Casual Friday Presents

Chronic Kidney Disease (CKD)

and the Gut Connection

A BIOGENETIX CLINICAL PRESENTATION

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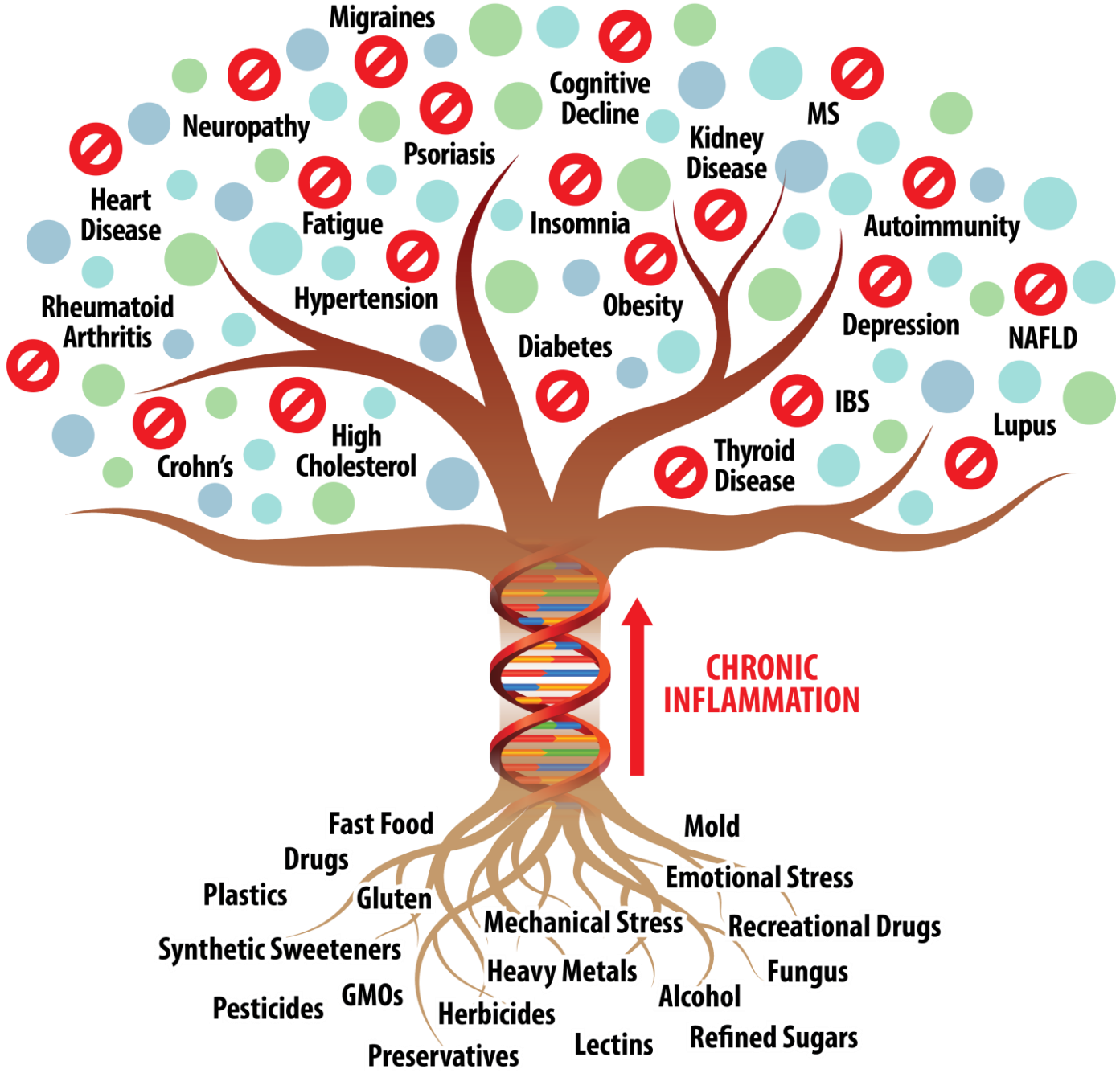
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

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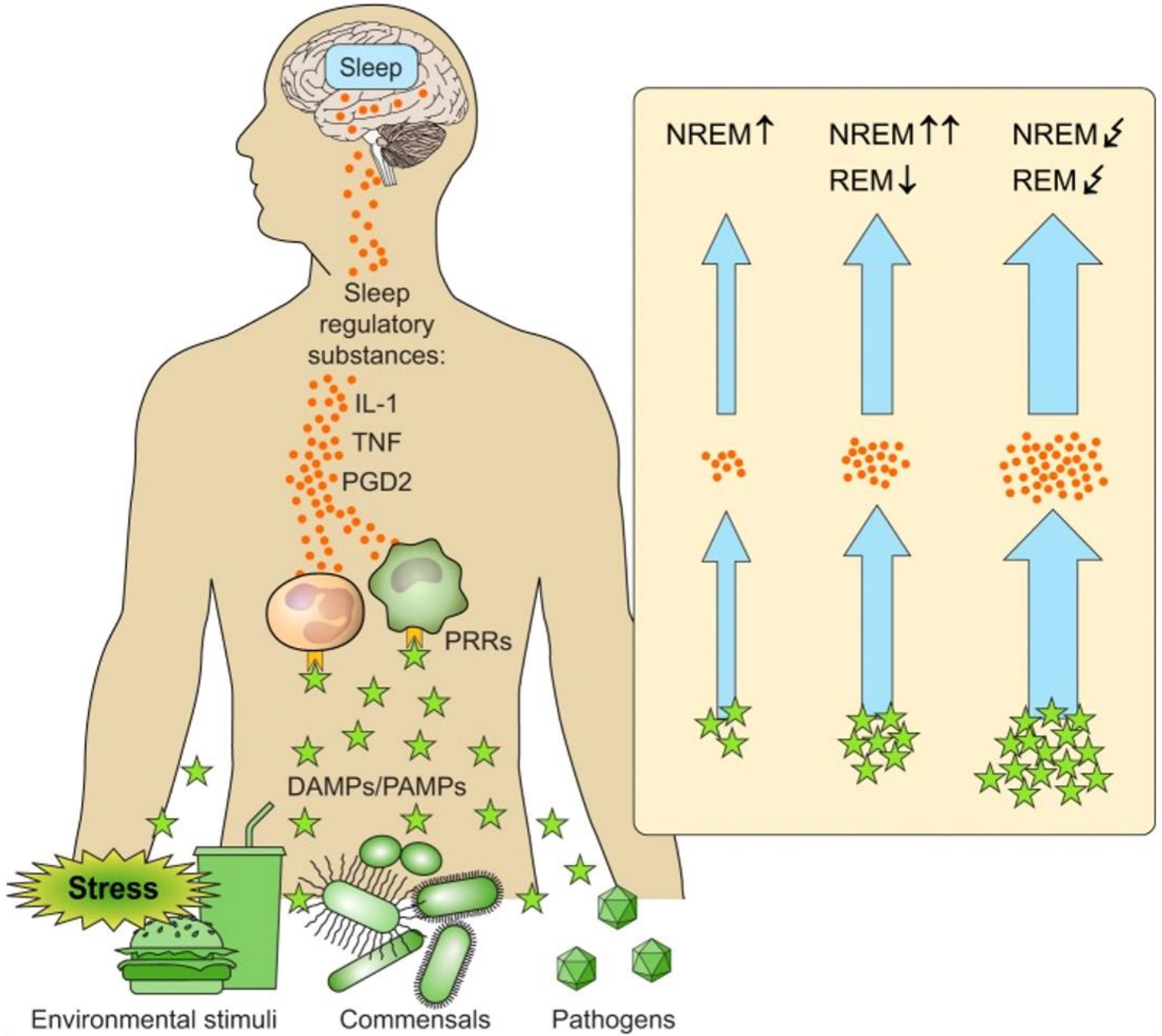

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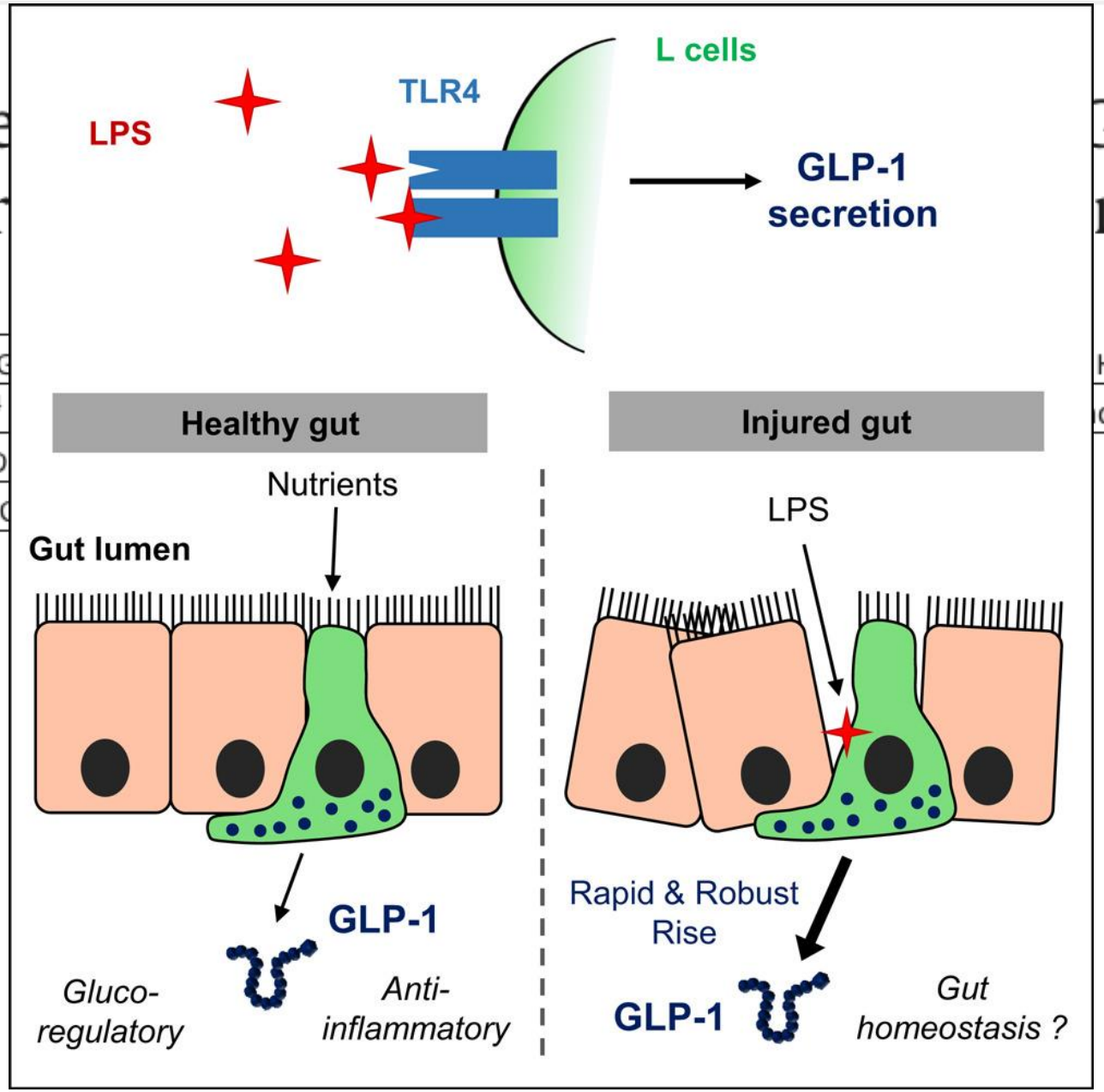

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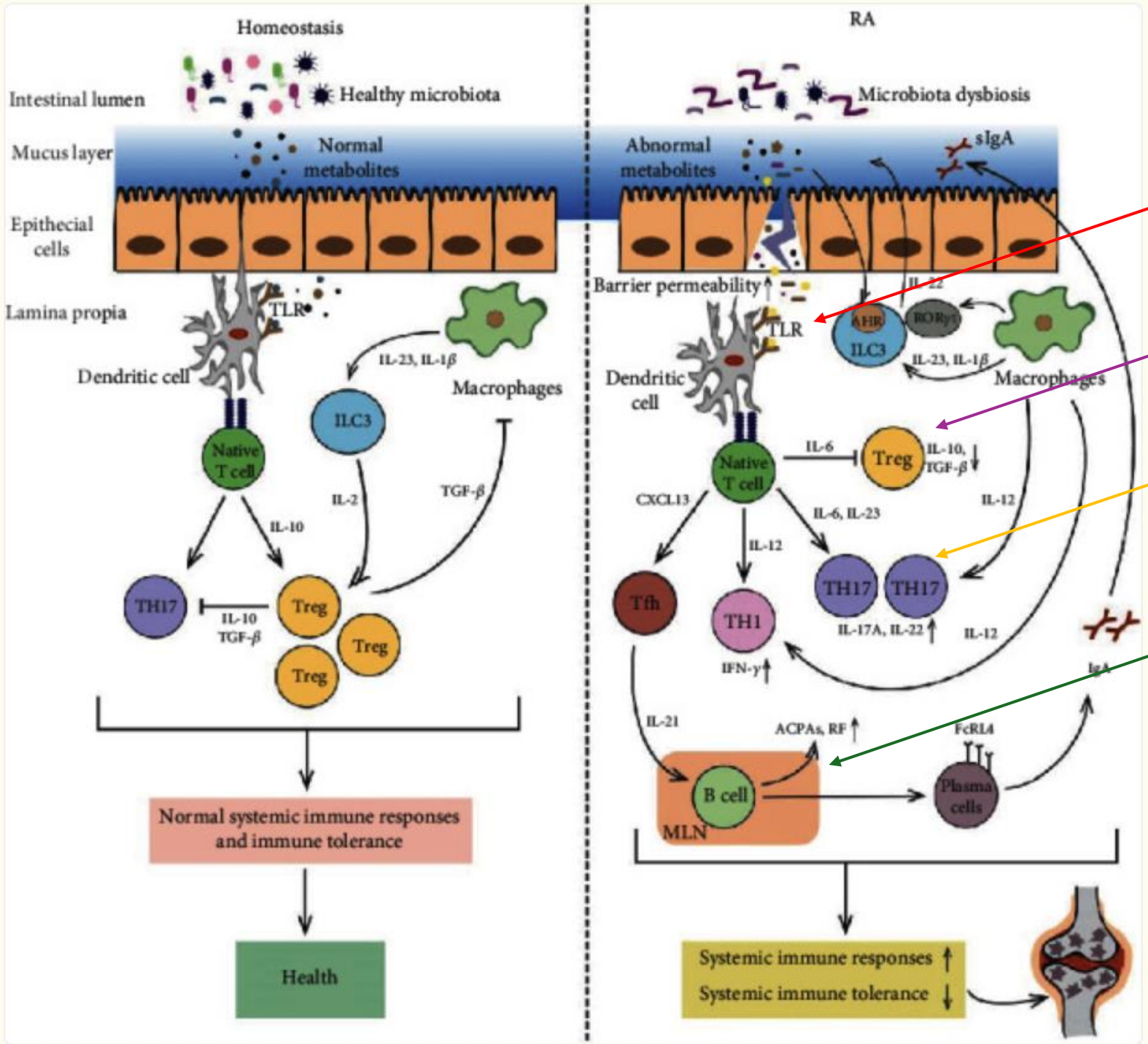
Homeostasis
Intestinal lumen
Healthy microbiota
Mucus layer
Normal metabolites
Epithecial cells
Lamina propia
TLR
Dendritic cell
IL-23, IL-1β
Macrophages
ILC3
Native T cell
IL-2
TGF-β
IL-10
TH17
IL-10 TGF-β
Treg
Treg
Treg
Normal systemic immune responses and immune tolerance
Health
RA
Microbiota dysbiosis
Abnormal metabolites
sIgA
Barrier permeability
IL-22
AHR
RORγt
ILC3
TLR
Dendritic cell
IL-23, IL-1β
Macrophages
Native T cell
IL-6
Treg
IL-10, TGF-β
CXCL13
IL-6, IL-23
IL-12
IL-12
Tfh
TH1
IFN-γ
TH17
TH17
IL-17A, IL-22
IL-12
IgA
IL-21
ACPAs, RF
FcRL4
B cell
Plasma cells
MLN
Systemic immune responses
Systemic immune tolerance

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The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease

Tao Yang [1], Elaine M Richards [1], Carl J Pepine [2], Mohan K Raizada [1,*]

Chronic kidney disease (CKD) affects approximately 10% of the global population and has a financial impact of ~$48 billion per year in the United States alone[1]. Hypertension is an important risk factor for CKD, and approximately 85–90% of patients with stage 3–5 CKD have hypertension[2]. Long-term hypertension leads to high intraglomerular pressure, which subsequently impairs glomerular filtration[3]. Thus, blood-pressure lowering is an important and widely used approach to slow CKD progression. Current management of early-stage CKD focuses on blood pressure control, reduction of protein and salt intake, prevention of acute kidney injury and glycaemic control[4]. No cure or strategy for prevention of CKD exists, and timely treatment is extremely challenging owing to a lack of symptoms in the early stages of the disease[5]. Moreover, with the exception of dialysis and kidney transplantation, effective treatments for end-stage renal disease (ESRD) are lacking. Thus, paradigm-shifting concepts and innovative approaches are needed to detect, manage, control and ultimately cure these diseases.

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Increasing evidence indicates an important role of the gut microbiota in the development of hypertension and CKD. The gut microbiota constantly communicates with vital organ systems of the host, such as the brain[6], bone marrow[7], vasculature[8], kidney[9], immune system[10] and autonomic nervous system (ANS)[11,12]. This communication contributes to the homeostasis and health of the host. Bone-marrow-derived immune cells are activated by the gut microbiota, leading to low-grade inflammation that affects the brain, ANS and the kidney via the circulation[13–15]. Peripheral stimuli influence the ANS to subsequently modify neural inputs to the kidney, intestine and lymphoid organs[16]. In addition, immune and gut microbiota-derived products affect renal function and have important effects on CKD[17]. Gut dysbiosis has an important role in many chronic diseases, and amelioration of this dysbiosis could be a potential strategy for the prevention and management of these diseases[18].

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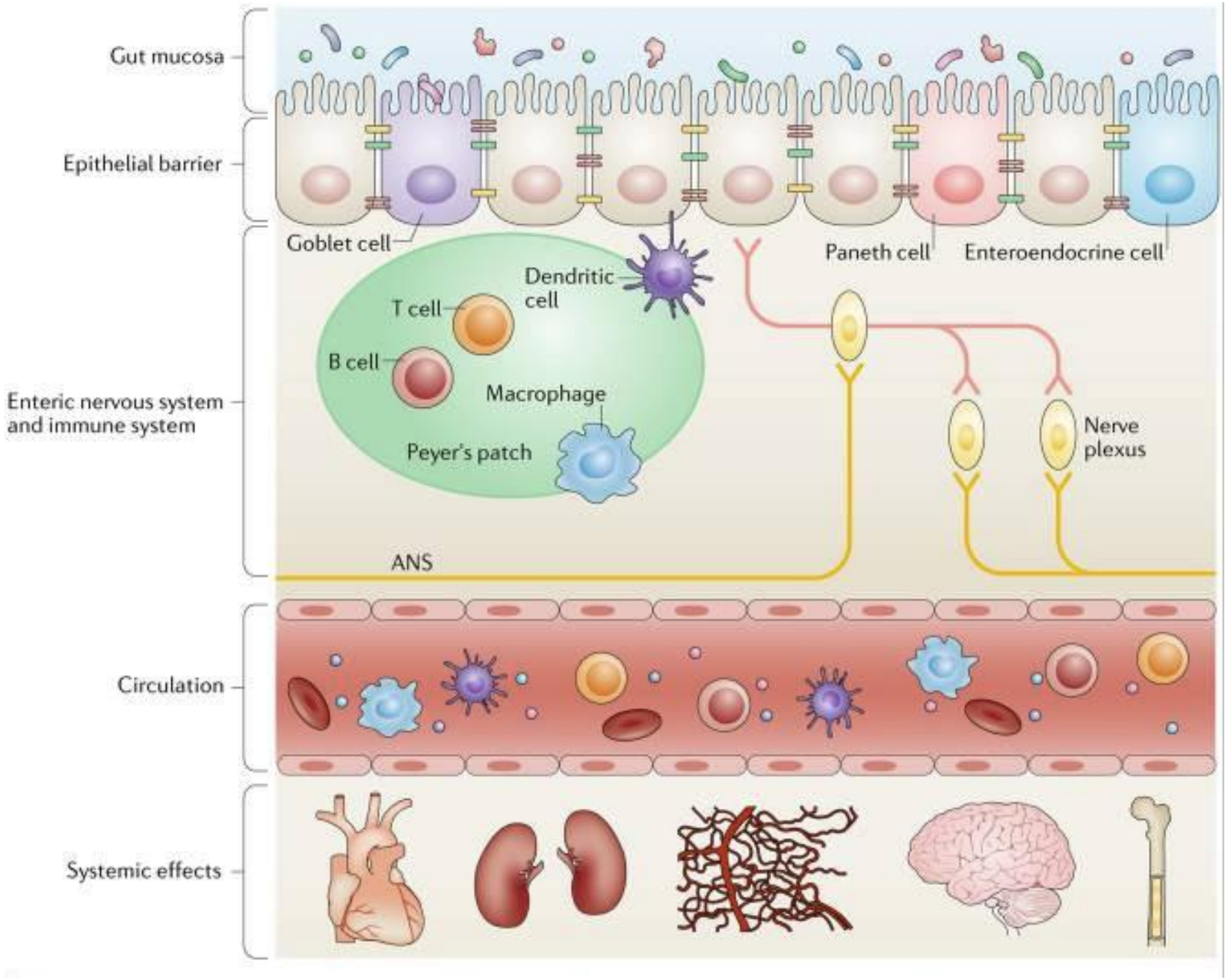
Gut mucosa
Epithelial barrier
Goblet cell
Paneth cell
Enteroendocrine cell
Dendritic cell
T cell
B cell
Macrophage
Peyer's patch
Enteric nervous system and immune system
Nerve plexus
ANS
Circulation
Systemic effects

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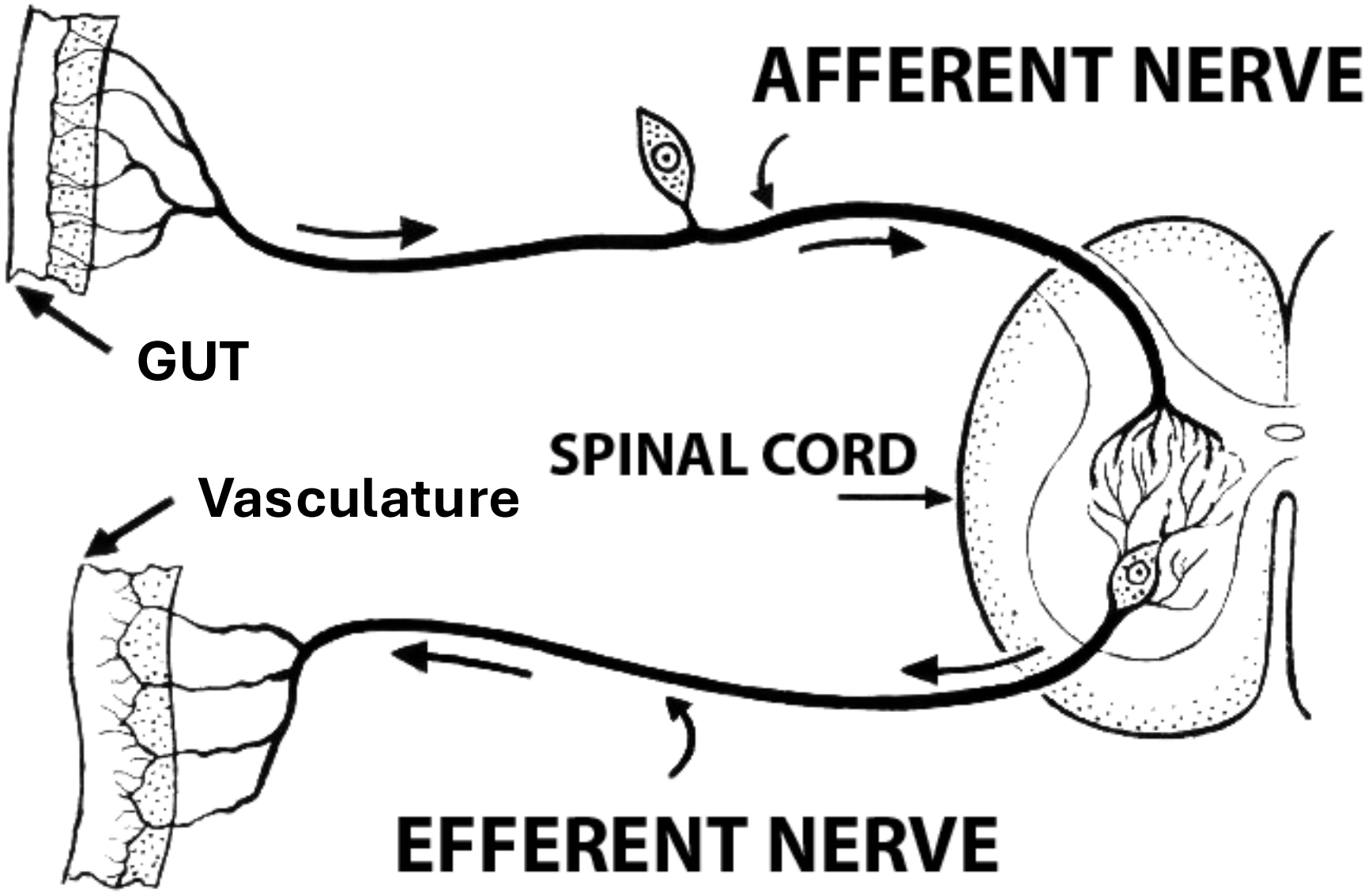
Tao Y

Neural control of the gut.

Intricate neural control of gastrointestinal function is achieved through the autonomic (extrinsic) and enteric (intrinsic) nervous systems[38]. The ANS conveys physiological conditions in the gut, such as acidity, levels of nutrients, osmolarity and pain, to the brain[49]. The enteric nervous system (ENS), which consists of the myenteric plexus and submucosal plexus, contributes to in situ neural communication within the intestine and connection to the ANS[38].

The ENS communicates bidirectionally with the brain through the vagus nerve, which sends sensory signals from the gut to the nucleus of the solitary tract (NTS) in the CNS. In a rat model of obesity, changes in the gut microbiota induced by an energy-dense diet were associated with alterations in brain-gut vagal (NTS) communication[53], which may alter vagal satiety signalling and stimulate energy intake and adiposity[54]. A series of beneficial effects of treatment with probiotics *(Lactobacillus rhamnosus* and *B. longum)* on stress and anxiety have been demonstrated to be vagus-nerve-dependent[11,12]. Vagal afferents express receptors that sense SCFAs[55], and activation of this pathway has been implicated in glucose homeostasis[56].


AFFERENT NERVE
GUT
SPINAL CORD
Vasculature
EFFERENT NERVE

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The gut microbiota in hypertension

Dysregulation of multiple contributing factors has been demonstrated in hypertension[80], including the reninangiotensin system[81,82], the ANS[82,83] and the immune system[84]. Environmental factors in association with epi-genetic[85] and genetic[86] components have critical roles in the initiation, maintenance and progression of hyper-tension. In addition, emerging evidence indicates that the gut microbiota has an essential role in hypertension development.

Gut dysbiosis has been reported in animal models[87–89] and in patients with hypertension[87,90] (Table 1). Moreover, spontaneously hypertensive rats (SHRs) showed patho-physiological changes in the gut, including decreased numbers of goblet cells and villi length and increased fibrosis compared with age-matched normotensive Wistar Kyoto (WKY) controls[91]. Although these changes were more profound in adult SHRs than in juvenile SHRs that had not yet developed hypertension, the prehypertensive juvenile SHRs had reduced levels of multiple tight junction proteins but similar gut permeability compared with juvenile WKY rats[91]. These findings indicate that gut pathology occurs before the onset of blood pressure elevation in the SHRs. Further evidence for a causative role of gut dysbiosis in the genesis of hypertension came from faecal microbiota transplantation (FMT) experiments in which transferring dysbiotic faecal samples from patients with hypertension to germ-free mice[90] or faeces from hypertensive stroke-prone SHRs to normotensive WKY rats[92] increased blood pressure in the recipients. As gut pathophysiological changes, immune responses and autonomic responses to FMT were not evaluated, further investigation is required to identify the potential mechanisms that underlie this FMT-induced increase in blood pressure.

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Changes in the gut microbial composition in hypertension and CKD

Bacteria	Hypertension		CKD	
	Change (organism)	Refs	Change (organism)	Refs
Actinobacteria				
Bifidobacterium	↓ (rat)	87,89	↓ (human and rat)	103,217
Bacteroidetes				
Bactemides	↓ (human and rat)	87,89,90,95	↓ (human and rat)	101,104
Prevotella	↑ (human)	90	↓ (human)	107,110
Parabactewides	↑ (human and rat)	87,90	↑ (human)	110
Firmicutes				
Lactobacillus	↓ (human and mouse)	92	↓ (human and rat)	101,104
Ruminococcaceae	NA	NA	↓ (human)	107
Roseburia	↓ (human)	90	↓ (human)	107
Allobaculum	↓ (rat)	87	NA	NA
Enterococcus	NA	NA	↑ (human)	107
Faecalibacterium	↓ (human)	90	↓ (human)	107
Proteobacteria				
Enterobacteriaceae	NA	NA	↑ (human)	101,105
Klebsiella	↓ (human)	203	↑ (human)	107
Verrucomicrobia				
Akkermansia	↓ (human and rat)	87,90	NA	NA

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The gut-kidney axis

The gut-kidney axis can be subdivided into metabolism-dependent and immune pathways[9]. The metabolism-dependent pathway is primarily mediated by metabolites produced by the gut microbiota that have the capability to regulate host physiological functions. In the immune pathway, components of the immune system (for example, lymphocytes, monocytes and cytokines) have a critical role in communication between the gut and the kidney (FIG. 2). Crosstalk between the metabolism-dependent and immune pathway also has an important role in maintaining the balance of the gut-kidney axis.

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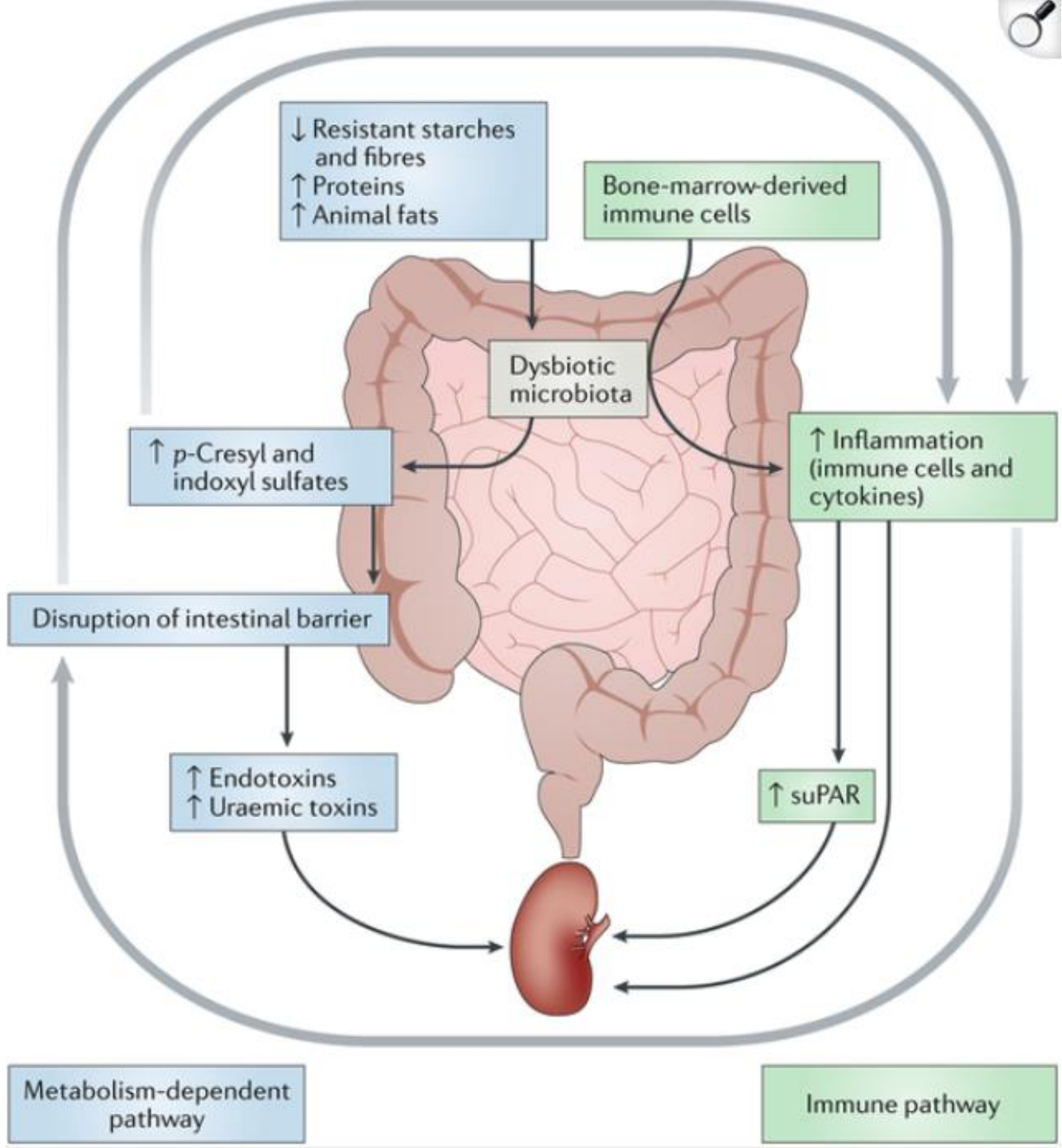
Diet is increasingly recognized to be a fundamental regulator of gut microbiomes. Dietary fermentable fibres, rather than protein, are the main source of energy for gut epithelial cells[111]. With sufficient supply of dietary fibres, the protein-derived α-amino nitrogen is almost totally incorporated into the faecal biomass. Lack of dietary fibres or excessive protein or animal fats leads to overaccumulation of α-amino nitrogen, which can be converted into uraemic toxins by the gut microbiota[112]. Patients on haemodialysis who had intact colons had significantly higher levels of *p*-cresyl sulfate and indoxyl sulfate than those who did not have colons, indicating an important contribution of colonic microorganisms to the production of uraemic toxins[113]. Colonic transit time is a modifiable determinant of uraemic toxin production[114]. A prolonged transit time decreases the availability of carbohydrates in the colon, facilitating increased protein fermentation and expanding the proteolytic bacterial population[9]. Therefore, the colonic microbiota makes a considerable contribution to the production of uraemic toxins.


↓ Resistant starches and fibres
↑ Proteins
↑ Animal fats
Bone-marrow-derived immune cells
Dysbiotic microbiota
↑ p-Cresyl and indoxyl sulfates
↑ Inflammation (immune cells and cytokines)
Disruption of intestinal barrier
↑ Endotoxins
↑ Uraemic toxins
↑ suPAR
Metabolism-dependent pathway
Immune pathway

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In CKD, a reduction in renal filtering capacity results in the deposition and accumulation of waste products in the blood. Accumulation of products of protein fermentation (for example, α-amino nitrogen) in the intestine and blood increases the gut intraluminal pH, deranges gut homeostasis and triggers intestinal disorders[102]. In addition, as renal function declines, the colon replaces the kidney as the primary site of excretion of urea and uric acid[115]. Constant exposure of colonic epithelial cells to urea reduces their viability and decreases epithelial barrier function in vitro[116] and disrupts colonic tight junction proteins (for example, claudin 1, occludin and zonula occludens 1) both in vitro and in vivo[116,117]. Consequently, the levels of endotoxins and bacterial products in the circulation are elevated in patients with CKD compared with healthy individuals[118,119]. Deficits in renal function associated with a leaky gut exacerbate the accumulation of metabolic wastes in the blood and may eventually cause uraemia.

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Immune pathway.

Another pathway that links the gut microbiota and the kidney is mediated by the immune system. Colonization of commensal microbiota in germ-free mice induced changes in the inflammatory cytokine profile in the bone marrow[120], which is the primary site of origin of immune cells. Cytokines have important effects in haematopoiesis, and antibiotic-mediated depletion of the intestinal microbiota in mice led to the suppression of multipotent progenitors in the bone marrow[7]. Therefore, the gut microbiota modulates not only the activation of intestinal immune cells but also the profile of immune progenitor cells in the bone marrow.

The relationship between the bone marrow, cardiovascular system, hypertension and CKD has long been recognized[15,121]. Following bone marrow ablation, reconstitution of WKY rats with bone marrow from SHRs led to an elevation in blood pressure and inflammation, whereas reconstitution of SHRs with WKY bone marrow had the opposite effect[15]. In a clinical setting, renal dysfunction has been found in recipients of bone marrow transplants[122], suggesting a contributory role of the bone marrow in the initiation of kidney inflammation. As the levels of pro-inflammatory cytokines positively correlate with the development of albuminuria and proteinuria, early intrarenal inflammation has been suggested as an important pathogenic mechanism in the onset of kidney disease[123]. In addition, immature myeloid cells derived from the bone marrow have been reported to be responsible for elevation in the circulating levels of soluble urokinase plasminogen activator surface receptor (suPAR)[124], which has been implicated in the onset and progression of CKD[125]. Evidence also indicates that multipotent cells in bone marrow repair damaged tissues, including the vasculature and kidney, by undergoing proliferation, mobilization, differentiation and eventually incorporation into these tissues[126–128].

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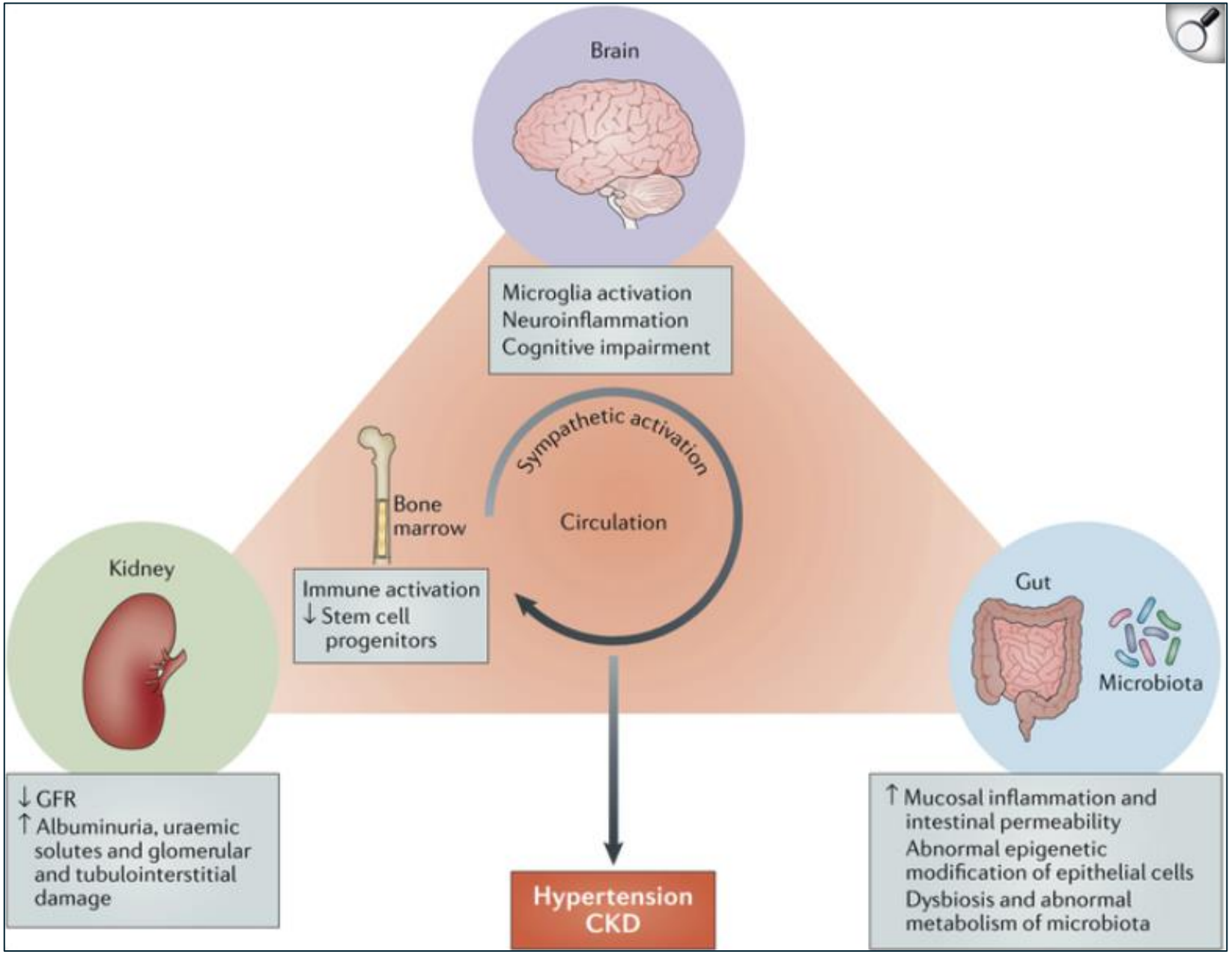
After exiting from the bone marrow, mature immune cells in the gut are activated by the gut microbiota in peripheral lymphoid organs, such as GALT[129]. Gut per meability leads to accumulation of bacteria and bacterial products in the circulation and substantially contributes to chronic and systemic low-grade inflammation.

Low-grade inflammation has a critical role in the maintenance of many chronic diseases, including hypertension and CKD[130,131]. A number of studies have demonstrated contributory roles for macrophages[132], T cells[133] and B cells[134] in the genesis of hypertension. For example, the blood pressure of germ-free mice is comparable to that of conventionally raised mice[8], but angiotensin-II-induced increases in blood pressure are blunted in germ-free mice, likely owing to inefficient induction of oxidative stress and inflammation by angiotensin II[8]. In the prehepatic portal hypertension model, mice with absent intestinal bacteria exhibited lower portal pressure than controls with intestinal microbiota; this lower portal pressure was associated with reduced densities of intestinal lymphatic and blood vessels[135]. These data suggest the involvement of gut microbiota in the immune-cell-mediated genesis of hypertension.

The gut microbiota also has a crucial role in systemic metabolic syndrome and CKD[136–138]. Mice with adenine-induced renal failure housed in germ-free conditions had significantly lower levels of uraemic toxins than those housed in SPF conditions[138]. However, more severe renal damage was observed in the germ-free mice, presumably owing to reduced production of renoprotective SCFAs and inefficient utilization of amino acids compared with the SPF mice. This finding highlights the importance of maintaining an exquisitely balanced gut microbiota in CKD.


Brain
Microglia activation
Neuroinflammation
Cognitive impairment
Sympathetic activation
Circulation
Bone marrow
Immune activation
↓ Stem cell progenitors
Kidney
↓ GFR
↑ Albuminuria, uraemic solutes and glomerular and tubulointerstitial damage
Hypertension CKD
Gut
Microbiota
↑ Mucosal inflammation and intestinal permeability
Abnormal epigenetic modification of epithelial cells
Dysbiosis and abnormal metabolism of microbiota

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