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Microbiota and Gut–Liver Axis: New Scope on Fibrotic Liver Disease

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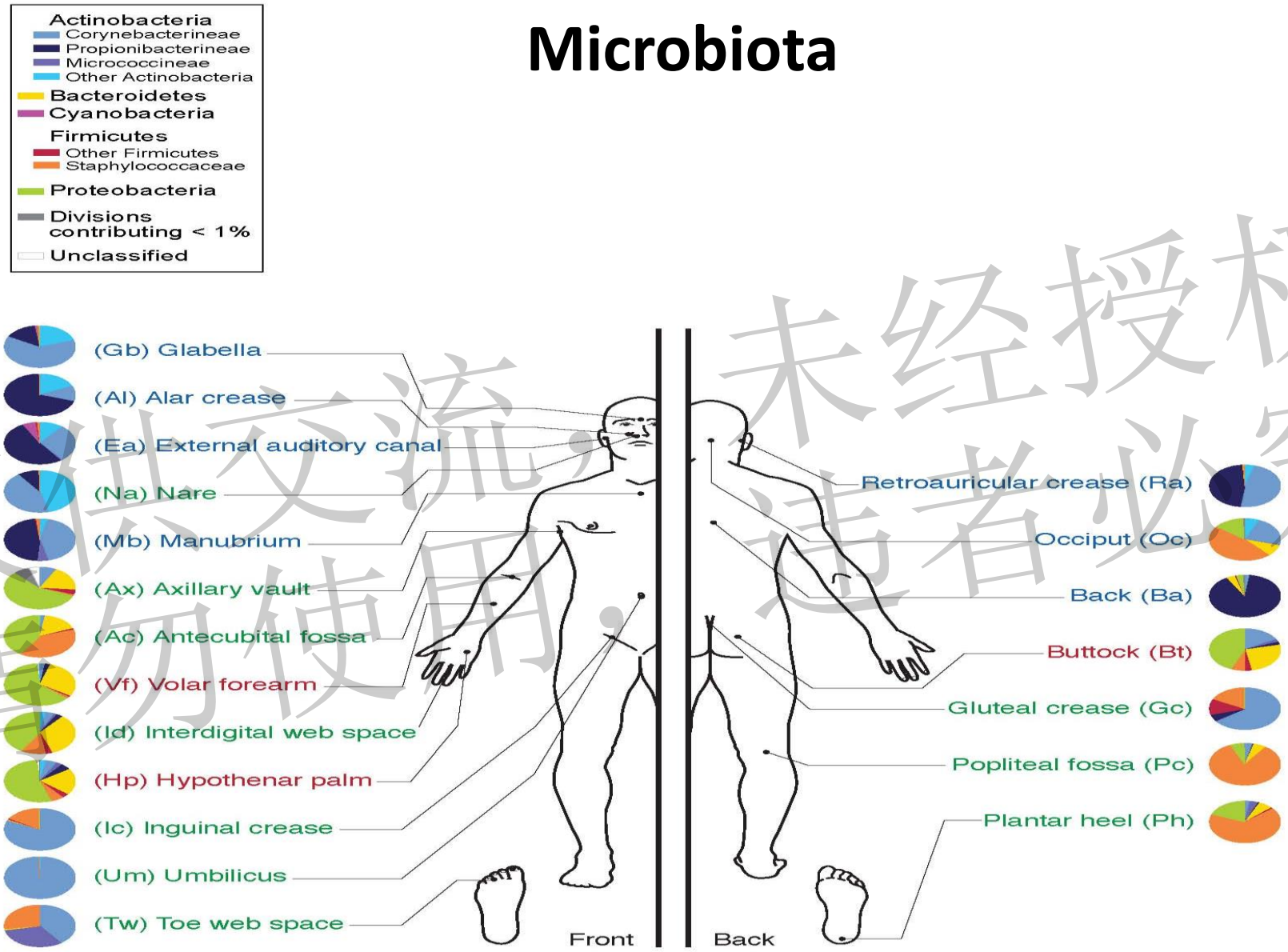
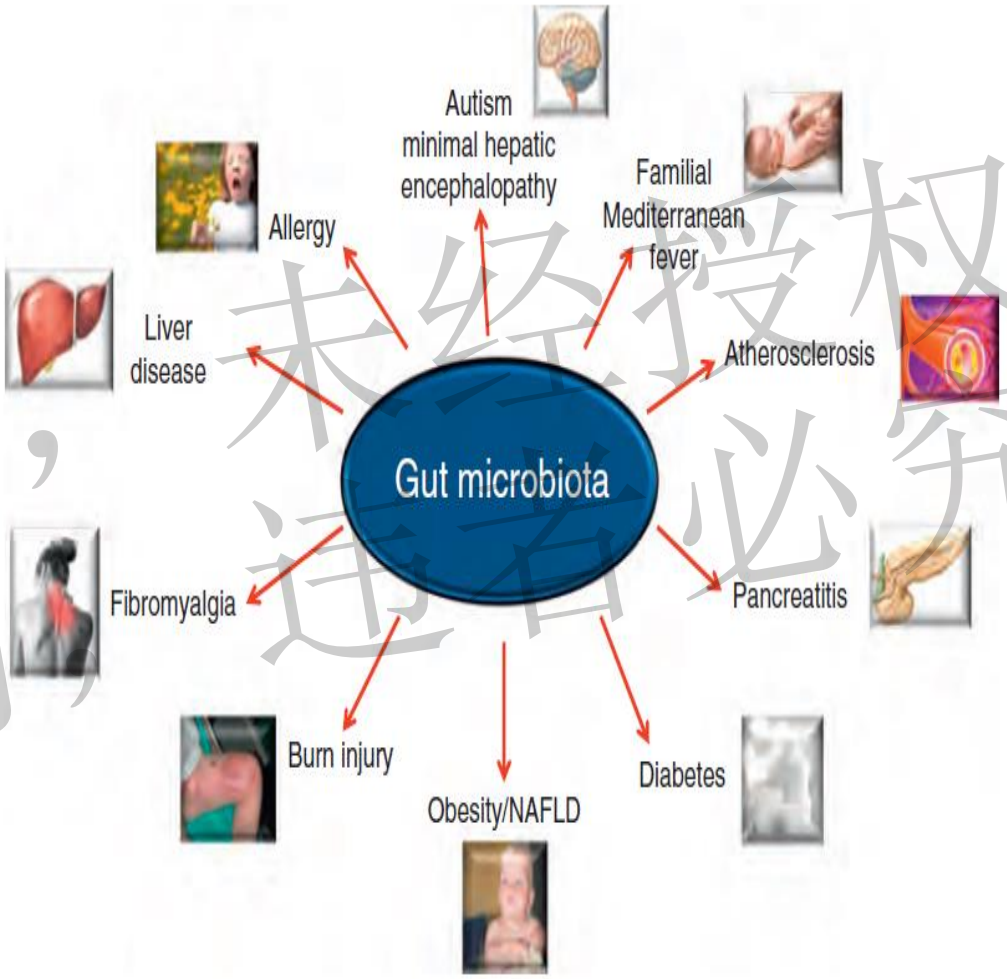
Microbiota



Gut Microbiota

- *Dysbiosis*
- *Inflammasomes*
- *Lipopolysaccharide (LPS)*
- *Lipoteichoic acid*
- *Metabonome/metabolome*
- *Metagenomics*
- *Microbiome*
- *Microbiota*
- *'Omic' methods*
- *Pathobiont*
- *Phenome*



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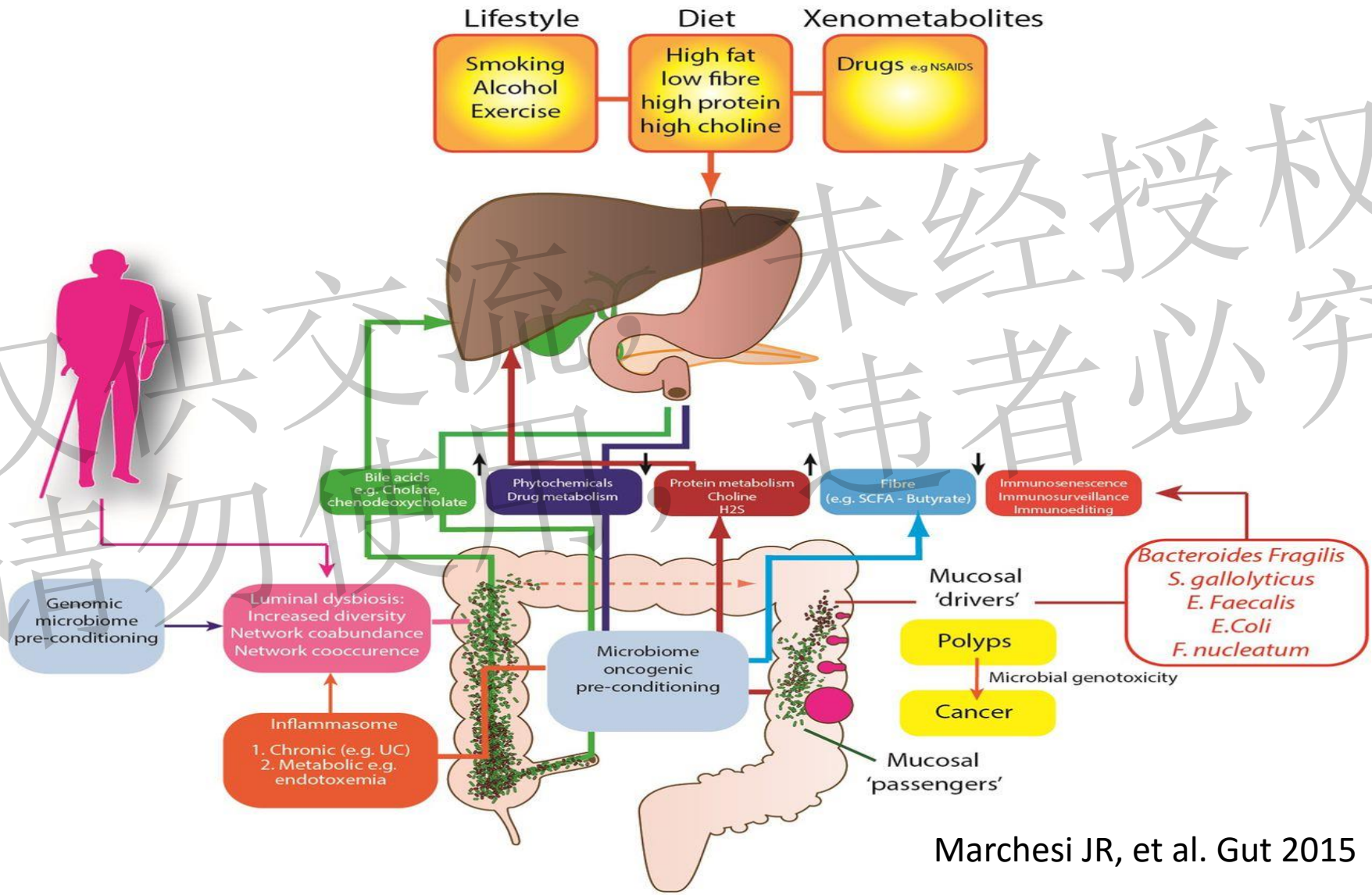
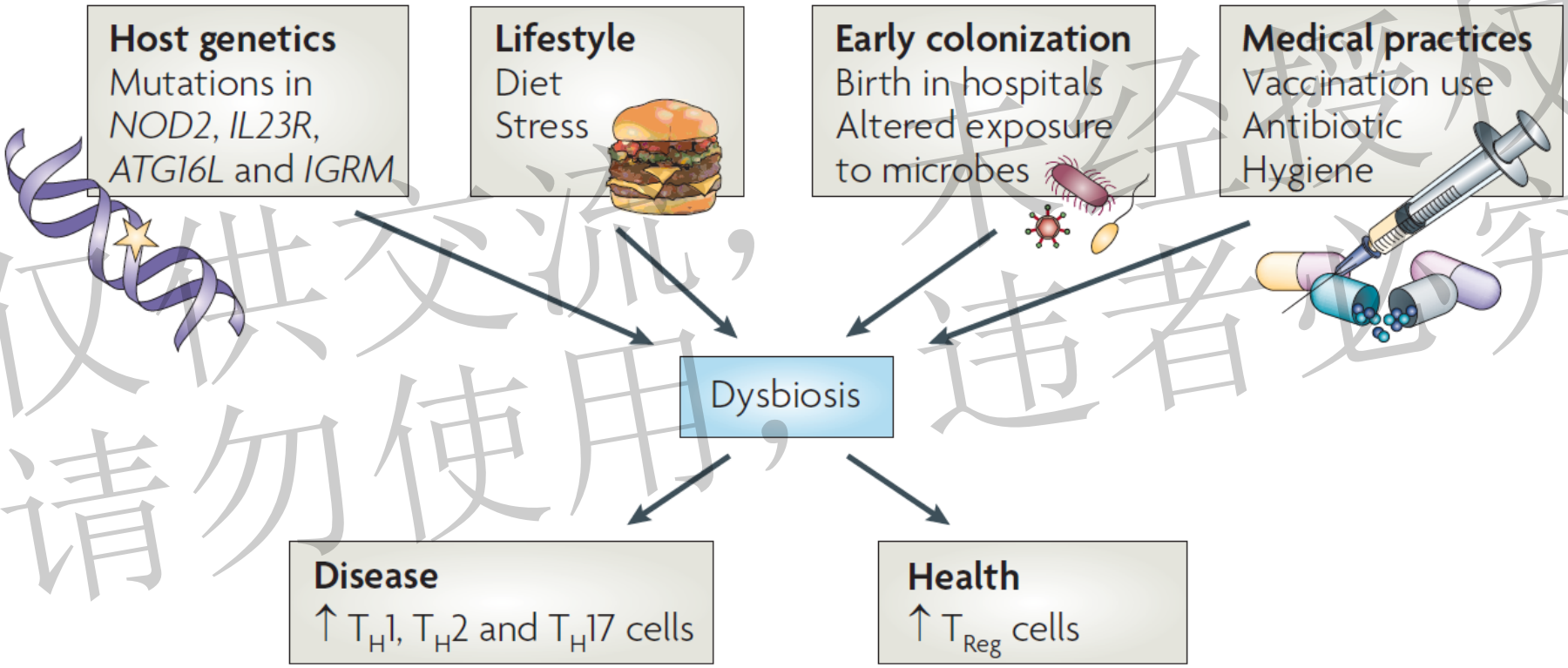
Sellitto M, et al.. PLoS One 2012;7: e33387.; Turnbaugh PJ, et al. Nature. 2006;444:1027–31.

The Gut Microbiota and Host Health: A New Clinical Frontier



Marchesi JR, et al. Gut 2015

Proposed Causes of Dysbiosis of The Microbiota



June L. Round, et al. Nature Review Immunology. 2009

Gut – Liver Axis in Fibrotic Liver DIseases

- Gut microbia diversity
- Intestinal barrier function
- Mucosal innate immune response
- Antigen trafficking
- Liver insult
- Metabolic disorders

Beneficial Gut Bacteria Promote Homeostasis

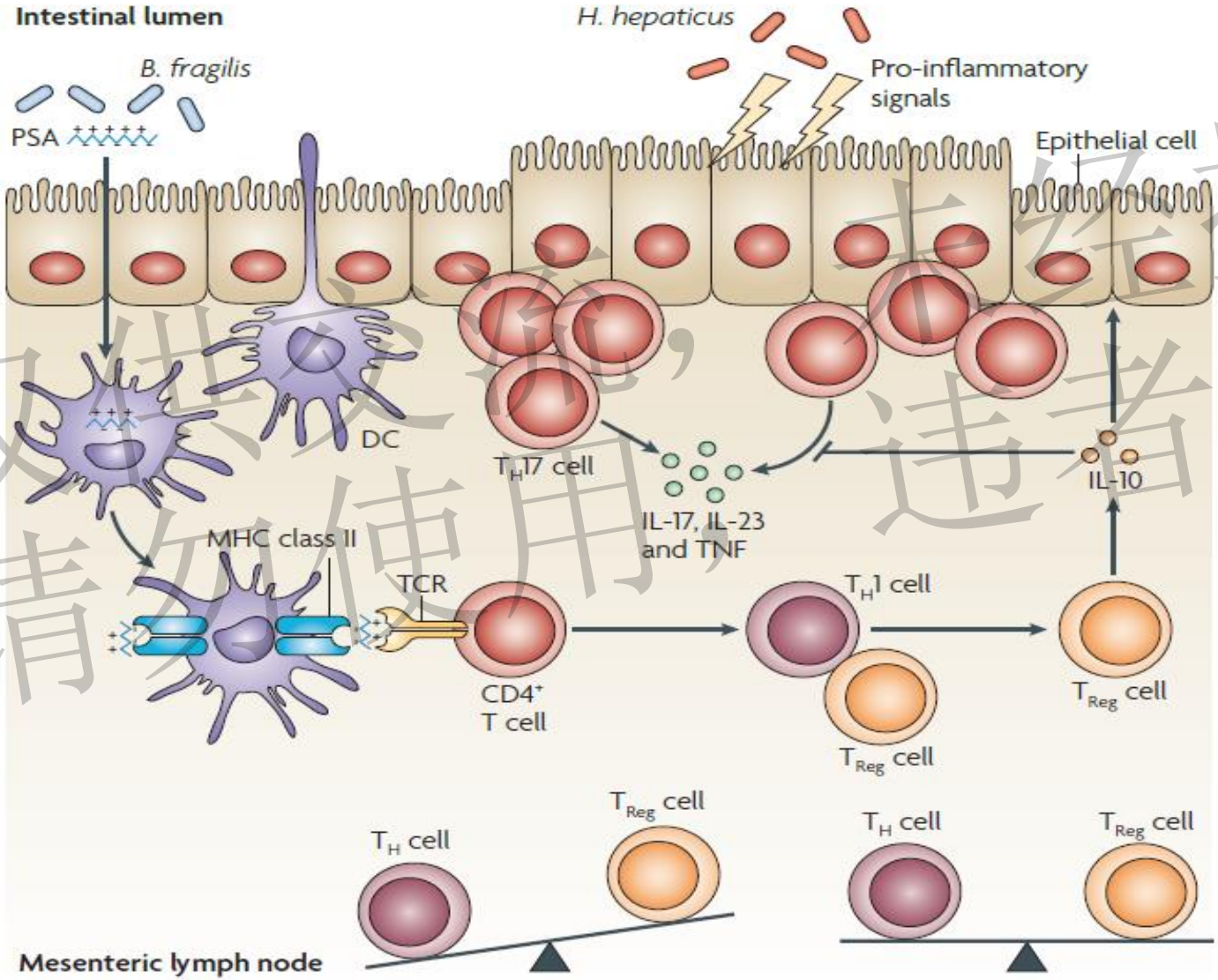
Table 2 | **Bacteria shown to be protective in inflammatory bowel disease**

Bacterial strain	Model system	Disease type or model	Mechanism of disease suppression
VSL#3*	Human and mouse	Pouchitis, ulcerative colitis and TNBS-induced colitis	Induction of IL-10- and TGFβ-expressing T cells
Bifidobacteria lactis	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS
Bifidobacteria infantis	Mouse	*Salmonella enterica*-induced enteritis	Induction of T_{Reg} cells and inhibition of NF-κB activation
Escherichia coli Nissle 1917	Human and mouse	Ulcerative colitis and DSS-induced colitis	Decreased colonic inflammation induced by TLR2 and TLR4 activation
Lactobacillus rhamnosus GG	Mouse and rat	TNBS-induced colitis and HLA-B27-associated colitis	Induction of T_{Reg} cells
Lactobacillus salivarius	Mouse	TNBS-induced colitis	Decreased colonic inflammation
Lactobacillus reuteri	Mouse	IL-10-deficient mice	Upregulation of NGF and decreased levels of IL-8 and TNF in cell lines
Lactobacillus plantarum 299v	Mouse	IL-10-deficient mice	Decreased levels of IFNγ and IL-12p40
Lactobacillus fermentum	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS
Lactobacillus casei	Rat	TNBS-induced colitis	Decreased levels of colonic cyclooxygenase 2
Bacteriodes thetaiotaomicron	Rat	*S. enterica*-induced enteritis	Decreased levels of IL-8 and TNF in colorectal adenocarcinoma cell line
Bacteriodes fragilis	Mouse	T cell transfer and TNBS-induced colitis	Production of $CD4^+$ T cell-derived IL-10
YO-MIX Y109 FRO 1000‡	Mouse	TNBS-induced colitis	ND
Faecalibacterium prausnitzii	Mouse	TNBS-induced colitis	Decreased levels of NF-κB, IL-8 and TNF and increased IL-10 production

*A mixture of *Lactobacillus* spp. (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Lactobacillus delbrueckii* subspecies *bulgaricus*), *Bifidobacterium* spp. (*Bifidobacterium longum*, *Bifidobacterium breve* and *Bifidobacterium infantis*) and *Streptococcus salivarius* subspecies *thermophilus*. ‡A mixture of *S. thermophilus*, *L. acidophilus* and *B. longum*. DSS, dextran sulphate sodium; IFNγ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; ND, not determined; NF-κB, nuclear factor-κB; NGF, nerve growth factor; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TNBS, trinitrobenzene sulphonic acid; TNF, tumour necrosis factor; T_{Reg}, regulatory T.

June L. Round, et al. Nature Review Immunology. 2009

Model for Bacteroides Fragilis-mediated Protection from Disease Induced by *Helicobacter hepaticus*



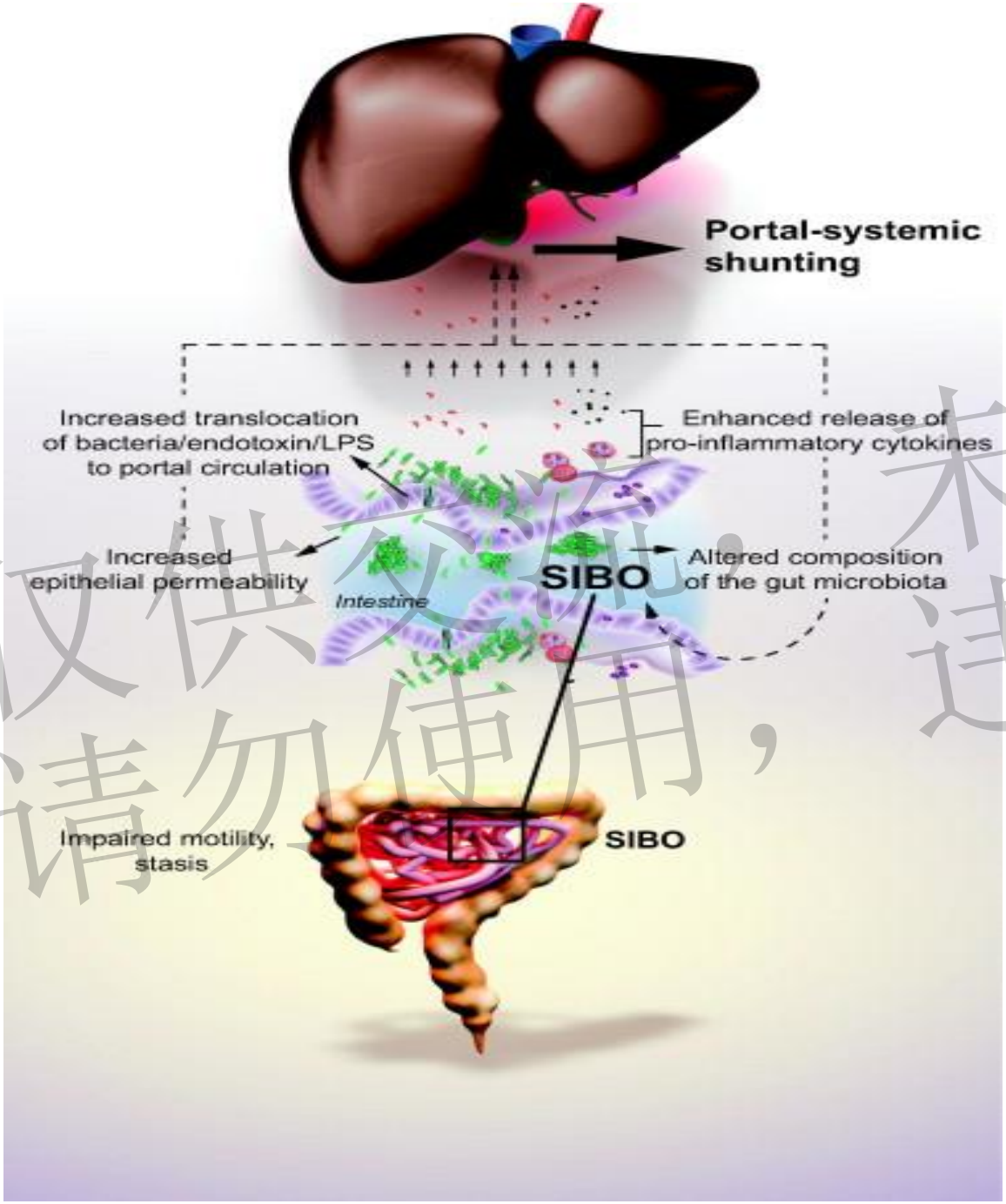
June L. Round, et al. Nature Review Immunology. 2009

Specific Microbiota Signature Highly Influenced by the Western Diet

	Obesity	Celiac disease	Inflammatory bowel diseases	Irritable bowel syndrome	Allergic diseases	Type 2 diabetes mellitus
Enhanced bacterial growth	Firmicutes	Gram- negative Bacteroides Provetella; Escherichia coli	Enterobacteriaceae; Bacteroidetes Enterococci; C difficile; Escherichia coli; Shigella flexneri; Listeria spp	Vellonella; Enterobacteriaceae	Staphylococcus aureus; E coli; Bifidobacterium adolescentis; Lactobacilli; B fragilis	B-Proteobacteria; Bacteroides; Parabacteroides
Reduced bacterial growth	Bacteroides, Bifidobacteria Staphylococcus aureus	Gram-positive Bifidobacteria Clostridium histolyticum, C liteseburense, Faecalibacterium prausnitzii	Firmicutes; Eubacterium rectale; Bacteroides fragilis; B vulgatus; Ruminococcus albus; R callidus; R bromii; F prausnitzii	Bifidobacteria Collinsella aerofaciens; Coprococcus eutactus; C cocleatum	Bifidobacteria	Firmicutes; Clostridia; Bifidobacteria; B vulgatus

Li JV, et al. Gut 2011;60:1214–23.

Small intestinal bacterial overgrowth (SIBO)



- Li Z, et al. Hepatology 2003;37:343–50. Abu-Shanab A, et al. Nat Rev Gastroenterol Hepatol 2010; 7:691–701.
- Miele L, et al. Hepatology 2009;49:1877–87. Harte AL, et al. J Inflamm (Lond) 2010;7:15.

Leaky Gut Hypothesis

Precirrhotic Liver Diseases

Highfat Diet (HFD)

NAFLD

Chronic Alcohol Abuse

Dysbiosis-induced Intestinal Inflammation

NF-kB, TNF-a

NLRP3 and NLRP6 deficiency

CCL5

Endotoxemia

TNFR-1

PAMPs - **TLRs**

increased intestinal permeability

Microbial products translocate to the liver

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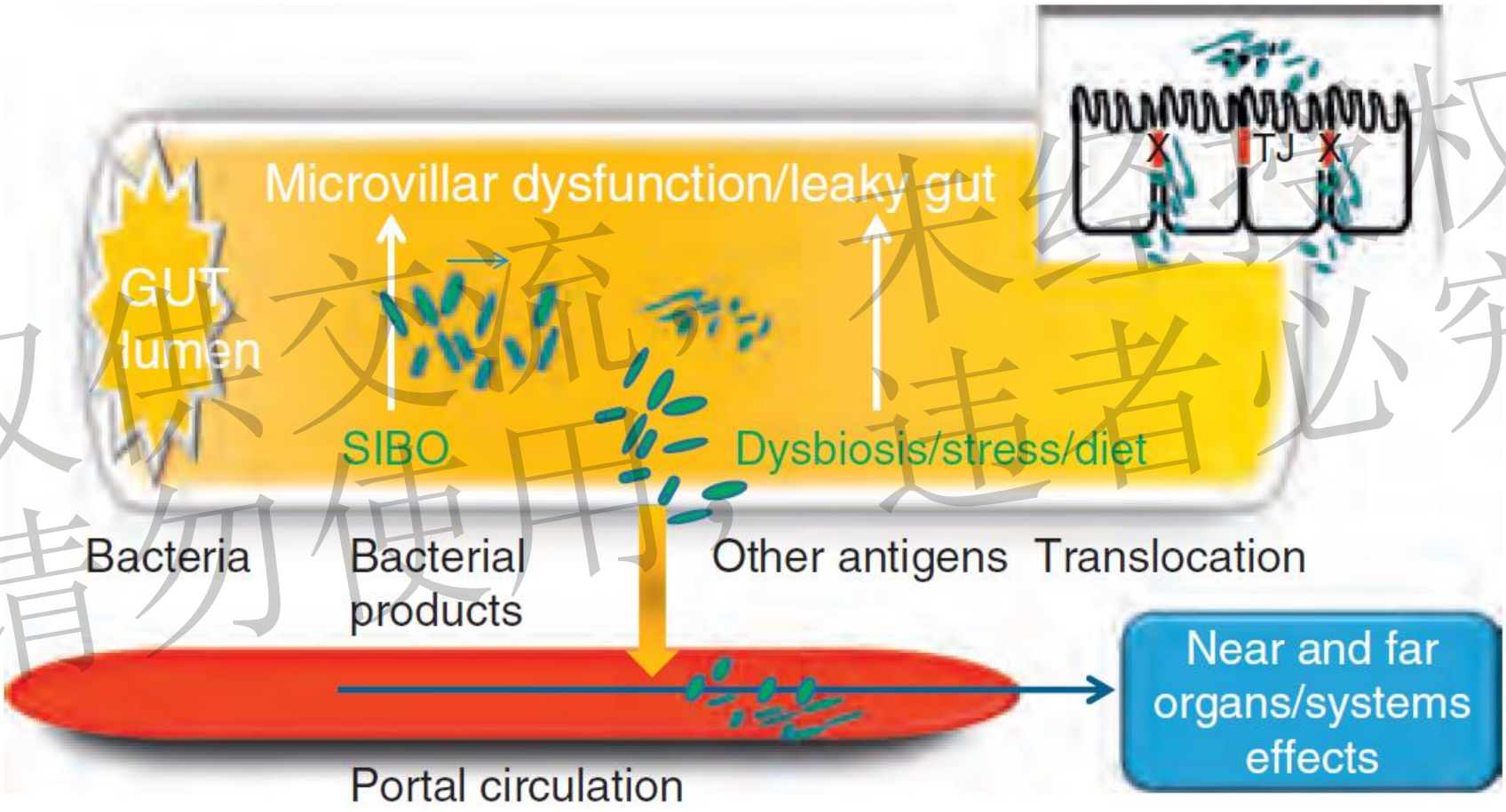
Alisi A, et al. J Pediatr. Gastroenterol Nutr 2010;50:645－649.
Farhadi A, et al. Liver Int 2008;28:1026－1033.
Cani PD, et al. Diabetes. 2007;56:1761－1772.
Teixeira TF, et al. Clin Nutr 2012;31:735－740.
Miele L, et al. Hepatology 2009;49:1877－1887.
Keshavarzian A, et al. Am J Gastroenterol 1994;89:2205－2211.

Intestine Mucosal



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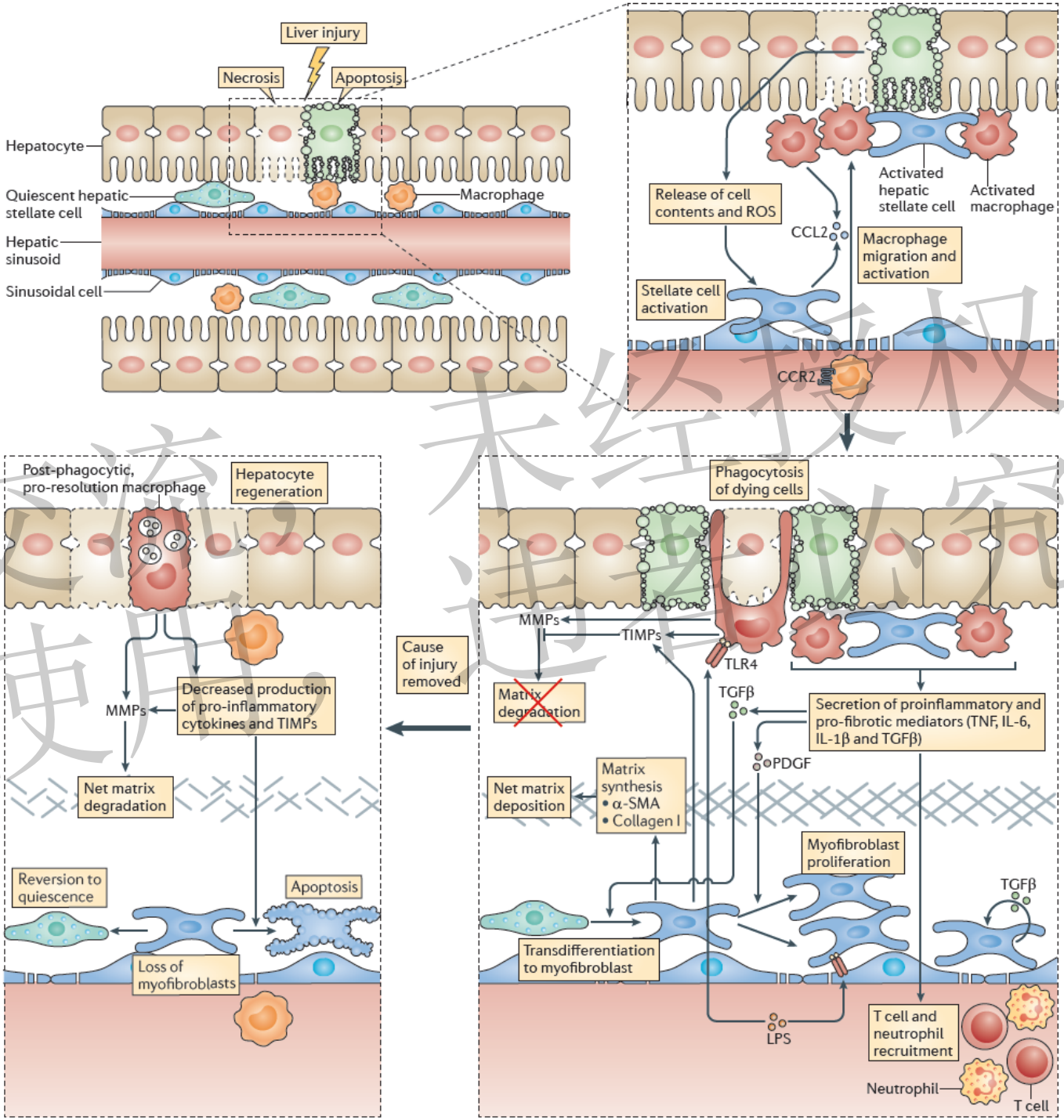
Cascade of signals following liver injury



Antonella Pellicoro, et al. nature review immunology. 2014, 14. 181-194

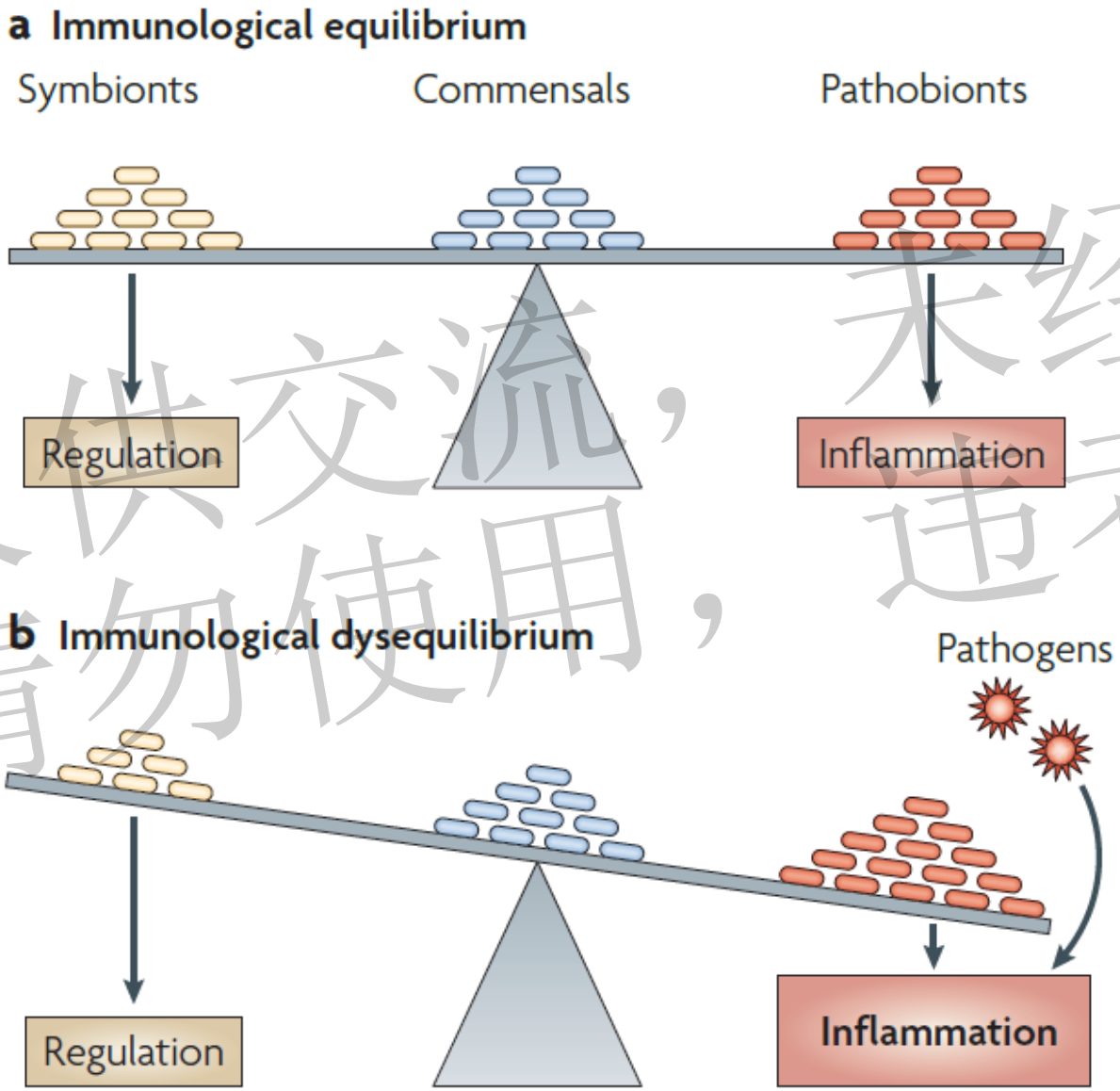
Intestinal immunological defects in germ-free mice

Immunological defect	Site	Phenotype in germ-free mice compared with conventionally housed mice
Development of small intestine	Peyer's patches	Fewer and less cellular
	Lamina propria	Thinner and less cellular
	Germinal centres	Fewer plasma cells
	Isolated lymphoid follicles	Smaller and less cellular
Development of mesenteric lymph nodes	Germinal centres	Smaller, less cellular and with fewer plasma cells
$CD8^+$ T cells	Intestinal epithelial lymphocytes	Fewer cells and with reduced cytotoxicity
$CD4^+$ T cells	Lamina propria	Fewer cells; decreased T_H17 cells in the small intestine but increased T_H17 cells in the colon
$CD4^+CD25^+$ T cells	Mesenteric lymph nodes	Reduced expression of FOXP3 and reduced suppressive capacity
Expression of angiogenin 4	Paneth cells	Reduced
Expression of REG3γ	Paneth cells	Reduced
Production of secretory IgA	B cells	Reduced
Levels of ATP	Intestine	Reduced
Expression of MHC class II molecules	Intestinal epithelial cells	Reduced
Expression of TLR9	Intestinal epithelial cells	Reduced
Levels of IL-25	Intestinal epithelial cells	Reduced

FOXP3, forkhead box P3; IL-25, interleukin 25; REG3γ; regenerating islet-derived 3γ; T_H17, T helper 17; TLR9, Toll-like receptor 9.

June L. Round, et al. Nature Review Immunology. 2009

Immunological dysregulation associated with dysbiosis of the microbiota



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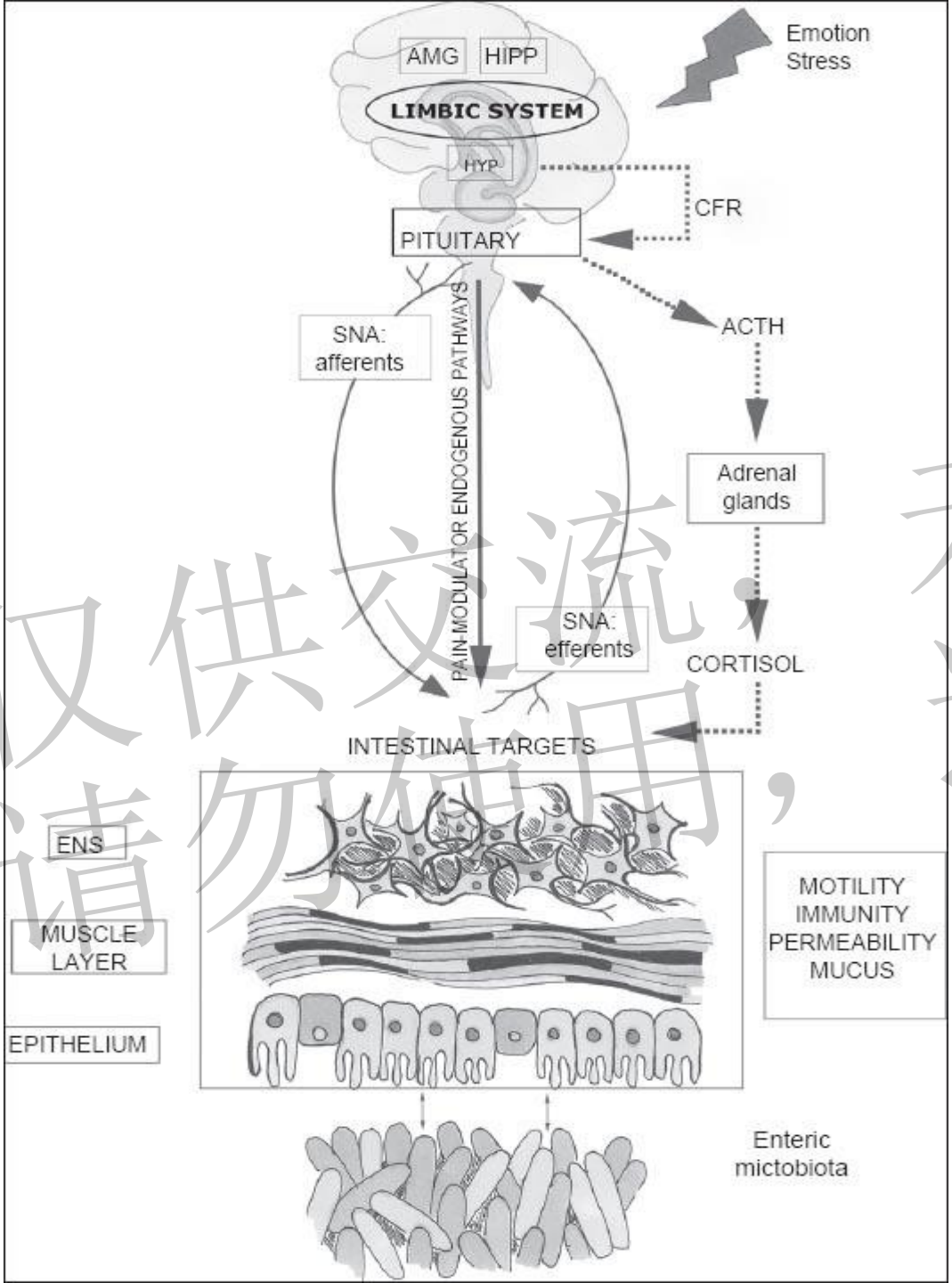
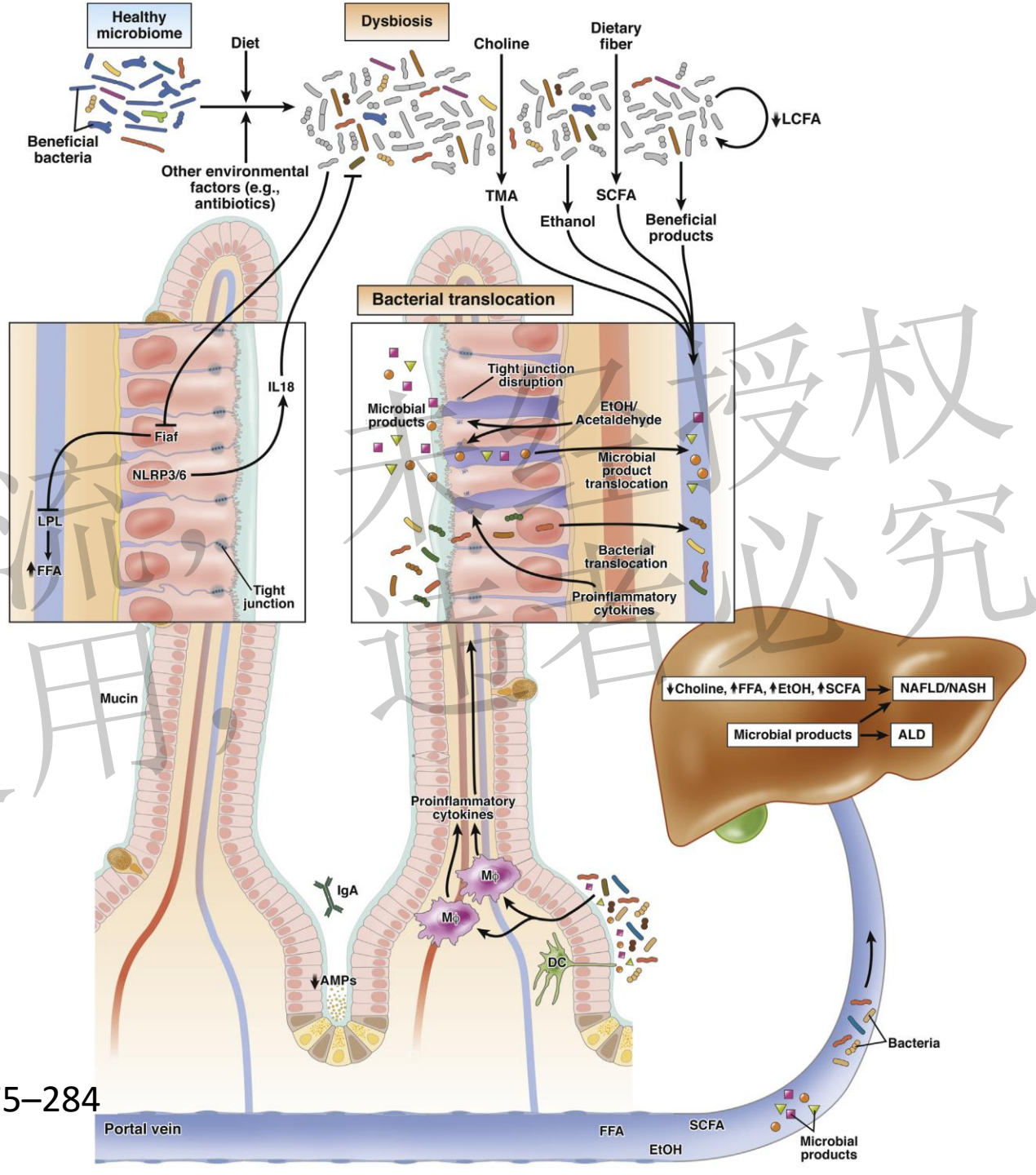


Gut–Brain–Liver Axis
The LPS-Endocannabinoid System Regulatory Loop

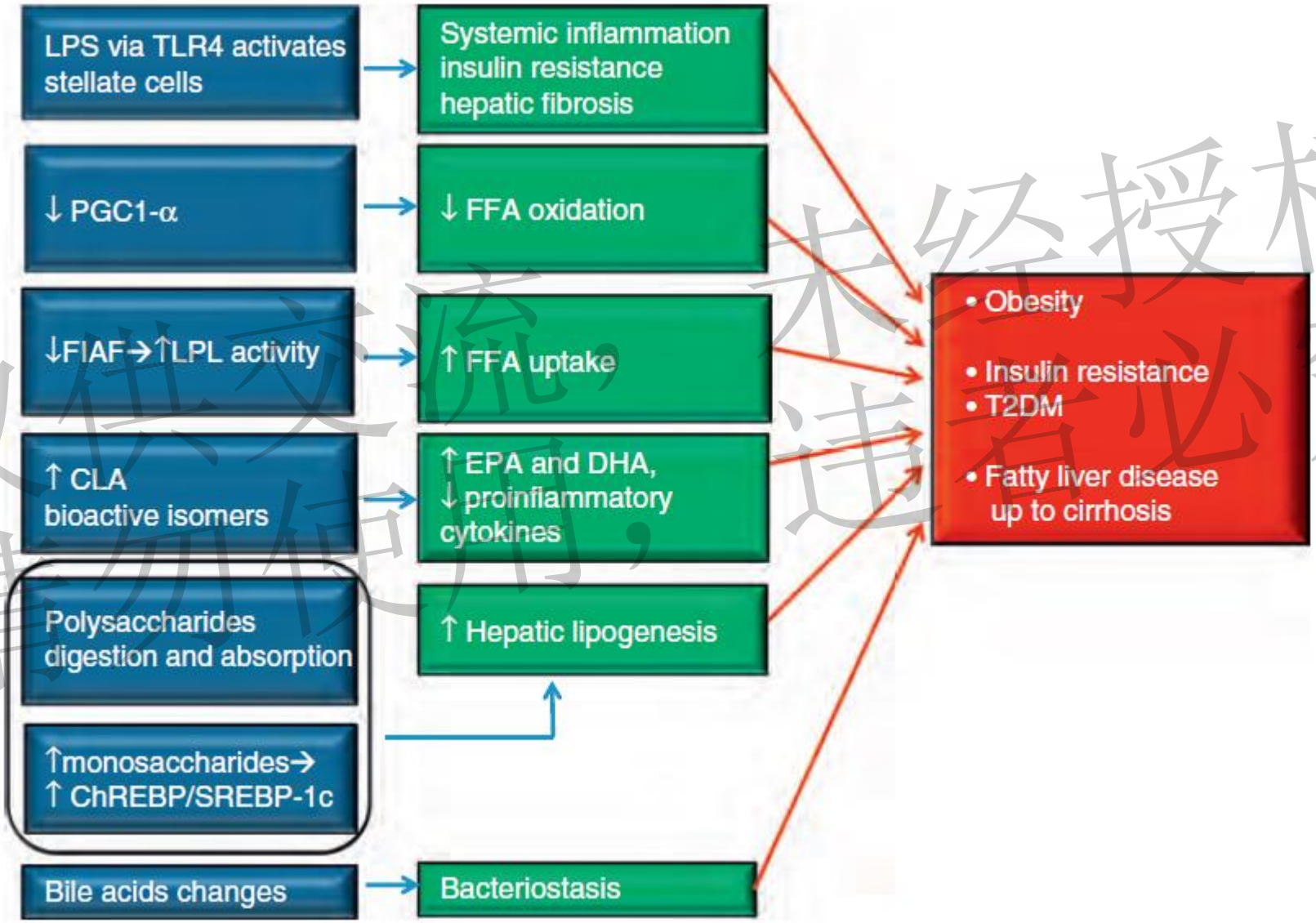
Marilia Carabotti , et al. Ann Gastroenterol. 2015; 28(2): 203–209.

Host–microbiome interactions during Fibrotic liver disease



Cristina Llorente, et al. Cell Mol Gastroenterol Hepatol 2015;1:275–284

Microbiota, Gut - Liver Axis, and Obesty Interaction



Vajro P, et al. J Pediatr Gastroenterol Nutr. 2013;56(5):461-8

Modulation of The Microbiota as A Therapy in Chronic Liver Disease

- ***Antibiotics***: polimixine B, tetracycline, and metronidazole
- ***Probiotics***: Lactobacillus bulgaricus, Streptococcus thermophiles, Lactobacillus GG
- ***Prebiotics***: Lactulose
- ***Symbiotics***: Combinations of a probiotic with a prebiotic, Faecal microbiota transplantation

Sajjad A, et al. Aliment Pharmacol Ther 2005;22:291–9.

Antibiotics

- Intestinal decontamination improves experimental ALD as a preventive strategy and as an intervention.

- Nonabsorbable antibiotics have a beneficial effect on toxic and cholestatic liver fibrosis and NASH.

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Summary

- The gut microbiome influences both normal physiology and disease susceptibilities through its collective metabolic activities and host interactions.
- Dysbiosis affects intestinal homeostasis and causes the progression of liver disease by triggering an increase in intestinal permeability.
- Genetic factors (single nucleotide polymorphisms, gene copy numbers, etc.) are involved in shaping the composition of the gut microbiota and modulating disease susceptibility or resistance.
- Given that germ-free mice are more susceptible to experimental liver fibrosis, there might be hepatoprotective microbial metabolites.
- The ultimate goal should be to design therapies that restore intestinal eubiosis and homeostasis. This could be achieved by either targeting the microbiota or the intestine of the host.