Casual Friday Presents

The Gut-Joint Axis

and Intervention Development

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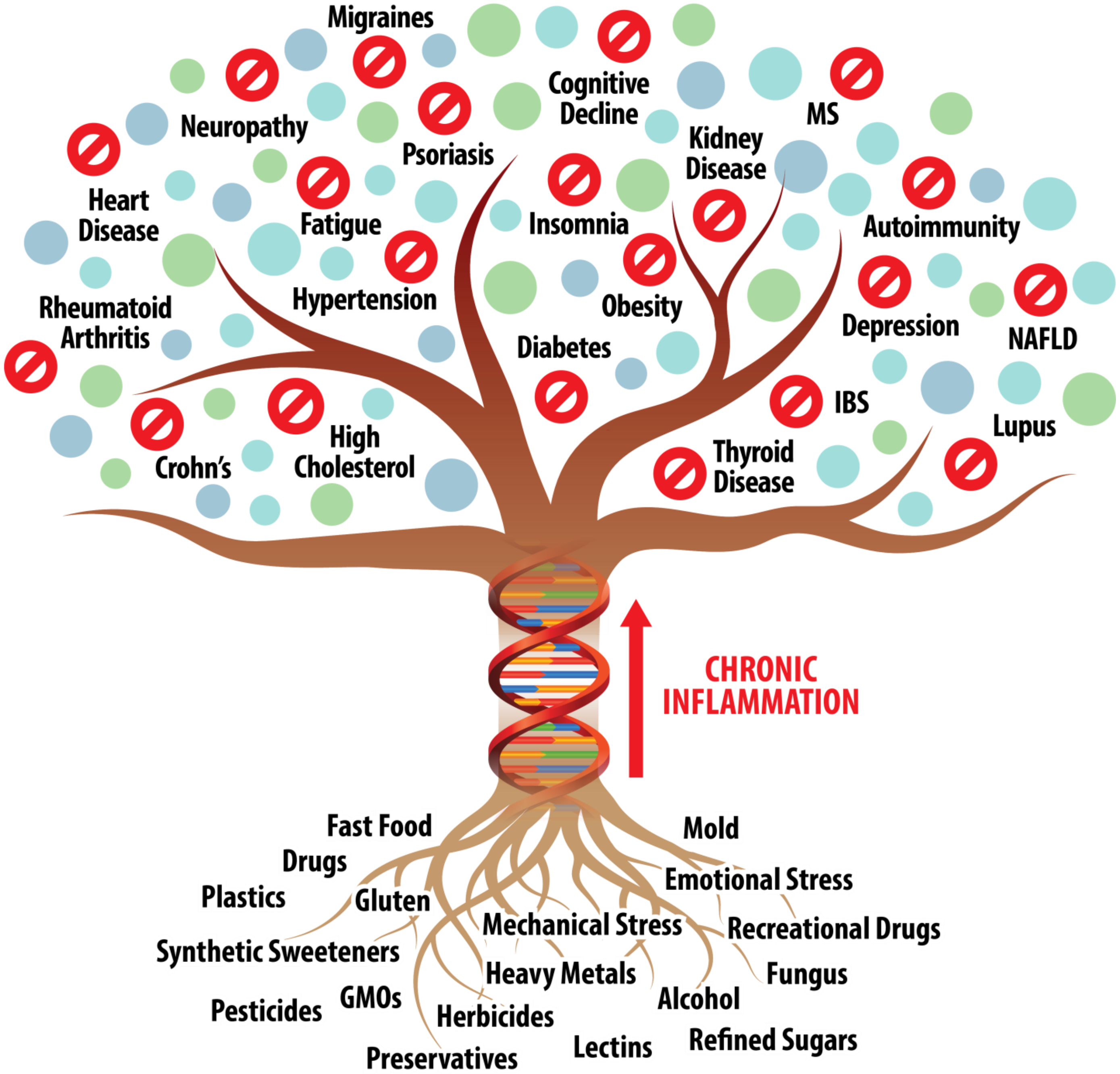

Migraines

Neuropathy

Psoriasis

Cognitive Decline

MS

Kidney Disease

Heart Disease

Fatigue

Insomnia

Autoimmunity

Rheumatoid Arthritis

Hypertension

Obesity

Depression

NAFLD

Diabetes

IBS

Lupus

High Cholesterol

Crohn's

Thyroid Disease

CHRONIC INFLAMMATION

Fast Food

Drugs

Plastics

Gluten

Synthetic Sweeteners

Pesticides

GMOs

Preservatives

Herbicides

Heavy Metals

Mechanical Stress

Lectins

Mold

Emotional Stress

Recreational Drugs

Fungus

Alcohol

Refined Sugars

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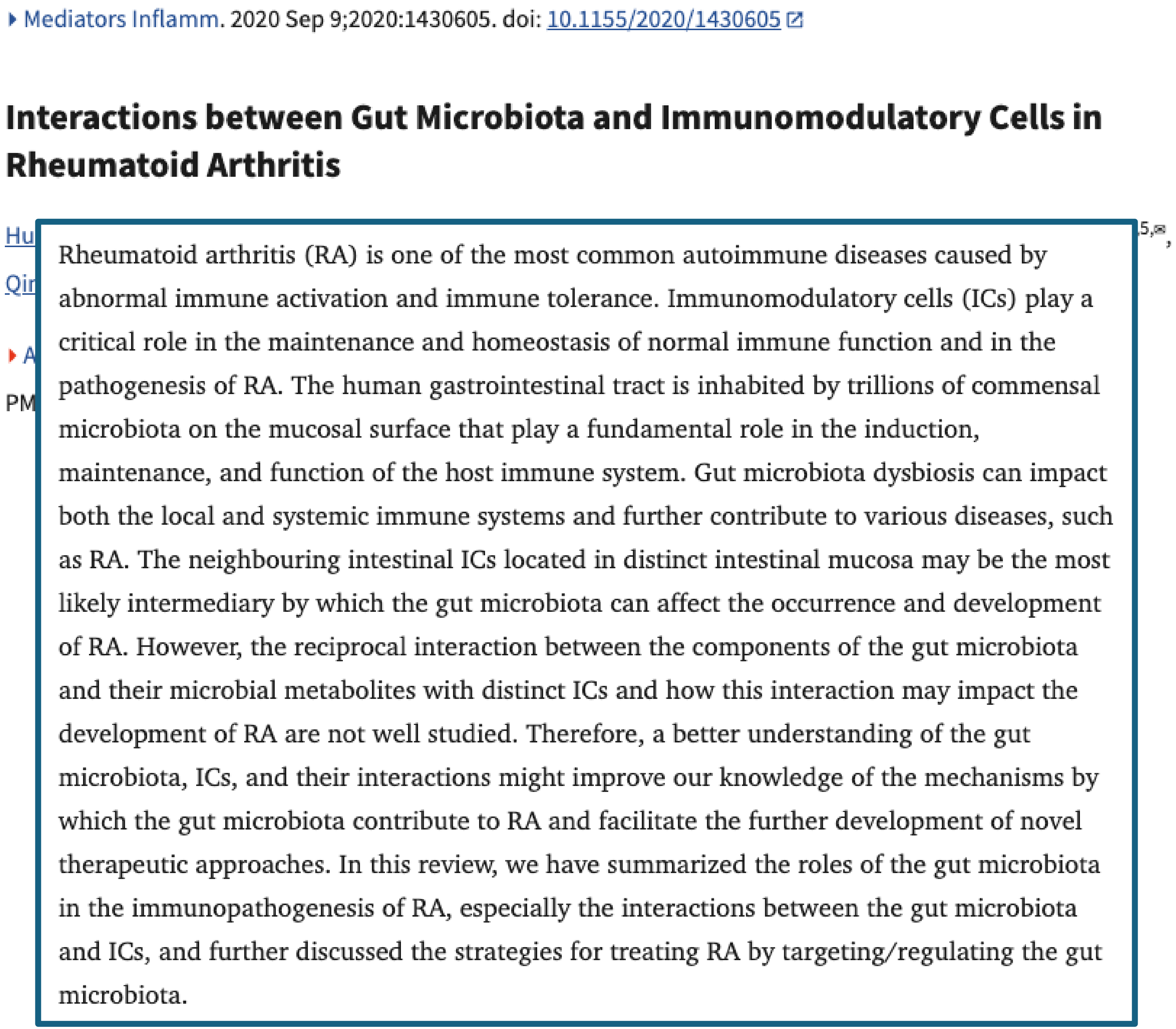

Mediators Inflamm. 2020 Sep 9;2020:1430605. doi: 10.1155/2020/1430605

Interactions between Gut Microbiota and Immunomodulatory Cells in Rheumatoid Arthritis

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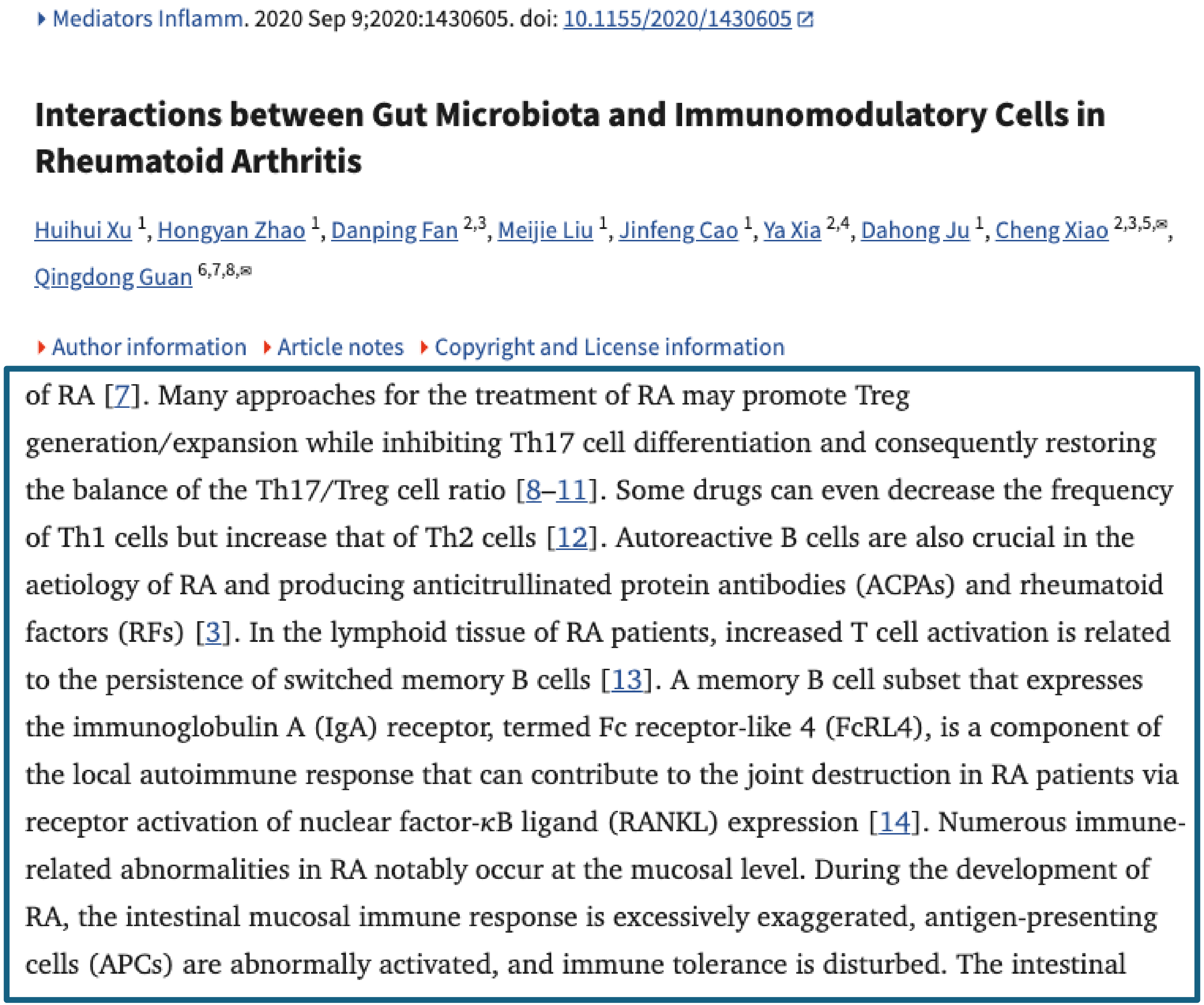
Rheumatoid arthritis (RA) is one of the most common autoimmune diseases caused by abnormal immune activation and immune tolerance. Immunomodulatory cells (ICs) play a critical role in the maintenance and homeostasis of normal immune function and in the pathogenesis of RA. The human gastrointestinal tract is inhabited by trillions of commensal microbiota on the mucosal surface that play a fundamental role in the induction, maintenance, and function of the host immune system. Gut microbiota dysbiosis can impact both the local and systemic immune systems and further contribute to various diseases, such as RA. The neighbouring intestinal ICs located in distinct intestinal mucosa may be the most likely intermediary by which the gut microbiota can affect the occurrence and development of RA. However, the reciprocal interaction between the components of the gut microbiota and their microbial metabolites with distinct ICs and how this interaction may impact the development of RA are not well studied. Therefore, a better understanding of the gut microbiota, ICs, and their interactions might improve our knowledge of the mechanisms by which the gut microbiota contribute to RA and facilitate the further development of novel therapeutic approaches. In this review, we have summarized the roles of the gut microbiota in the immunopathogenesis of RA, especially the interactions between the gut microbiota and ICs, and further discussed the strategies for treating RA by targeting/regulating the gut microbiota.



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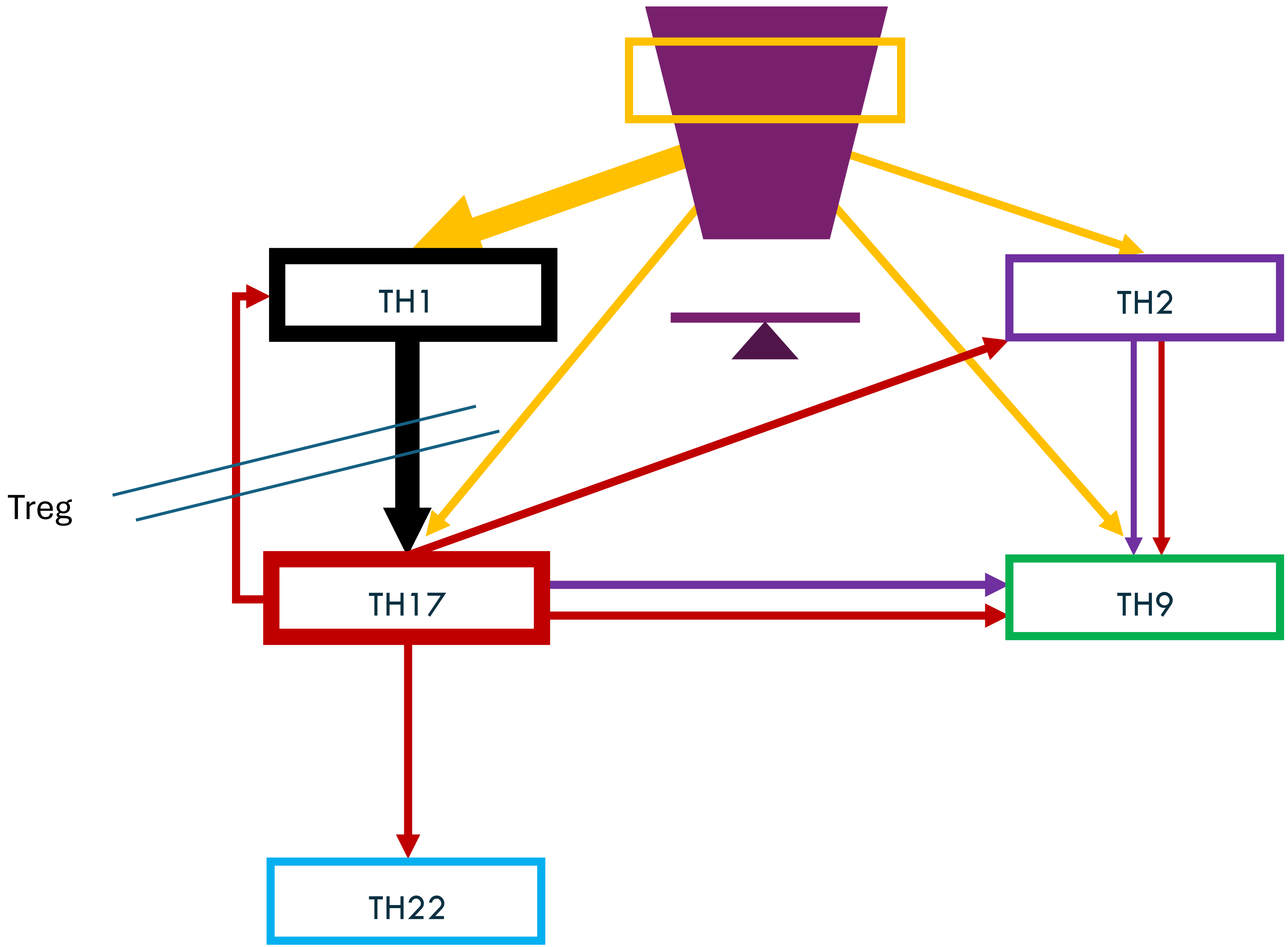
Interactions between Gut Microbiota and Immunomodulatory Cells in Rheumatoid Arthritis

Huihui Xu [1], Hongyan Zhao [1], Danping Fan [2,3], Meijie Liu [1], Jinfeng Cao [1], Ya Xia [2,4], Dahong Ju [1], Cheng Xiao [2,3,5,✉], Qingdong Guan [6,7,8,✉]

of RA [7]. Many approaches for the treatment of RA may promote Treg generation/expansion while inhibiting Th17 cell differentiation and consequently restoring the balance of the Th17/Treg cell ratio [8–11]. Some drugs can even decrease the frequency of Th1 cells but increase that of Th2 cells [12]. Autoreactive B cells are also crucial in the aetiology of RA and producing anticitrullinated protein antibodies (ACPAs) and rheumatoid factors (RFs) [3]. In the lymphoid tissue of RA patients, increased T cell activation is related to the persistence of switched memory B cells [13]. A memory B cell subset that expresses the immunoglobulin A (IgA) receptor, termed Fc receptor-like 4 (FcRL4), is a component of the local autoimmune response that can contribute to the joint destruction in RA patients via receptor activation of nuclear factor-κB ligand (RANKL) expression [14]. Numerous immune-related abnormalities in RA notably occur at the mucosal level. During the development of RA, the intestinal mucosal immune response is excessively exaggerated, antigen-presenting cells (APCs) are abnormally activated, and immune tolerance is disturbed. The intestinal



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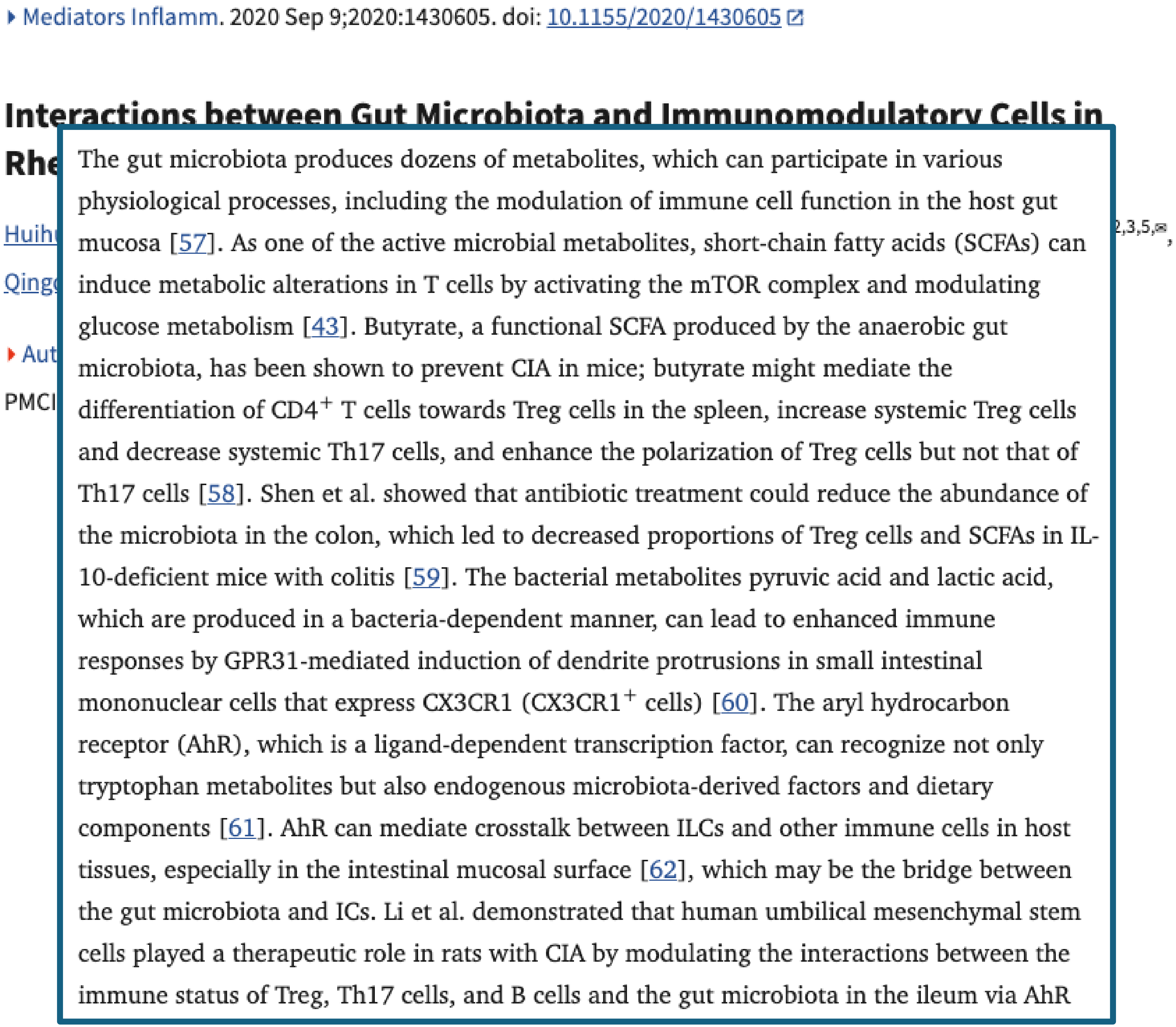

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Interactions between Gut Microbiota and Immunomodulatory Cells in Rhe

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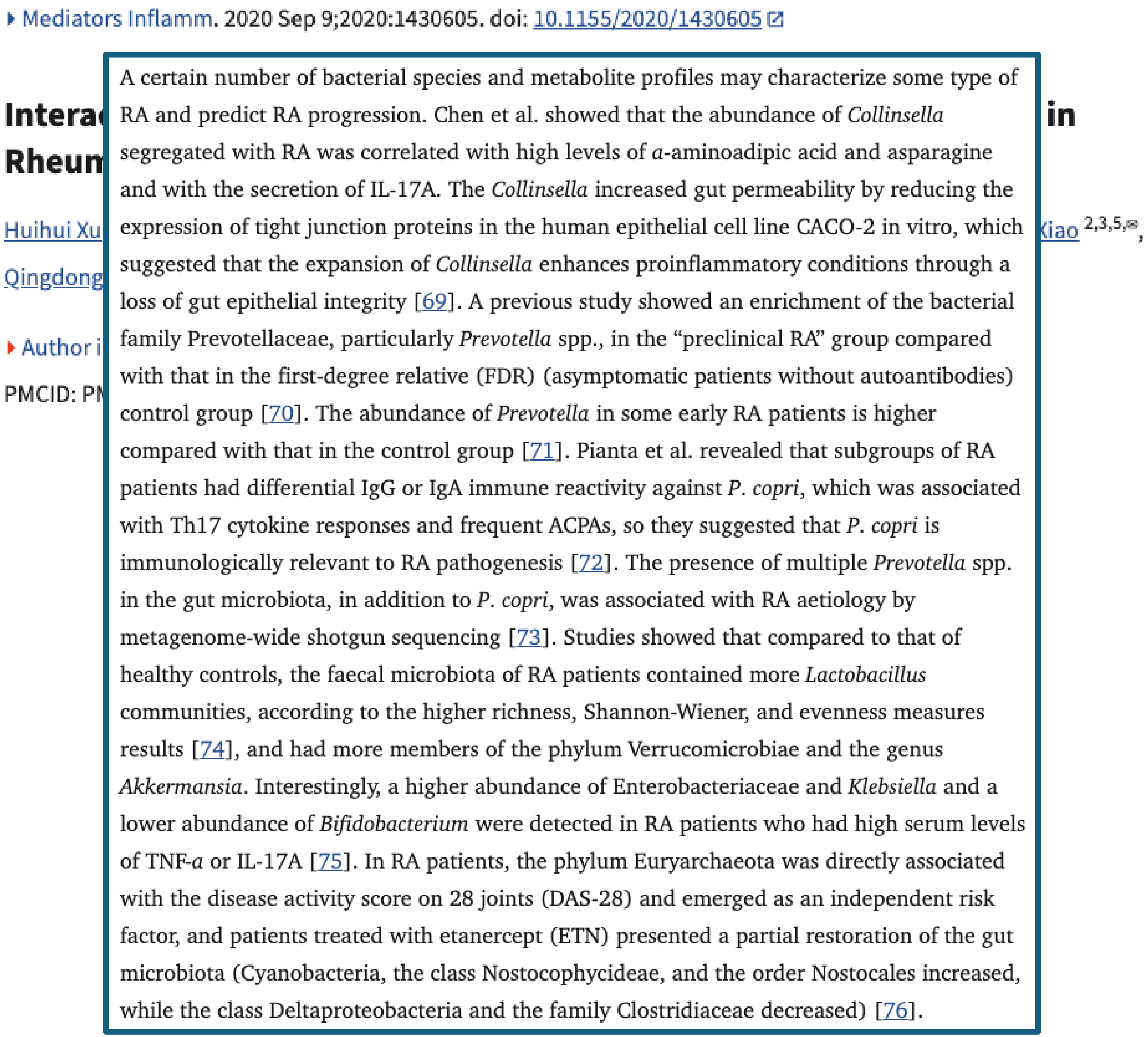
The gut microbiota produces dozens of metabolites, which can participate in various physiological processes, including the modulation of immune cell function in the host gut mucosa [57]. As one of the active microbial metabolites, short-chain fatty acids (SCFAs) can induce metabolic alterations in T cells by activating the mTOR complex and modulating glucose metabolism [43]. Butyrate, a functional SCFA produced by the anaerobic gut microbiota, has been shown to prevent CIA in mice; butyrate might mediate the differentiation of $CD4^+$ T cells towards Treg cells in the spleen, increase systemic Treg cells and decrease systemic Th17 cells, and enhance the polarization of Treg cells but not that of Th17 cells [58]. Shen et al. showed that antibiotic treatment could reduce the abundance of the microbiota in the colon, which led to decreased proportions of Treg cells and SCFAs in IL-10-deficient mice with colitis [59]. The bacterial metabolites pyruvic acid and lactic acid, which are produced in a bacteria-dependent manner, can lead to enhanced immune responses by GPR31-mediated induction of dendrite protrusions in small intestinal mononuclear cells that express CX3CR1 ($CX3CR1^+$ cells) [60]. The aryl hydrocarbon receptor (AhR), which is a ligand-dependent transcription factor, can recognize not only tryptophan metabolites but also endogenous microbiota-derived factors and dietary components [61]. AhR can mediate crosstalk between ILCs and other immune cells in host tissues, especially in the intestinal mucosal surface [62], which may be the bridge between the gut microbiota and ICs. Li et al. demonstrated that human umbilical mesenchymal stem cells played a therapeutic role in rats with CIA by modulating the interactions between the immune status of Treg, Th17 cells, and B cells and the gut microbiota in the ileum via AhR



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Rheum

Huihui Xu … Xiao [2,3,5,✉],

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A certain number of bacterial species and metabolite profiles may characterize some type of RA and predict RA progression. Chen et al. showed that the abundance of *Collinsella* segregated with RA was correlated with high levels of *α*-aminoadipic acid and asparagine and with the secretion of IL-17A. The *Collinsella* increased gut permeability by reducing the expression of tight junction proteins in the human epithelial cell line CACO-2 in vitro, which suggested that the expansion of *Collinsella* enhances proinflammatory conditions through a loss of gut epithelial integrity [69]. A previous study showed an enrichment of the bacterial family Prevotellaceae, particularly *Prevotella* spp., in the "preclinical RA" group compared with that in the first-degree relative (FDR) (asymptomatic patients without autoantibodies) control group [70]. The abundance of *Prevotella* in some early RA patients is higher compared with that in the control group [71]. Pianta et al. revealed that subgroups of RA patients had differential IgG or IgA immune reactivity against *P. copri*, which was associated with Th17 cytokine responses and frequent ACPAs, so they suggested that *P. copri* is immunologically relevant to RA pathogenesis [72]. The presence of multiple *Prevotella* spp. in the gut microbiota, in addition to *P. copri*, was associated with RA aetiology by metagenome-wide shotgun sequencing [73]. Studies showed that compared to that of healthy controls, the faecal microbiota of RA patients contained more *Lactobacillus* communities, according to the higher richness, Shannon-Wiener, and evenness measures results [74], and had more members of the phylum Verrucomicrobiae and the genus *Akkermansia*. Interestingly, a higher abundance of Enterobacteriaceae and *Klebsiella* and a lower abundance of *Bifidobacterium* were detected in RA patients who had high serum levels of TNF-*α* or IL-17A [75]. In RA patients, the phylum Euryarchaeota was directly associated with the disease activity score on 28 joints (DAS-28) and emerged as an independent risk factor, and patients treated with etanercept (ETN) presented a partial restoration of the gut microbiota (Cyanobacteria, the class Nostocophycideae, and the order Nostocales increased, while the class Deltaproteobacteria and the family Clostridiaceae decreased) [76].

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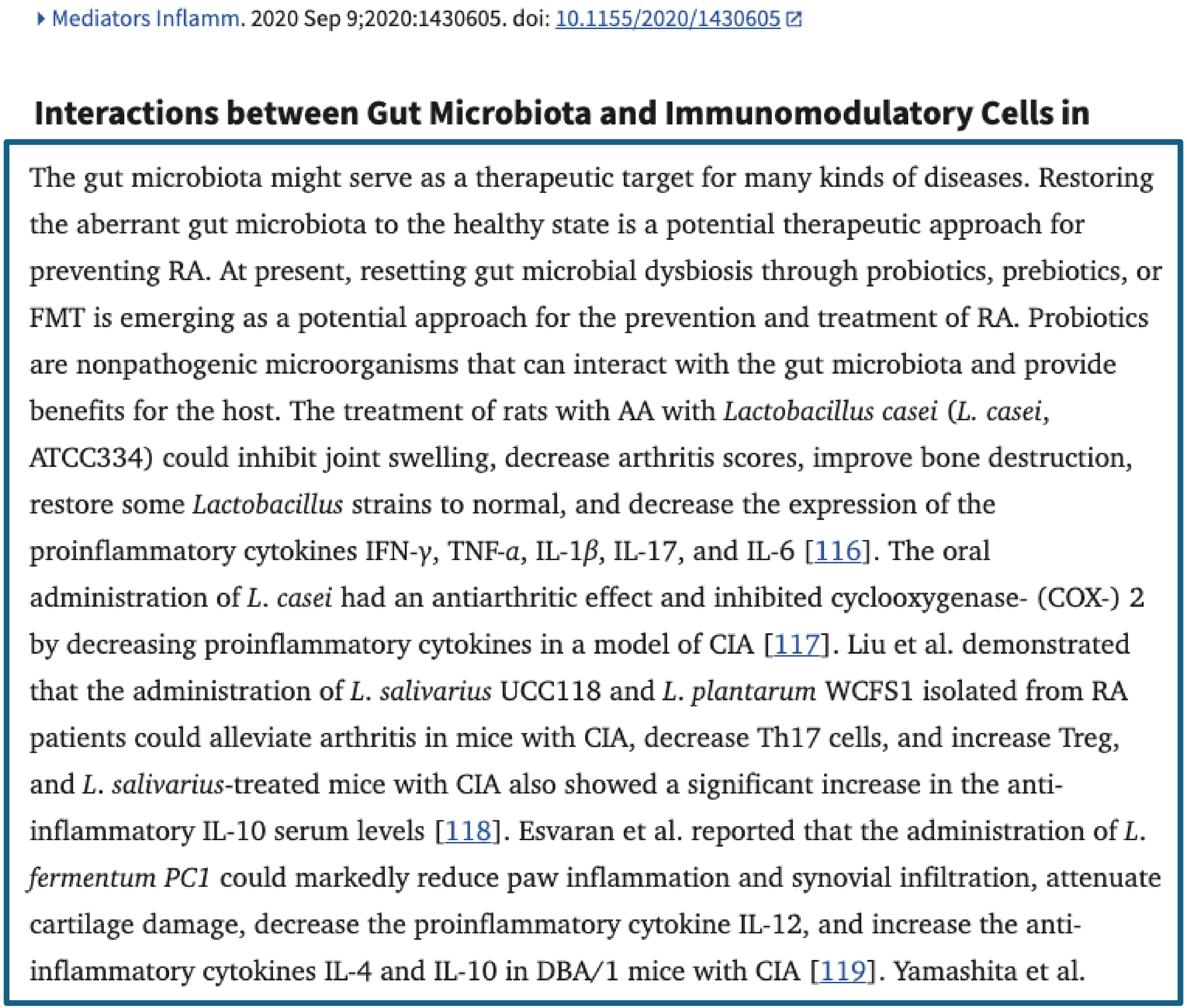

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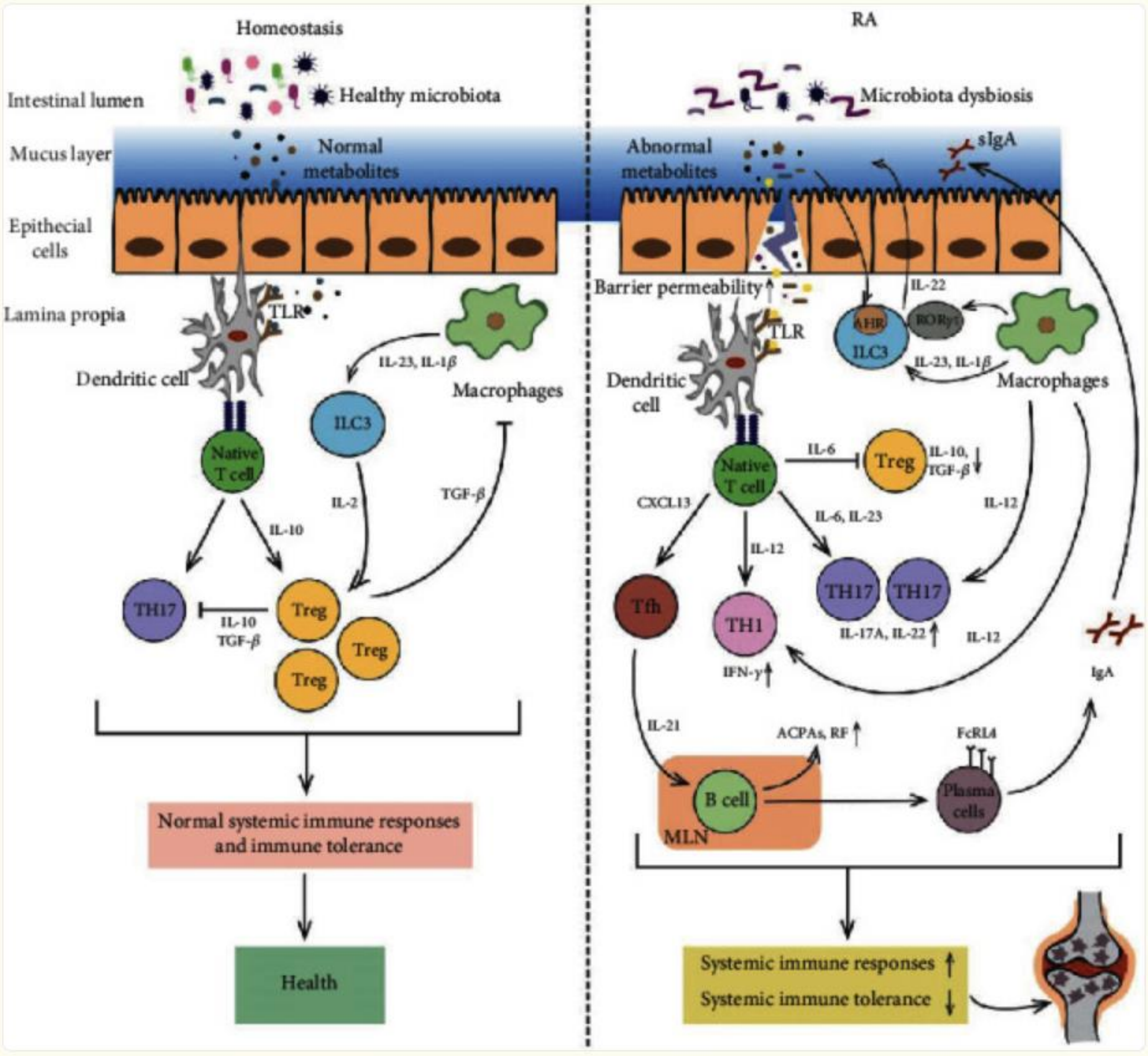
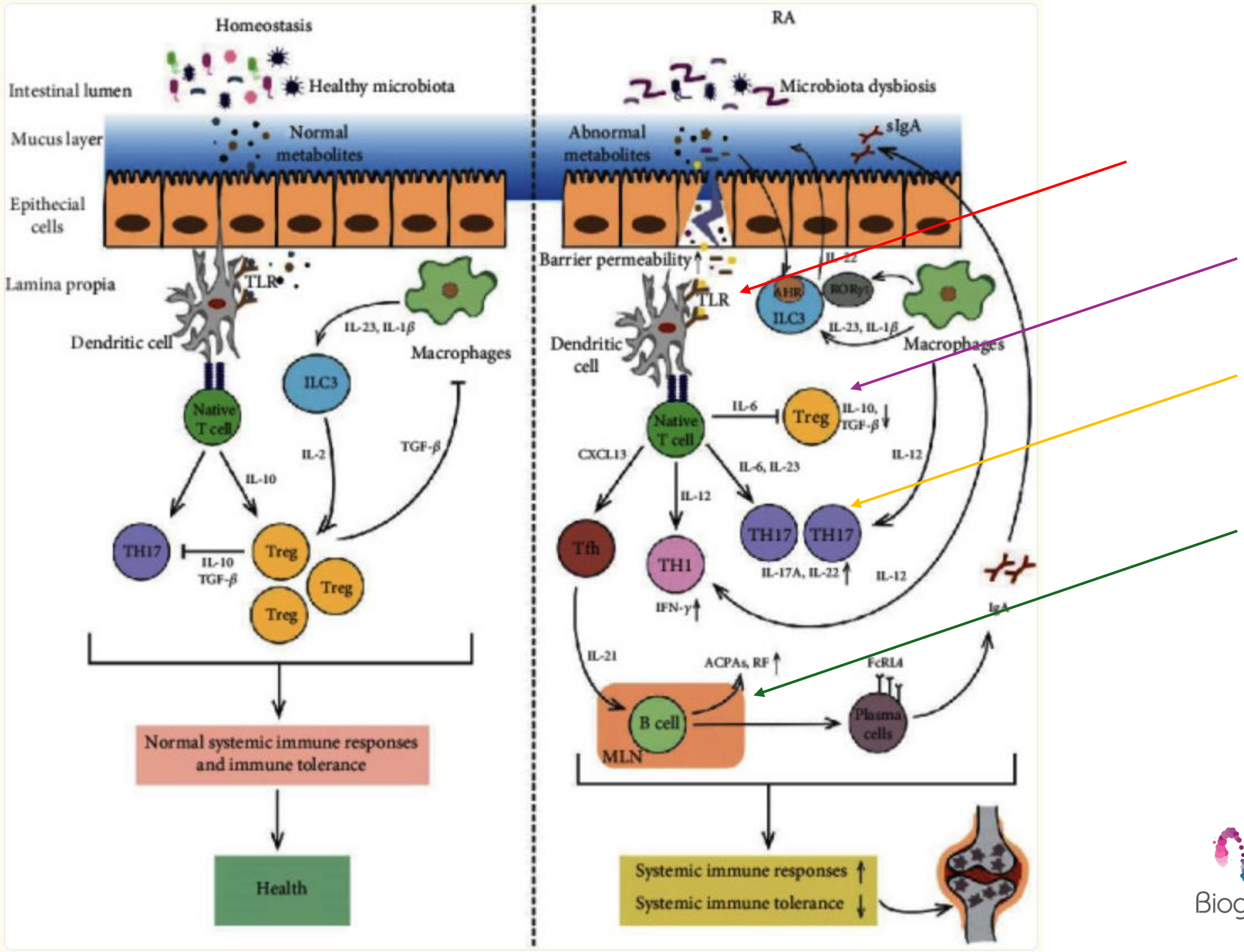
Interactions between Gut Microbiota and Immunomodulatory Cells in

The gut microbiota might serve as a therapeutic target for many kinds of diseases. Restoring the aberrant gut microbiota to the healthy state is a potential therapeutic approach for preventing RA. At present, resetting gut microbial dysbiosis through probiotics, prebiotics, or FMT is emerging as a potential approach for the prevention and treatment of RA. Probiotics are nonpathogenic microorganisms that can interact with the gut microbiota and provide benefits for the host. The treatment of rats with AA with *Lactobacillus casei* (*L. casei*, ATCC334) could inhibit joint swelling, decrease arthritis scores, improve bone destruction, restore some *Lactobacillus* strains to normal, and decrease the expression of the proinflammatory cytokines IFN-*γ*, TNF-*a*, IL-1*β*, IL-17, and IL-6 [116]. The oral administration of *L. casei* had an antiarthritic effect and inhibited cyclooxygenase- (COX-) 2 by decreasing proinflammatory cytokines in a model of CIA [117]. Liu et al. demonstrated that the administration of *L. salivarius* UCC118 and *L. plantarum* WCFS1 isolated from RA patients could alleviate arthritis in mice with CIA, decrease Th17 cells, and increase Treg, and *L. salivarius*-treated mice with CIA also showed a significant increase in the anti-inflammatory IL-10 serum levels [118]. Esvaran et al. reported that the administration of *L. fermentum PC1* could markedly reduce paw inflammation and synovial infiltration, attenuate cartilage damage, decrease the proinflammatory cytokine IL-12, and increase the anti-inflammatory cytokines IL-4 and IL-10 in DBA/1 mice with CIA [119]. Yamashita et al.


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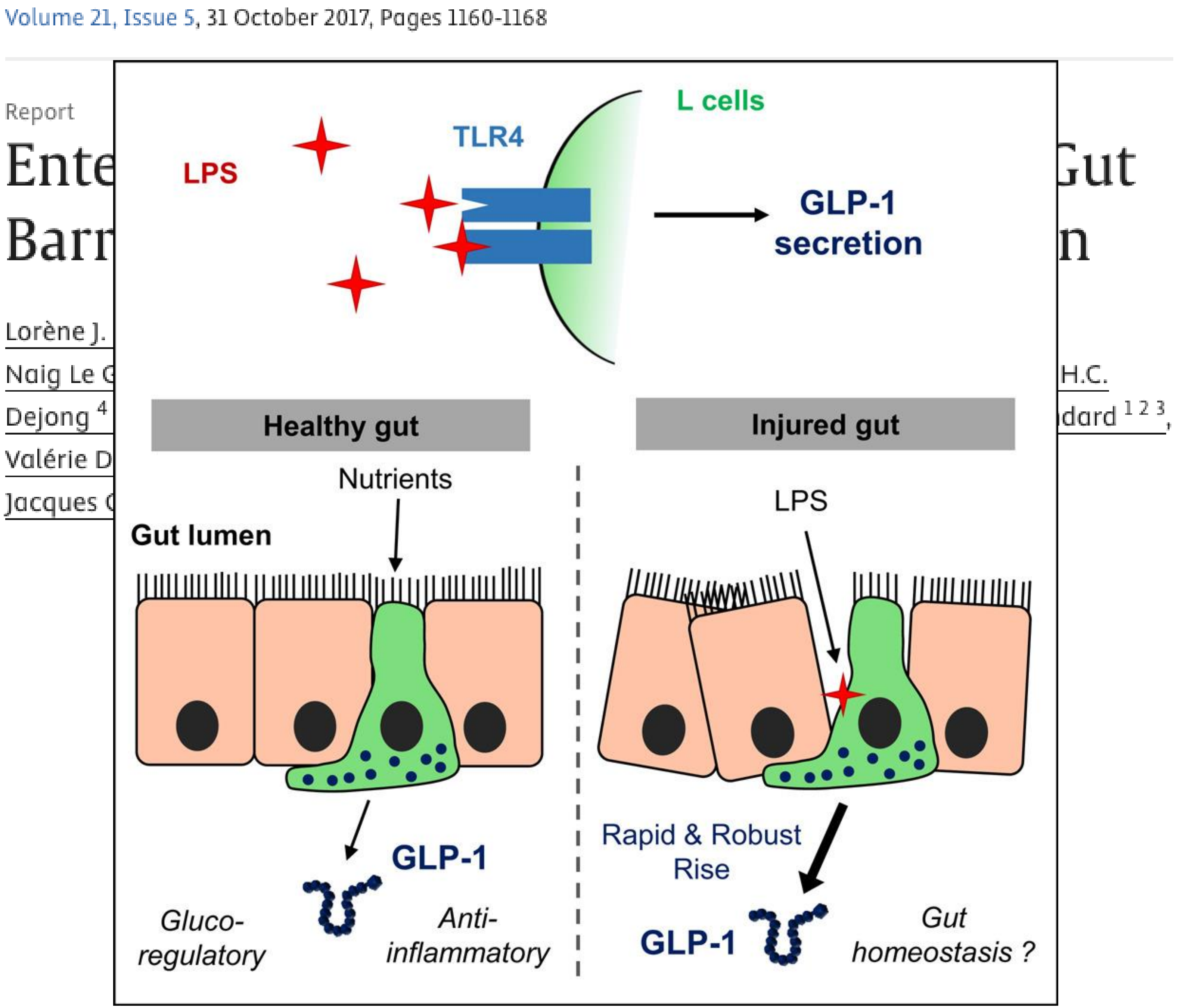

Volume 21, Issue 5, 31 October 2017, Pages 1160-1168

Report

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Naig Le G H.C.
Dejong [4] dard [1 2 3],
Valérie D
Jacques C

Gut Inflammatory Markers

Test Name	Comments	Current	Ref Range	Prev
S100A12	S100A12 is primarily secreted by activated neutrophils in response to pro-inflammatory stimuli. Its release is a component of the immune response to bacterial overgrowth and other microbial pathogens, particularly during infections or dysbiosis. Elevated levels of S100A12 indicate heightened neutrophil activity and active inflammation, typically associated with inflammatory bowel disease (IBD). Increased S100A12 levels correlate with disease severity and immune system activation, which can lead to mucosal damage and gut barrier dysfunction. Symptoms include rectal bleeding and persistent diarrhea, frequently observed in conditions such as ulcerative colitis (UC) and Crohn's disease.	39.0	≤50.0	
Calprotectin	Calprotectin, a protein released by neutrophils, is a hallmark of inflammation in the gastrointestinal tract. Elevated calprotectin levels indicate active disease and immune cell infiltration, which can result in tissue damage and disrupted gut function. Symptoms may include abdominal pain and loose stools. The presence of elevated calprotectin in stool serves as a marker of neutrophil activity and gastrointestinal inflammation. This makes it a valuable biomarker for conditions such as inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease, and for distinguishing these conditions from irritable bowel syndrome (IBS), which typically does not involve significant inflammation.	313.6 H	≤50.0	
Fecal Lactoferrin	Lactoferrin, a glycoprotein released by neutrophils, serves as a marker of gastrointestinal inflammation. It is released in response to bacterial infections and immune activation, indicating significant neutrophil infiltration and active inflammation, often associated with inflammatory bowel disease (IBD). Elevated lactoferrin levels suggest ongoing immune activity and mucosal damage, which can lead to symptoms such as abdominal discomfort and blood in the stool, commonly observed in IBD subtypes such as active Crohn's disease and ulcerative colitis.	2.3	≤6.4	

Digestion And Immune Balance

Test Name	Comments	Current	Ref Range	Prev
Fecal Zonulin	Zonulin, a regulatory protein involved in intestinal permeability, is a marker for "leaky gut." It is produced by intestinal epithelial cells and hepatocytes in response to gut microorganisms, gluten, and other environmental triggers, regulating the integrity of tight junctions in the gut lining. Elevated fecal zonulin levels are associated with metabolic syndrome, obesity, Crohn's disease, and increased gut permeability. High levels indicate disrupted tight junctions, resulting in symptoms such as bloating, diarrhea, food sensitivities, and fatigue. Zonulin is a key marker of gut dysbiosis and systemic metabolic disorders.	344.3 H	25.1-160.8	
pH	Fecal pH reflects the acidity or alkalinity of stool, with a normal pH averaging around 6.6. A high fecal pH, indicating stool alkalinity above the normal average, is typically associated with insufficient acid production or the presence of undigested food in the gastrointestinal tract. This condition may suggest digestive enzyme insufficiency or imbalances in the gut microbiota that hinder proper digestion. Symptoms associated with high fecal pH include bloating, abdominal pain, and digestive inefficiencies, which can lead to nutrient malabsorption and, eventually, malnutrition. Evaluating and managing alkaline stool levels is crucial for addressing potential metabolic or digestive dysfunctions and maintaining overall health.	6.5	6.1-7.8	

Gut barrier disruption allows microbial fragments into circulation

Barrier integrity weakens (for example with high zonulin & inflammation):

Small microbial molecules, toxins, foods cross the gut wall:

- LPS
- peptidoglycan
- bacterial DNA
- Flagellin
- Phosphates, metals, molds

These are detected by immune receptors like:

- Toll-like receptors

Activation leads to systemic cytokines:

- TNF-α
- IL-6
- IL-1β

Those cytokines circulate and affect distant tissues—including joints.

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Prevotella expansion → Th17 immune activation

Key disturbances:

- *Prevotella copri*
- *Prevotella spp.*

Metabolomic activity

- succinate production
- branched-chain amino acid metabolism
- inflammatory lipopolysaccharides

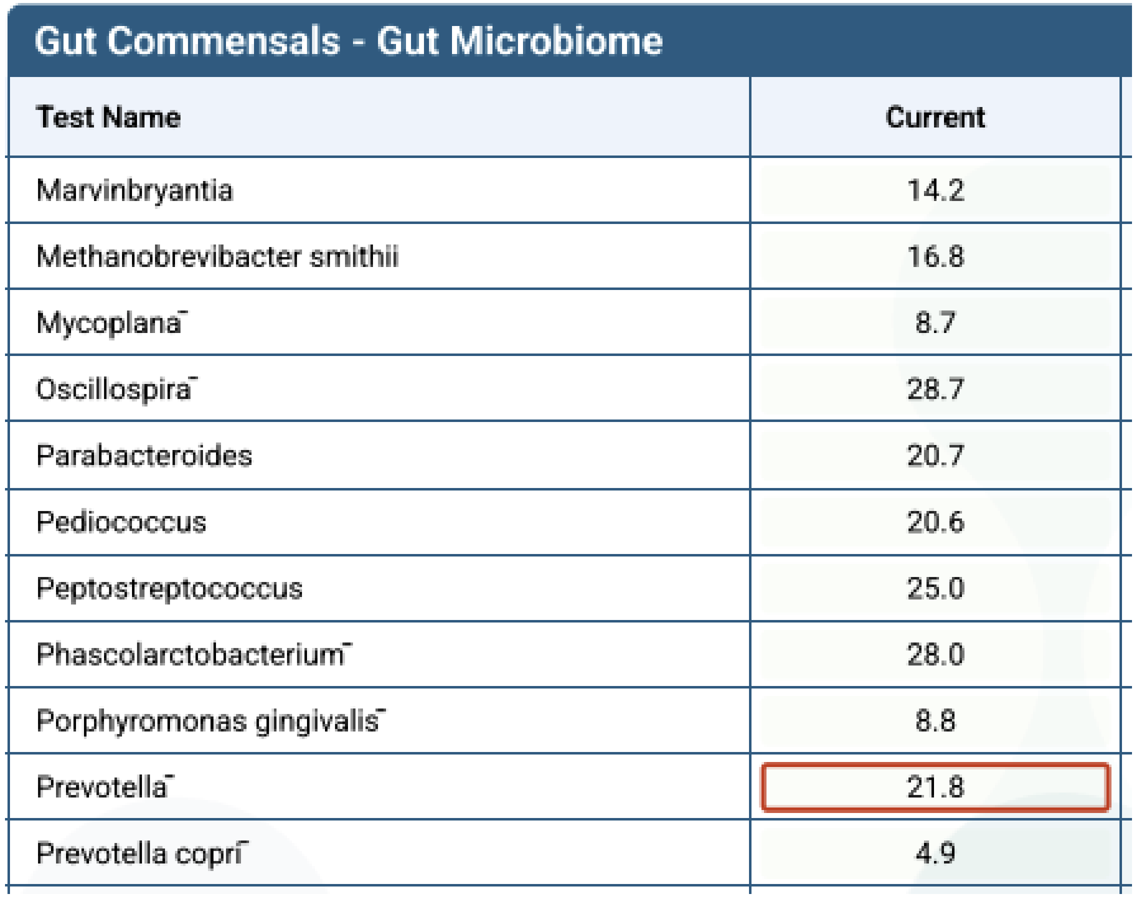
Immune consequence

- stimulates Th17 cells
- increases IL-17 and IL-23 signaling

These cytokines are central in:

- rheumatoid arthritis
- ankylosing spondylitis
- psoriatic arthritis

Many RA studies show Prevotella expansion before disease onset.



Gut Commensals - Gut Microbiome

Test Name	Current
Marvinbryantia	14.2
Methanobrevibacter smithii	16.8
Mycoplanaˉ	8.7
Oscillospiraˉ	28.7
Parabacteroides	20.7
Pediococcus	20.6
Peptostreptococcus	25.0
Phascolarctobacteriumˉ	28.0
Porphyromonas gingivalisˉ	8.8
Prevotellaˉ	21.8
Prevotella copriˉ	4.9

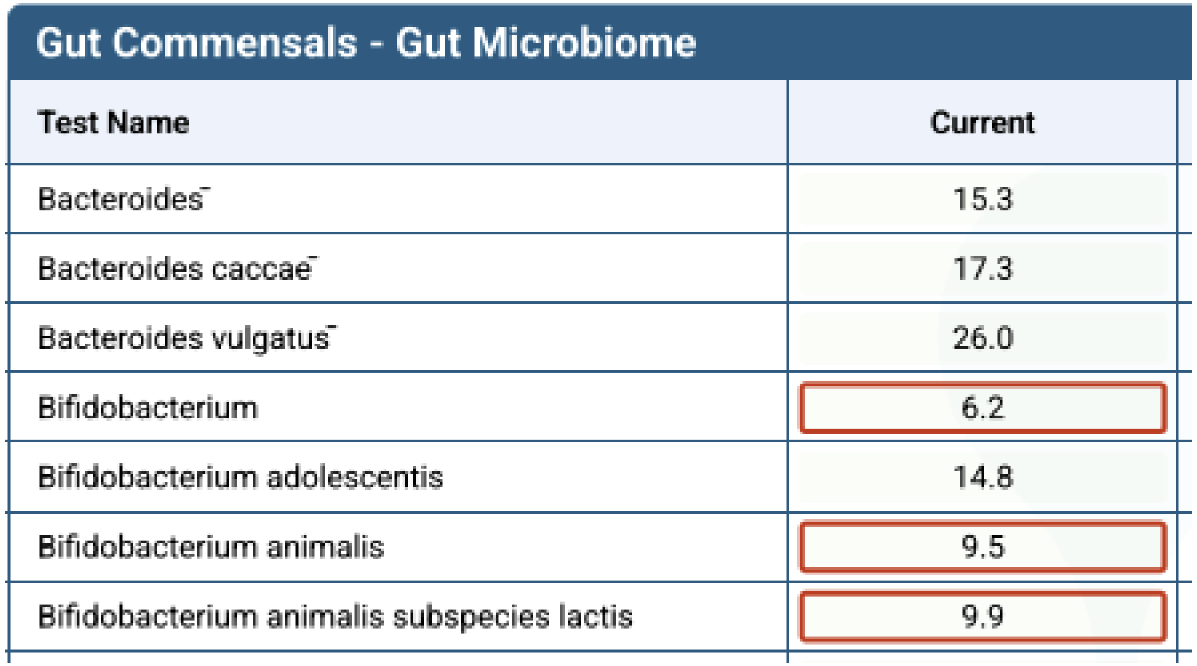
Loss of Bifidobacterium → reduced anti-inflammatory metabolites

Key findings decreased:
- *Bifidobacterium animalis*
- *Bifidobacterium dentium*
- low total *Bifidobacterium*

Metabolomic consequences
Reduced production of:
- acetate
- indole-lactate
- folate derivatives
- anti-inflammatory peptides

These normally:
- promote T-regulatory immune cells
- suppress IL-6 and TNF

Loss of these microbes shifts the immune balance toward autoimmune inflammation.



Gut Commensals - Gut Microbiome

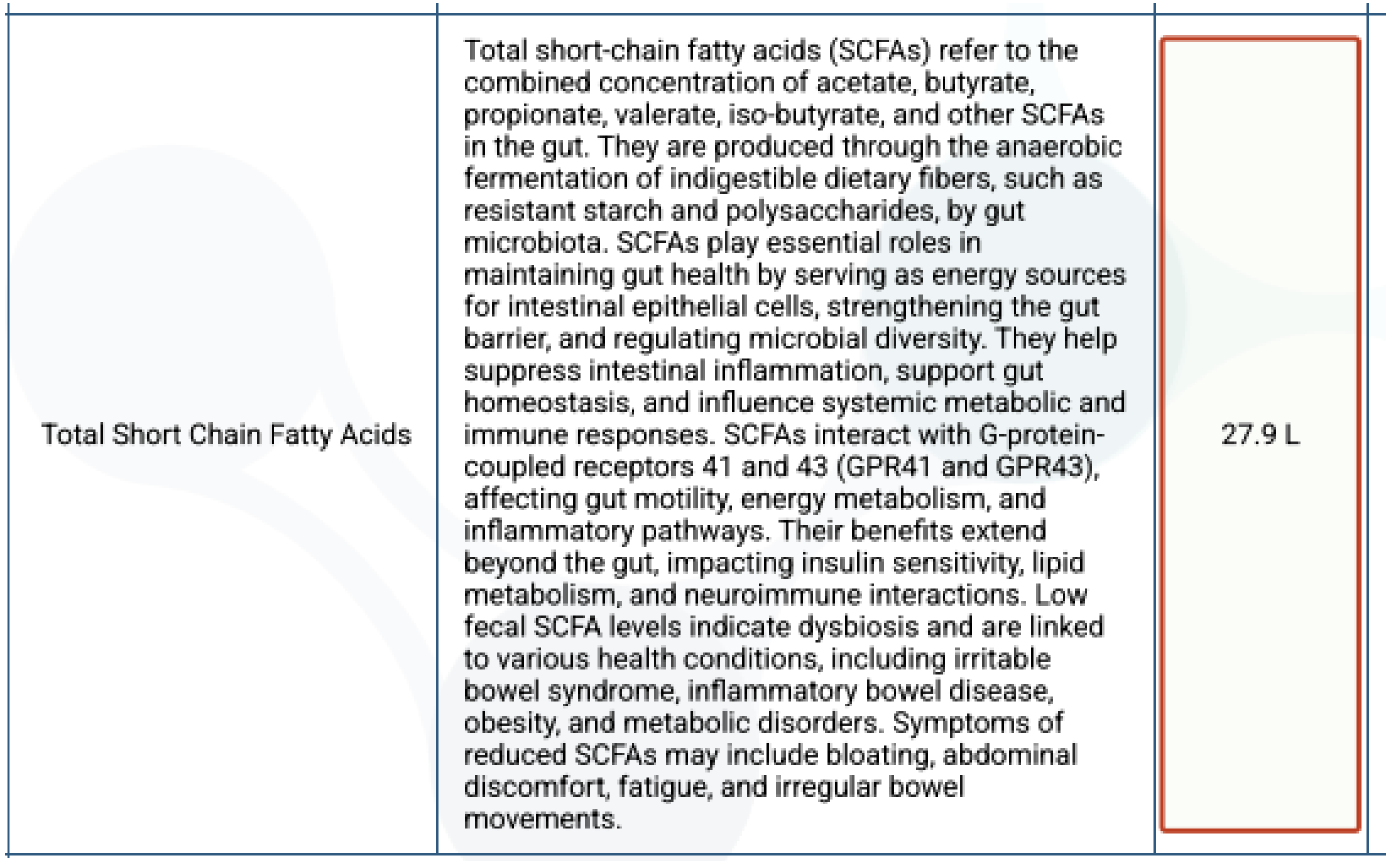
Test Name	Current
Bacteroides¯	15.3
Bacteroides caccae¯	17.3
Bacteroides vulgatus¯	26.0
Bifidobacterium	6.2
Bifidobacterium adolescentis	14.8
Bifidobacterium animalis	9.5
Bifidobacterium animalis subspecies lactis	9.9

Reduced SCFA production → immune dysregulation

Key metabolites
- butyrate
- propionate
- acetate

They regulate:
- Treg cells
- epithelial barrier integrity
- inflammatory cytokines

Low SCFAs are linked with:
- rheumatoid arthritis
- ankylosing spondylitis
- IBD-associated arthritis



Total Short Chain Fatty Acids	Total short-chain fatty acids (SCFAs) refer to the combined concentration of acetate, butyrate, propionate, valerate, iso-butyrate, and other SCFAs in the gut. They are produced through the anaerobic fermentation of indigestible dietary fibers, such as resistant starch and polysaccharides, by gut microbiota. SCFAs play essential roles in maintaining gut health by serving as energy sources for intestinal epithelial cells, strengthening the gut barrier, and regulating microbial diversity. They help suppress intestinal inflammation, support gut homeostasis, and influence systemic metabolic and immune responses. SCFAs interact with G-protein-coupled receptors 41 and 43 (GPR41 and GPR43), affecting gut motility, energy metabolism, and inflammatory pathways. Their benefits extend beyond the gut, impacting insulin sensitivity, lipid metabolism, and neuroimmune interactions. Low fecal SCFA levels indicate dysbiosis and are linked to various health conditions, including irritable bowel syndrome, inflammatory bowel disease, obesity, and metabolic disorders. Symptoms of reduced SCFAs may include bloating, abdominal discomfort, fatigue, and irregular bowel movements.	27.9 L

Enterococcus expansion → inflammatory metabolites

Key players:

- *Enterococcus faecalis*
- *Enterococcus spp.*

These produce:

- reactive oxygen species
- cytolysins
- inflammatory peptides

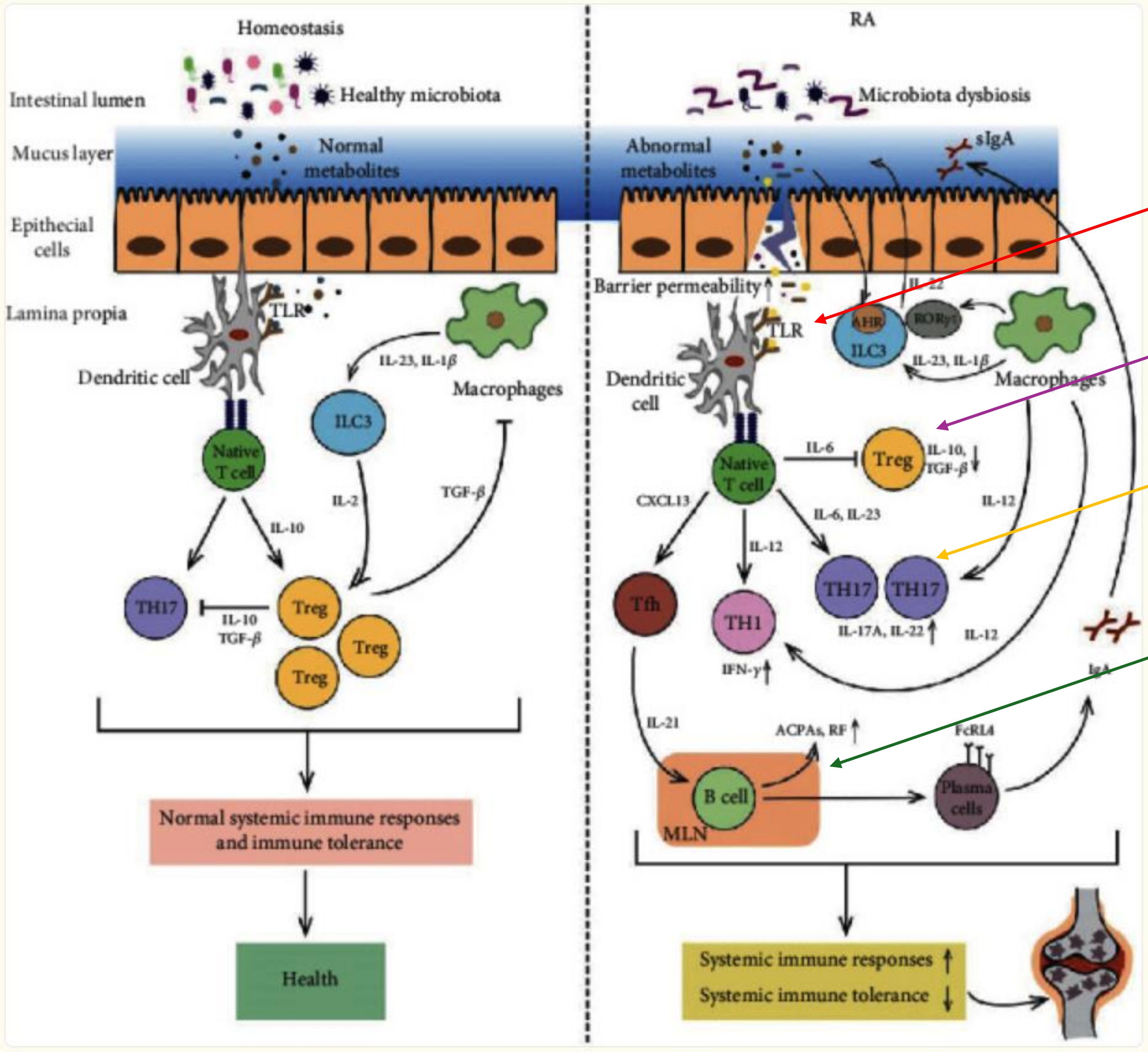
They can:

- damage epithelial barrier
- activate macrophages
- increase systemic inflammation

Enterobacteria¯	14.3
Enterobacteriaceae¯	18.6
Enterococcus	20.1
Enterococcus gallinarum	14.3
Escherichia coli¯	15.5

In autoimmune arthritis studies, Enterococcus expansion correlates with:

- higher TNF
- higher IL-6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Health
Systemic immune responses ↑
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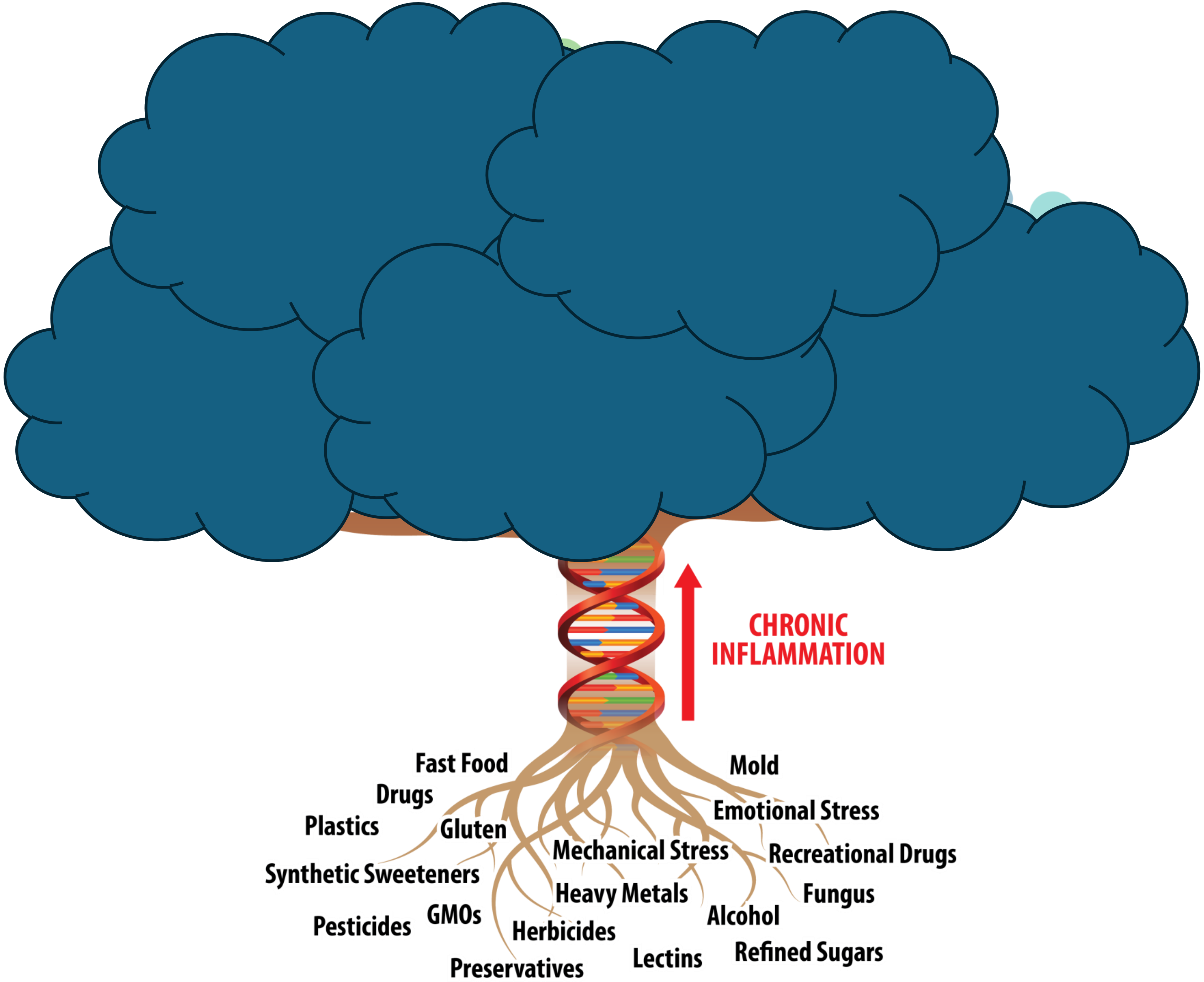
CHRONIC
INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Preservatives
Herbicides
Mechanical Stress
Heavy Metals
Lectins
Mold
Emotional Stress
Recreational Drugs
Fungus
Alcohol
Refined Sugars

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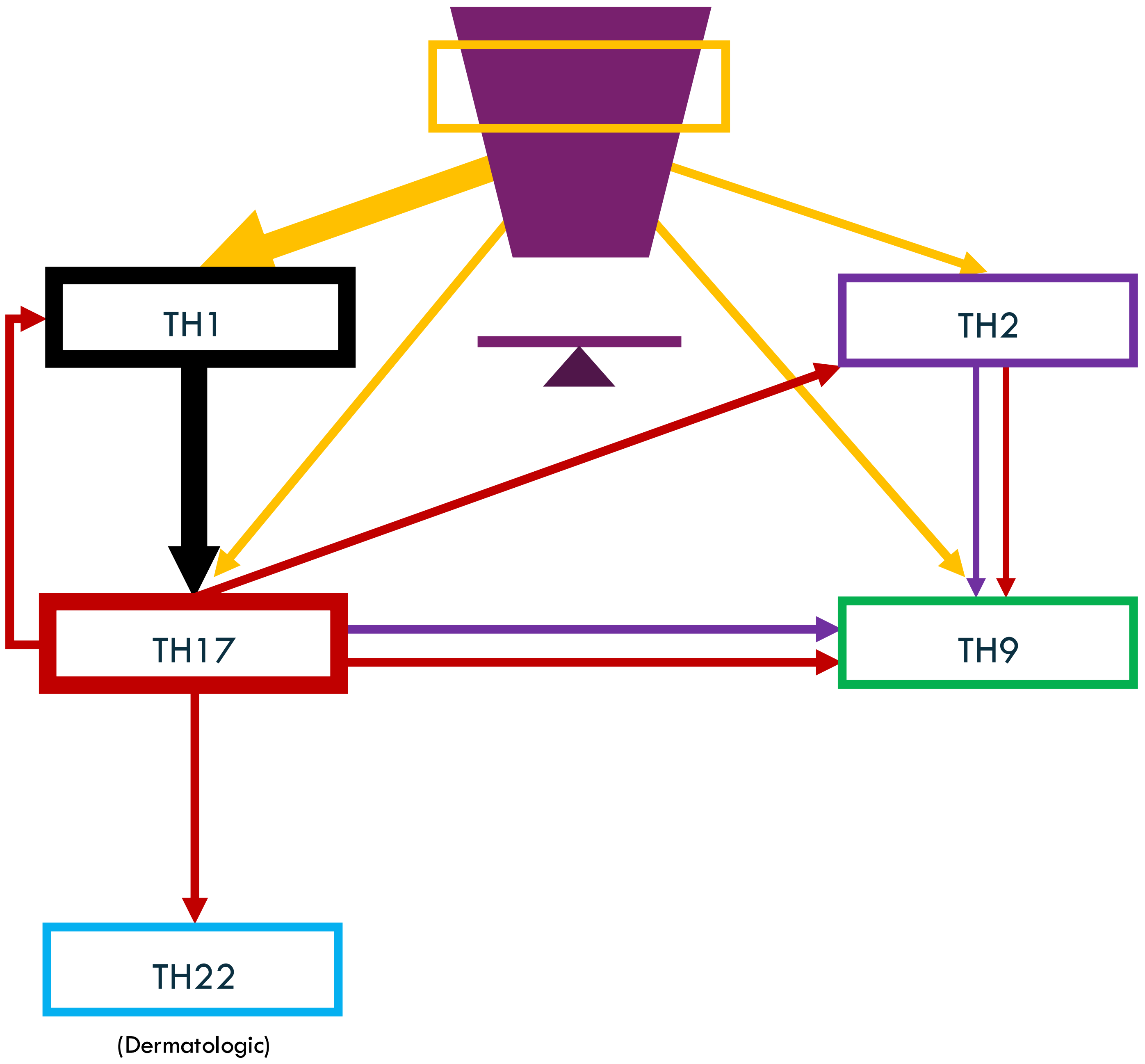
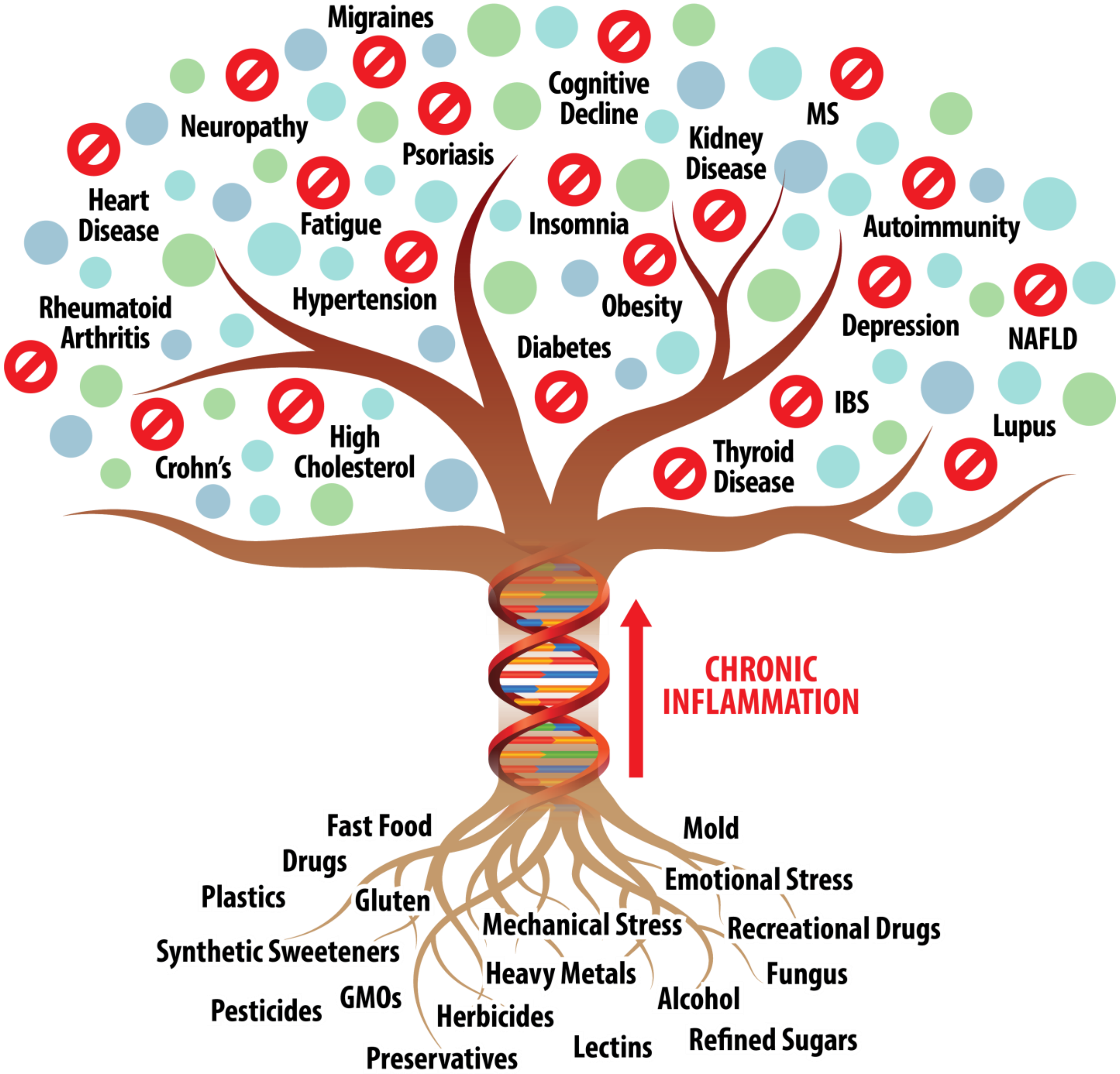

TH1
TH2
TH17
TH9
TH22
(Dermatologic)



Migraines

Neuropathy

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Cognitive Decline

MS

Kidney Disease

Heart Disease

Fatigue

Insomnia

Autoimmunity

Hypertension

Obesity

Rheumatoid Arthritis

Depression

NAFLD

Diabetes

IBS

Lupus

High Cholesterol

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Preservatives

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