

第六届(2022)猪营养国际论坛

The 6th (2022) International Swine Industry Symposium

主办：美国动物科学学会 | 中国畜牧业协会

承办：上海亘泰实业集团有限公司 | 中国畜牧业协会生物产业分会 | 中畜传媒

协办：美国大豆出口协会 | 上海优久生物科技有限公司 | 上海征泰生物科技集团有限公司

免疫和粘膜—猪健康的驱动力 Immunity and Mucosa—The Driver of Swine Health

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南达科他州立大学 (布鲁金斯) South Dakota State University

Brookings SD

展望营养科技的应用对养猪行业可持续性的帮助

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目录

Credits

- 幻灯片 Slides
 - Kuby 免疫学 Kuby Immunology
 - 免疫生物学，第八版 Immunobiology, 8th edition
 - David Topham, 罗彻斯特大学 David Topham, University of Rochester
- 电影/动画 Movies/Animations
 - 免疫生物学，第八版 Immunobiology, 8th edition



大纲

Outline

- 体内平衡 Homeostasis
- 粘膜免疫 Mucosa Immunity
- 微生物群 Microbiome
- 肠道-肺轴-炎症 Gut-Lung Axis-Inflammation
- 细胞因子攻击 Cytokine Storm
- 调节炎症 Modulating Inflammation



体内平衡&免疫系统

Homeostasis & the Immune System

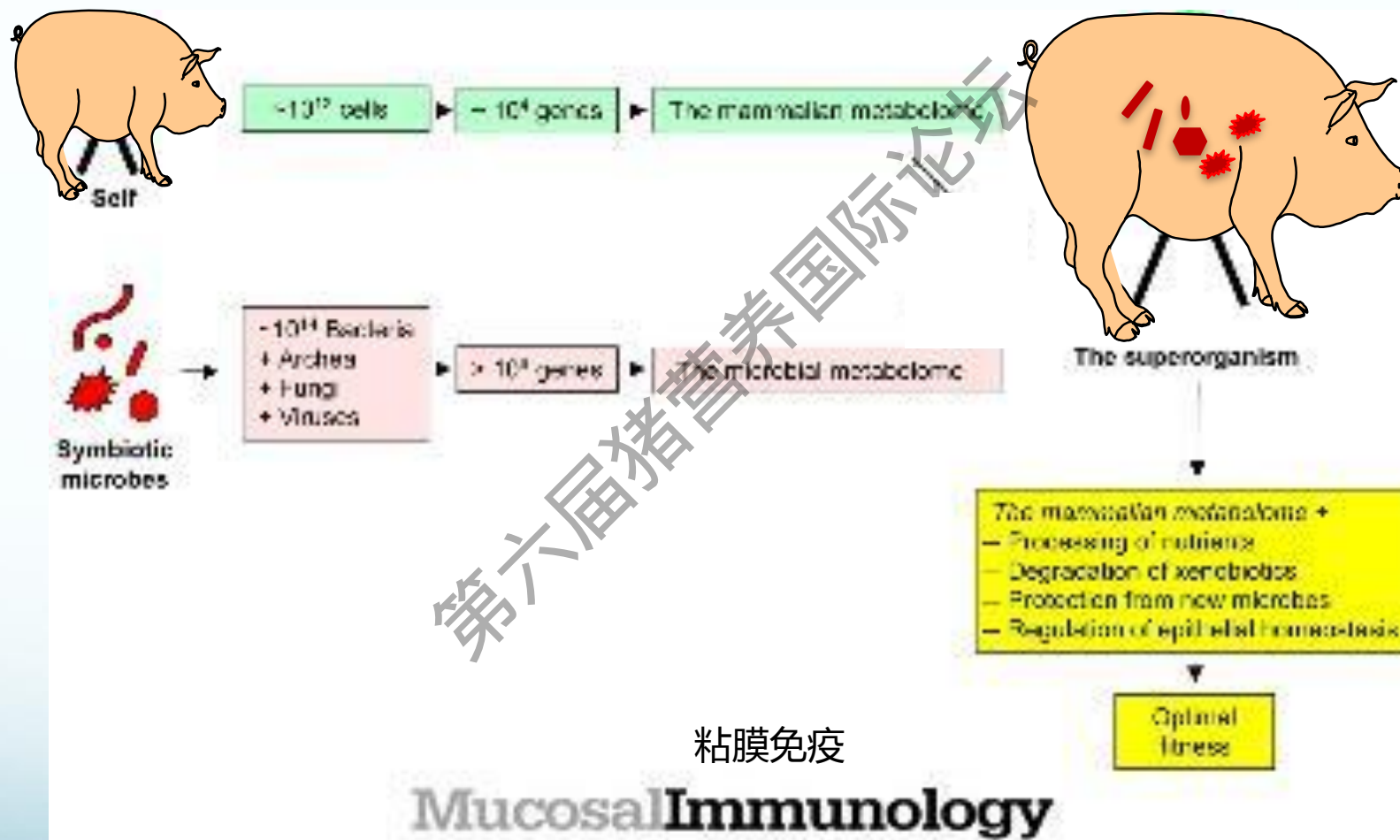
- 免疫系统的主要任务是维持健康。Main “task” of the immune system is to maintain health.
- 体内稳态是动物维持稳定、健康的内部环境的过程。Homeostasis is the process by which the animal maintains a stable, healthy internal environment.
- 免疫系统是维持体内平衡的整个过程的一部分。The immune system is part of the overall process of maintaining homeostasis.
- 免疫系统识别并攻击被称为病原体的有害入侵生物实体。The immune system identifies and attacks harmful invasive biological entities called pathogens.



体内平衡

Homeostasis

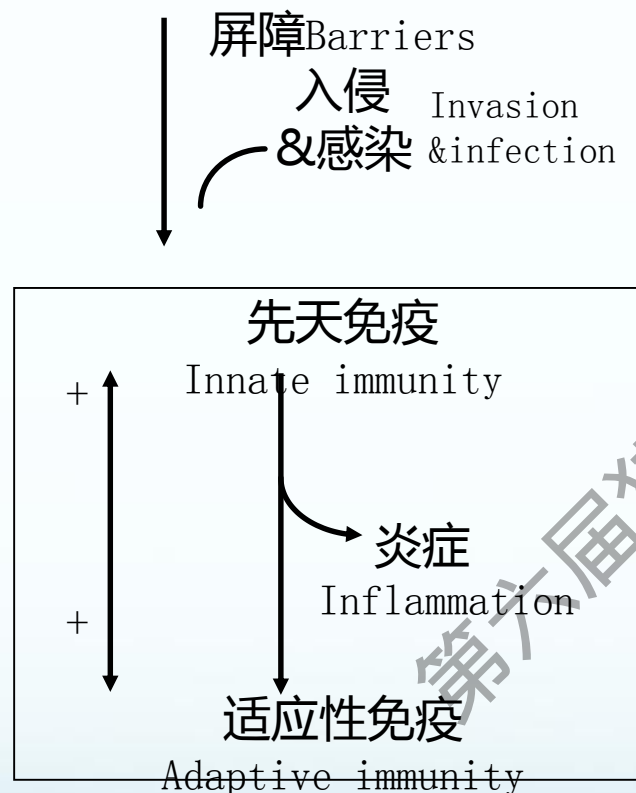
超个体 Superorganism



Mucosal Immunology (2010) 3, 450–460

免疫应答

IMMUNE RESPONSES



• 第一道防线 1st Line of Defense

• 屏障 Barriers

人体最大的免疫器官 Largest Immune Organ in the Body

皮肤、粘膜和分泌物 Skin & Mucous membranes and secretions
屏障, 快速再生的表皮, 蠕动, 溶菌酶, 皮脂腺/粘液分泌物, 胃酸, 共生生物
Barrier, rapidly regenerating surfaces, peristaltic movement, lysozyme, sebaceous/mucous secretions, stomach acid, commensal organisms

第二道防线 2nd Line of Defense

体液和细胞成分 Humoral and Cellular Components

细胞, 细胞因子和蛋白质防御干扰素, 防御素, 趋化因子, 细胞因子(促炎和T刺激), 补体蛋白, TLRs, 吞噬作用, NK细胞

Cellular, cytokine and protein defenses

Interferons, defensins, chemokines, cytokines (pro-inflammatory and stimulatory), complement proteins, TLRs, phagocytosis, NK cells

第三道防线 3rd Line of Defense

Humoral and Cellular Components 体液和细胞成分

Cellular and humoral defenses

Antibodies, cytokines, chemokines,

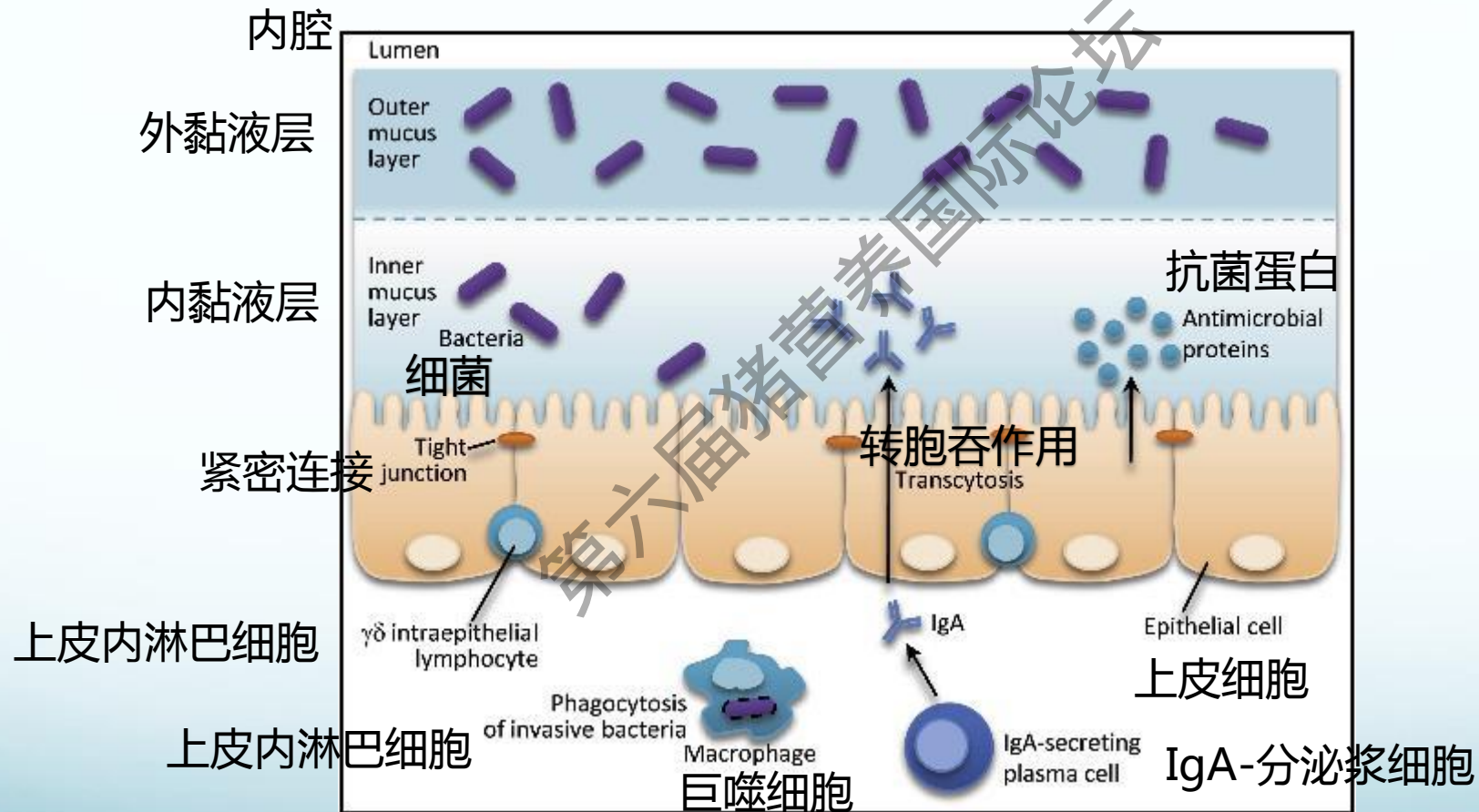
T helper cells, cytotoxic T cells

细胞和体液防御抗体

细胞因子, 趋化因子, 辅助T细胞, 细胞毒性T细胞

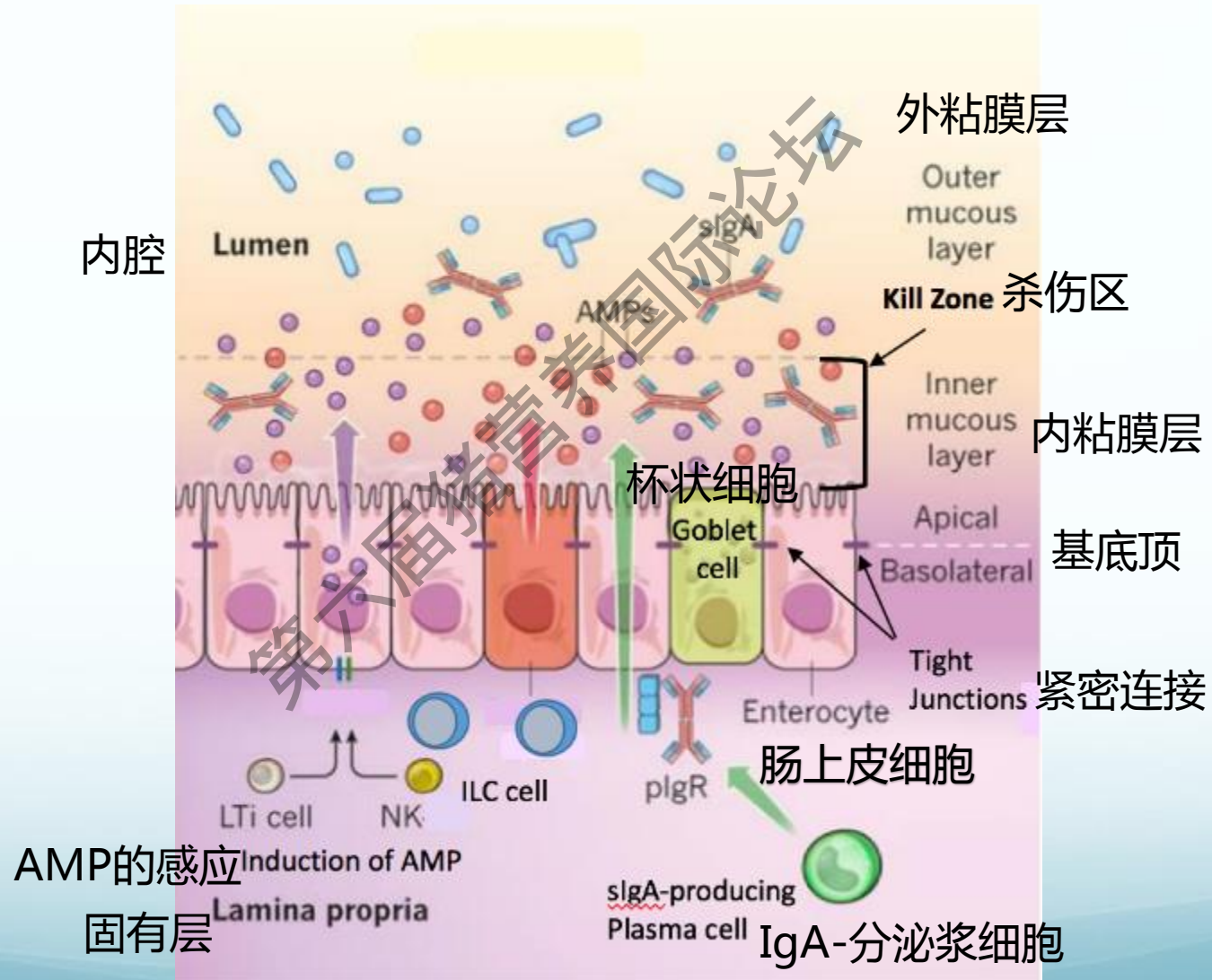
上皮屏障

Epithelial Barriers



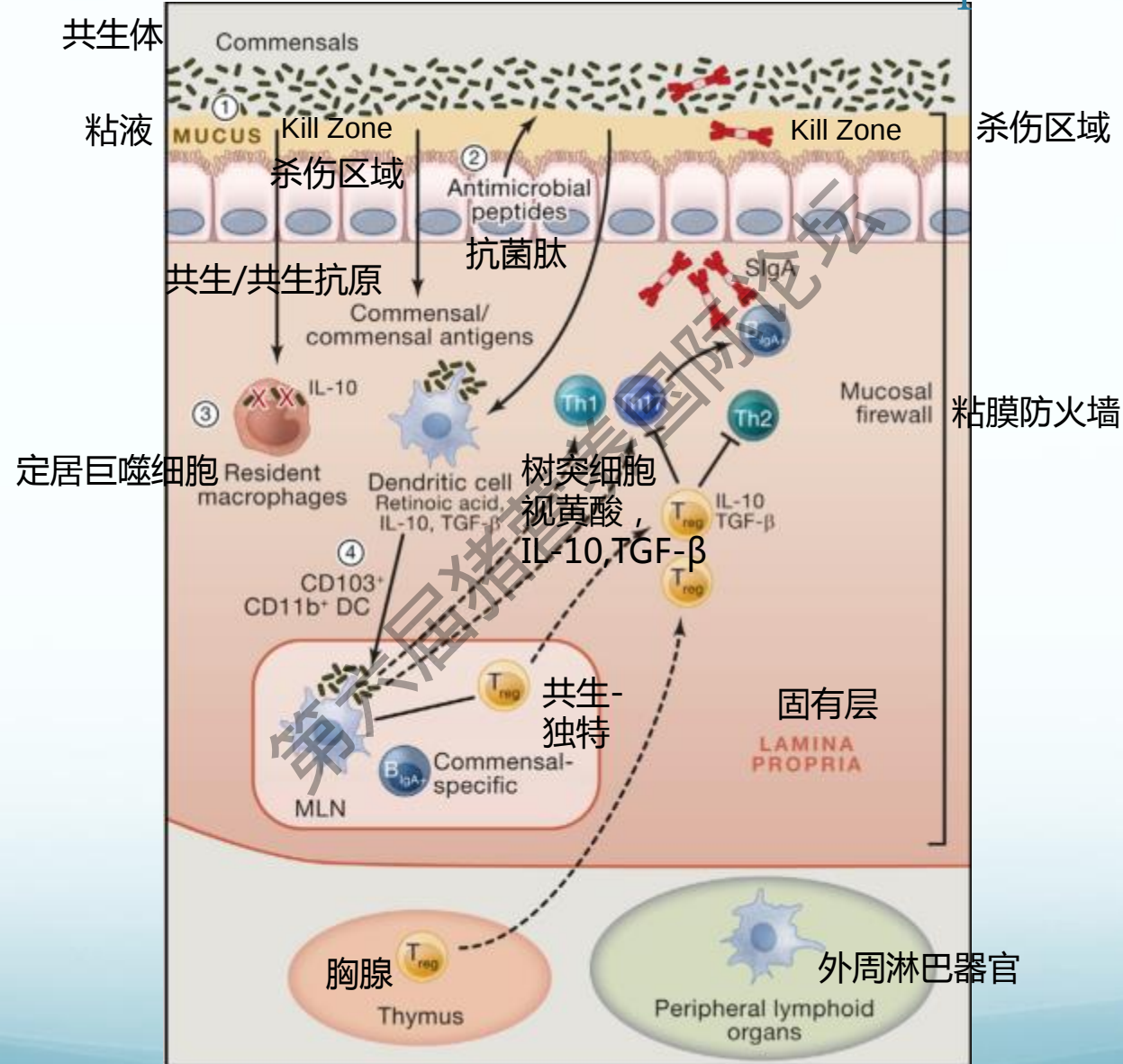
上皮细胞和杀伤区

Epithelium and Kill Zone



防火墙-黏膜+固有层

Firewall-Mucosa + Lamina Propria



上皮细胞与免疫功能

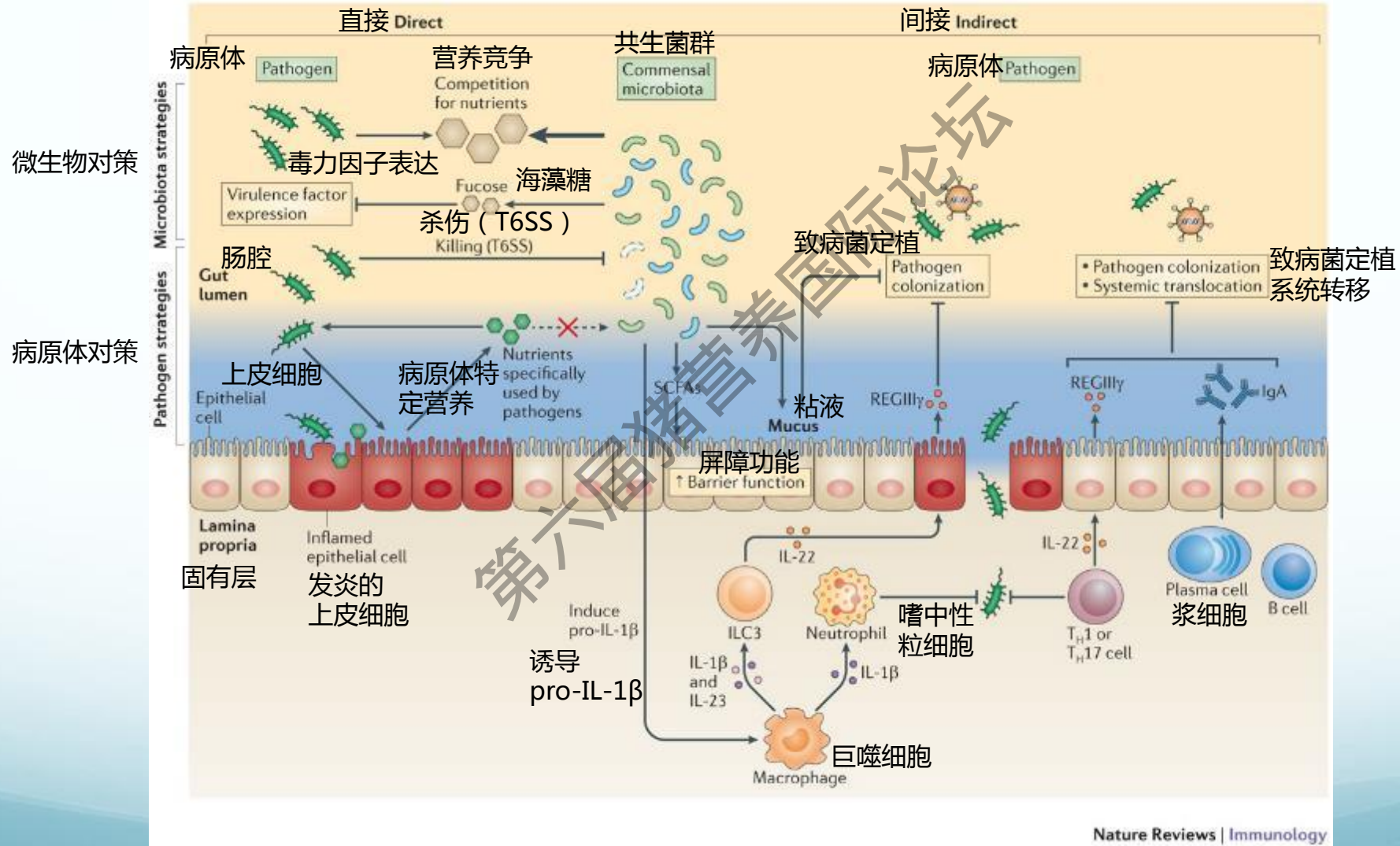
Epithelium and Immune Function

第六届猪营养国际论坛



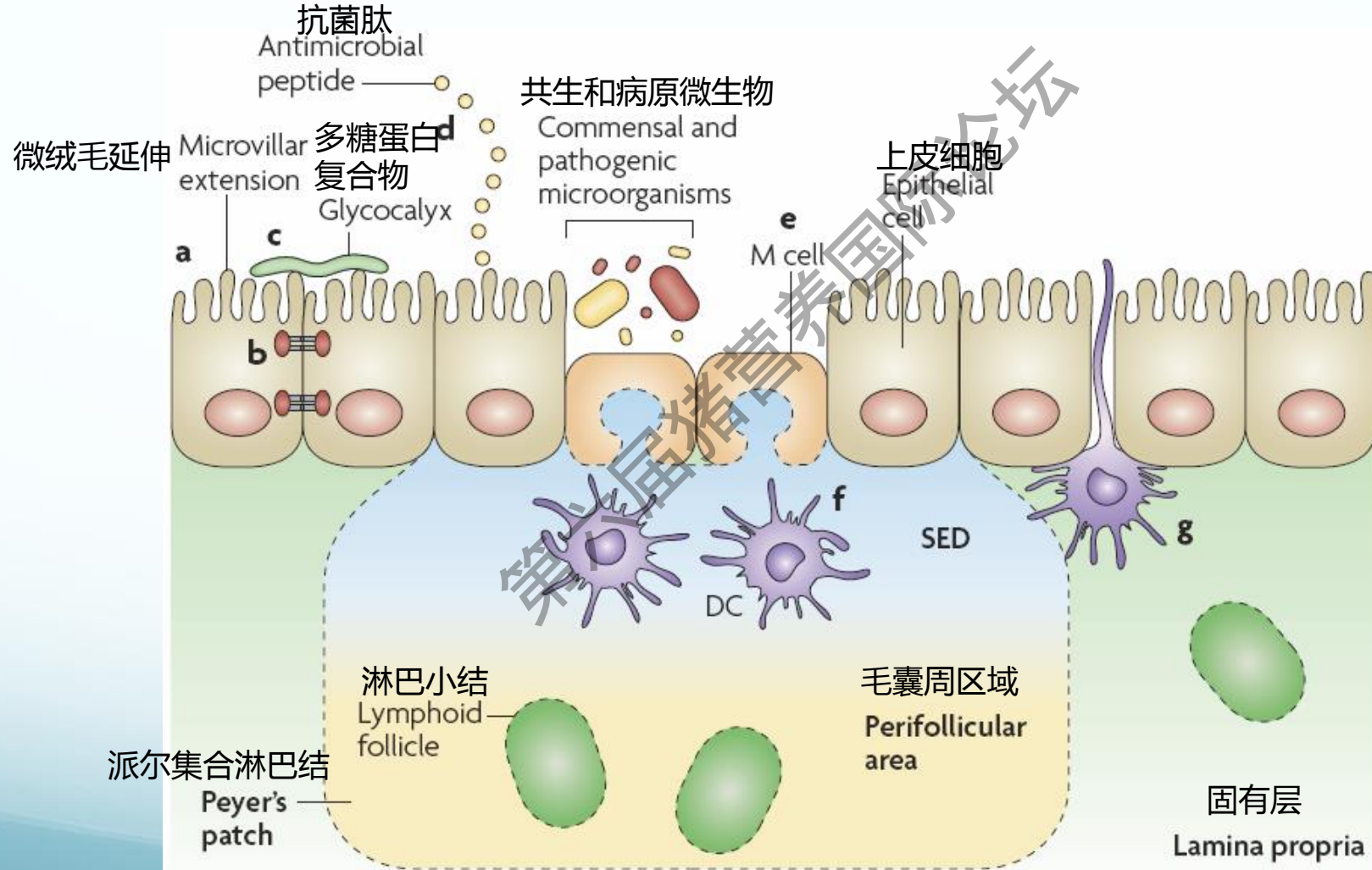
共生体及其诱导的免疫改变

Commensals and their Induced Immune Changes

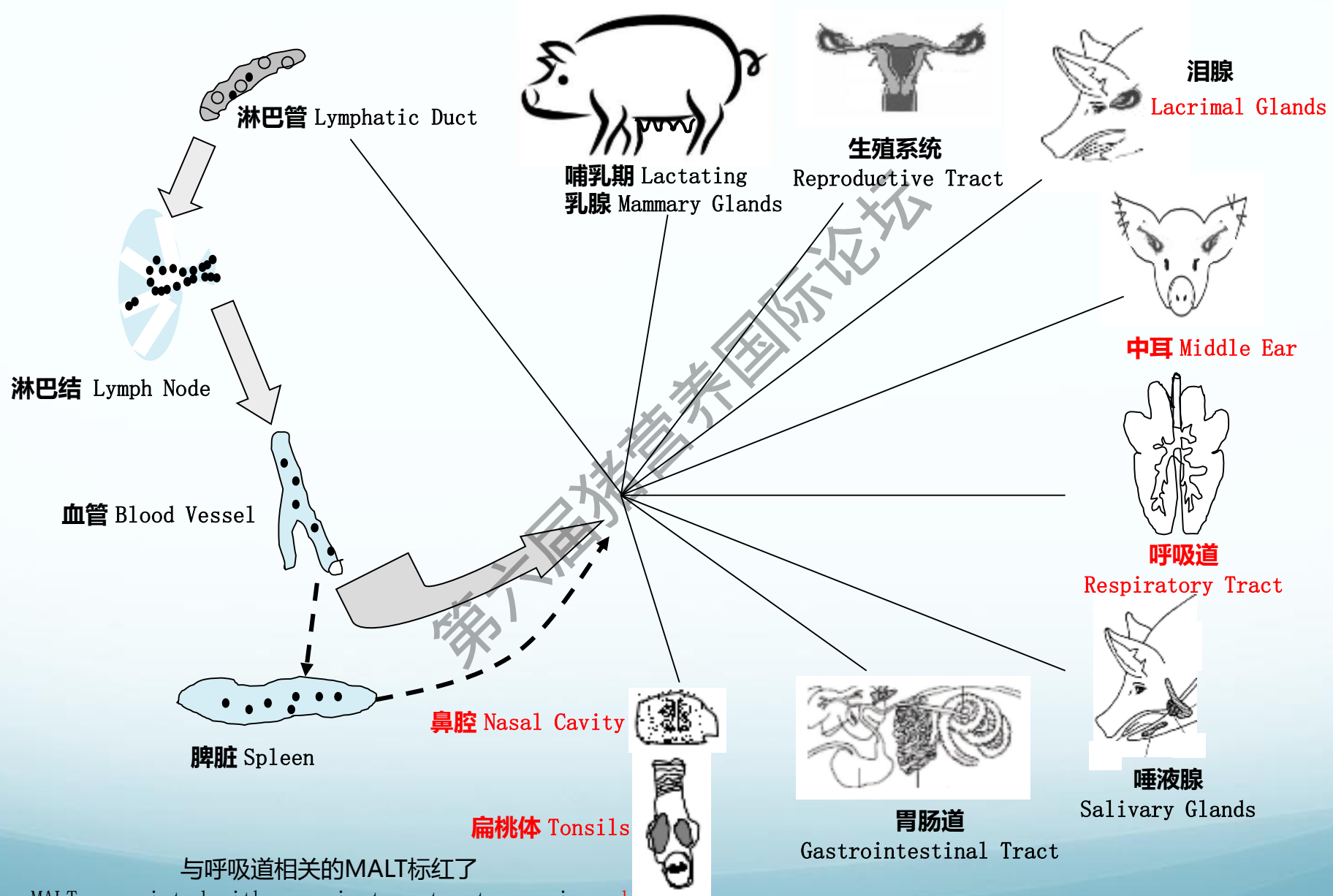


黏膜免疫

Mucosal Immunity



普通粘膜免疫系统 Common Mucosal Immune System



MALT associated with respiratory tract are in red

改编自黏膜免疫学和疫苗开发 Adapted from Mucosal Immunology and Vaccine Development

卫生学说

Hygiene hypothesis

- 微生物和过敏原的存在对新生儿的免疫发育至关重要 The presence of microorganisms and allergens is essential for immune development of the neonate
- 重要的肠道和呼吸道健康 Essential gut and respiratory health



微生物群(微生物区系)

Microbiota (Microflora)

- 在我们体内和身体上发现的生物集合——非常特定的位置和个体(遗传分) The collection of organisms found in and on our body- very location specific and individual specific (genetic component).
- 胃肠道微生物是最多样化的，与黏膜和食源性超微生物的相互作用最大 Gastrointestinal microbiota is the most diverse and has the largest interaction both with mucosa and ingesta- “superorganism”.



共生体

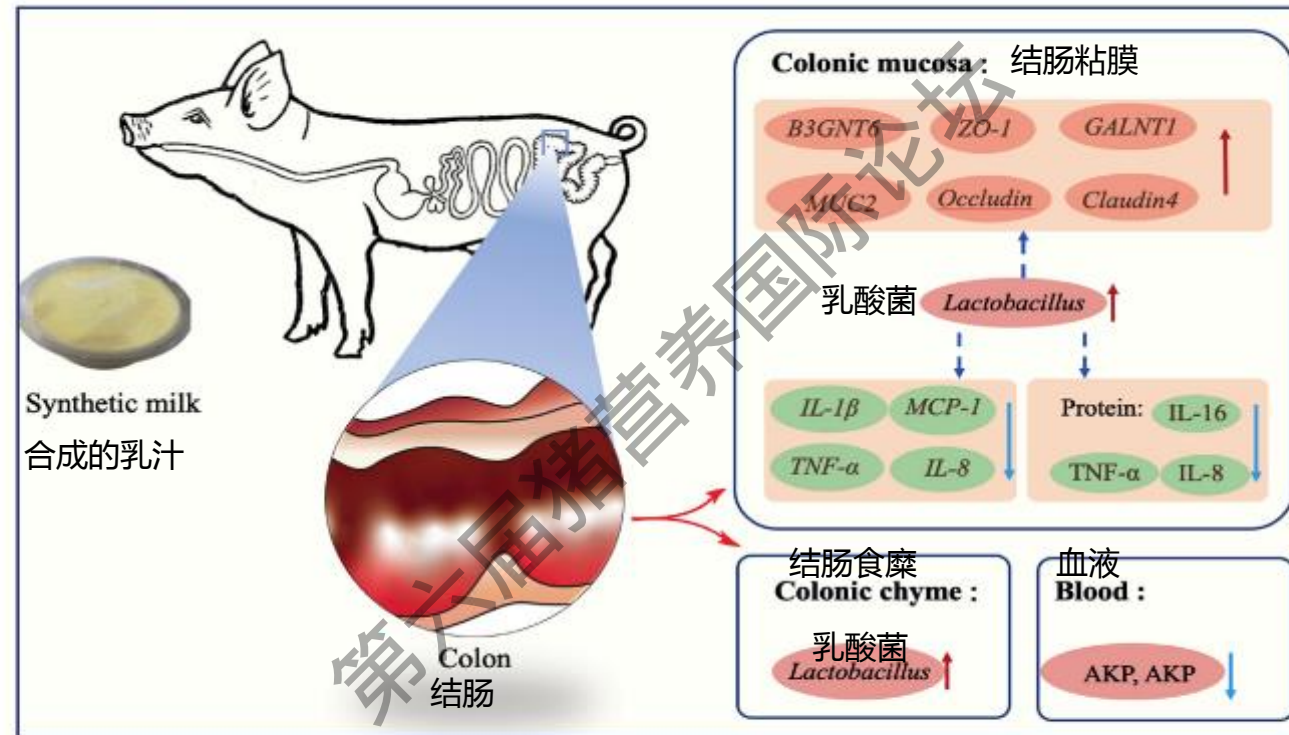
Commensal Organisms

- 10^{14} 种生物——真核生物、古细菌和细菌 10^{14} organisms—eukarya, archae and bacteria
- 10^{12} 个共生体细菌/ml-比人体细胞和干细胞结合的高10倍 10^{12} commensal bacteria/ml- 10X higher than the combined somatic and stem cells in man.
- 共生体对免疫发育至关重要 Commensals are essential for immune development.
- 寄主免疫状况对共生菌组成的影响 Composition of commensal bacteria influenced by the host immune status.



共生细菌

Commensal Bacteria



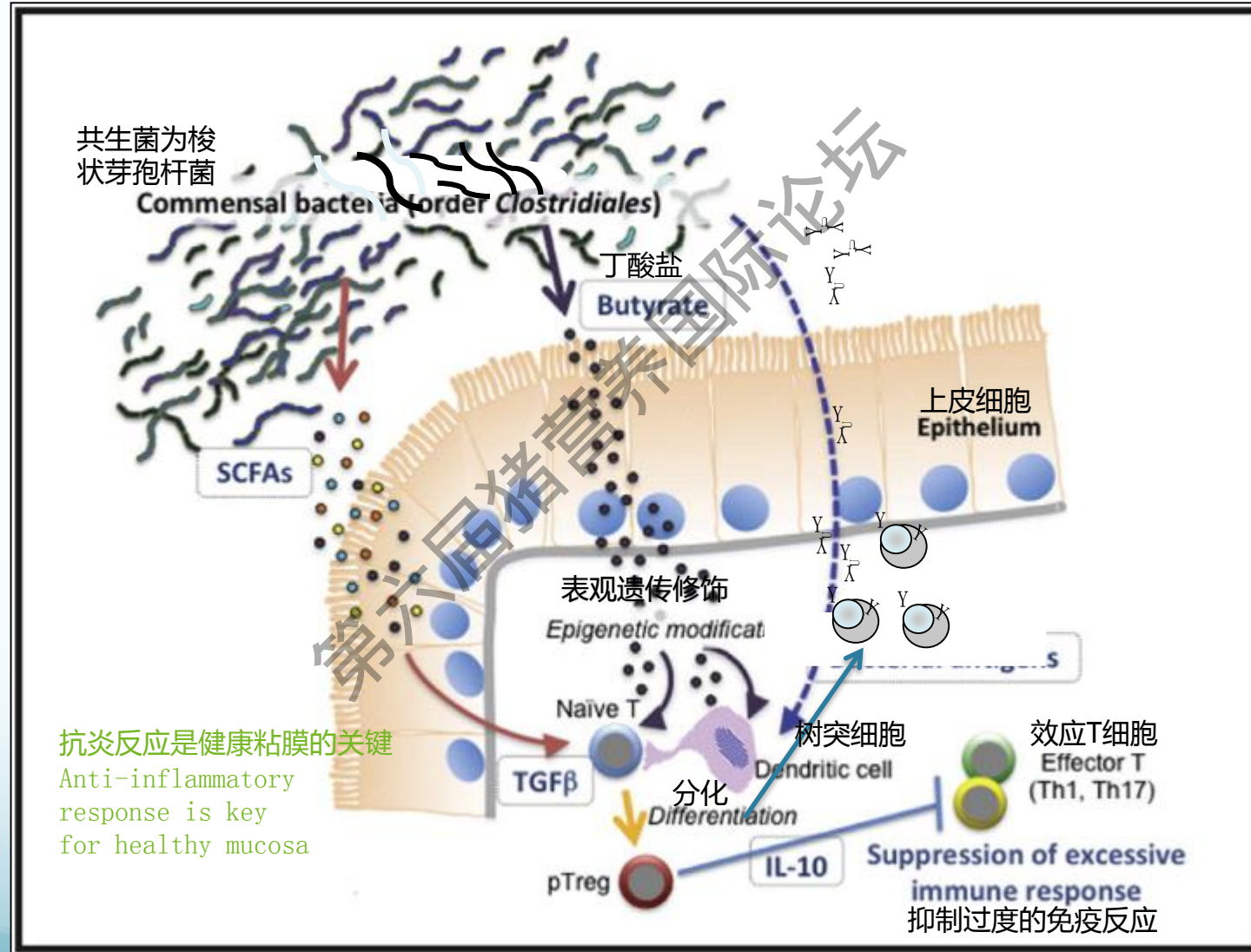
早期营养干预通过肠道菌群改善仔猪生长性能和肠道健康:一种可能的机制

FIGURE 10 | Early-life nutrition interventions improved growth performance and intestinal health via the gut microbiota in piglets: a possible mechanism.

Luo, C., Xia, B., Zhong, R., Shen, D., Li, J., Chen, L., Zhang, H., 2022. Early-Life Nutrition Interventions Improved Growth Performance and Intestinal Health via the Gut Microbiota in Piglets. *Frontiers Nutrition* 8, 783688. <https://doi.org/10.3389/fnut.2021.783688>

微生物与先天免疫调节-快乐的肠道

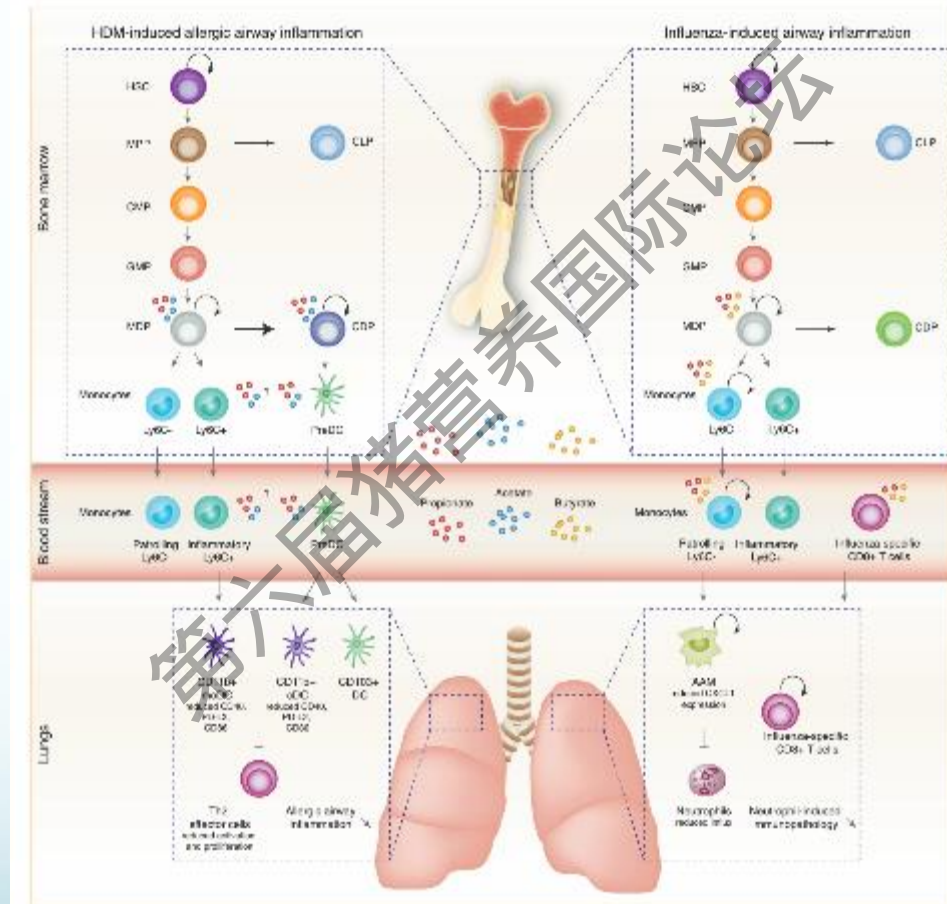
Microbes and Regulating Innate Immunity-Happy Gut Happy Calf



Adapted from Cell 156, Issues 1 - 2, 2014, Pages 7

微生物与先天免疫调节-快乐的肠道

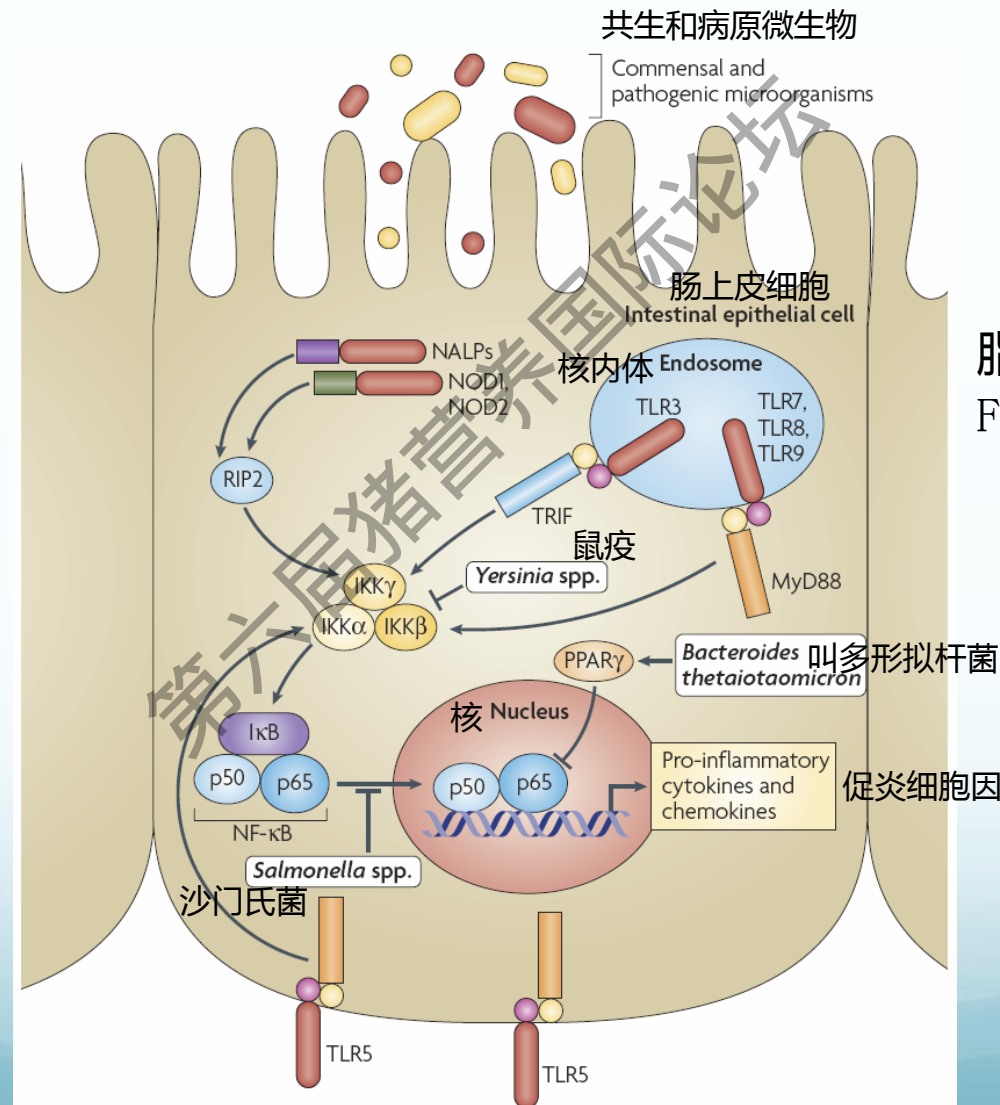
Microbes and Regulating Innate Immunity-Happy Gut Happy Calf



Dang, A.T., Marsland, B.J., 2019. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol* 12, 843-850. <https://doi.org/10.1038/s41385-019-0160-6>

共生细菌-抑制促炎反应

Commensal Bacteria-Inhibit proinflammatory responses

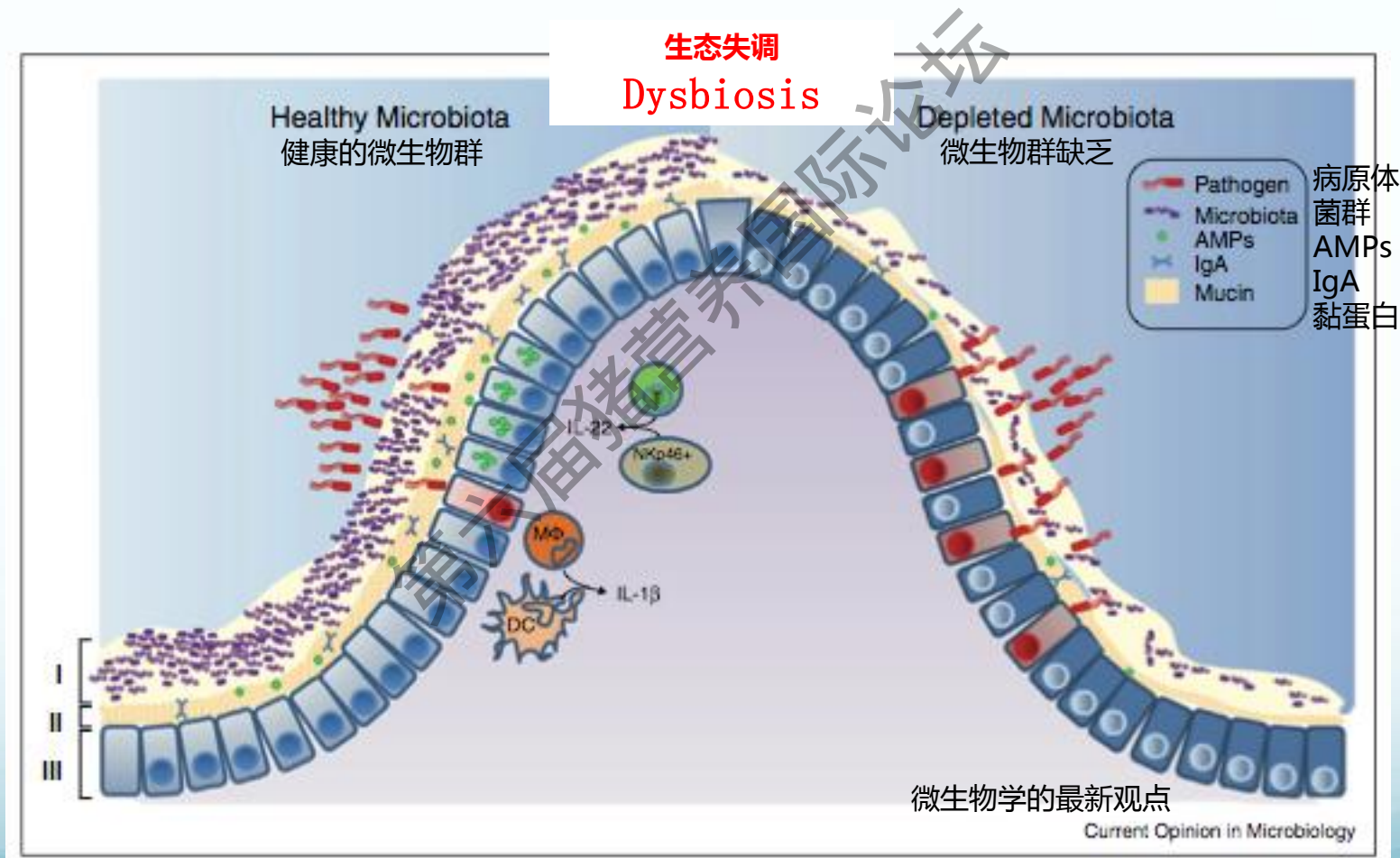


脂肪酸丁酸盐
Fatty acids butyrate

促炎细胞因子和趋化因子

共生体及其诱导的免疫改变

Commensals and their Induced Immune Changes



Khosravi and Mazmanian, Current Opinion in Microbiology 2013, 16:221–227

微生物、日粮和应激

Microflora, Diet and Stress

- 营养不仅仅是饲喂动物，也是喂养微生物

Nutrition isn't just feeding the "animal" it is also feeding the "microbes".

- V的生产

Production of vitamins.

- 更高效的细菌-增加肥胖的机会

More efficient bacteria- increase opportunity for obesity.

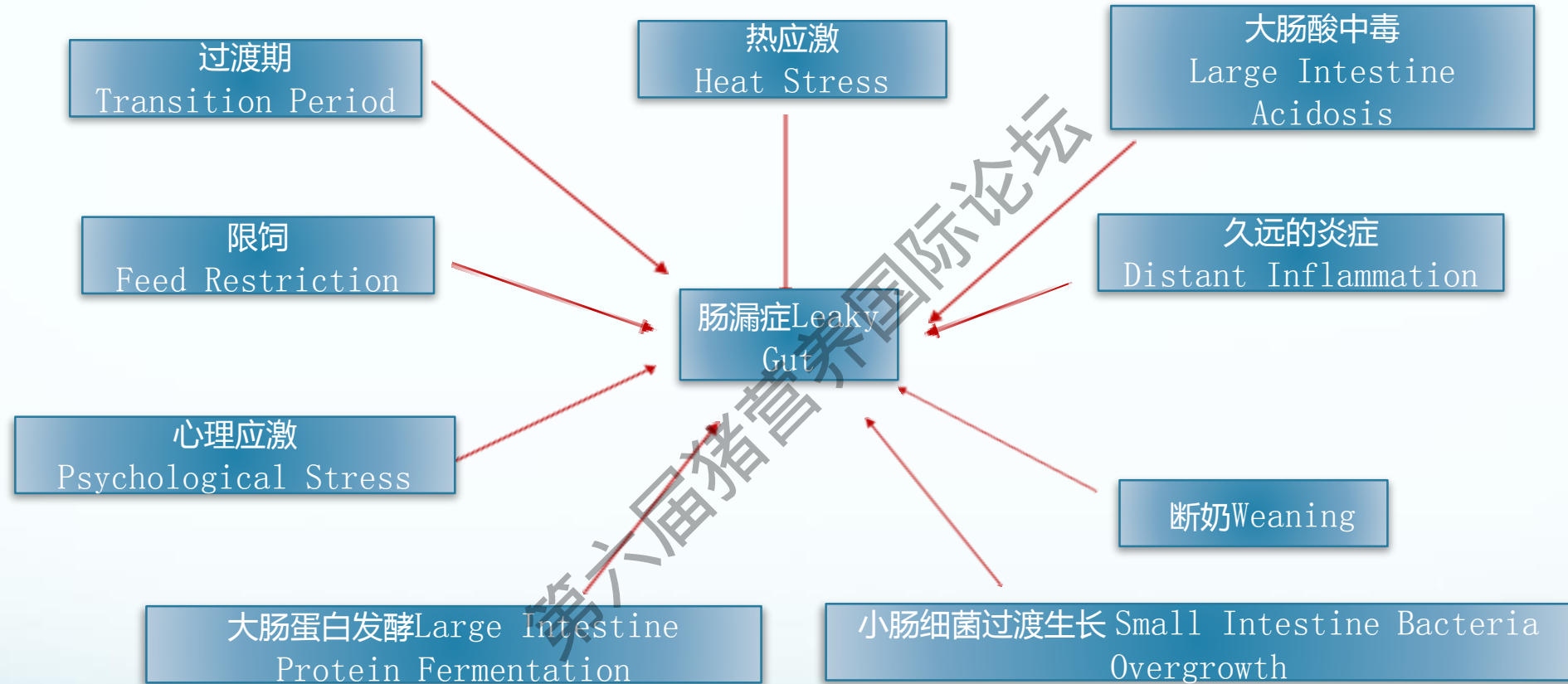




Adapted from Zeineldin M, Lowe J, Aldridge B. Contribution of the Mucosal Microbiota to Bovine Respiratory Health. *Trends Microbiol.* May 2019. doi:10.1016/j.tim.2019.04.005.

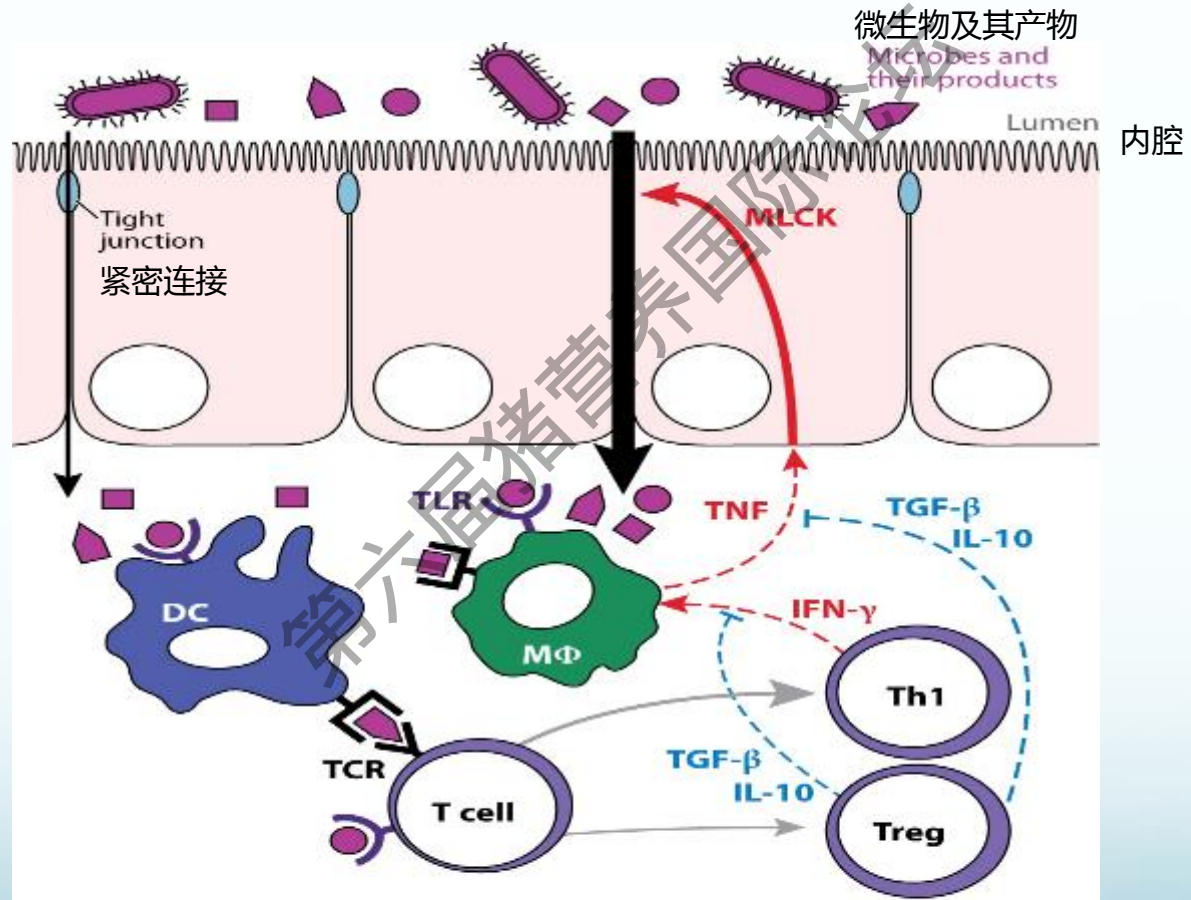
肠通透性增加的原因(肠漏)

Documented Causes of Increased Intestinal Permeability (“leaky gut”)



Baumgard L, International Symposium on Dairy Cattle Nutrition, Wageningen NL October 26, 2017

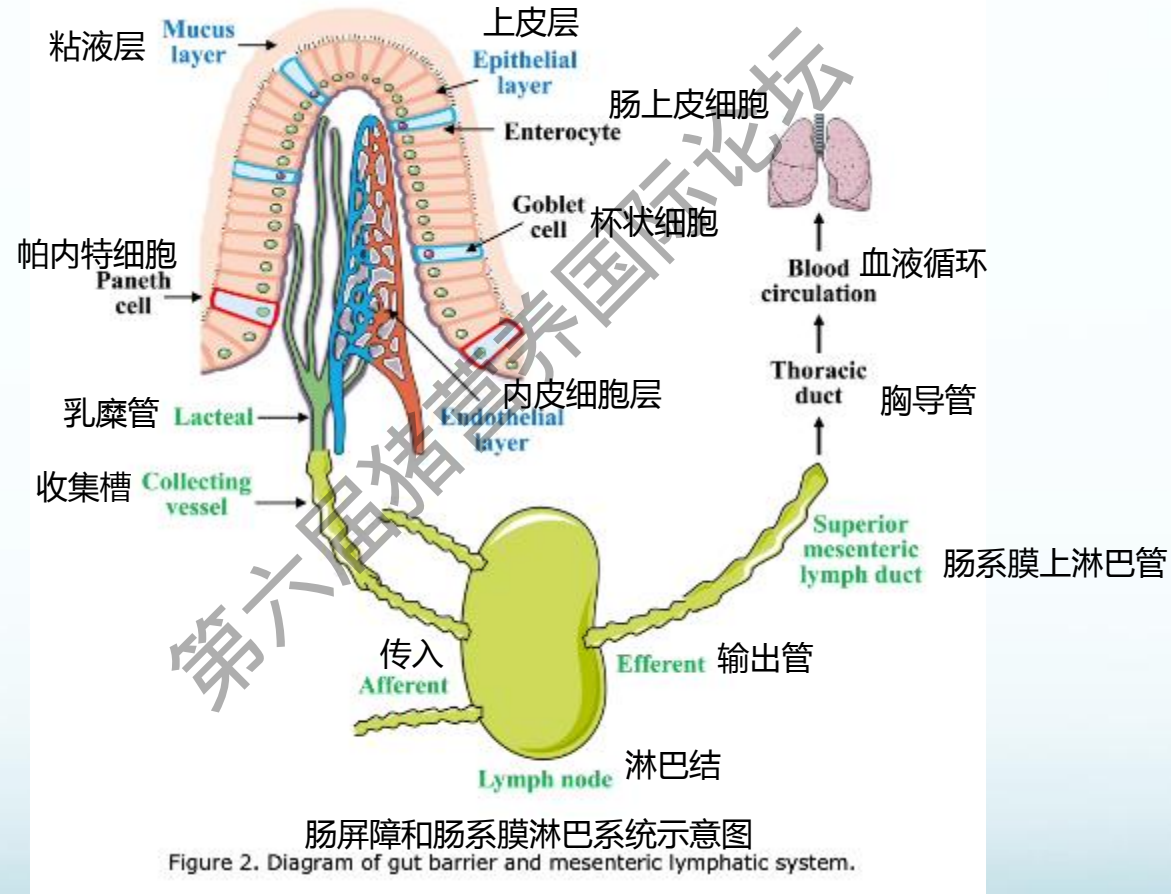
肠漏 Leaky Gut



AR Marchiando AM, et al. 2010.
Annu. Rev. Pathol. Mech. Dis. 5:119–44

肠-肺炎症轴

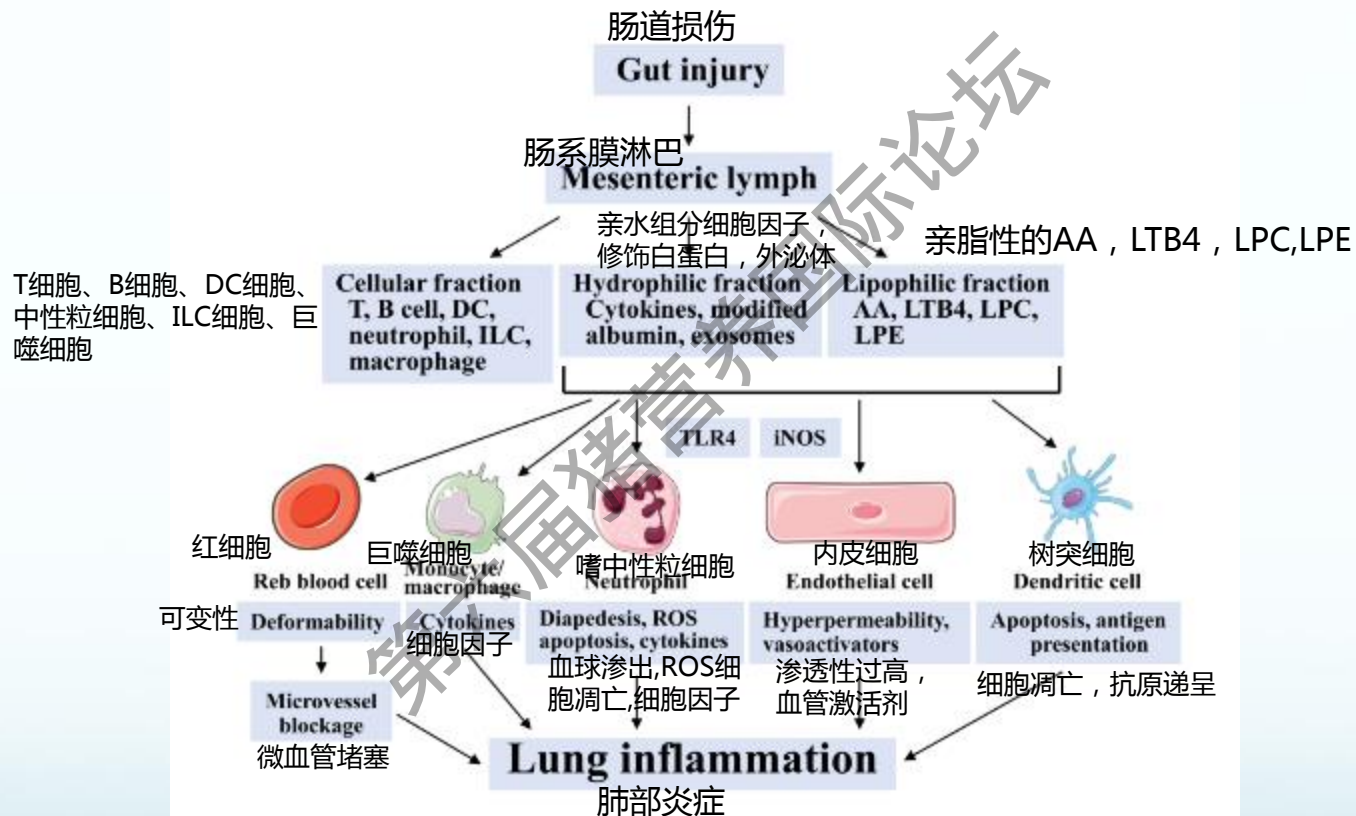
Gut-Lung Inflammatory Axis



Ma, Y., Yang, X., Chatterjee, V., Wu, M., Yuan, S.Y., 2020. The Gut-Lung Axis in Systemic Inflammation: Role of Mesenteric Lymph as Conduit. Am J Resp Cell Mol. <https://doi.org/10.1165/rcmb.2020-0196tr>

肠-肺炎症轴

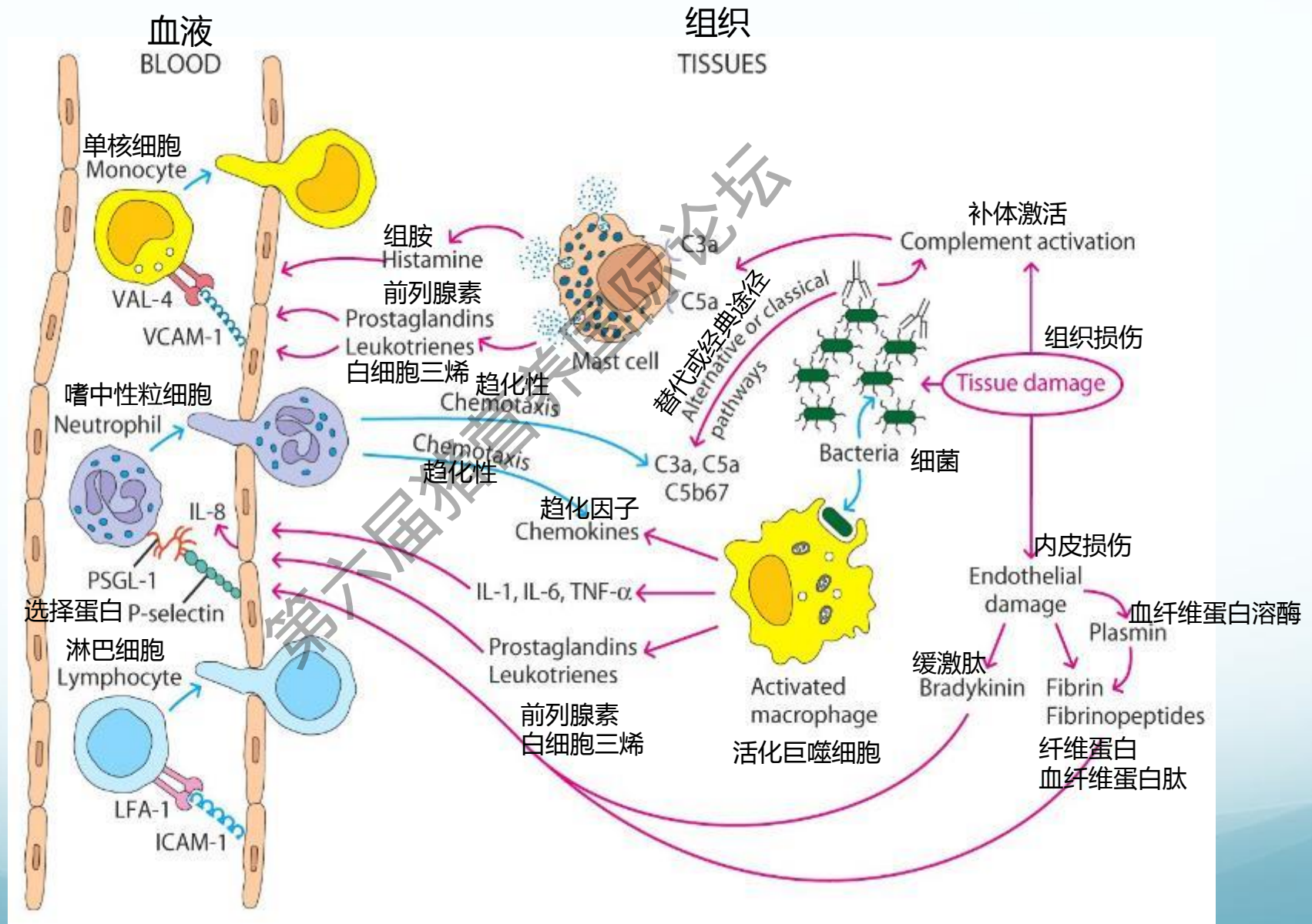
Gut-Lung Inflammatory Axis



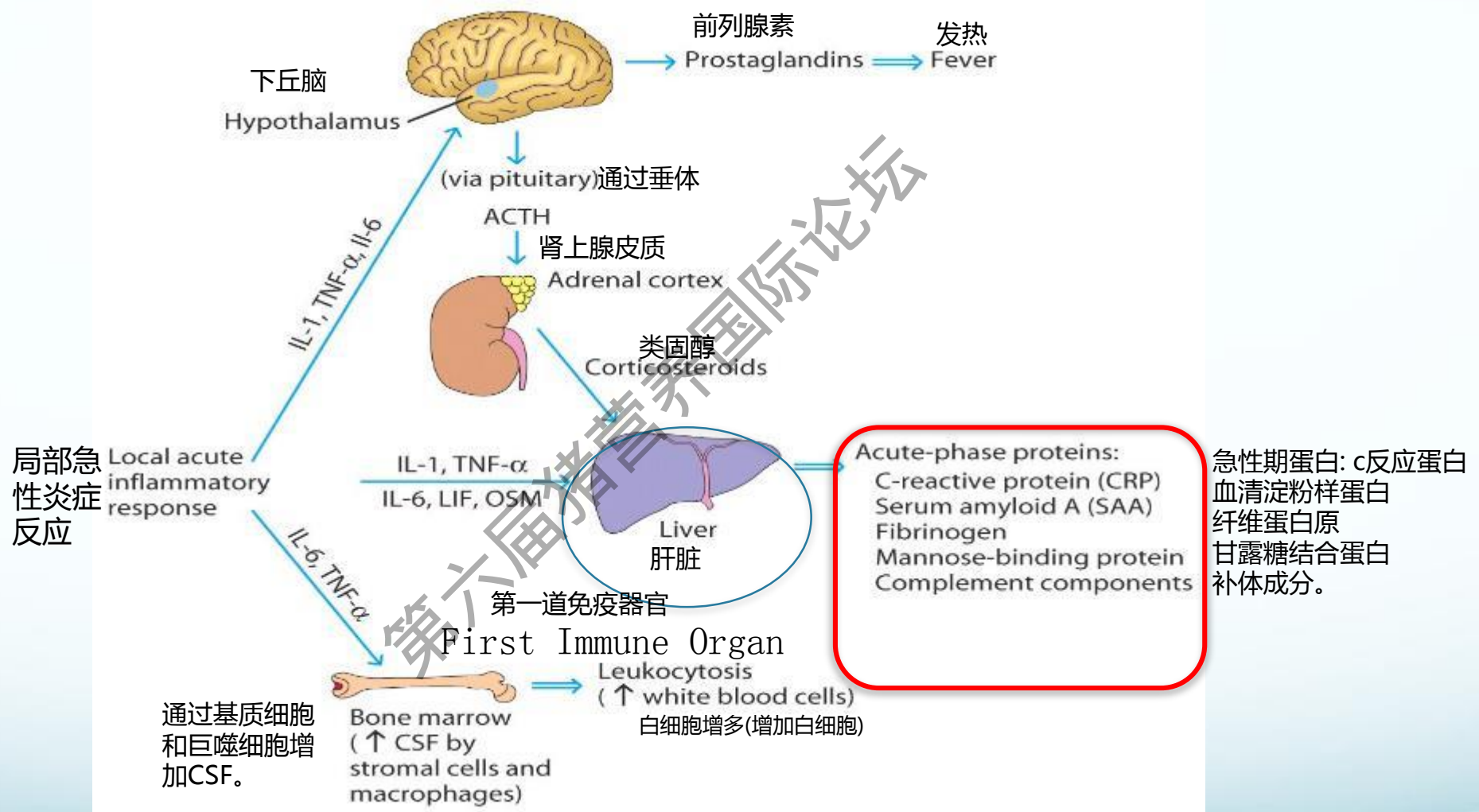
肠系膜淋巴诱导肺损伤的机制示意图
Figure 3. Mechanistic diagram of mesenteric lymph inducing lung injury.

Ma, Y., Yang, X., Chatterjee, V., Wu, M., Yuan, S.Y., 2020. The Gut-Lung Axis in Systemic Inflammation: Role of Mesenteric Lymph as Conduit. Am J Res Cell Mol. <https://doi.org/10.1165/rcmb.2020-0196tr>

炎症反应 Inflammatory Response



炎症反应 Inflammatory Response



系统反应 Systemic response

过犹不及 Too Much of A Good Thing

评论 COMMENT

CREATIVITY Why did Goethe write a scandalous novel about breeding? p.188

FLY Biopic: The Fly Room centres on the crucible of early genetics p.189

INDEPENDENT Call for conflict-of-interest rules for panel-report authors p.170

CONSERVATION Manage military training grounds for environmental value too p.179



The often harmless fungus *Aspergillus fumigatus* can cause severe pulmonary disease in people with leukaemia.

不要用病原体这个词

Ditch the term pathogen

Disease is as much about the host as it is the infectious agent — the focus on microbes is hindering research into treatments, say Arturo Casadevall and Liise-anne Pirofski.

The term pathogen started to be used in the late 1890s to mean a microbe that can cause disease. Ever since, scientists have been searching for properties in bacteria, fungi, viruses and parasites that account for their ability to make us ill. Some seminal discoveries have resulted — such as the roles of various bacterial and fungal toxins in disease. Indeed, our oldest and most reliable vaccines, such as those for diphtheria and tetanus, work by prompting the body to produce antibodies

that neutralize bacterial toxins.

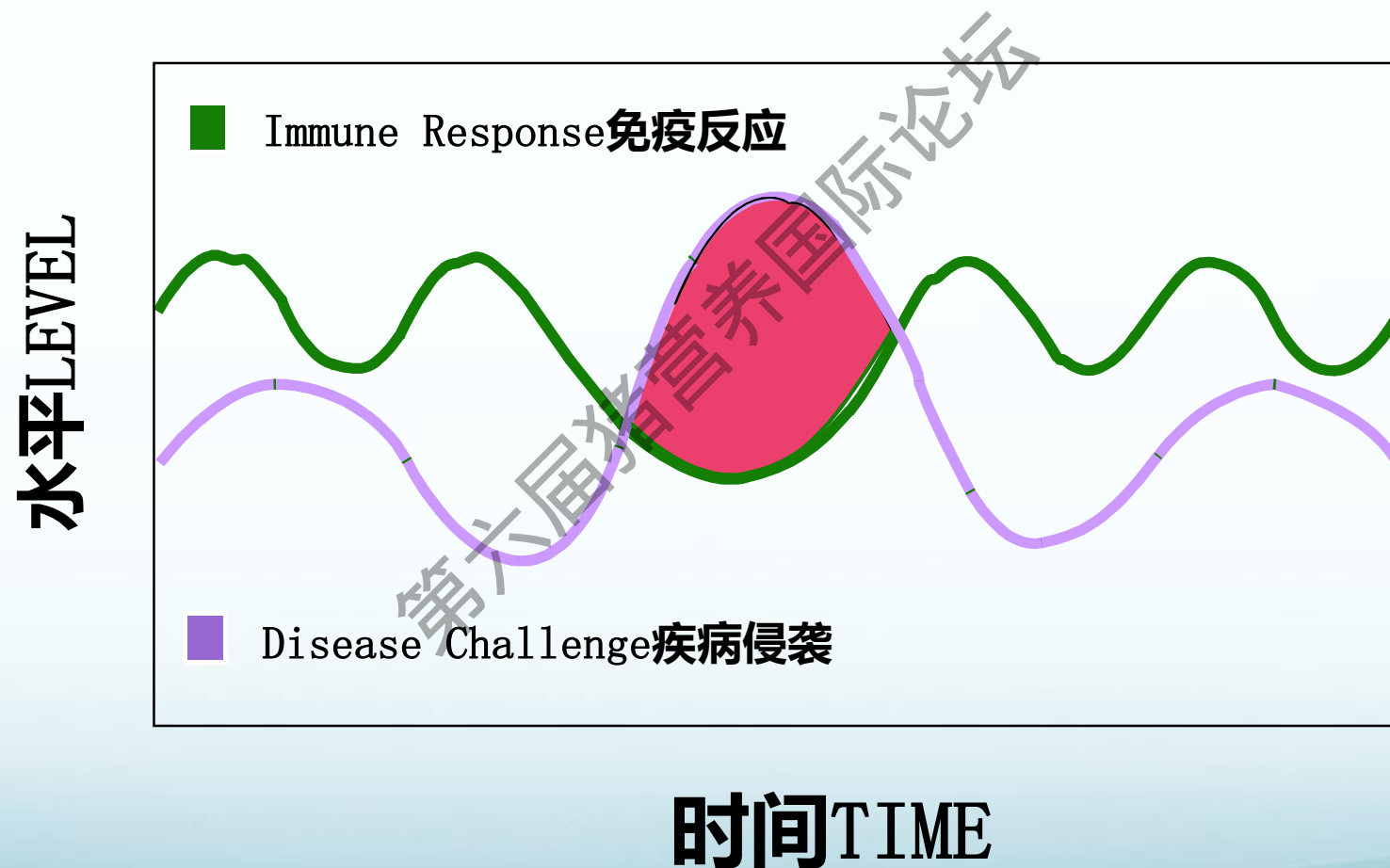
Yet a microbe can not cause disease without a host. What actually kills people with diphtheria, for example, is the strong inflammatory response that the diphtheria toxin triggers, including a thick grey coating on the throat that can obstruct breathing. Likewise, it is the massive activation of white blood cells triggered by certain strains of *Staphylococcus* and *Streptococcus* bacteria that can lead to toxic-shock syndrome.

Disease is one of several possible outcomes of an interaction between a host and a microbe. It sounds obvious spelled out in this way. But the issue here is more than just semantics: the use of the term pathogen sustains an unhelpful focus among researchers and clinicians on microbes that could be hindering the discovery of treatments. In the current Ebola epidemic in West Africa, for instance, much attention has been focused on the ill and the dead, even though crucial clues to curbing the outbreak may

Arturo Casadevall和Liise-anne Pirofski说，疾病既与宿主有关，也与传染因子有关-对微生物的关注阻碍了治疗的研究。

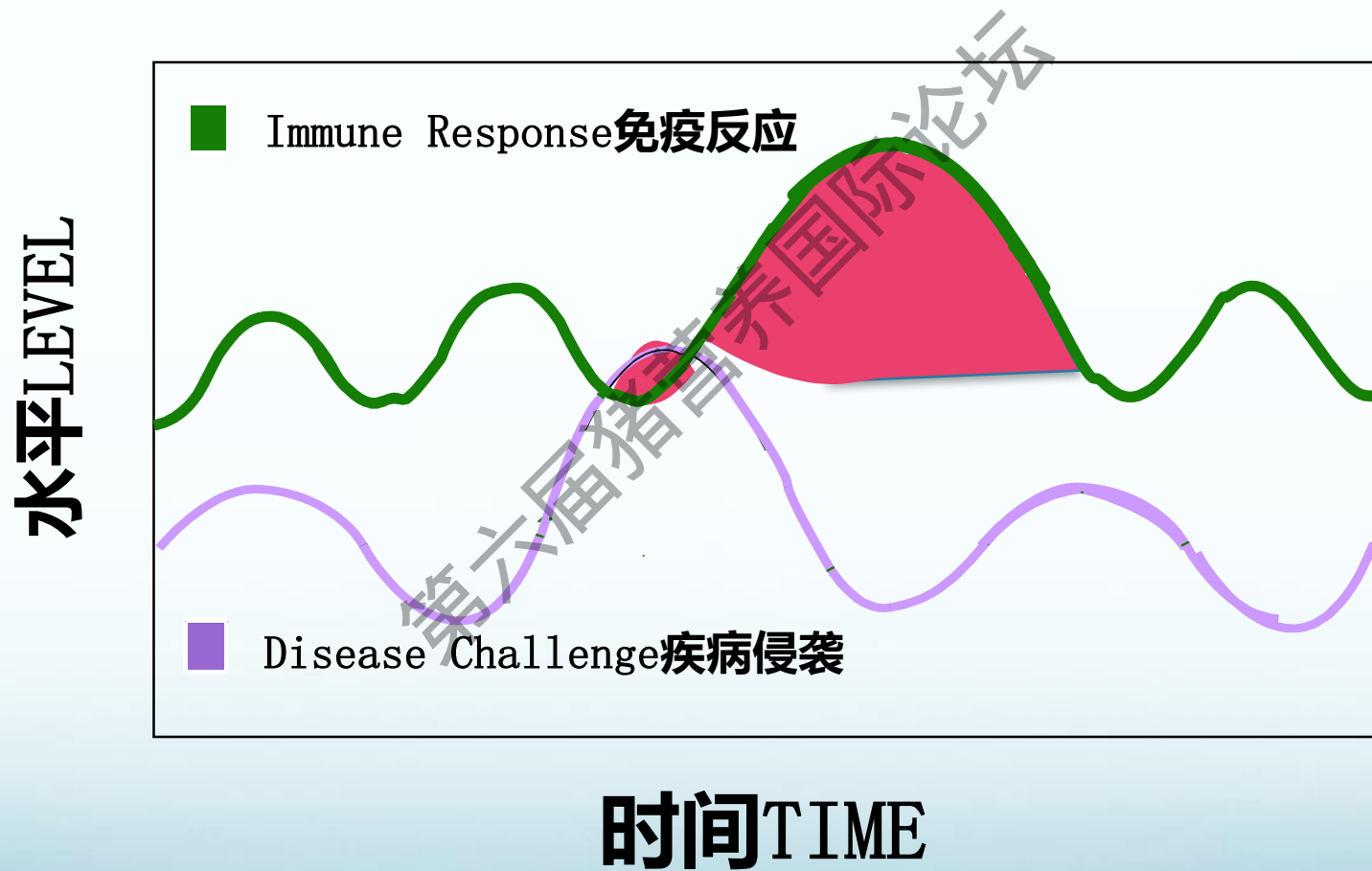
免疫不够

Not Enough of A Good Thing



免疫过度

Too Much of A Good Thing



炎症反应

Inflammatory Response

What Does Stress Do to Neutrophil Motility and Phagocytosis?

应激如何影响中性粒细胞的活动和吞噬作用

第六届猪营养国际论坛

Neutrophil Chemotaxis and Phagocytosis

中性粒细胞趋化作用和吞噬作用



未被控制的炎症反应

Uncontrolled Inflammatory Response

第六届猪营养国际论坛

Neutrophil Fungal Killing 中性粒细胞杀伤真菌

What does pro-inflammatory response do to Neutrophil Function? 促炎反应如何影响中性粒细胞功能



中性粒细胞爆炸

Neutrophils-Blowing Up

第六届猪营养国际论坛



过度炎症反应

Overactive Inflammatory Response

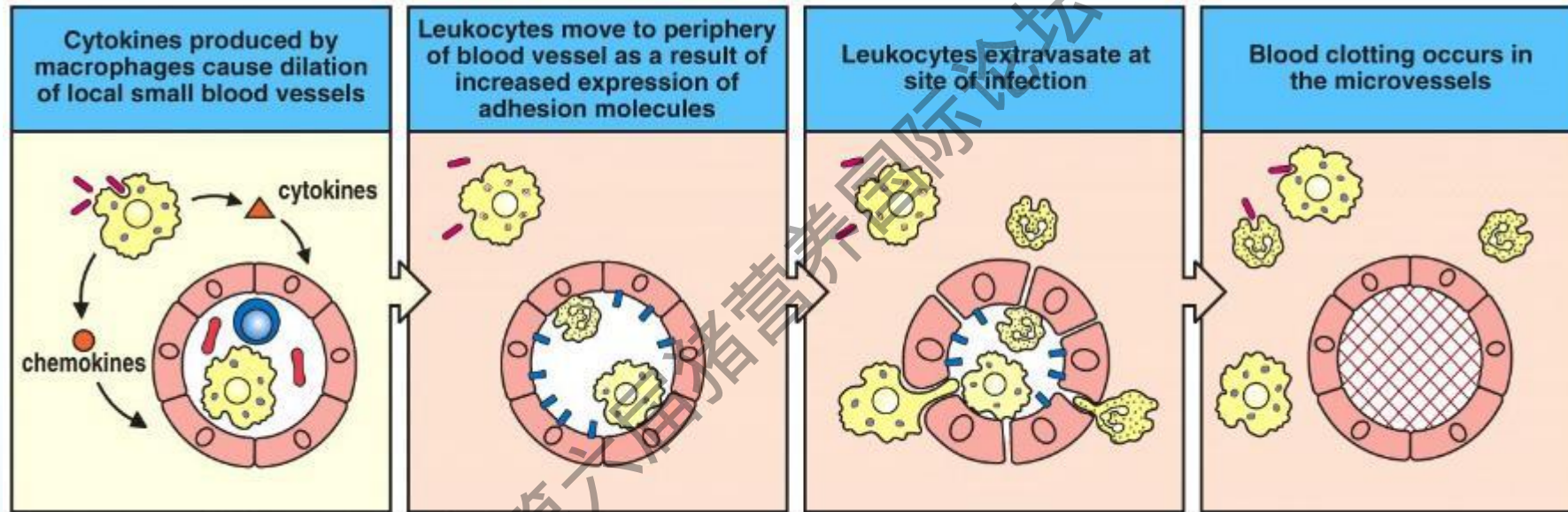


Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)

巨噬细胞产生的炎症因子导致附件小血管扩张

随着粘附分子表达的增加，淋巴细胞移动到血管周围

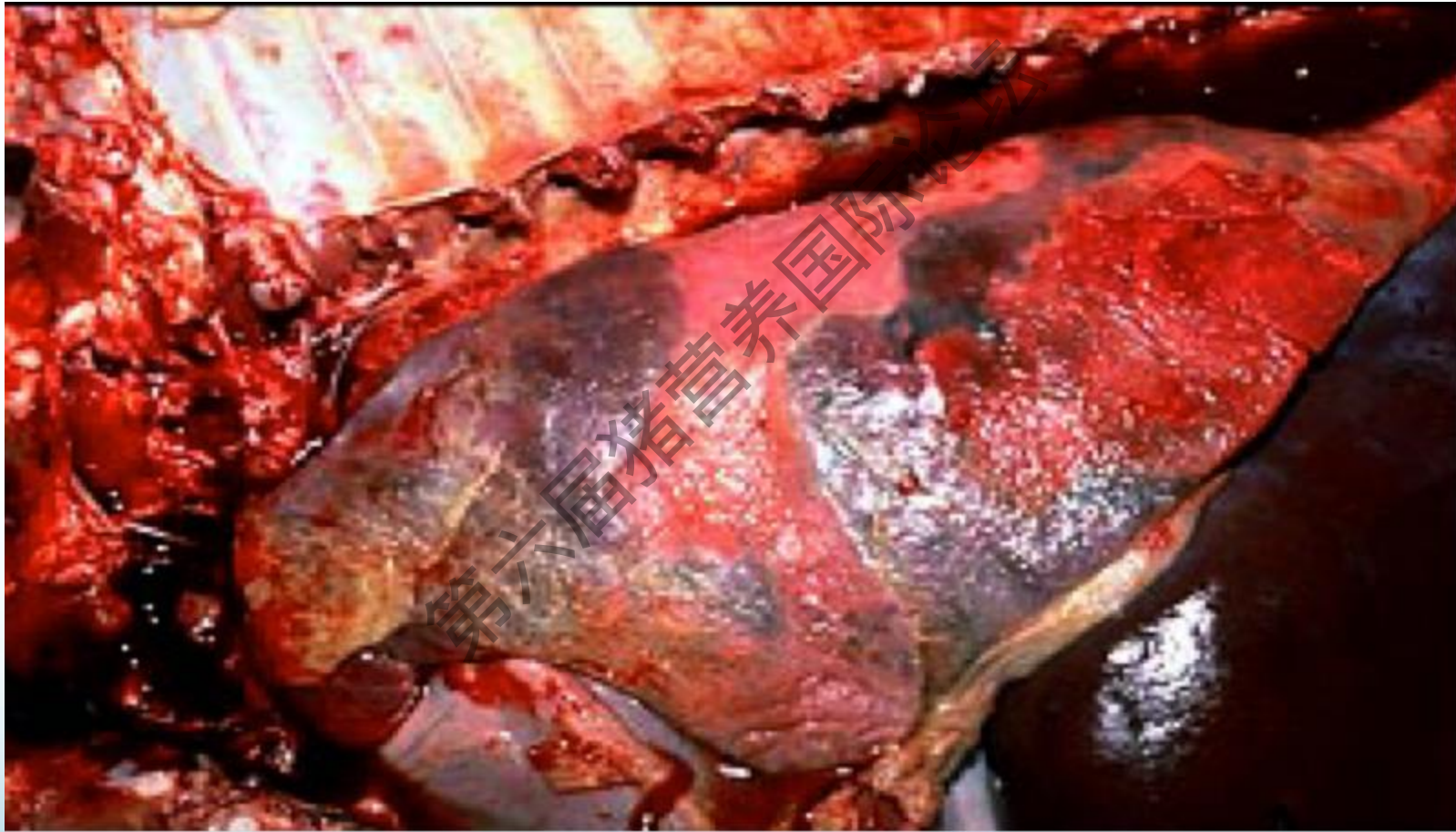
淋巴细胞外渗到感染部位

微血管发生血液凝固

Tissue Damage 组织损伤

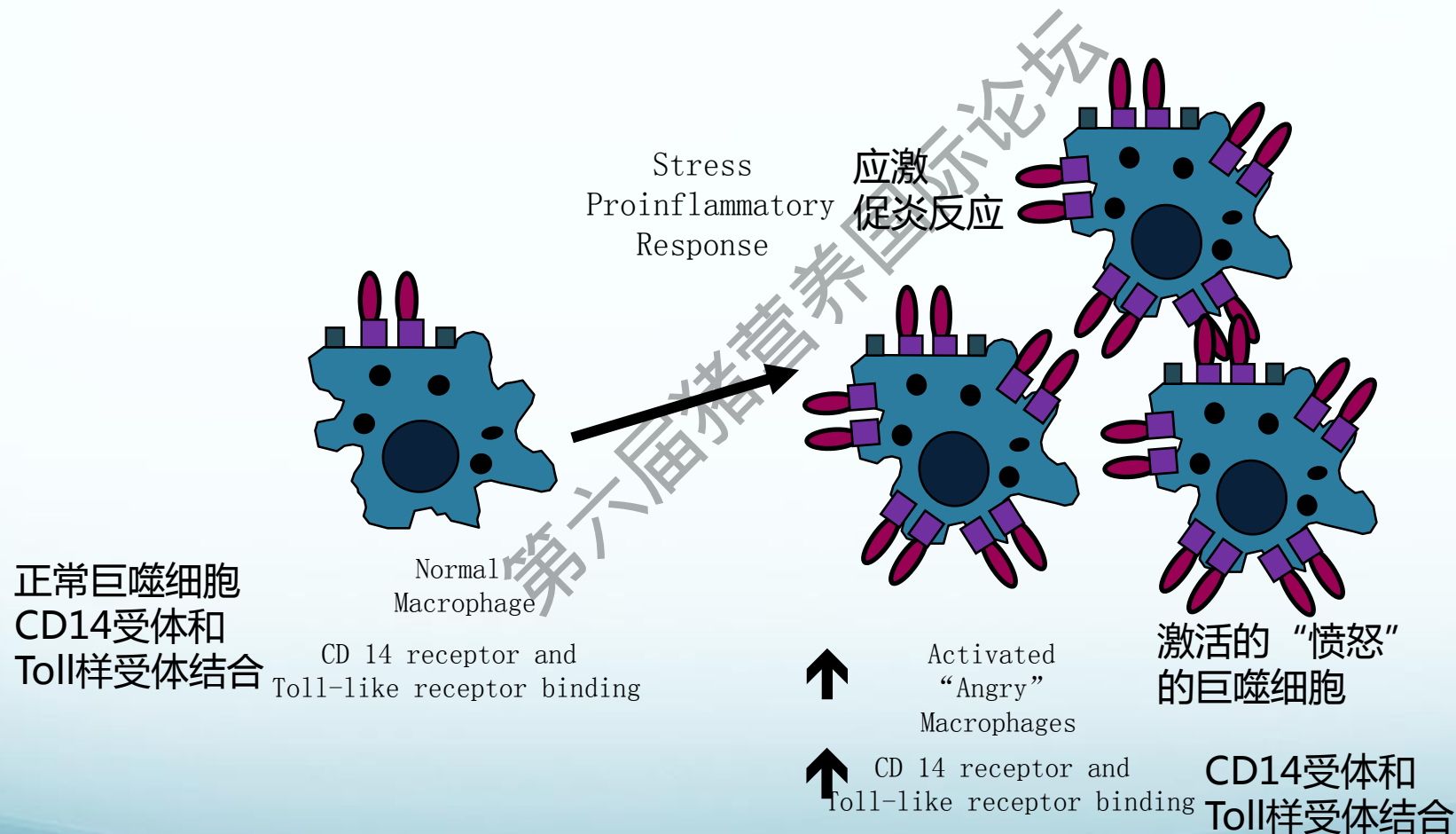
组织损伤——过度活化免疫系统

Tissue Damage-Overactive Immune System



巨噬细胞是免疫系统的眼睛和第一反应者

Macrophages are the Immune System's Eyes and First Responder



活化的巨噬细胞招募和激活嗜中性粒细胞作为对病原体的第一反应者

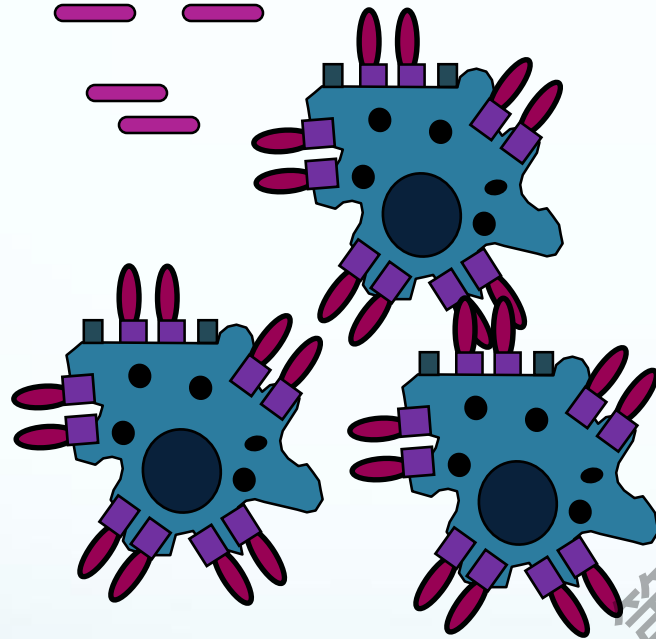
Activated Macrophages Recruit and Activate Neutrophils as First Responder in Response to Pathogens

Gram Negative bacteria 革兰氏阴性菌

M. haemolytica

H. somni

P. multocida



Activated “Angry”
Macrophages

激活的“愤怒”的巨噬细胞

Innate Cytokines

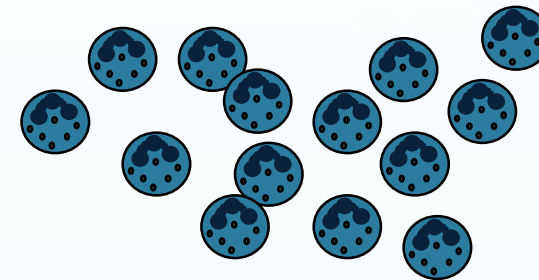
先天细胞因子

IL-1 β

IL-6

IL-8

Produce
Proinflammatory
Cytokines
产生促炎因子



Recruits Neutrophils
召集中性粒细胞

针对细胞外病原体的巨噬细胞效应机制

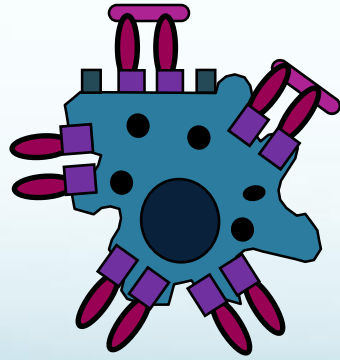
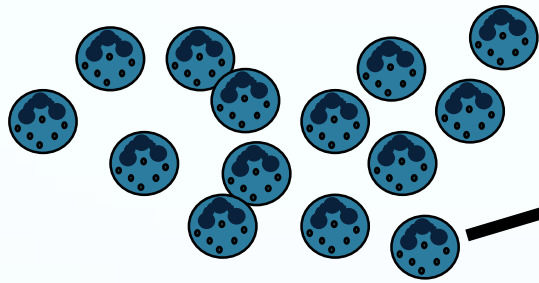
Macrophage effector mechanisms against extracellular pathogens

Gram Negative bacteria 革兰氏阴性菌

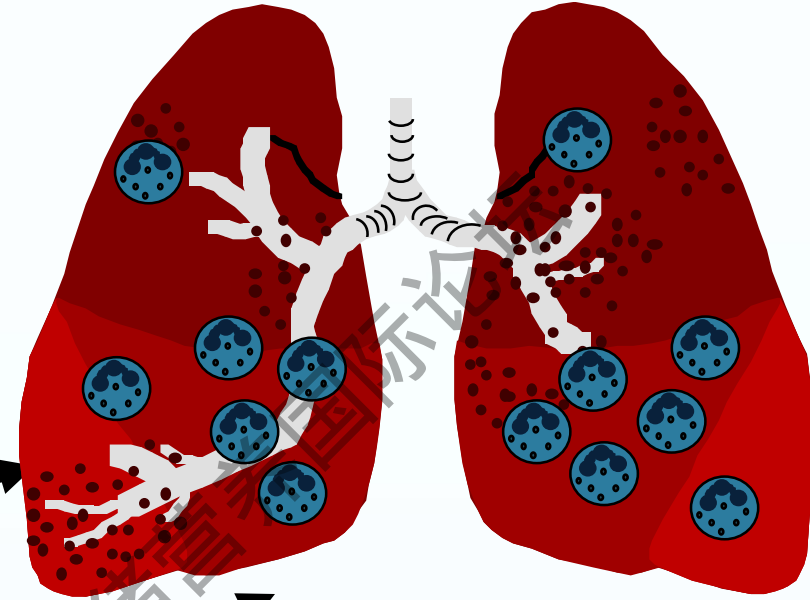
M. haemolytica

H. somni

P. multocida



Activated “Angry”
Macrophages
激活的“愤怒”的巨噬细胞



Recruits Neutrophils
召集中性粒细胞

Innate Cytokines

先天细胞因子

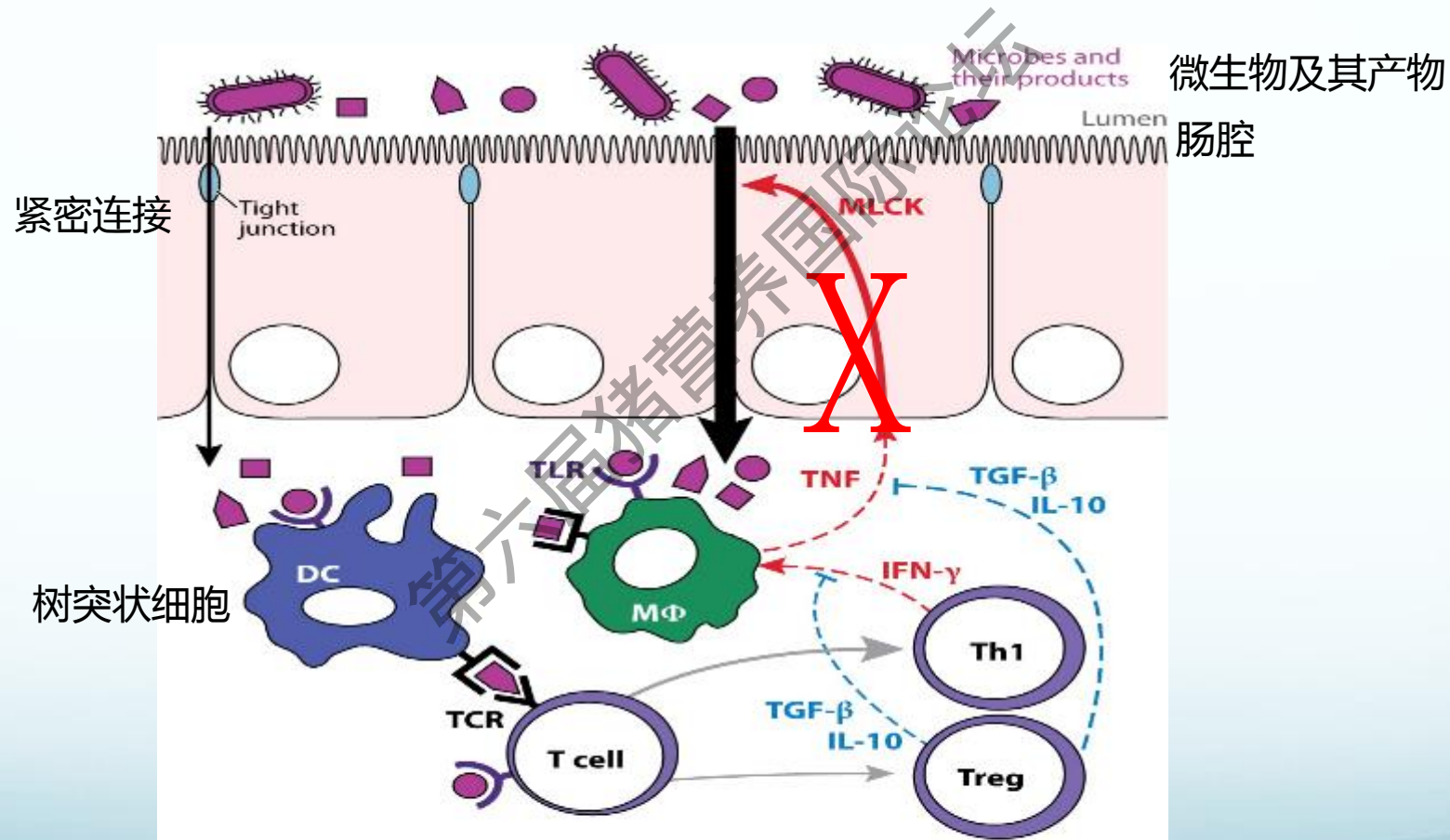
IL-1 β

IL-6

IL-8

炎症反应——上皮细胞

Inflammatory Response-Epithelial Cells



Marchiando AM, et al. 2010.

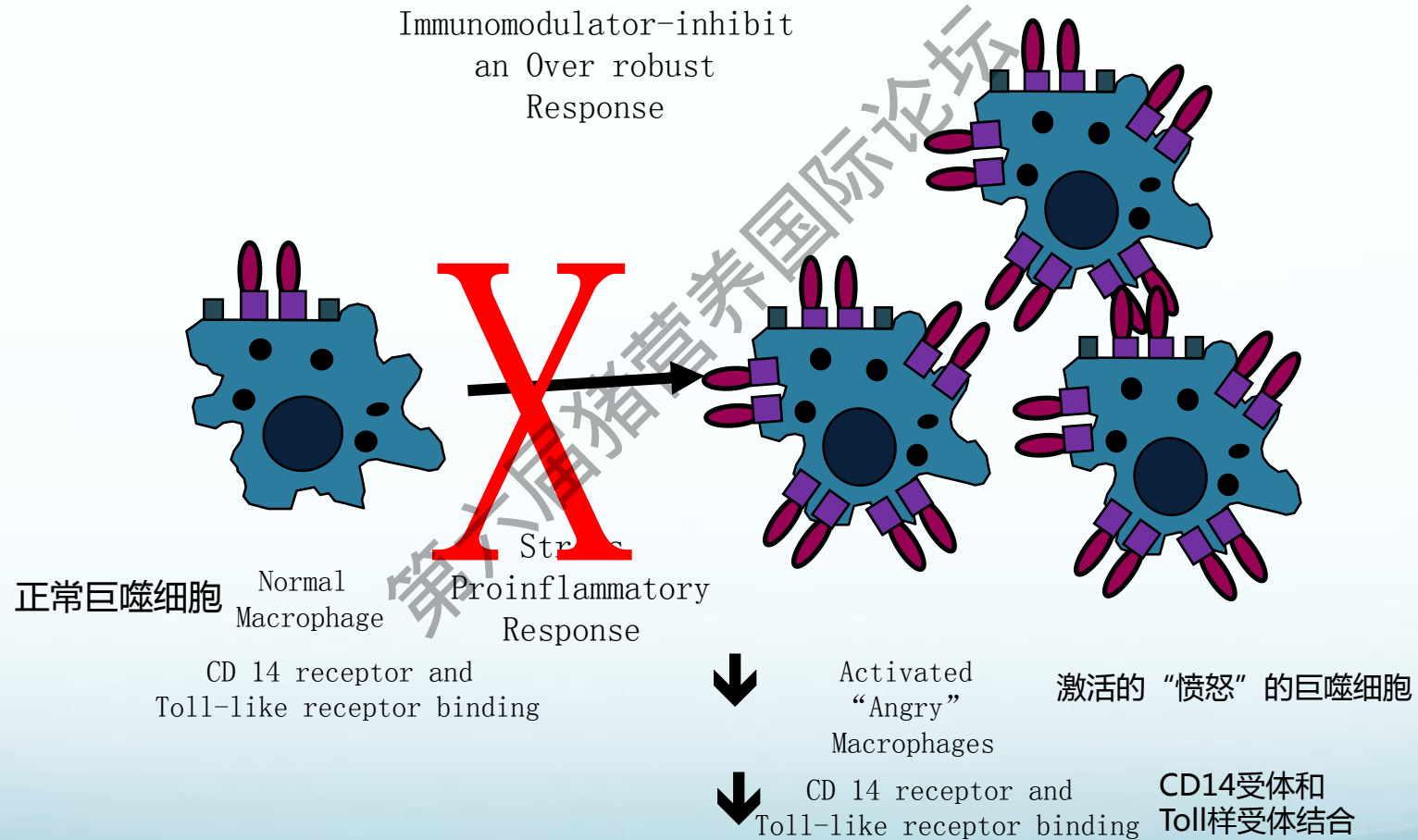
Annu. Rev. Pathol. Mech. Dis. 5:119-44

巨噬细胞-维持体内平衡

Macrophages- Maintains Homeostasis

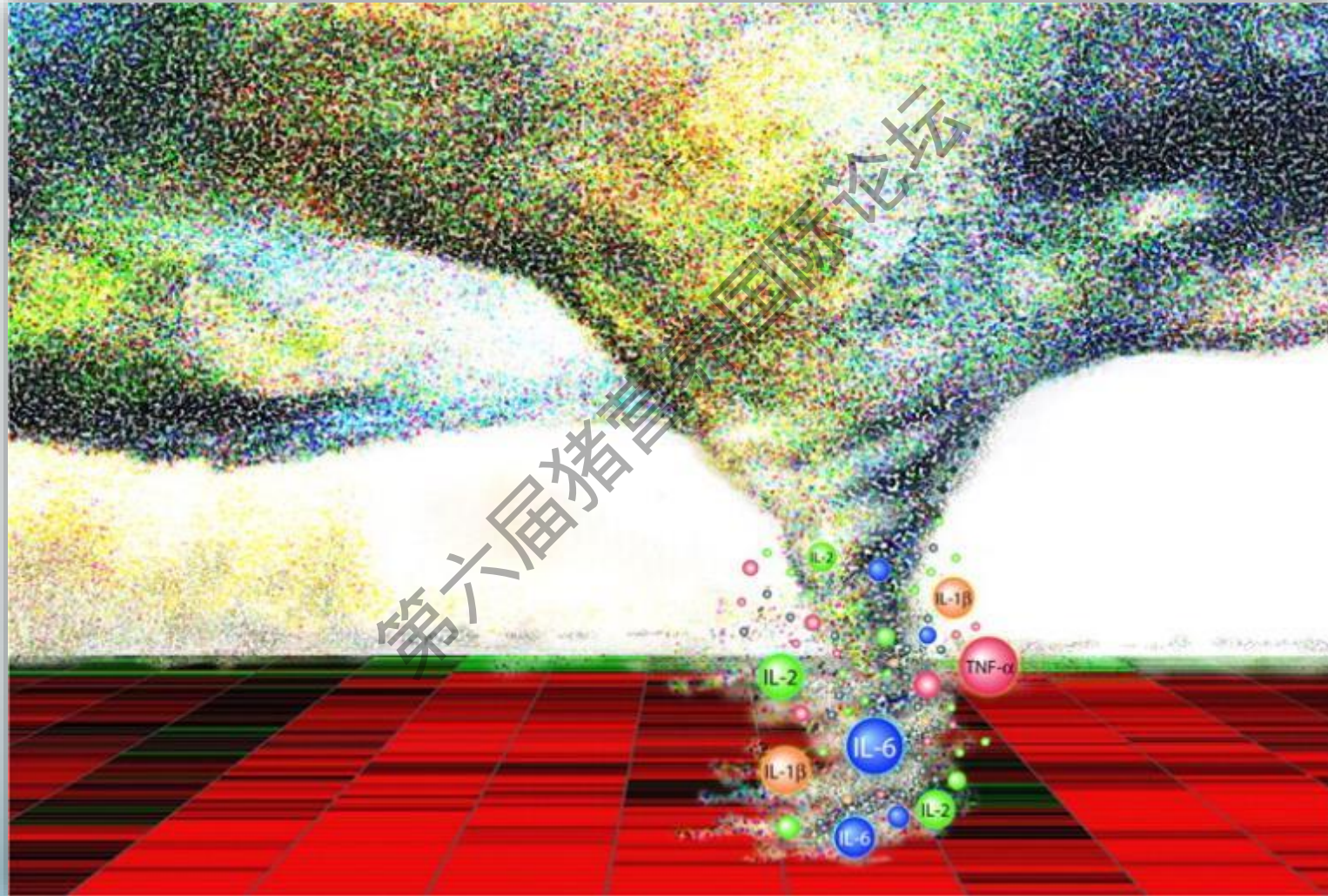
免疫调节——阻止过度免疫反应

Immunomodulator-inhibit
an Over robust
Response



细胞因子风暴

Cytokine Storm



Tisoncik J R et al. Microbiol. Mol. Biol. Rev. 2012;76:16-32

细胞因子风暴

Cytokine Storm

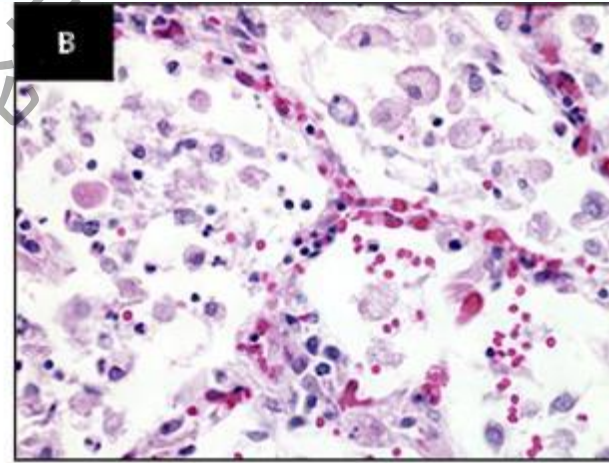
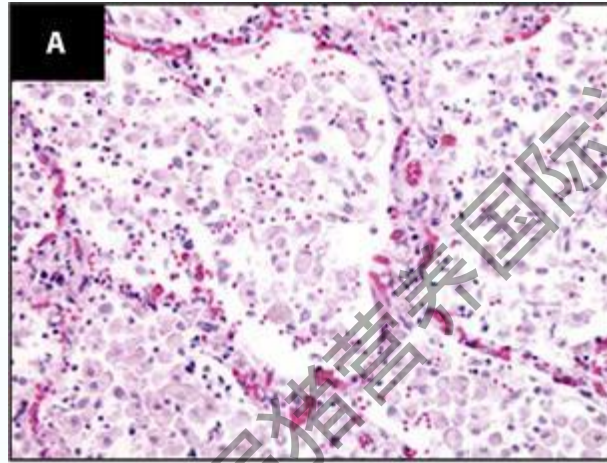
- 高温 High Temps- 104°-106°F
- 呼吸系统疾病 Respiratory Disease-
 - 急性肺损伤 Acute Lung Injury
 - 急性呼吸系统综合征 Acute Respiratory Disease Syndrome
- Is BRSV??? 是牛呼吸道合胞病毒吗？
- Is Vaccination or Aspirin the Answer? 解决办法是疫苗还是阿司匹林？



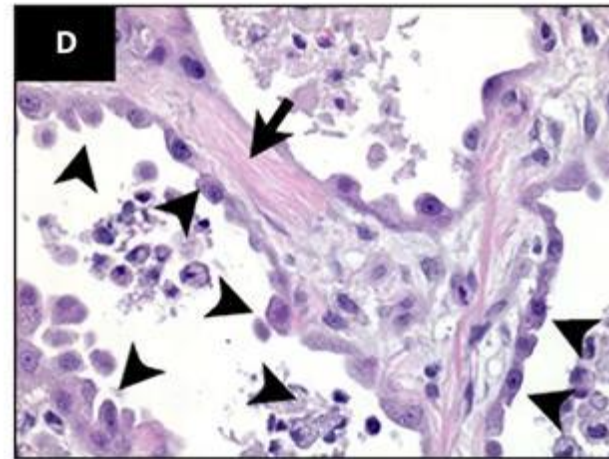
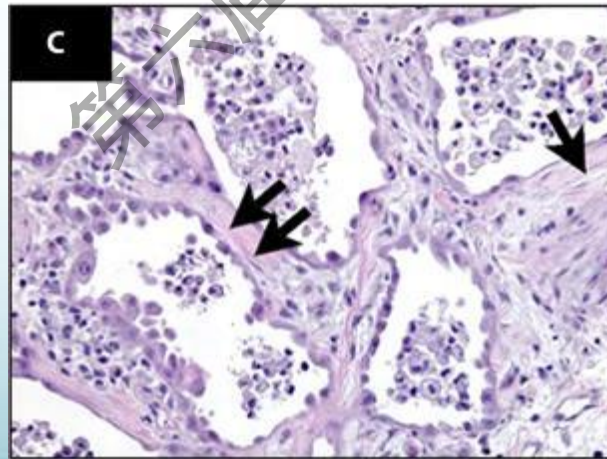
急性呼吸系统综合征

Acute Respiratory Disease Syndrome

Acute
急性

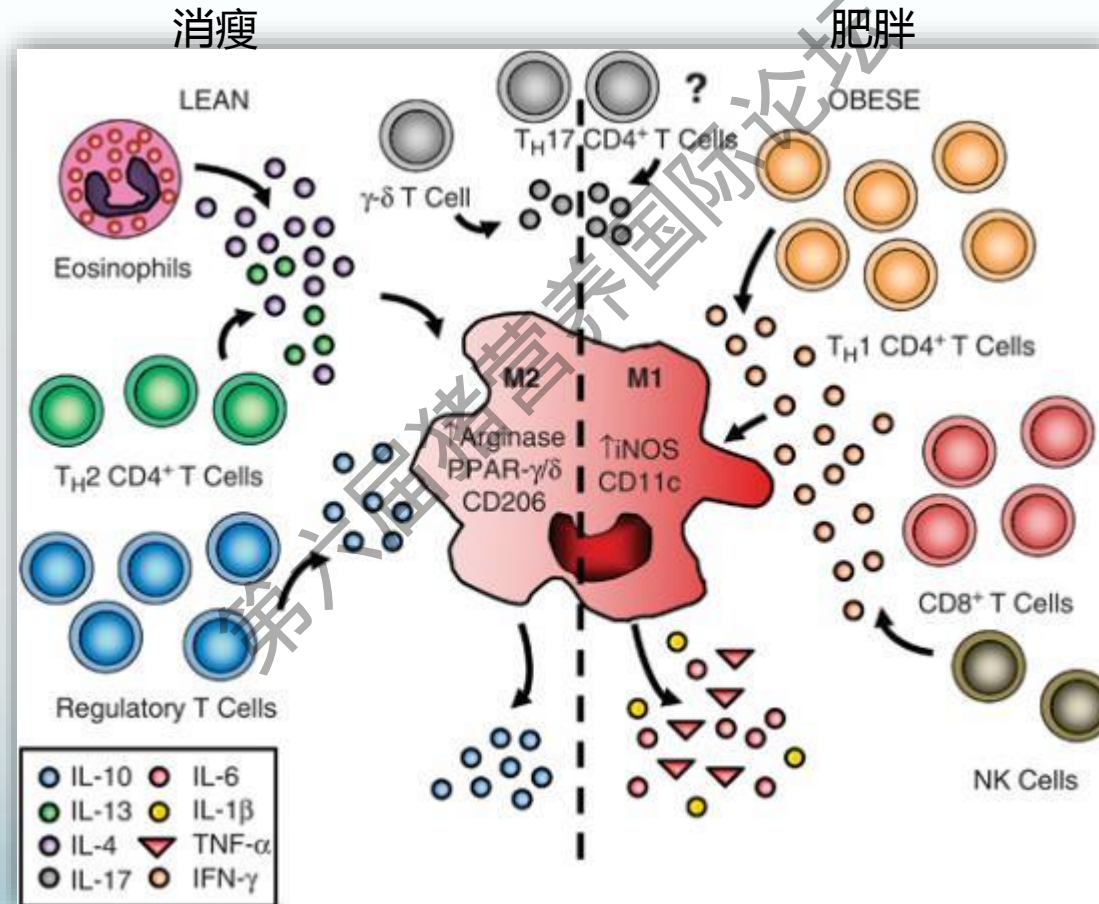


Chronic
慢性



炎症和机体状况

Inflammation And Body Condition

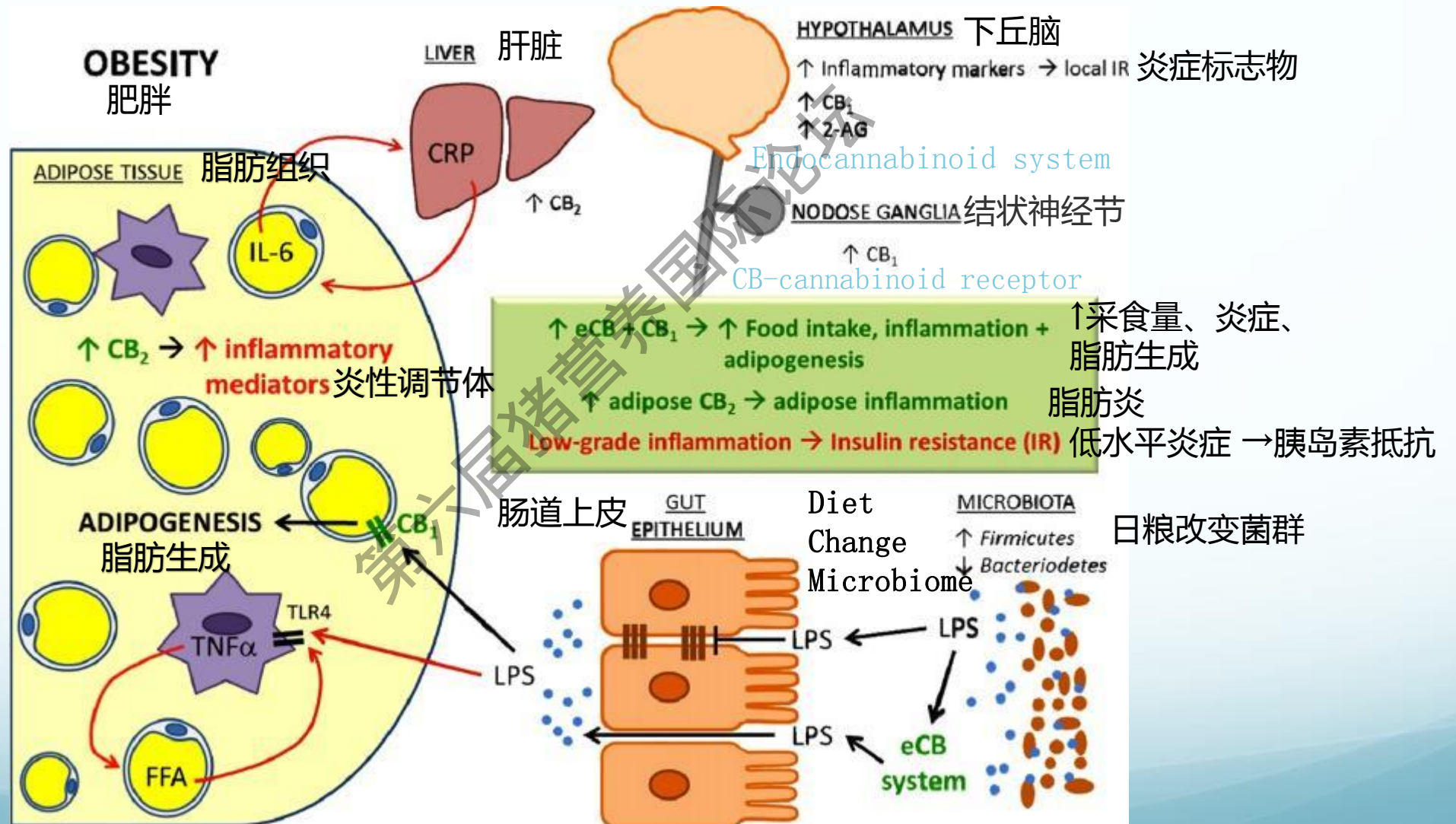


Winer and Winer, Immunology and Cell Biology (2012), 1 - 8

脑-肠-微生物轴 Brain-Gut-Microbiota axis

炎症和肥胖——过肥的断奶仔猪、育肥猪、围产期母猪

Inflammation and Obesity-Overconditioned Weaned pIgs, Finishing Hogs, Sows Pre- & Post-farrowing-



Cluny, N.L., et al. Cannabinoid signaling regulates inflammation and energy balance: The importance of the brain-gut axis. Brain Behav. Immun. (2012), doi:10.1016/j.bbi.2012.01.004

炎症与肥胖

Inflammation and Obesity

- 基因——影响生产性能和胴体品质、健康

Genetics-Negative Impact of Production and Carcass Traits on Health

- 炎症表型——巨噬细胞

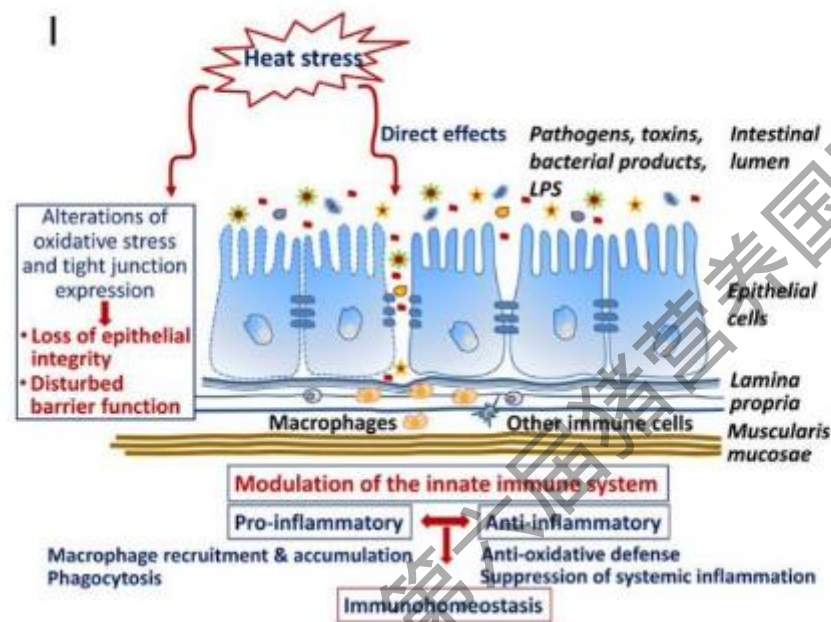
Inflammatory phenotype- Macrophages

- 肺动脉高压与慢性心力衰竭

Pulmonary Hypertension and Chronic Heart Failure

热应激的其它危害

Additive Effect of Heat Stress



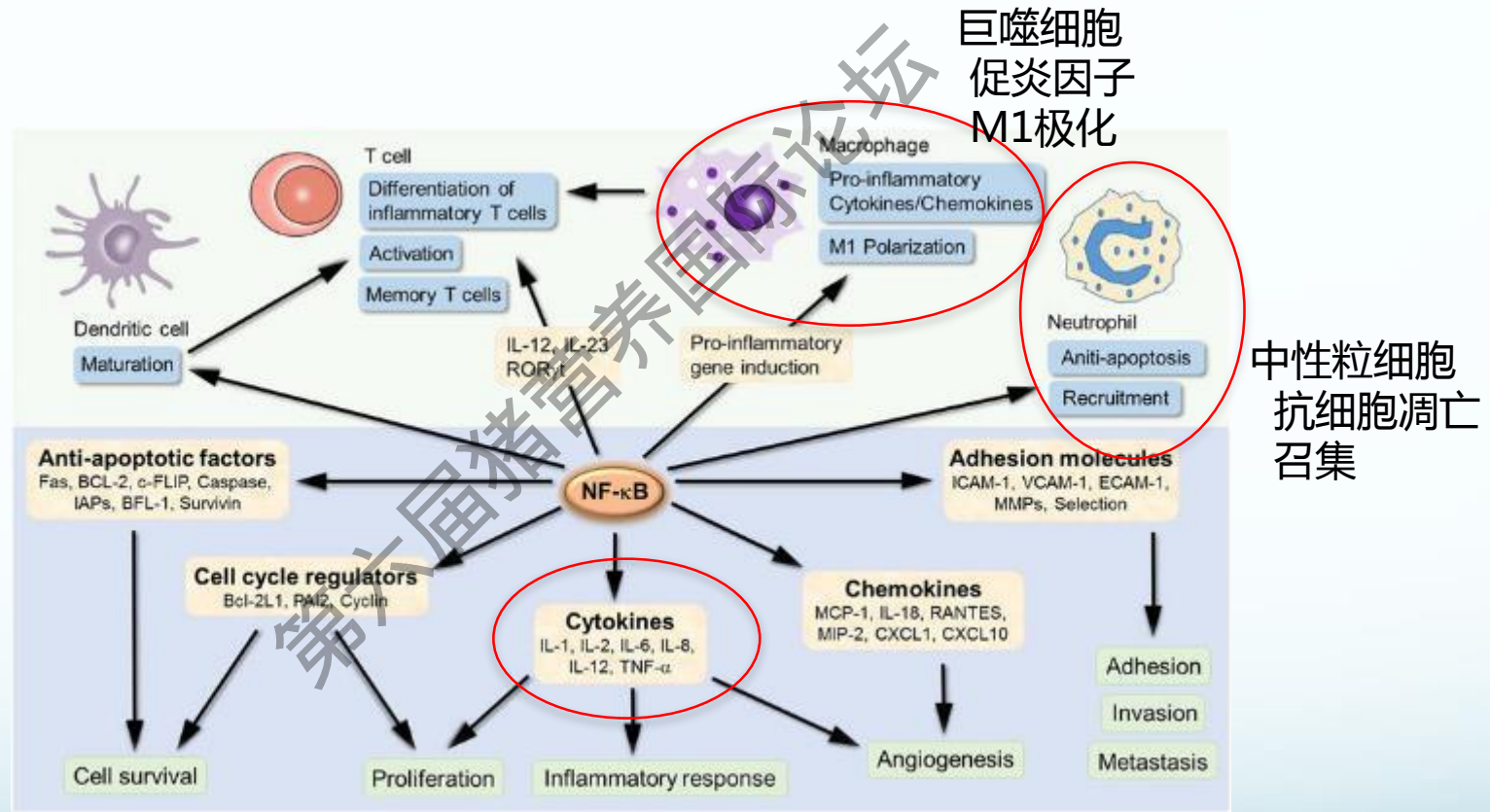
肠漏症的细胞学、分子学机理

The cellular and molecular underpinnings of leaky gut

Heat stress directly impairs gut integrity and recruits distinct immune cell populations into the bovine intestine
Franziska Koch, Ulrike Thom, Elke Albrecht, Rosemarie Weikard, Wietje Nolte, Björn Kuhla, Christa Kuehn
Proceedings of the National Academy of Sciences May 2019, 116 (21) 10333-10338; DOI: 10.1073/pnas.1820130116

激活NF-kB旁路

Activation of NF- κ B Pathway



细胞因子

炎症及其对生产指标的影响

Inflammation and Effect on Production Parameters

- Increase Sickness Behavior-listlessness
- Decrease feed intake- Inappetence-
- Increase body temperature sweats
- Decreased feed conversion
- Decrease gain
- Decrease milk production
- Increased Mastitis
- Increased Metritis
- Increased PRD
- 增加疾病行为-无精打采
- 减少采食量-食欲不振
- 增加体温出汗
- 饲料转化率降低
- 降低增重
- 减少牛奶产量
- 乳腺炎增加
- 增加子宫炎
- PRD增加

炎症和疾病-维持稳态

Inflammation and Disease-Maintain Homeostasis-Steady State



小结 – 炎症平衡行动

Summary-Inflammation Balancing Act

- Just enough to prevent/control disease 足以预防/控制疾病
- Too much of a good thing- immune pathology 免疫过度——免疫病理学
- Too little response- pathogen wins 免疫反应太少——病原获胜
- Immune response is not always a good thing 免疫反应并不总是一件好事
- Maintain homeostasis 维持稳态



健康肠道是必须的-益生菌和益生元怎么样？

A Healthy Gut is a Necessity-What About Probiotic and Prebiotics?

- 细菌培养物、酵母、细胞壁产品、蛋IgY对肠道健康有益

Bacterial cultures, Yeast, cell wall products, Egg IgY are good for gut health

- 问题：如何评估

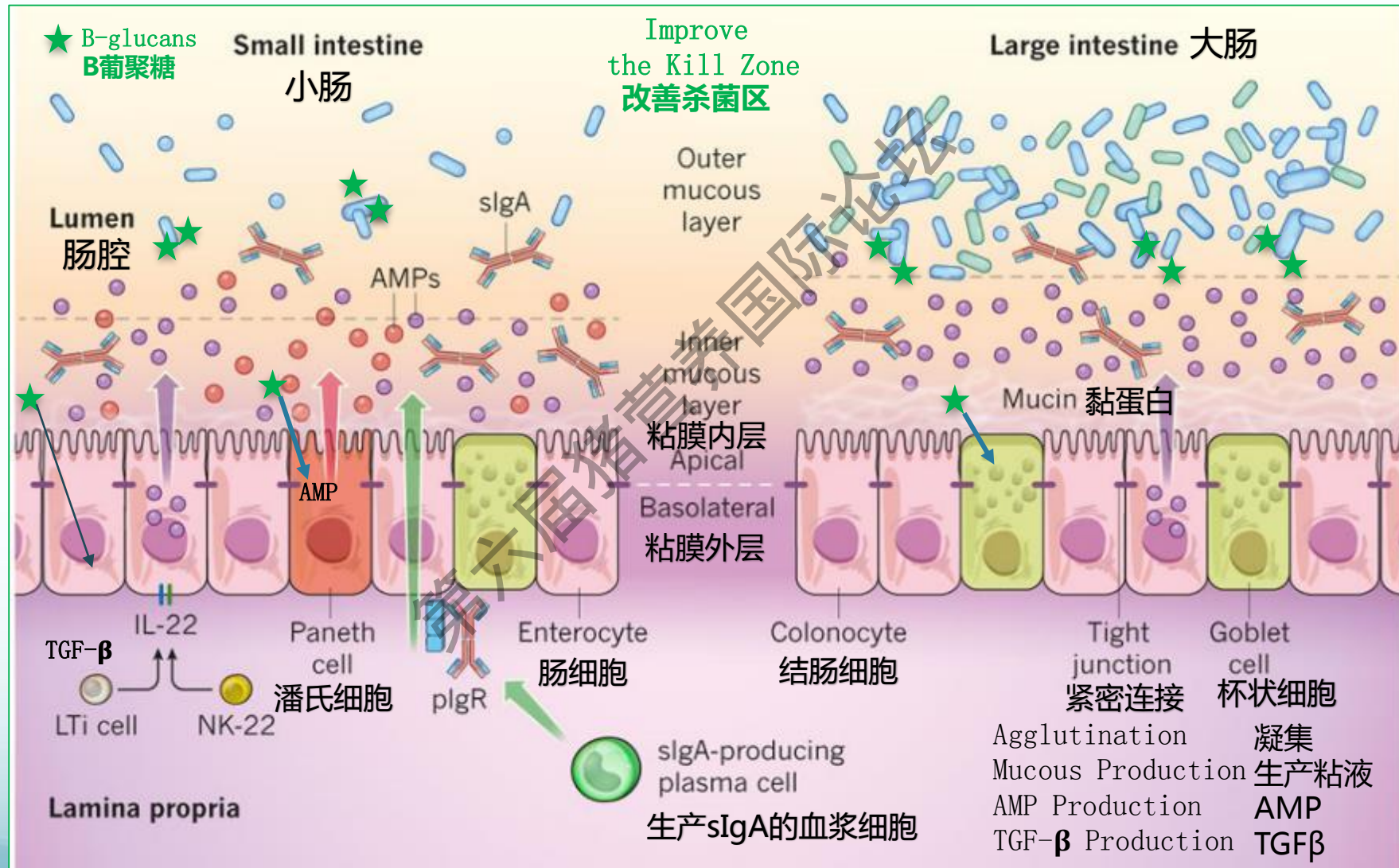
Problem: how do we measure it

- 需要一直使用吗？不是-应激的时候

Do we need them all the time? No- times of stress

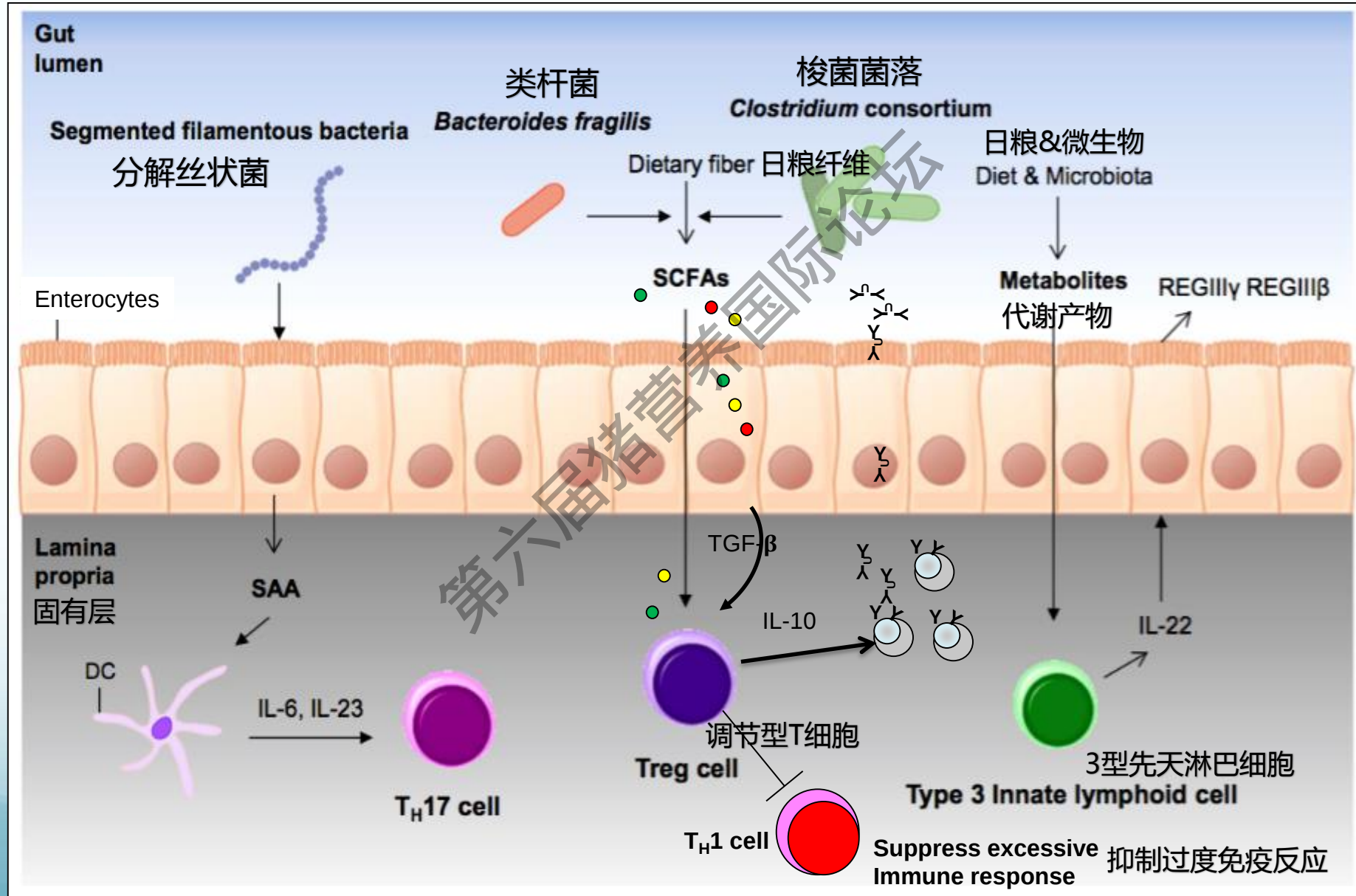


抵抗机制 Defense Mechanisms

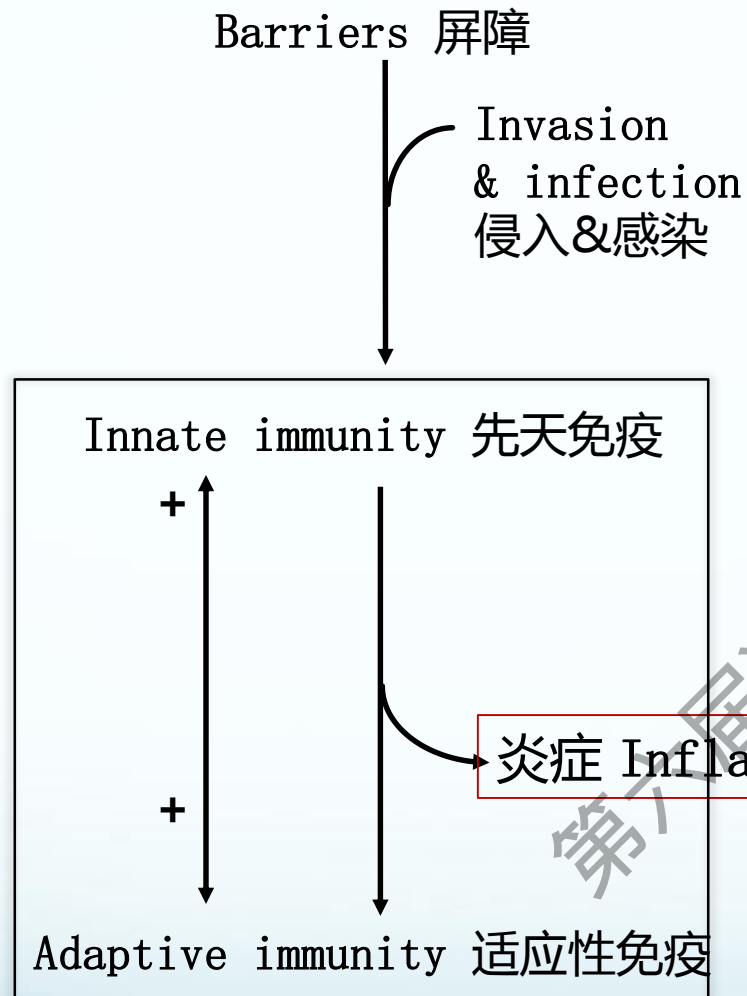


益生菌和益生元 – 作用机理？

Probiotic and Prebiotics–Modes of Action?



两个目标 Two Targets



1st Line of Defense 第一道防线

Barriers 屏障

mucous, tears, gastric pH, saliva, skin, AMP 粘膜、眼泪、胃ph、唾液、皮肤、AMP

Strength 加强

2nd Line of Defense 第二道防线

Cellular and humoral defenses

细胞体液免疫

interferon, cytokines (pro-inflammatory and T stimulatory), complement proteins, phagocytosis, NK cells

干扰素、细胞因子(促炎因子、T激活因子)、补体蛋白、吞噬、NK细胞

Minimize

3rd Line of Defense 第三道防线

Cellular and humoral defenses 细胞体液免疫

Antibodies, cytokines, T helper cells,

cytotoxic T cells 抗体、细胞因子、辅助T细胞
细胞毒性T细胞

总结

Summary

- Homeostasis 稳态
- Mucosa and Immunity 粘膜和免疫
- Microbiome- Happy? 微生物-快乐?
- Leaky Gut 肠漏症
- Cytokine Storm 细胞因子风暴
- Role of Probiotics and Prebiotics 益生菌和益生元作用



关键点

Take Aways

- 需要管理微生物菌落，不被扰乱 – 日粮、干燥、摄入

Microbiome needs to be managed and not upset– diet, dehydration, intakes

- 益生元和益生菌 – 它们在何处适应体内平衡？

Pre- and Probiotics– where do they fit in with homeostasis?





Harvey Dunn (1884-1952) *Prairie is My Garden*,
South Dakota Art Museum

哈维·杜恩(1884-1952)，大草原是我的花园
南达科他州艺术博物馆

主办：美国动物科学学会 | 中国畜牧业协会

承办：上海亘泰实业集团有限公司 | 中国畜牧业协会生物产业分会 | 中畜传媒

协办：美国大豆出口协会 | 上海优久生物科技有限公司 | 上海征泰生物科技集团有限公司

THE END