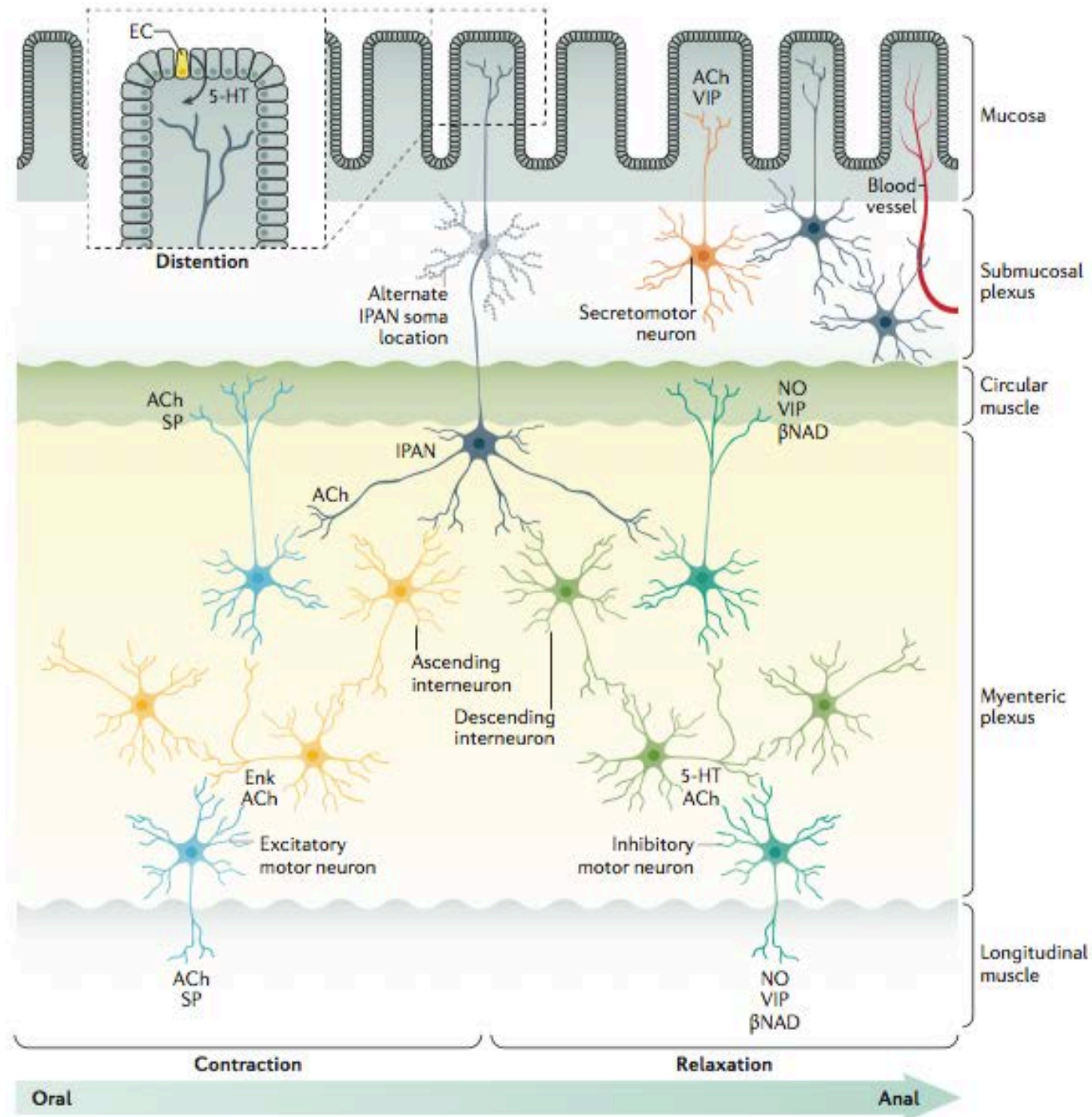
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The ENS

- Discovered in the late 1900's
- Part of the autonomic nervous system
- “On Site” control of gut behavior
- Can alert the organism to danger & influence response (**Unconscious**)
- 90% of Vagus Nerve information flow is from the gut to the brain



a**b**



Peristalsis - 1

- **Luminal distention or distortion triggers** direct activation of mechanoreceptive endings of **intrinsic primary afferent neurons (IPANs)**, as well as indirect activation of IPANs upon serotonin (5-HT) release by enterochromaffin cells (ECs) in the epithelium.
- IPANs activate **ascending and descending interneurons**, which stimulate excitatory and inhibitory motor neurons, respectively.
- Motor neuron activity leads to **oral contraction and anal relaxation of intestinal smooth muscle**, which propels luminal contents in the proximal–distal direction.

Peristalsis - 2

- **ACh** refers to neurons that contain acetylcholine
- **SP** refers to neurons that contain Substance P
- **Enk** refers to enkephalin-expressing ascending interneurons
- **NO** and **VIP** indicate inhibitory motor neurons secreting nitric oxide and vasoactive intestinal peptide
- **βNAD** refers to inhibitory motor neurons secreting the purine, β-nicotinamide adenine dinucleotide
- **Secretomotor & vasomotor** neurons of the submucosal plexus secrete ACh or VIP

2. The ENS – CNS Interactions

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The CNS & ENS - 1

- Innervation of the gastrointestinal tract regulates **secretions, sphincter control, motility, blood flow and enteroendocrine function**
- The enteric nervous system (ENS) is an autonomous neural network with a comparable number of neurons to the spinal cord, and chiefly comprises **myenteric ganglia** (between the longitudinal and circular muscle layers of the gut wall) and **submucosal ganglia**
- The myenteric plexus circumferentially encases the gut from the **upper oesophagus to the internal anal sphincter**, whereas the submucosal plexus is predominantly present in the **small and large intestine**

The CNS & ENS - 2

- The three main types of neuron in the ENS are **primary sensory neurons, interneurons and primary motor neurons**; these neurons directly synapse with each other to mediate ENS intrinsic reflexes
- Although the small and large intestine are the key sites of autonomous ENS circuitry, it is important to appreciate that the ENS is closely integrated and **in extensive communication with the central nervous system (CNS)**
- The main lines of communication between the ENS and CNS are the **vagus nerve** (proximal gastrointestinal tract) and **the spinal nerves** (including thoracolumbar and lumbosacral networks, which innervate the distal small bowel and colon), all of which contain **both sensory (afferent) and motor (efferent) pathways**

The CNS & ENS - 3

- Vagal afferents detecting **nutrients, chemicals or luminal contents (chemoreceptors), and distention or movement** (mechanoreceptors or tension receptors) project to the nucleus tractus solitarius (NTS) via the dorsal and ventral vagal trunks
- Vagal efferents originating in the NTS and nucleus ambiguus directly innervate striated muscle (e.g. oesophagus), but mostly synapse with enteric nerves to mediate motor functions (e.g. **motility, secretions, sphincter relaxation**)
- **The thoracolumbar spinal nerves** are composed of sensory neurons with cell bodies in the dorsal root ganglia and efferent sympathetic fibres, which **innervate blood vessels and synapse with myenteric and submucosal ganglia**
- **The pelvic spinal nerves** innervate the rectum and distal colon, and include sensory (including pain fibres) and motor pathways

3. The Gut Immune System

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The Mucosal Immune System -1

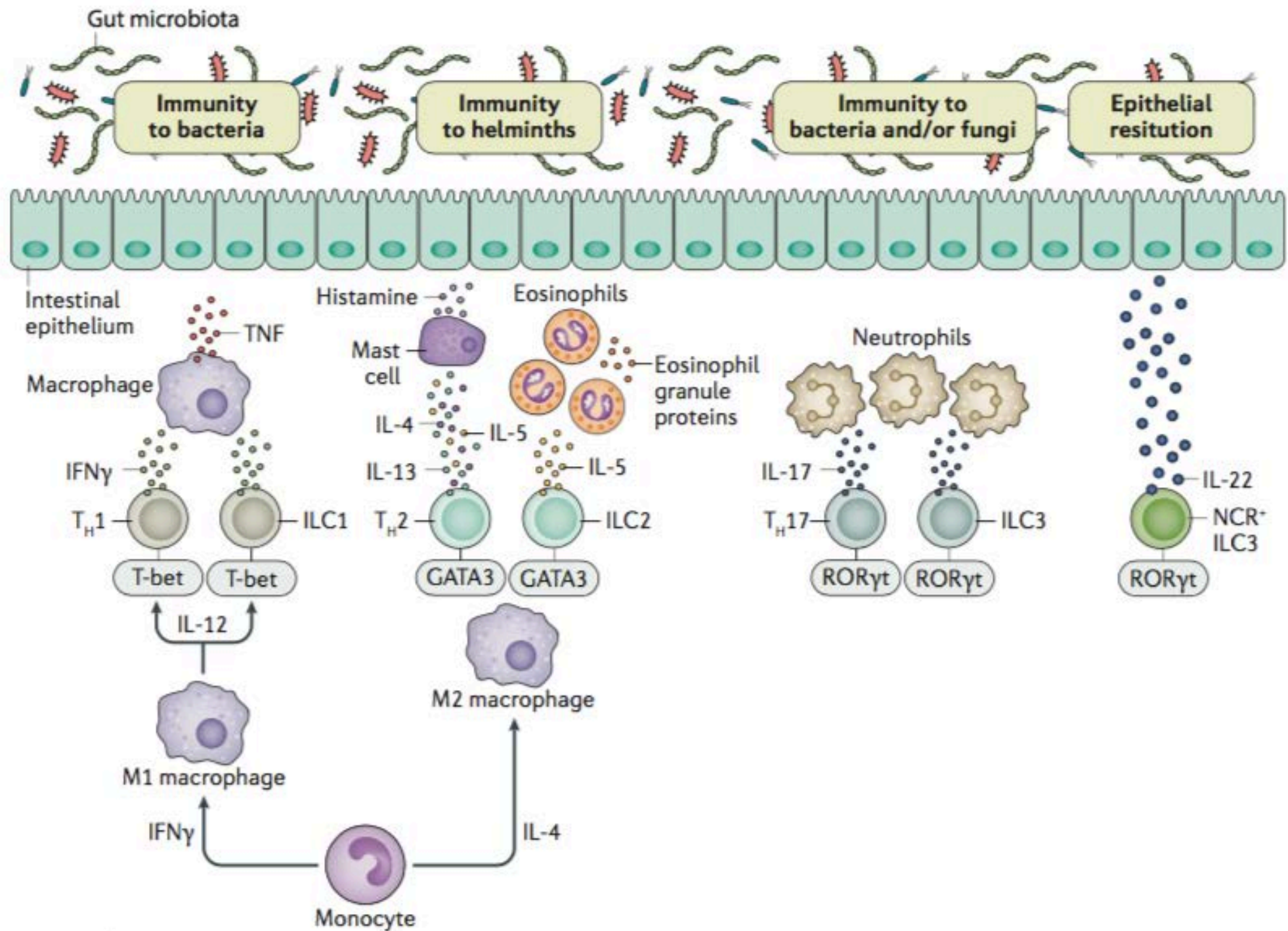
- CD4+ effector T- cell subsets are defined by the expression of specific transcription factors and by the pattern of cytokines produced.
- **Type 1 T helper (TH₁) cells** produce IFN γ and TNF, which have many pro-inflammatory actions, including activation of macrophages.
- **Type 2 T helper (TH₂) cells** produce IL-4, IL-5 and IL-13, which promote activation, survival and maintenance of tissue mast cells and eosinophils; the TH₂ response is implicated in host immunity to multicellular pathogens, such as helminths.
- **Type 17 T helper (TH₁₇) cells** produce IL-17A, IL-17F and IL-22, which support the recruitment and activation of neutrophils and have an important role in host resistance to extracellular bacteria and fungi.
- **Regulatory T cells** expressing the transcription factor FOXP3 serve to counterbalance overly exuberant effector responses and dampen down inflammation; they secrete immunosuppressive cytokines, such as IL-10 and TGF β , and are one of the main immunoregulatory mechanisms in the gut (and beyond)

The Mucosal Immune System - 2

- Key cells of the mucosal innate immune compartment include cells of the mononuclear phagocyte system (MPS), such as monocytes, macrophages and dendritic cells.
- **Intestinal macrophages**, which are continually replenished by circulating monocytes, are mostly anti-inflammatory cells in the steady state, producing immunoregulatory cytokines such as IL-10; however, under inflammatory conditions they are a potent source of inflammatory cytokines, including TNF, IL - 6 and IL - 1 β .
- **Tissue macrophages** exist as M₁ (classically activated) and M₂ (alternatively activated) subsets. M₁ macrophages are activated by IFN γ , but also support TH₁ activation or differentiation through IL-12.
- **IL-4** is a major stimulus driving alternative activation of M₂ macrophages. M₂ macrophages are also a source of IL-4, which supports TH₂ cells.
- **Intestinal MPS** cells are activated by bacterial products (such as lipopolysaccharide) that trigger Toll-like receptors (TLRs).

The Mucosal Immune System - 3

- **Innate lymphoid cells** (ILCs) are a heterogeneous population of newly described innate lymphocytes that resemble the effector CD4⁺ lineages with respect to the expression of lineage defining transcription factors, cytokine production profiles and functional roles.
- Key subsets are **ILC₁** (express T-bet and produce IFN γ), **ILC₂** (express GATA₃ and produce IL-5 and IL-13) and **ILC₃** (express ROR γ t and produce IL-22 and/or IL-17A). ILCs contribute to **host defense** against different mucosal pathogens, including helminths (ILC₂) and bacterial infections (ILC₁ and ILC₃).
- IL-22-producing ILC₃ also serve to **promote epithelial stem cell growth and recovery** from injury, indicating that these cells are crucial to long-term intestinal epithelial homeostasis.
- **Immune-cell trafficking** to the gut is dependent on the expression of selective homing molecules, including the chemokine receptor CCR9 and the integrin $\alpha_4\beta_7$. The regulation of immune cell trafficking to the gut is now of major interest as monoclonal antibodies blocking these pathways have emerged into clinical practice to treat intestinal inflammation.



4. The Gut Microbiome

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The Gut - Brain Axis

- Within the first few days of life the human gut is colonized by commensal intestinal microbiota
- Commensal, probiotic, and pathogenic bacteria in the gastrointestinal tract can activate neural pathways and central nervous system signaling systems
- 400 – 500 species of bacteria, **Anaerobes >>> Aerobes**

Bidirectionality

Gut Microbiota to Brain

- Production, expression & turnover of 5-HT, GABA & BDNF
- Protection of intestinal barrier & tight junction integrity
- Modulation of enteric sensory afferents
- Bacterial metabolites
- Mucosal immune regulation

Brain to Gut Microbiota

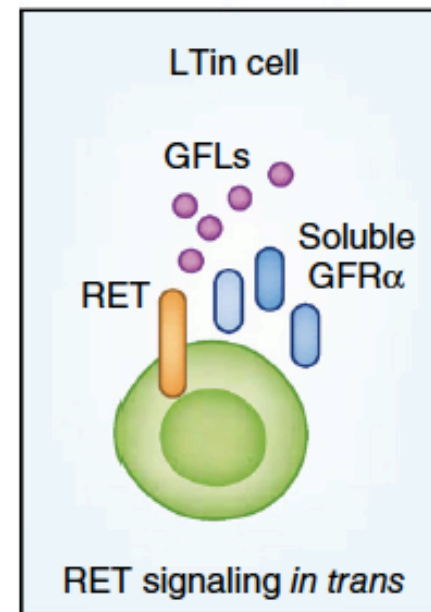
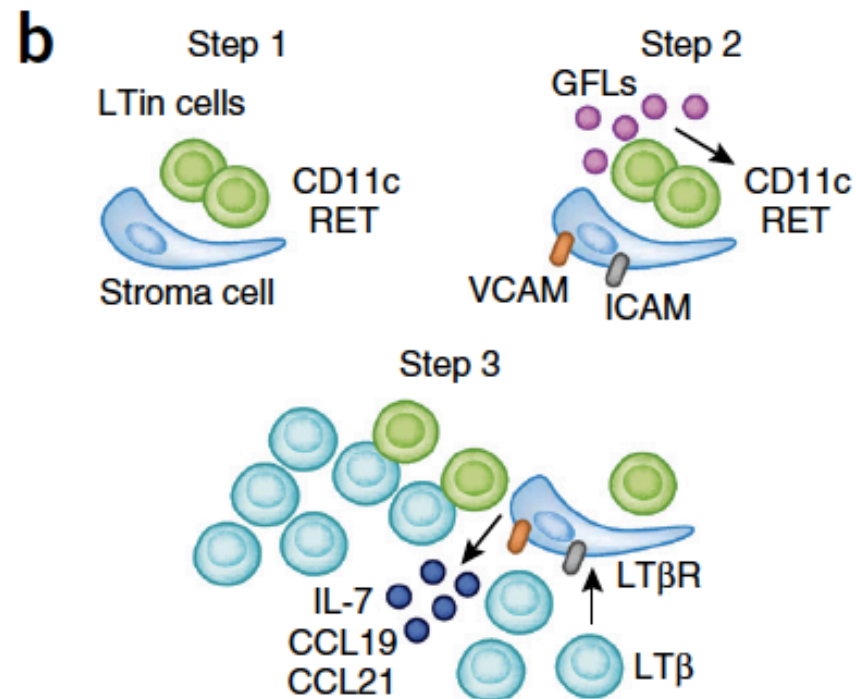
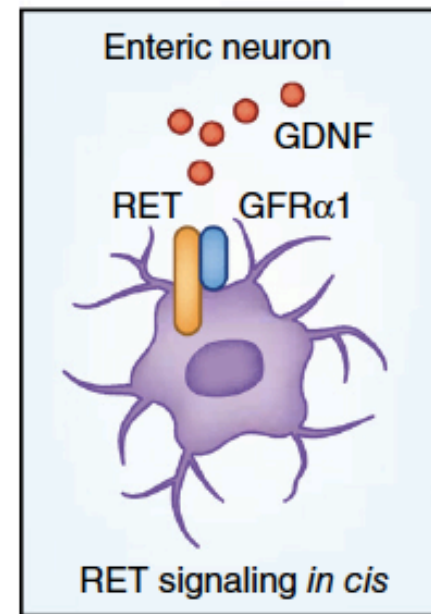
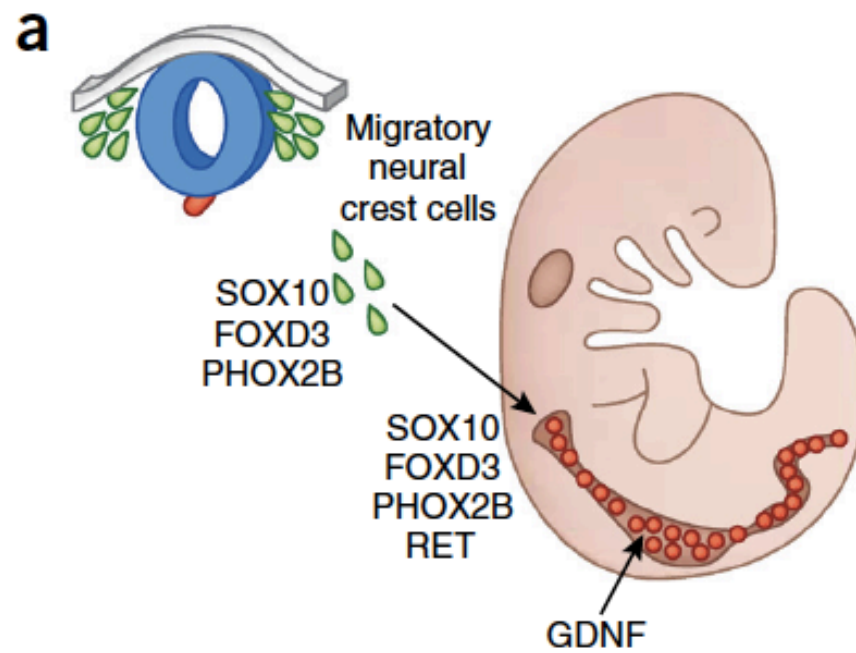
- **Alteration in**
 - Mucus & biofilm production
 - Motility
 - Intestinal permeability
 - Immune function

4.1. Developmental Issues

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Gut & Brain Tissue

- The brain and the gut both develop from the same tissue – during foetal development, one part becoming the central nervous system, while the other develops into the enteric nervous system.
- The connection - **Vagus nerve**

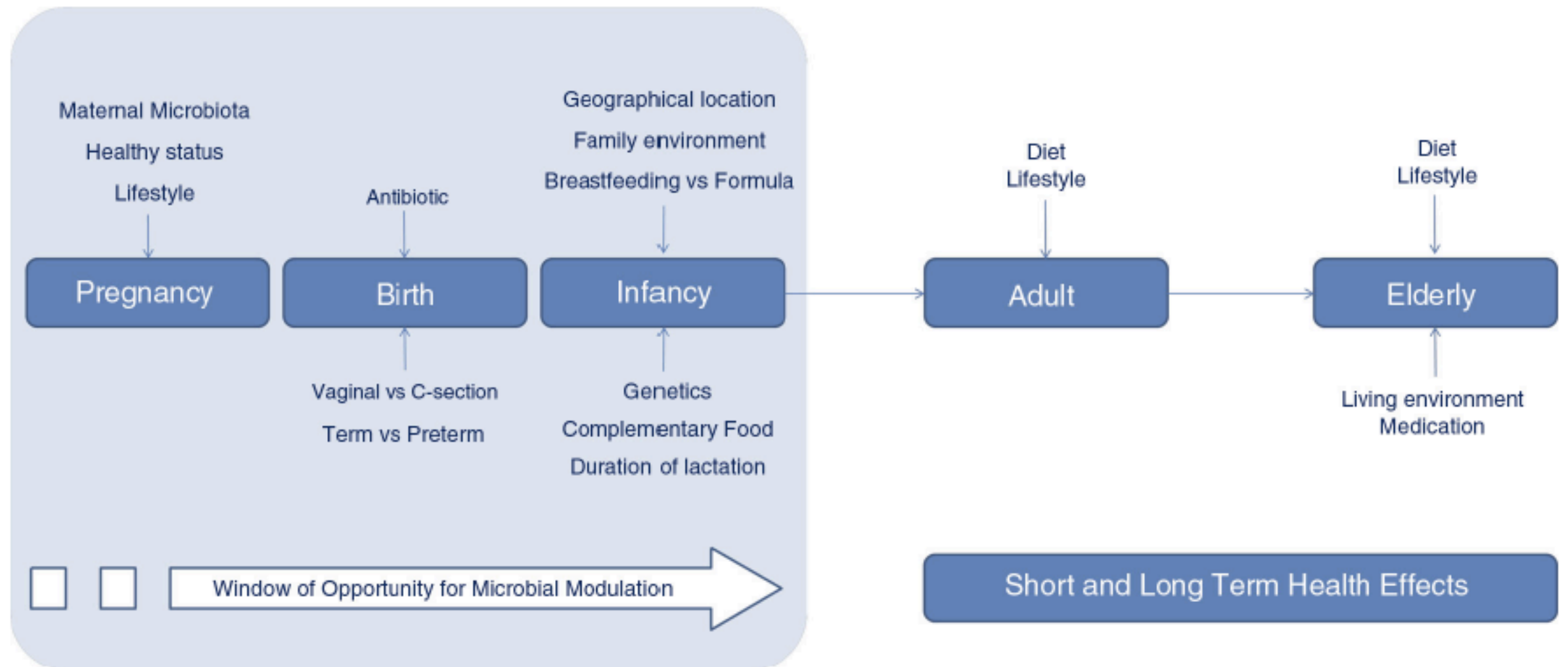


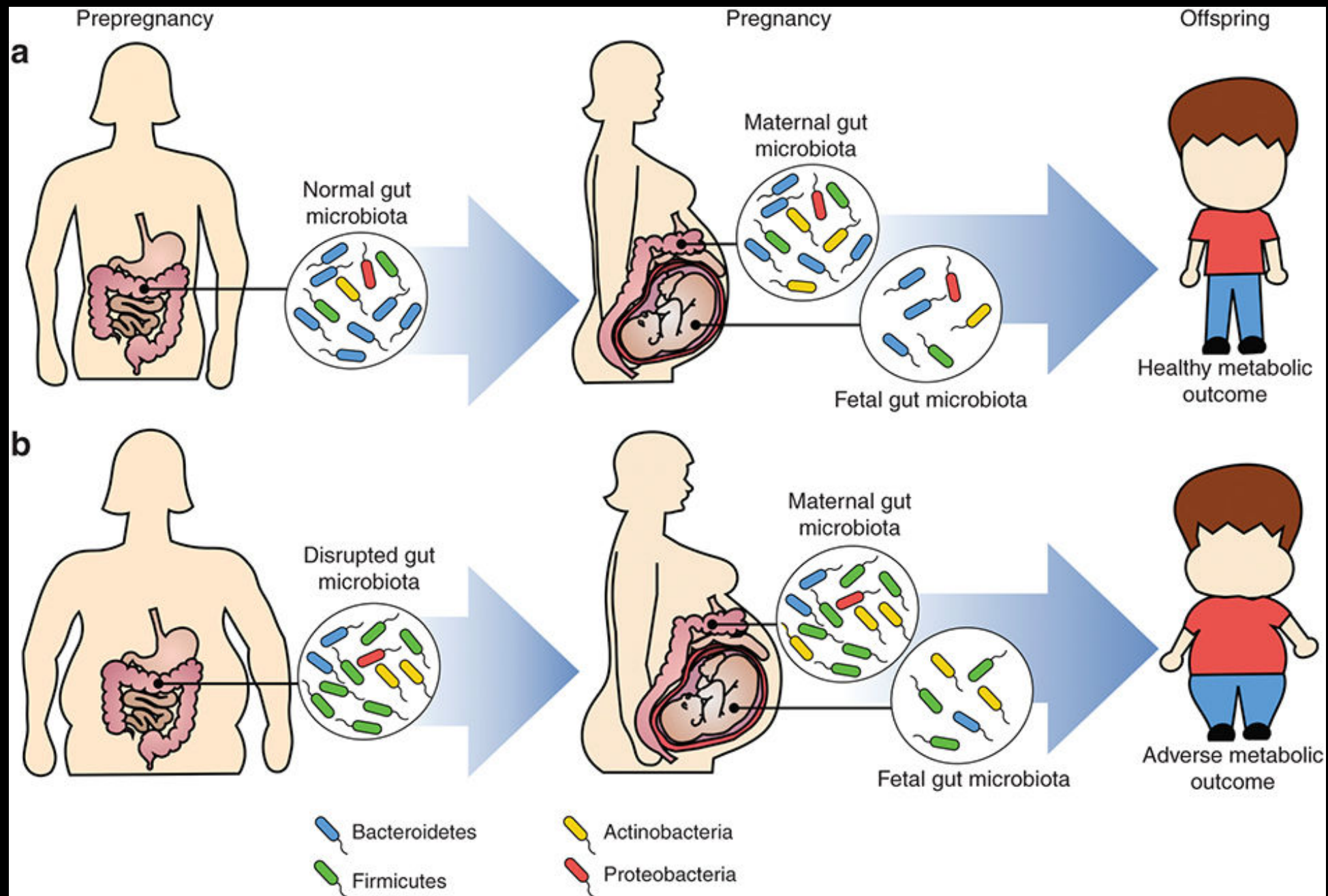
Development & Homeostasis

Common regulatory mechanisms of neuronal and lymphoid organogenesis in the gut:

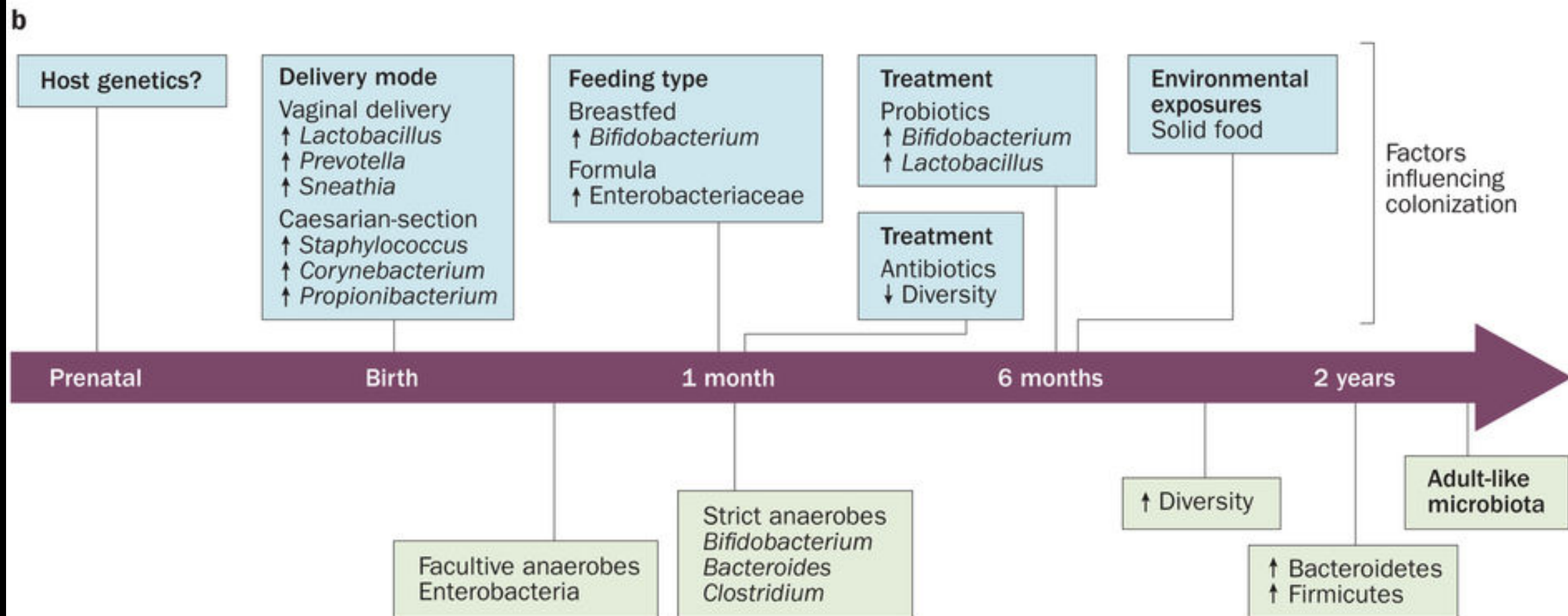
- **Neural-crest-derived progenitor cells** invade the foregut during embryogenesis and migrate rostro-caudally to colonize the full length of the gut, giving rise to enteric neurons and glial cells. Early ENS **progenitor cells express the transcription factors SOX10, FOXD3 and PHOX2B, which drives the expression of RET**. In turn, a GDNF gradient in the fetal intestine activates RET *in cis*, which ensures **cell survival and enteric neurogenesis**.
- The development of PPs follows a multi-step process of immune-cell and stromal-cell interactions.
 - LT_{in} cells in the vicinity of sessile stroma cells express RET (step 1).
 - LT_{in} cells are activated by soluble GFLs *in trans* and, in turn, prime stromal cells to produce the adhesion molecules VCAM and ICAM (step 2).
 - Initial chemokine-independent, adhesion-mediated arrest of LT_i cells leads to further maturation of stroma cells that initiate the production of chemokines (step 3).
 - Subsequently, gradients of stroma-cell-derived chemokines and cytokines (such as IL-7, CCL19 and CCL12) further attract additional LT_i cells, which gives rise to PP anlagen (step 3).

CD11c, integrin; LT β and LT β R, lymphotoxin- β and its receptor (in the diagram)





a	Intestinal location	Stomach	Duodenum	Jejunum	Ileum	Colon
	Microbes/gram	1×10^1	1×10^3	1×10^4	1×10^7	1×10^{12}
	Composition	<i>Lactobacillus</i> <i>Helicobacter</i> <i>Veillonella</i>	<i>Streptococcus</i> <i>Lactococcus</i> <i>Staphylococcus</i>	<i>Lactobacillus</i> <i>Streptococcus</i> <i>Enterococcus</i>	SFB Enterobacteriaceae <i>Bacteroides</i> <i>Clostridium</i>	<i>Bacteroides</i> <i>Clostridium</i> Lachnospiraceae Proteobacteria Actinobacteria Prevotellaceae

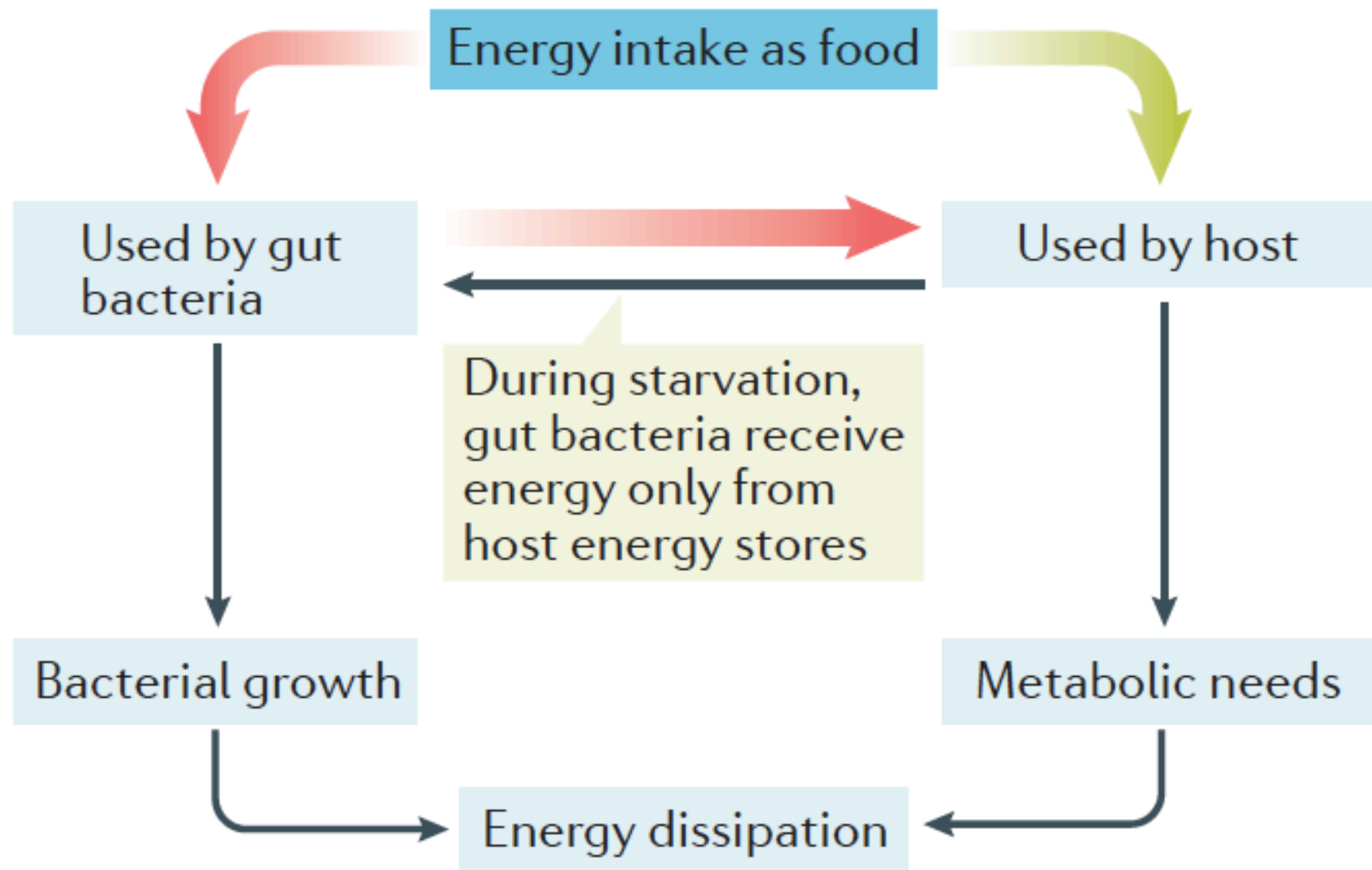


Lactation & Microbiota

- Milk **contains SIgA**, which prevents translocation of aerobic bacteria from the gut to the draining lymph nodes (*SIgA = Secretory IgA*)
- Maternal IgA ameliorated colonic damage after Dextran Sulfate administration

4.2. Energetics

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Host energy use:



Direct



Indirect

5. The Microbiota – NS Interactions

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Neurotransmitter Production & Modulation

Production

- **Norepinephrine:** Escherichia, Bacillus, Saccharomyces
- **Serotonin:** Streptococcus, Escherichia, Enterococcus
- **Dopamine:** Bacillus, Serratia

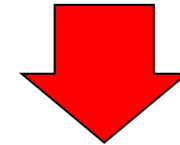
Modulation

- **Lactobacillus acidophilus:** expression of **cannabinoid receptors** in the spinal cord
- **Bif. Infantis:** increases plasma tryptophan levels and thereby **modulates 5-HT**
- **Lactobacillus rhamnosus:** alters **central GABA receptor** expression

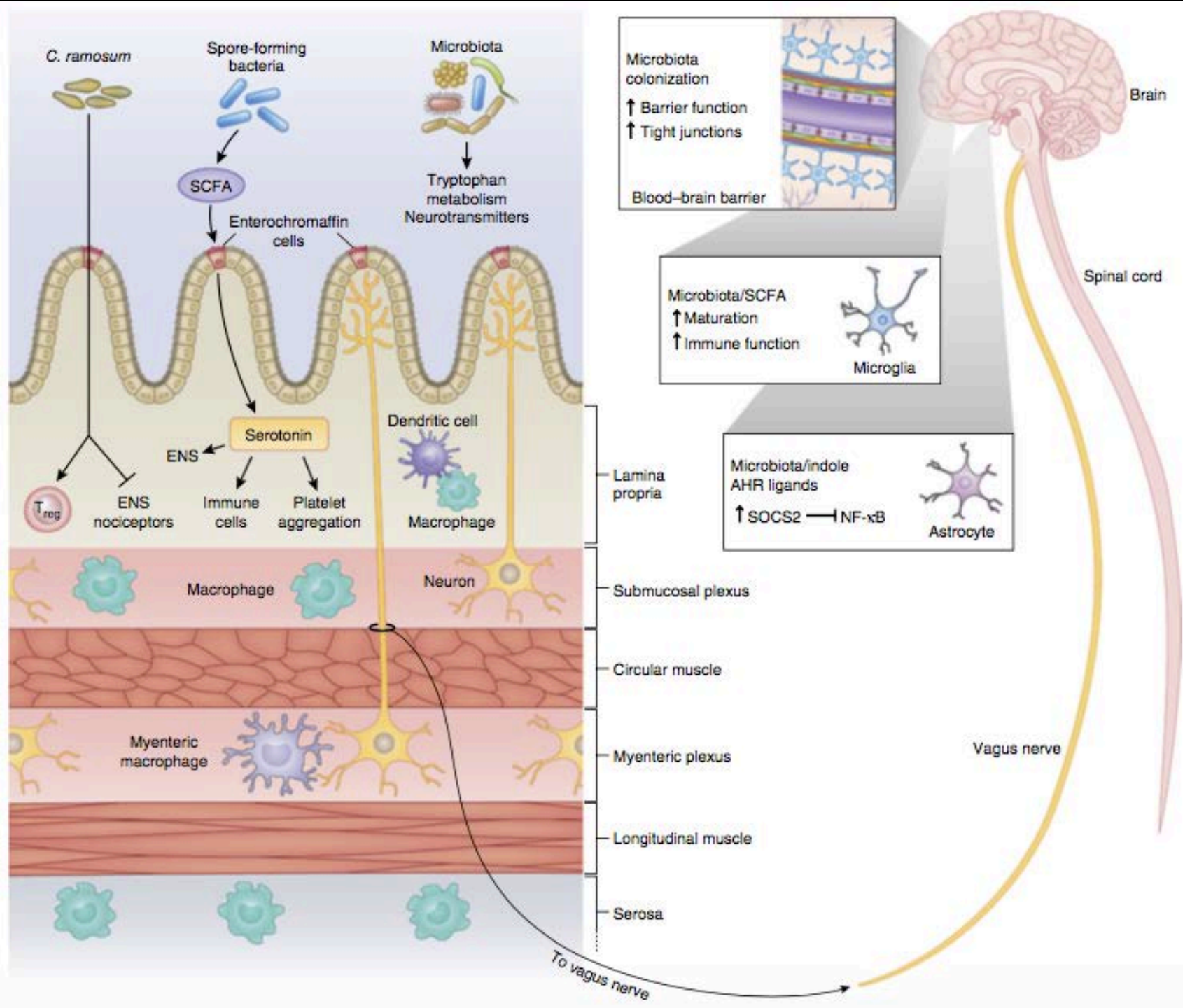
Factors Affecting The Gut Microbiome

- Host genetics
- Stress
- Pollution
- Diet
- Psychological status
- Microbial exposure
- Pharmacological agents

Commensals



Pathogens



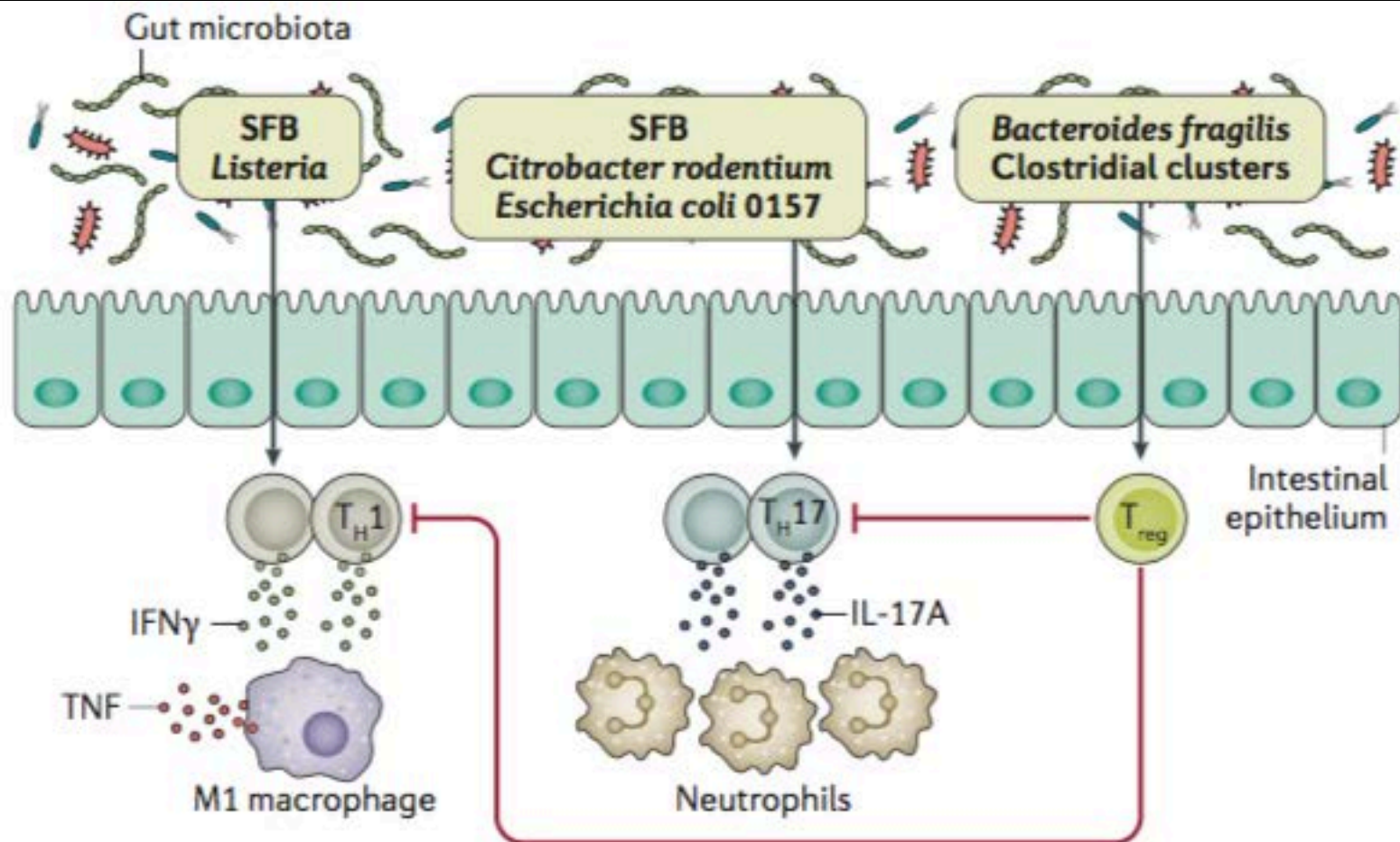


Figure 4 | The gut microbiota directly influences T-cell differentiation. Specific bacterial constituents of the gut microbiota are required for lineage differentiation of different T-cell subsets. Bacteria, including segmented filamentous bacteria (SFB), *Citrobacter rodentium* and *Escherichia coli* 0157 (which are all epithelial adherent bacteria) are permissive for T helper (T_H)17 differentiation. SFB and *Listeria* are also implicated in the differentiation of T_H1 cells. Regulatory T-cell (T_{reg}) numbers are boosted by the presence of selective clostridial clusters and *Bacteroides fragilis*.

Intestinal Microbiota & Neuroinflammation - 1

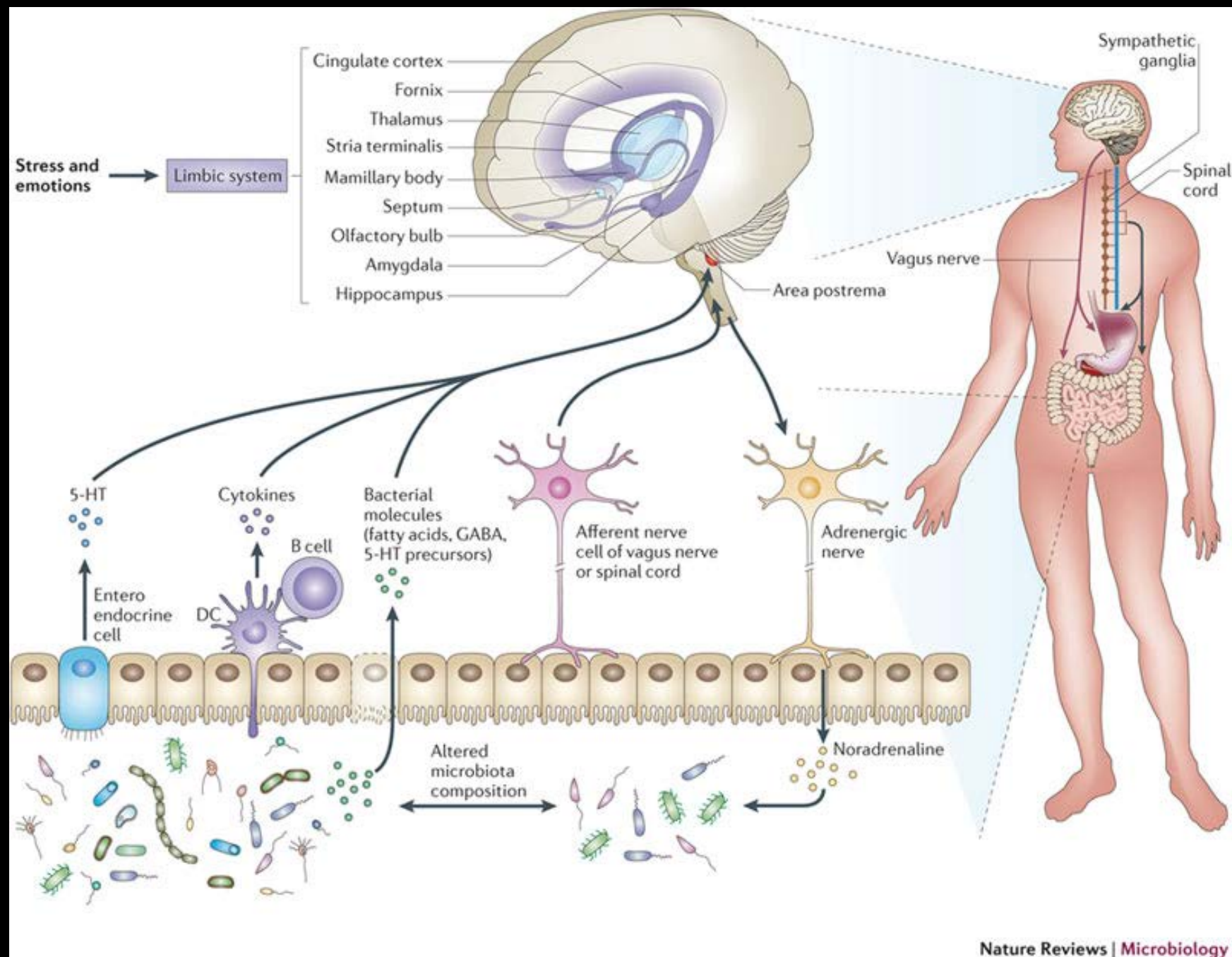
- Multiple members of the microbiota, such as Escherichia, Lactobaccillus, Bifidobacterium, Enterococcus and Truchuris, **produce neurotransmitters and neuropeptides** including dopamine, acetylcholine, gamma-aminobutyric acid, serotonin and brain-derived neurotrophic factor
- Spore-forming bacteria, primarily Clostridium spp., modulate the colonic luminal metabolome, including SCFAs, thus inducing **serotonin biosynthesis by enterochromaffin cells** and thereby affect intestinal motility and platelet function in mice
- In the colon, C. ramosum induces ROR γ t⁺ T_{reg} cells but also **represses** neuronal-specific transcripts, particularly those encoding **nociceptive neuropeptides**

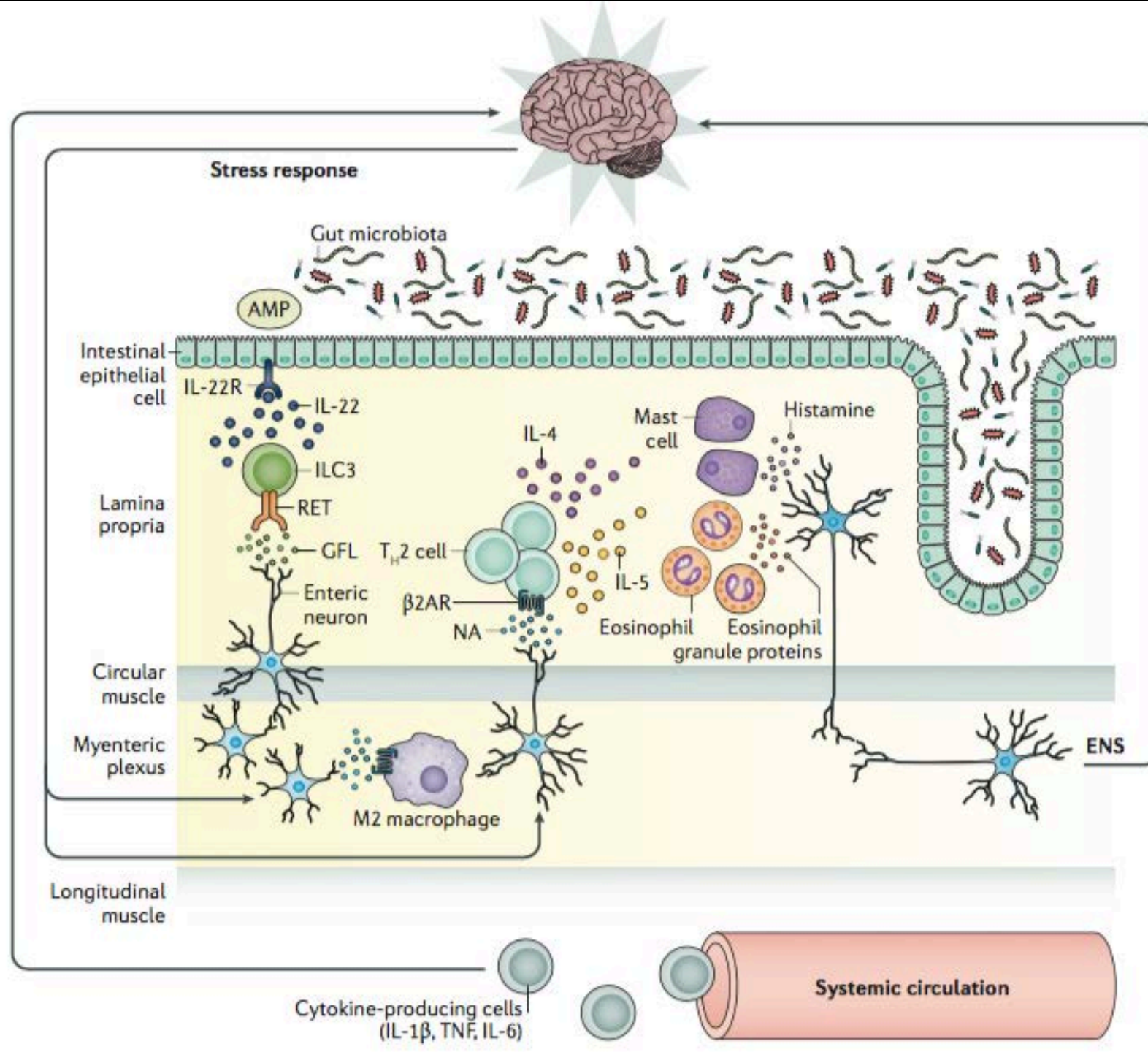
Intestinal Microbiota & Neuroinflammation - 2

- Afferent neurons within the enteric nervous system (ENS) can communicate intestinal conditions to intestinal muscularis macrophages via β_2 - adrenergic receptors and also to the brain via the Vagus Nerve
- Intestinal colonization by the microbiota increases blood–brain tight junctions and barrier function, although microbiota-derived SCFAs can gain access to the brain and promote microglia differentiation and function.
- Microbiota-dependent metabolism of tryptophan into AHR ligands engages AHR on astrocytes, thus leading to an increase in astrocyte expression of the inhibitor protein SOCS2 and consequently inhibiting activation of the transcription factor of NF- κ B and thereby limiting inflammation (AHR = Aryl Hydrocarbon Receptor)

6. Stress

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The HPA Axis & The Stress Response - 1

- Activation of the stress response affects both brain and gut function and profoundly influences dialogue between these organ systems
- After exposure to perceived threat, sensory inputs are directed and processed by limbic system structures in the forebrain, including the **amygdala, hippocampus and prefrontal cortex**
- The amygdala directly innervates the **hypothalamus** stimulating release of **corticotropin-releasing hormone** into the hypophyseal portal system, triggering release of **adrenocorticotrophic hormone** from the anterior pituitary gland
- Adrenocorticotrophic hormone stimulates **cortisol production** by the zona fasciculata of the adrenal cortex

The HPA Axis & The Stress Response - 2

- The amygdala also innervates the catecholaminergic **locus coeruleus** in the brainstem, which is the principle source of noradrenaline in the brain, serving to augment arousal, focus and attention
- Immediate sympathetic activation occurs after **integration of stress signals at the paraventricular nuclei** (PVN) of the hypothalamus, which can be considered the command centre of the autonomic stress response
- Neurons from the PVN project to sympathetic targets in the brain stem, spinal cord and preganglionic noradrenergic nuclei to activate the sympathetic arm of the autonomic **stress response at target organs**; direct and indirect (via synapses at the nucleus tractus solitarius) projections exist to the locus coeruleus for induction of centrally acting noradrenaline release

The HPA Axis & The Stress Response - 3

- Neurons from the PVN also directly innervate **immune tissue in the gut**, including mesenteric lymph nodes and gut - associated lymphoid tissue
- The adrenal medulla is directly innervated by post - ganglionic sympathetic fibres, stimulating catecholamine release into the bloodstream; the **adrenal medulla predominantly produces adrenaline** and, to a lesser extent noradrenaline, whereas the postsynaptic sympathetic fibres innervating the **gut (and other organs) are noradrenergic**

The HPA Axis & The Stress Response - 4

- **Noradrenergic neurons in the gut** release noradrenaline (NA), which ligates the β_2 adrenergic receptor (β_2 AR) on **macrophages** in the myenteric plexus (supporting differentiation towards the M_2 phenotype) and T cells, which limits T helper (TH_1) differentiation (indirectly favouring TH_2 and TH_{17} differentiation).
- **Mast cells** and **eosinophils** are found degranulating next to enteric neurons, providing a mechanism for sensory excitation (which can be perceived by the ENS & CNS).
- **Gut immune cells** (e.g. $\gamma\delta$ T cells) differentiating in the gut can traffic to the brain under some circumstances (e.g. after brain injury).
- Blood - borne **cytokines** generated in the gut can also signal in the brain.

The HPA Axis & The Stress Response - 5

- **Enteric glial** cells also produce glial-cell-derived neurotrophic factor family ligands (GFL), which stimulate IL-22 production by innate lymphoid cell (ILC₃) (acting on the specific receptor RET)
- **IL-22** acts on an epithelial-restricted receptor (IL-22R) to stimulate epithelial proliferation, antimicrobial peptide production
- **IL-4 and IL-5** (potentially generated locally by TH₂ cells support activation of mast cells and eosinophils, respectively)
- *AMP = antimicrobial peptides, in the diagram*

Microbe-derived molecules

- SCFAs (microglia maturation and function)
- Tryptophan metabolites, AHR ligands (astrocyte function)
- MAMPs (LPS, PGN)

Neuroactive molecules

- Intestinal neurotransmitter biosynthesis
- Regulation of neurotransmitter signaling

Neuronal signaling

- Vagal nerve stimulation



Central nervous system

Tissue Inflammation, Injury and repair

- T_H1 (IFN γ), T_H2 (IL-4), T_H17 (IL-17A), T_{reg} (IL-10)

Neurogenesis

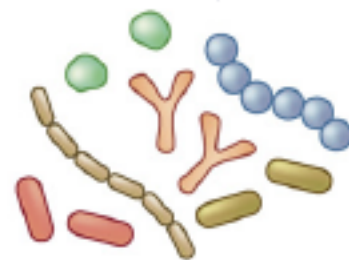
- $Ly6C^+$ monocytes

Neural development and connectivity

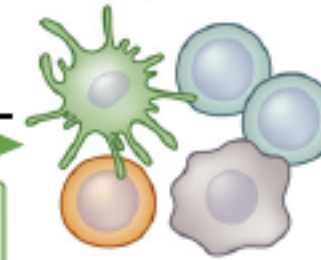
- IL-17A (cortical development)
- IFN γ (neural connectivity)

Neuroendocrine signaling

- HPA axis (microbiome composition, intestinal permeability/motility, immune regulation)



Gut microbiota



Peripheral immune system

Microbial-derived molecules

- SCFAs
- MAMPs (PSA, TLR and NLR ligands)

Immune pathways impacted

- T_{reg} differentiation
- T_H17 differentiation
- Antibody production
- Antigen presentation
- Mononuclear phagocyte function

7. Psychiatric Disorders

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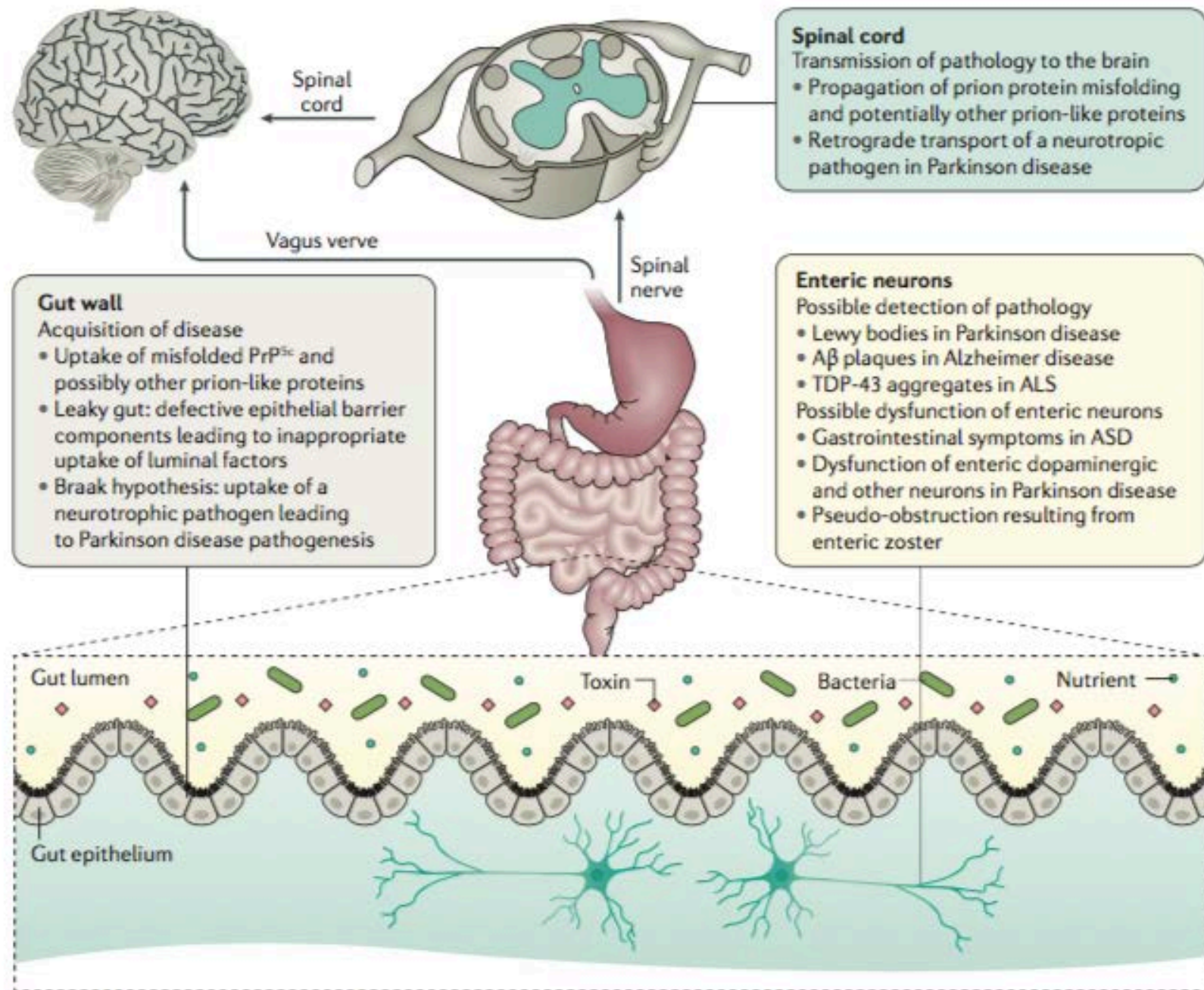
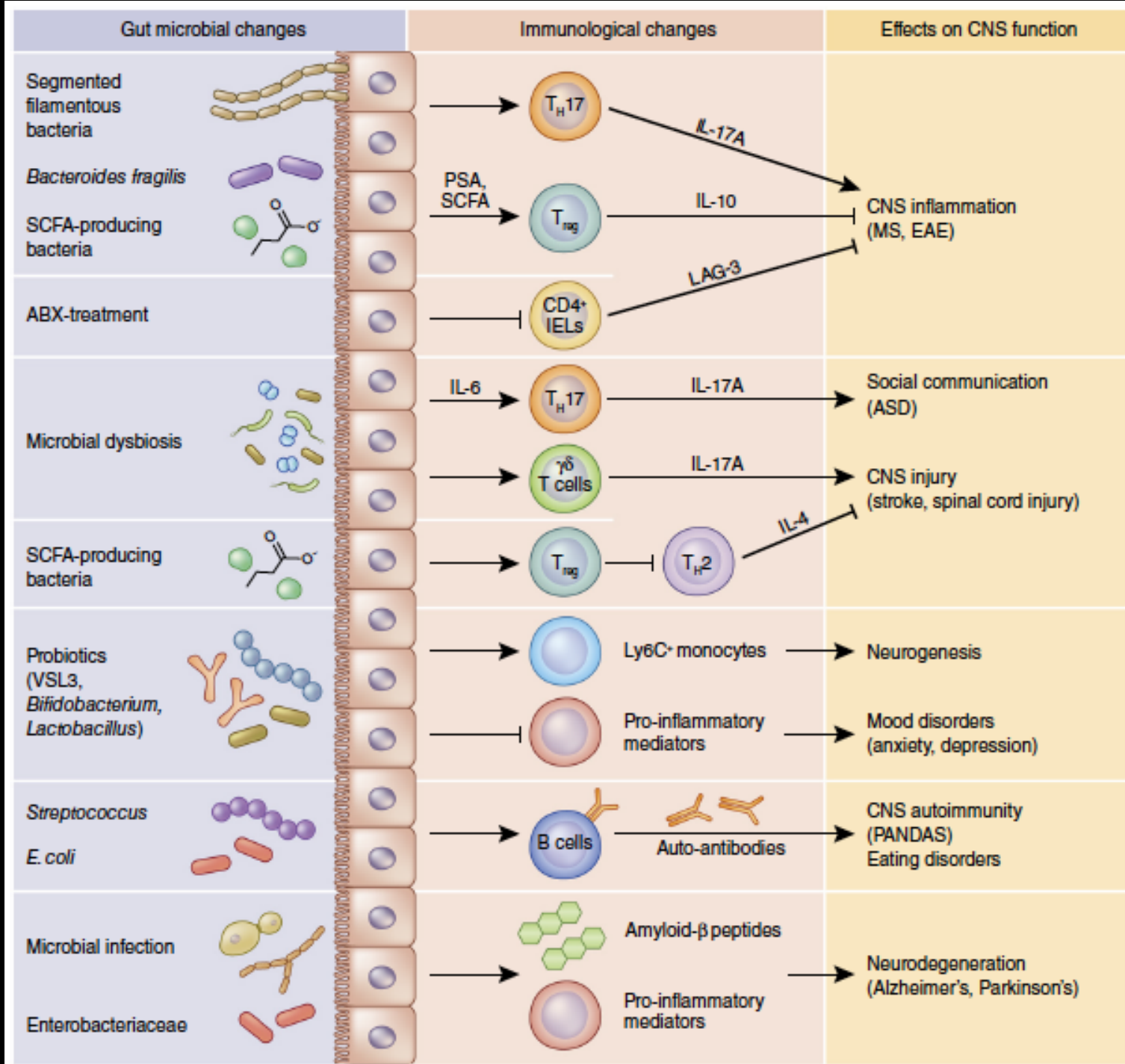


Figure 4 | **Summary of primary disease interactions between the gut and brain.** A β , amyloid-beta; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; PrP^{Sc}, prion protein scrapie.



Note:

Dysbiosis – Imbalance in the microbiota

SCFA – Short Chain Fatty Acids (Dietary modification in ASD)

PSA – Polysaccharide A

EAE – Experimental Autoimmune / Allergic Encephalomyelitis

MIA – Maternal Immune Activation

Figure 2 Effects of the microbiota on peripheral immune cells and CNS function. Intestinal microbes in the gastrointestinal tract regulate peripheral immune responses, CNS function and behavior. Intestinal colonization by specific members of the microbiota is associated with activation of pro- or anti-inflammatory CD4⁺ T cell responses that regulate susceptibility to EAE. The maternal immune activation (MIA) model of ASD leads to microbial dysbiosis that is associated with elevated T_H17 cell responses, which are sufficient to trigger social and behavioral defects. Mouse models of CNS injury (stroke, spinal cord injury) also appear to be regulated by microbiota-immune interactions. Oral administration of probiotics can elicit a population of Ly6C⁺ monocytes that increase hippocampal neurogenesis and enhance memory responses. Probiotics such as *Bifidobacterium* and *Lactobacillus* have potent anti-inflammatory properties that reduce behaviors associated with anxiety and depression. Furthermore, microbial infections can trigger antibody-dependent CNS autoimmunity and promote neurodegeneration. Collectively, regulation of peripheral immune responses is a critical pathway by which the intestinal microbiota and exogenous microbial challenges influence CNS function and behavior. ABX, antibiotic treatment of SPF mice; IELs, intraepithelial lymphocytes; LAG-3, lymphocyte activation gene-3.

Microbiota & ASD

- GI disturbances
- Severity of dysbiosis a/w severity of ASD
- **Bacteroidetes** more, **Firmicutes** less
- Oral treatment of MIA offspring with *B. fragilis* corrects gut permeability, alters microbial composition, may ameliorate ASD symptomatology

The Dresden Parkinson Model

- Chronic intra-gastric administration of **Rotenone** (pesticide) to mice
- Almost complete production of the syndrome
- Rotenone induces α -synuclein release from enteric neurons into extra-synaptic space
- Uptake by non-neuronal cells or presynaptic neurons
- Retrograde transport to soma & accumulation
- Trans-synaptic cell to cell transmission upto CNS
- Dorsal Motor Nucleus of Vagus, Intermediolateral Nucleus of Spinal Cord
- α -synuclein impairs Mitochondrial Complex 1 activity leading to inflammation (SN dopaminergic neurons are highly sensitive) & degeneration
- Substantial α -synuclein burden in upper GI, but the earliest GI symptoms are defecatory dysfunction & constipation

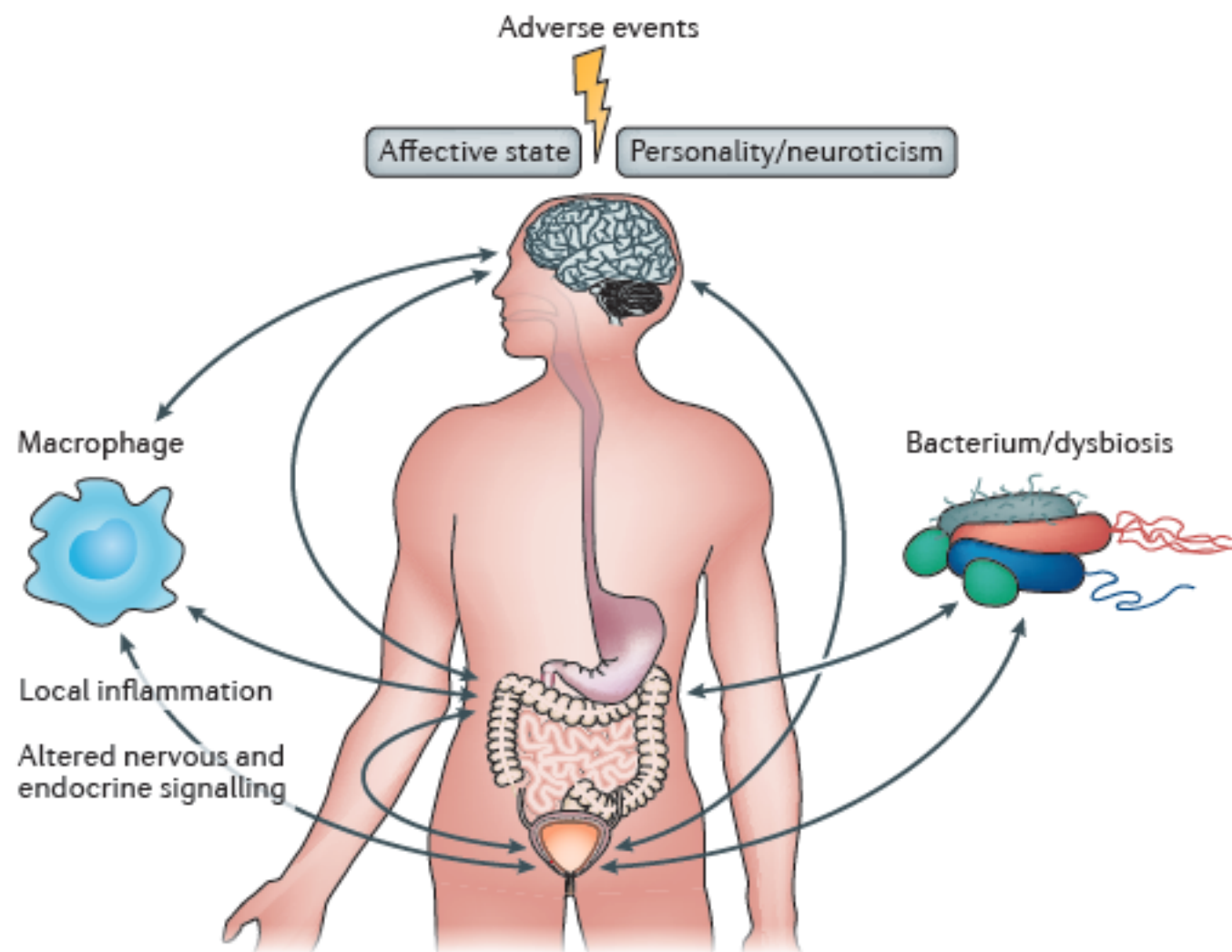


Figure 1 | The threatening environment and the bladder-gut-brain axis (BGBA). External psychological and/or physical adverse events can negatively affect the body via the BGBA, which can also be affected by internal threats such as infections or dysbiosis. Emotional, cognitive, and behavioural consequences include functional urological and gastrointestinal disorders, parts of which might be related to altered immunological, endocrine, and nervous system signalling.

7. 1. Treatment

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Interfering With GBA

- Interventions directed at either the brain or gut aspect of the axis might be anticipated to alleviate clinical features in both organ systems.
- For example, in patients in whom gut symptoms are primarily driving brain symptoms, modulation of the microbiota (e.g. faecal microbiota transplantation (FMT) or probiotic therapy) would directly alter host immune responses, alleviate local immune activation and simultaneously reduce immune-driven brain dysfunction.
- Likewise, targeting the stress response (e.g. psychotherapy or antidepressants) would alleviate brain symptoms, but would also limit autonomic activation of host immunity to suppress aberrant immune-driven gut symptoms.

Sources Of Probiotics & Prebiotics

Probiotics

Choose carefully as some may not be very effective

- Kefir – water or milk
- Yogurt, Lassi, Buttermilk
- Cultured vegetables – Sauerkraut
- Sourdough (contains Lactobacilli)
- Miso (fermented Soy paste)
- Tempeh (fermented Soybeans)
- Soft cheeses (like Gouda)

Prebiotics

- While probiotics contain live bacteria, prebiotic foods feed the good bacteria already living in the digestive system
- Found in foods such as Asparagus, Jerusalem artichokes, Bananas, Oatmeal, Red wine, Honey, Maple syrup, and Legumes

Targets For Psychobiotics

- **Depression / Anxiety**

- L. helveticus + B. longum (Messaoudi et al, 2011)

- **Chronic Fatigue Syndrome**

- L. casei (Rao et al, 2009)

- **Irritable Bowel Syndrome**

- (Whelan & Quigley, 2013)

Current approach



Probiotics



Limited activity



FMT



Limited/
transient activity



Prebiotics



Limited targets
and specificity



Integrated personalized approach

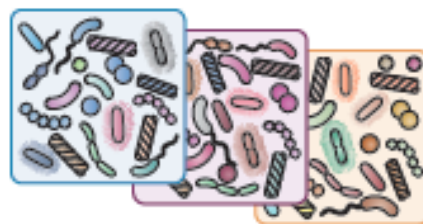


Metabolites (postbiotics)

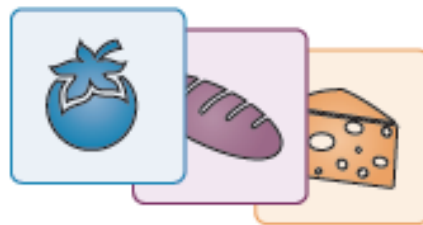


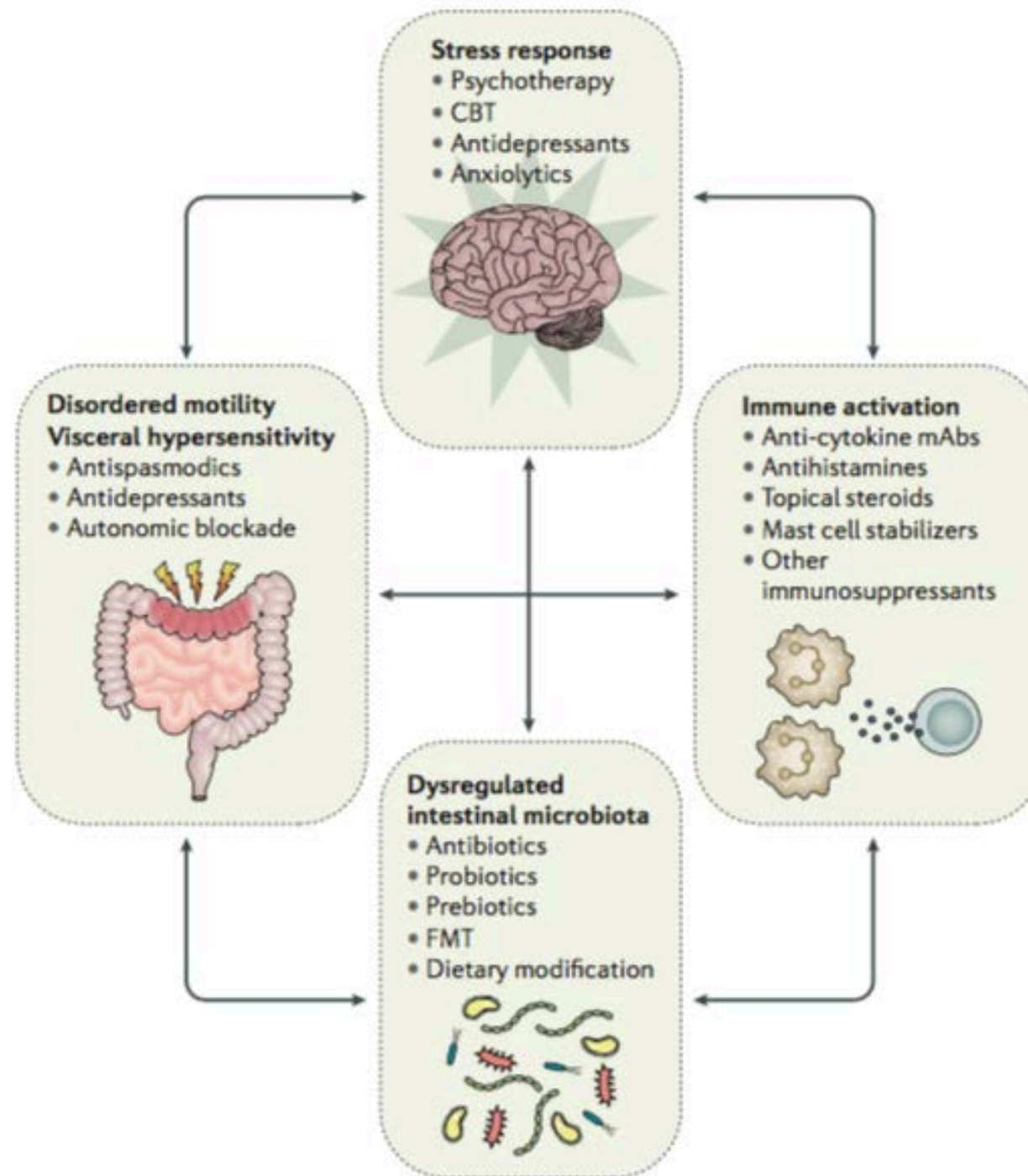
Direct effect on the host

Personalized FMT (probiotics)



Personalized nutrition (prebiotics)





8. Future Trends

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Endocannabinoid – Microbiota Crosstalk

- Role of bioactive lipids in the adipose tissue – gut microbiota axis
- Specific roles of bioactive lipids & endocannabinoid analogues
- Specific bacterial metabolites & endocannabinoid system (receptors, synthesis & degradation)
- Modulation of gut microbiota (Prebiotics, probiotics, etc.)
- Relevance of the endocannabidiome in the management of obesity & metabolic disorders

Strains, functions and dynamics in the expanded Human Microbiome Project

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The characterization of baseline microbial and functional diversity in the human microbiome has enabled studies of microbiome-related disease, diversity, biogeography, and molecular function. The National Institutes of Health Human Microbiome Project has provided one of the broadest such characterizations so far. Here we introduce a second wave of data from the study, comprising 1,631 new metagenomes (2,355 total) targeting diverse body sites with multiple time points in 265 individuals. We applied updated profiling and assembly methods to provide new characterizations of microbiome personalization. Strain identification revealed subspecies clades specific to body sites; it also quantified species with phylogenetic diversity under-represented in isolate genomes. Body-wide functional profiling classified pathways into universal, human-enriched, and body site-enriched subsets. Finally, temporal analysis decomposed microbial variation into rapidly variable, moderately variable, and stable subsets. This study furthers our knowledge of baseline human microbial diversity and enables an understanding of personalized microbiome function and dynamics.

9. References

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Juan Miguel Rodríguez¹, Kiera Murphy^{2,3}, Catherine Stanton^{2,3},
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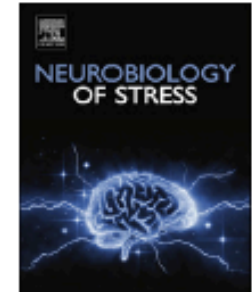
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Thank You