WCJD 世界华人消化杂志®

在线投稿: http://www.baishideng.com/wcjd/ch/index.aspx
帮助平台: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.11569/wcjd.v24.i15.2361

世界华人消化杂志 2016年5月28日; 24(15): 2361-2367
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

肥胖–肠道菌群–Toll样受体交互调控作用的研究进展

司原成, 苗维纳, 何嘉悦, 王晓芳, 汪弋力, 丁维俊

司原成, 苗维纳, 何嘉悦, 王晓芳, 汪弋力, 丁维俊, 成都中医药大学基础医学院 四川省成都市 610072

司原成, 主要从事中医防治代谢性疾病的基础及应用方面的研究.

基金项目: 国家自然科学基金资助项目, No. 81273899.

作者贡献分布: 本文由司原成、苗维纳、何嘉悦、王晓芳及汪弋力共同完成; 丁维俊审校.

通讯作者: 丁维俊, 教授, 610072, 四川省成都市十二桥路37号, 成都中医药大学基础医学院. dingwj123@163.com
电话: 028-61800158

收稿日期: 2016-02-14
修回日期: 2016-04-04
接受日期: 2016-04-11
在线出版日期: 2016-05-28

Intricate interactions of obesity, intestinal flora and Toll-like receptors

Yuan-Cheng Si, Wei-Na Miao, Jia-Yue He, Xiao-Fang Wang, Yi-Li Wang, Wei-Jun Ding

Yuan-Cheng Si, Wei-Na Miao, Jia-Yue He, Xiao-Fang Wang, Yi-Li Wang, Wei-Jun Ding, College of Basic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu 610072, Sichuan Province, China

Supported by: National Natural Science Foundation of China, No. 81273899.

Correspondence to: Wei-Jun Ding, Professor, College of Basic Medicine, Chengdu University of Traditional Chinese Medicine, 37 Shierqiao Road, Chengdu 610072, Sichuan Province, China. dingwj123@163.com

Received: 2016-02-14
Revised: 2016-04-04
Accepted: 2016-04-11
Published online: 2016-05-28

Abstract

The rapidly increasing incidence of obesity has resulted in a severe public problem globally. Obesity is associated with subclinical inflammation, causing elevated levels of inflammatory cytokines, as well as disorders of the immune function, which are involved in the dysfunction of intestinal flora. Intestinal flora maintains a dynamic equilibrium with intestinal mucosal immunity. Obesity-related inflammation is mainly trigged by endoplasmic reticulum stress, Toll-like receptor 4 (TLR4) activation and changes of gut flora. Among them, TLR4 plays a central role in sensing intestinal pathogens and inducing mucosal immunity. On the other hand, metabolism, genetics, gut flora and immune state are integrally regulating the TLR function. In the present paper we explore the intricate interactions of obesity, intestinal flora and TLRs, in order to find novel targets for the treatment of obesity.

Key Words: Obesity; Intestinal flora; Mucosal immunity; Subclinical inflammation; Toll-like receptors

Si YC, Miao WN, He JY, Wang XF, Wang YL, Ding WJ. Intricate interactions of obesity, intestinal flora and Toll-like receptors. Shijie Huaren Xiaohua Zazhi 2016; 24(15): 2361-2367 URL: http://www.wjgnet.com/1009-3079/full/v24/i15/2361.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i15.2361

摘要

肥胖发病率逐年上升, 已经成为全球性公共

背景资料
肥胖-肠道菌群-Toll样受体(Toll-like receptors, TLRs)三者之间存在紧密的生理病理联系. 肥胖引起肠道菌群结构与功能紊乱, 肠黏膜免疫异常; 肠道菌群、肠道免疫异常又反过来促进肥胖进程.

同行评议者
吴军, 研究员, 军事医学科学院生物工程研究所; 杜潇, 副教授, 四川大学华西医院胃肠外科; 王道荣, 主任医师, 江苏省苏北人民医院胃肠外科

研发前沿
以往研究肥胖多关注于脂质代谢方面, 缺乏肥胖-肠道菌群-免疫功能交互作用的整合性研究. 本文基于TLRs探究三者之间的关系, 有助于更完整揭示肥胖发生发展的整体性病理机制.

健康问题. 肥胖的发生常伴有亚临床炎症表现, 引起炎症水平升高与免疫功能紊乱, 而这又与肠道菌群紊乱密切相关. 肠道菌群与肠黏膜免疫构成动态平衡, 其结构及功能异常均可引起机体免疫紊乱. 肥胖性炎症反应的启动途径, 涉及Toll样受体(Toll-like receptors, TLRs)活化、内质网应激与肠道菌群改变. 其中, TLR4在感应肠道病原菌、诱导炎症与胰岛素抵抗进程中, 扮演中心角色. 另一方面, 代谢、遗传与免疫等因素, 整合性调控TLR功能. 因此, 我们从肥胖-肠道菌群-TLRs的复杂交互作用着手, 阐释肠道菌群、肠道免疫与肥胖等代谢性疾病的高度相关性, 以期发现这类疾病的新治疗靶点.

关键词: 肥胖; 肠道菌群; 肠黏膜免疫; 亚临床炎症反应; Toll样受体

核心提示: 肥胖是全球性公共卫生难题, 其形成和进展与肠道菌群紊乱, 以Toll样受体为代表的肠道黏膜免疫异常直接相关. 三者交互作用机制的研究, 可望深化肥胖病理认识, 提高肥胖疗效.

司原成, 苗维纳, 何嘉悦, 王晓芳, 汪弋力, 丁维俊. 肥胖-肠道菌群-Toll样受体交互调控作用的研究进展. 世界华人消化杂志 2016; 24(15): 2361-2367 URL: http://www.wjgnet.com/1009-3079/full/v24/i15/2361.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i15.2361

0 引言

肥胖发病率逐年上升, 已经成为全球性的公共健康问题[1]. 众多因素参与肥胖发展进程, 如能量代谢失衡、棕色脂肪减少、长期低水平炎症刺激等[2]. 近年研究[3]发现, 肠道菌群与机体的消化、免疫、能量代谢等紧密联系. 在免疫功能紊乱或者降低时, 病原微生物大量繁殖, 引起肥胖、糖尿病等多种疾病. 近期研究发现,肠道菌群与机体免疫功能异常, 同肥胖发生发展高度相关,但其具体作用机制与关键环节仍不十分清楚[4-6]. 因此, 本文综述相关研究进展, 以期阐释肠道菌群、肠道免疫与肥胖等代谢性疾病的高度相关性, 发现这类疾病的新治疗靶点.

1 肠道微生物与肥胖进程密切相关

人体肠道中寄生着大量的微生物, 种类超过10000种, 总量达10^{14}数量级, 是肠道微生态平衡的重要组成部分[7,8]. 肠道菌群与宿主具有复杂的交互作用关系. 在物质代谢方面, 机体供给肠道微生物生长所需养分, 而肠道微生物则合成维生素K等机体不能合成的营养物质, 并帮助机体消化纤维素[9]. 在免疫方面, 部分肠道细菌保持肠黏膜的完整性, 激活宿主免疫系统, 阻止有害病原体通过黏膜进入体内[10]. 但是, 肠道菌群也含有部分有害菌, 可以产生内毒素等物质, 引起炎症反应、糖尿病、肥胖及部分癌症.

肠道菌群在肥胖发生发展中起到重要作用. Harley等[11]发现肥胖患者肠道厚壁菌门/拟杆菌属的比值与患者肥胖程度呈正相关. 肠道菌群能够通过慢性炎症状态影响肥胖[12]. Zarrinpar等[13]发现饮食和进食方式的改变, 可引起肥胖患者肠道菌群的结构改变, 造成壁厚菌门和变形菌门水平升高, 拟杆菌门降低. 肠道菌群通过其代谢产物来调节脑-肠-菌轴, 促进肥胖进程. 短链脂肪酸中的丁酸和丙酸通过互补机制积极参与糖代谢. 丁酸通过增加肠上皮细胞cAMP的含量直接增加糖质新生基因的表达; 丙酸作为FFAR3激动剂, 通过脑-肠-菌轴诱导糖新生, 促进食物的吸收和糖代谢[14]. 超重者肠道丙酸呈显著性升高[15-18]. Poutahidis等[19]给予肥胖鼠口服PL60不仅可以降低肥胖鼠的腹部脂肪含量, 还能显著改变$CD4^+$ T细胞和白介素-10(interleukin 10, IL-10)依赖的免疫细胞功能. Walker等[20]也发现, 拟杆菌门具有明显的抑制脂肪细胞增长的作用. Ridaura等[21]通过大范围筛选出体质量差异明显的双胞胎, 将肥胖患者的肠道菌群植入到无菌小鼠体内, 发现小鼠的体质量相对植入不肥胖的正常组小鼠显著增加. 因此, 以肠道菌群为治疗肥胖靶点, 可望为减肥新药的研发提供新的思路.

2 肥胖常伴发亚临床炎症反应

炎症是机体对有害刺激做出的应激性反应, 以维持机体稳态. 肥胖患者存在明显慢性亚临床炎症反应[5,6], 其不仅涉及诸多经典炎症途径[22], 同时亦有其特殊性[23]. 肥胖性炎症源于过剩的营养物质堆积而引起的慢性炎症, 涉及长期能量代谢紊乱引起的固有免疫功能异常. 当体质量下降后, 脂肪细胞功能趋于正常, 慢性代谢炎症得以缓解甚至消除[24]. 肥胖进程中肿瘤坏死因子-α(tumor necrosis factor α,

TNF-α)、IL-1β、CCK等炎症细胞因子起到主要作用[25]. 巨噬细胞、肥大细胞及自然杀伤细胞(natural killer cell, NK)细胞等免疫细胞, 亦明显增加, 进而加重炎症反应[26].

脂肪组织是肥胖性炎症启动和产生的重要场所, 其分泌的炎性细胞因子可直接引发胰岛素抵抗. 如Guilherme等[27]发现肥胖患者TNF-α水平升高, 伴有胰岛素分泌和糖摄取降低. Solinas等[28]揭示, JNK、IKK、PKR等炎症反应之上游信号分子, 在炎症过程中起主要作用. Lu等[29]进一步阐明, 引起肥胖促进炎症因子释放的炎症激酶, 通过调节AP-1、核因子-κB(nuclear factor-κB, NF-κB)、IRF等炎症反应的下游信号通路, 维持慢性炎症反应. 此外, 在肥胖亚临床炎症中促炎症因子IL-6异常增高, 抑炎症信号过氧化物酶体增殖物激活受体-γ(peroxisome proliferator-activated receptor γ, PPAR-γ)活性显著下调, 亦有助于维持慢性炎症反应[30,31].

3 Toll样受体在调节肠道菌群引起的炎症反应中起重要作用

肥胖脂肪组织的慢性低水平的炎症, 是长期双向刺激产生的恶性循环. 这一刺激过程与肠道病原微生物密切相关. 健康状态下, 肠道菌群的各种细菌数量、结构达到一个相互制约、相互协同的平衡状态. 一旦菌群紊乱, 益生菌减少而病原菌相对增加, 肠道菌群产生的致炎因子增多, 遂引起机体低水平的炎症反应. 其中, Toll样受体(Toll-like receptors, TLRs)家族在调节肠道菌群引起的炎症反应中起重要作用.

TLRs是模式识别受体家族中的一种重要受体, 能够激活NF-κB、丝裂原活化蛋白激酶等炎症相关信号通路, 在肠道菌群介导的炎症反应中起着重要的桥梁作用[4]. TLRs最早发现在果蝇体内, 随后在无脊椎动物、脊椎动物及植物中陆续被发现. 不同物种的TLRs具有高度同源性, 均承担识别致病菌和启动防御机制等功能[32]. TLRs广泛存在于细胞膜、细胞质及细胞核内, 参与机体各种免疫应答过程, 尤其在诱导、促进炎症方面作用突出[33]. 在树突状细胞、B细胞、T细胞中发现大量TLRs, 在识别有害物质、启动免疫应答过程中起到关键作用[34]. 除开免疫细胞, TLRs还分布在成纤维细胞及黏膜上皮细胞[35], 参与慢性炎症等病理过程. TLR2主要检测细菌肽聚糖、脂多糖及磷壁酸的含量变化[36,37], 通过NF-κB通路诱导炎症反应[38]. TLR1、TLR6与TLR2是同源异构体, 均能识别LPS及脂肽[39]. TLR2与TLR6均能与支原体二酰基脂蛋白结合, 产生生物学效应[40]. TLR4是革兰阴性细菌脂多糖的重要结合配体[41], 其在肥胖鼠肠黏膜上皮细胞中呈现过度表达状态; 激活的TLR4可诱导多种促炎症细胞因子的产生, 引起并维持肥胖型低水平炎症[42]. 细菌鞭毛蛋白可激活TLR5信号通路, 产生炎症效应[43]. TLR3、TLR7、TLR8、TLR9存在于细胞质中, 参与病原体核酸等识别. 其中, TLR3识别肠道病原微生物中存在的大量病毒, 这些病毒在肥胖形成、发展进程中, 起到促进作用[44].

4 肥胖-肠道菌群-TLRs三者间的交互作用关系

4.1 肥胖对肠黏膜免疫功能造成多层次病理损伤

肠黏膜是人体最大的免疫器官, 监管着10^{14}数量级的肠道微生物[45-48]. 其包含的各种免疫细胞以及分泌的多种免疫因子协同作用, 构成对正常菌群与致病菌的精确辨别能力. 但是, 该能力容易受到饮食、肥胖等因素干扰. 免疫细胞同神经元一样, 均属于高能耗细胞, 对机体脂代谢及葡萄糖浓度极为敏感. 因此, 肥胖或其他代谢性疾病, 理论上都可引起免疫学功能改变[45-48]. 大量研究发现, 肥胖对肠道黏膜免疫系统、免疫细胞、免疫分子与免疫相关基因表达, 构成多层次的干扰. 如Mantovani等[46]发现, 肥胖鼠肝脏脂肪样变性源于肥胖诱导的淋巴细胞高反应性, 而减肥可以逆转该病理过程. 肥胖患者脂肪细胞所分泌的超量Leptin, 作为神经-内分泌-免疫系统之间的重要连接者, 通过多个信号轴调控免疫与炎症反应[47,48]. 肥胖患者脂肪细胞合成的大量炎症细胞因子, 导致炎症、自身免疫病及其他肥胖继发症的发病率增加[49].

4.2 肠道菌群失调在肥胖及肠黏膜免疫功能紊乱中扮演重要角色

肠道正常菌群参与机体代谢、营养、免疫等功能, 对维持黏膜免疫功能、肠壁稳定性与营养吸收等十分重要[49]. 例如, 脆弱类杆菌等益生菌, 合成两性离子多糖(zwitterionic polysaccharides, ZPS)、多糖A(polysaccharides A, PSA)等免疫调节多糖, 指导免疫系统发育[47]. 但是, 肥胖等代谢性疾病使患者肠道益生菌明显减少, 肠黏膜免疫功能发育与维持受到明显影响. 肠道菌群可直接影

相关报道

目前, 关于肥胖的研究还局限在某种方法干预下肠道菌群相关细菌种属升高或者降低, 进而推断该种属与肥胖的形成有关系, 如Zarrinpar等研究饮食及喂养方式对肠道菌群的动态变化的影响.

创新盘点

本文归纳和总结了近5年来研究肥胖的最新进展, 阐述肥胖-肠道菌群-TLRs之间的相互关系, 揭示TLRs在三者之间的桥梁作用, 为进一步深入探究肥胖成因, 寻找治疗肥胖的最佳治疗方法, 提供新的思路和研究平台.

响机体胆固醇、脂蛋白与胆盐代谢[45], 调整机体免疫防御功能与炎症水平. 肥胖患者胃肠道功能失调、高脂食物、胆盐代谢异常等, 均是肠道菌群失调的重要病因. Burcelin等[50]提出, 失调的肠道菌群产生炎性细胞因子、毒素等, 导致内毒素血症, 诱导肠黏膜上皮细胞免疫基因表达亢进, 进而引起慢性炎症、胰岛素抵抗与肥胖. 实际上, 失调的肠道菌群影响黏膜免疫功能, 黏膜免疫功能紊乱又通过改变肠道微环境加重肠道菌群失调, 从而构成恶性循环, 造成肥胖患者肠道黏膜免疫功能进一步紊乱. 基于其与肥胖、糖尿病等代谢性疾病高度相关, 肠道菌群与肠道免疫可望成为这类疾病新的治疗靶点[51].

4.3 TLRs是肠道黏膜免疫系统识别与清除病原菌的关键性整合分子 TLRs等固有免疫系统的病原菌感应分子, 是肠黏膜屏障、肠道菌群、免疫系统之间的交互作用界面[52-55]. 主要由肠道病原菌激活的TLRs通路, 与多种类型感染及炎症反应相关[52]. 另一方面, 肠道糖脂代谢环境、机体及肠道菌群遗传调控模式、宿主免疫状态等因素, 整合性调控TLR功能[52-55]. 因此, TLRs处于肥胖、肠道菌群失调与肠黏膜免疫的交互调控界面, 其基本功能包括: (1)识别不同病原成分: TLRs是识别肠道病原菌的主要受体, 是调控肠黏膜免疫的关键分子. 不同TLR识别不同的病原模体, 如TLR2识别革兰阳性细菌, TLR3识别双链RNA病毒, TLR5识细菌鞭毛, TLR8识别单链RNA病毒. 不同肠黏膜细胞的TLR谱, 实际上是其功能谱的基本体现[53-55]; (2)协调肠道免疫功能: TLRs是肠道微生物与肠壁黏膜免疫细胞之间的重要信使, 通过诱生抗菌肽、促进黏膜上皮细胞增殖等途径, 稳定肠黏膜免疫功能. TLRs广泛分布在多种肠壁细胞, 对维持肠道免疫功能稳定至关重要[55]; (3)维持肠黏膜结构完整: 如TLR2促进紧密连接蛋白产生, 维持肠黏膜完整. TLR4通过诱生IL-10调控多种肠道炎症反应, 维持肠黏膜免疫功能可塑性[54]; (4)促进免疫细胞成熟与抗体类别转换: IgA2对细菌合成消化酶的耐受性较强. He等[56]发现, TLRs感应肠道病原菌后, 诱导IgM抗体转换为IgA2抗体类型; (5)TLR具有重要诊断学意义: 在炎症性肠炎、肥胖等病理状况下, TLR的异常表达是重要的致病因子, 同时也具有重要的诊断学意义[4,57,58]; (6)TLR与肥胖性炎症反应直接相关: 肥胖导致肠道菌群改变, 降低肠壁完整性, 使得细菌脂多糖与脂肪酸渗漏入血增加, 激活TLR4与系统性炎症应答. 同时, 脂肪酸也通过启动内质网应急而激活TLR4. 因此, TLR4等与肥胖性炎症反应直接相关, 居于肥胖-肠道菌群-TLRs三者间的关键调控节点.

5 结论

肥胖的发生发展, 与肠道菌群及其以TLRs为代表的肠道黏膜免疫直接相关. 肥胖-肠道菌群-TLRs三者间的复杂交互作用机制, 正逐渐被揭示. 肥胖是引起肠道菌群失调与肠道黏膜免疫紊乱的重要因素, 肠道菌群与肠黏膜免疫构成动态平衡, 持续地受到肥胖等代谢性疾病的冲击, 进而出现恶性循环. TLRs作为肠道固有免疫反应中最主要的病原菌感受分子, 居于肥胖-肠道菌群-肠道黏膜免疫之间的关键调控节点. 因此, 通过肥胖-肠道菌群-TLRs的复杂交互作用研究, 可望阐释肠道菌群、肠道免疫与肥胖等代谢性疾病的高度相关性, 进而发现肥胖等代谢性疾病的新型治疗靶点.

6 参考文献

1 Speakman JR. Evolutionary perspectives on the obesity epidemic: adaptive, maladaptive, and neutral viewpoints. *Annu Rev Nutr* 2013; 33: 289-317 [PMID: 23862645 DOI: 10.1146/annurev-nutr-071811-150711]

2 Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, Jobin C, Lund PK. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* 2010; 5: e12191 [PMID: 20808947 DOI: 10.1371/journal.pone.0012191]

3 Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. *Int J Mol Sci* 2015; 16: 7493-7519 [PMID: 25849657 DOI: 10.3390/ijms16047493]

4 Velloso LA, Folli F, Saad MJ. TLR4 at the Crossroads of Nutrients, Gut Microbiota, and Metabolic Inflammation. *Endocr Rev* 2015; 36: 245-271 [PMID: 25811237 DOI: 10.1210/er.2014-1100]

5 闫美玲, 夏丽莎. 代谢炎症与肥胖相关研究进展. 中国动脉硬化杂志 2015; 23: 634-638

6 Okun E, Barak B, Saada-Madar R, Rothman SM, Griffioen KJ, Roberts N, Castro K, Mughal MR, Pita MA, Stranahan AM, Arumugam TV, Mattson MP. Evidence for a developmental role for TLR4 in learning and memory. *PLoS One* 2012; 7: e47522 [PMID: 23071817 DOI: 10.1371/journal.pone.0047522]

7 Kamada N, Núñez G. Regulation of the immune system by the resident intestinal bacteria. *Gastroenterology* 2014; 146: 1477-1488 [PMID: 24503128

DOI: 10.1053/j.gastro.2014.01.060]
8 Gerritsen J, Smidt H, Rijkers GT, de Vos WM. Intestinal microbiota in human health and disease: the impact of probiotics. *Genes Nutr* 2011; 6: 209-240 [PMID: 21617937 DOI: 10.1007/s12263-011-0229-7]
9 Maier E, Anderson RC, Roy NC. Understanding how commensal obligate anaerobic bacteria regulate immune functions in the large intestine. *Nutrients* 2015; 7: 45-73 [PMID: 25545102 DOI: 10.3390/nu7010045]
10 Ulluwishewa D, Anderson RC, McNabb WC, Moughan PJ, Wells JM, Roy NC. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr* 2011; 141: 769-776 [PMID: 21430248 DOI: 10.3945/jn.110.135657]
11 Harley IT, Karp CL. Obesity and the gut microbiome: Striving for causality. *Mol Metab* 2012; 1: 21-31 [PMID: 24024115 DOI: 10.1016/j.molmet.2012.07.002]
12 Cluny NL, Reimer RA, Sharkey KA. Cannabinoid signalling regulates inflammation and energy balance: the importance of the brain-gut axis. *Brain Behav Immun* 2012; 26: 691-698 [PMID: 22269477 DOI: 10.1016/j.bbi.2012.01.004]
13 Zarrinpar A, Chaix A, Yooseph S, Panda S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab* 2014; 20: 1006-1017 [PMID: 25470548 DOI: 10.1016/j.cmet.2014.11.008]
14 Moran CP, Shanahan F. Gut microbiota and obesity: role in aetiology and potential therapeutic target. *Best Pract Res Clin Gastroenterol* 2014; 28: 585-597 [PMID: 25194177 DOI: 10.1016/j.bpg.2014.07.005]
15 齐可民. 肠道菌群与肥胖发生. 中国儿童保健杂志 2015; 23: 337-339
16 Lin HV, Frassetto A, Kowalik EJ, Nawrocki AR, Lu MM, Kosinski JR, Hubert JA, Szeto D, Yao X, Forrest G, Marsh DJ. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLoS One* 2012; 7: e35240 [PMID: 22506074 DOI: 10.1371/journal.pone.0035240]
17 Gorissen L, Raes K, Weckx S, Dannenberger D, Leroy F, De Vuyst L, De Smet S. Production of conjugated linoleic acid and conjugated linolenic acid isomers by Bifidobacterium species. *Appl Microbiol Biotechnol* 2010; 87: 2257-2266 [PMID: 20556602 DOI: 10.1007/s00253-010-2713-1]
18 Million M, Maraninchi M, Henry M, Armougom F, Richet H, Carrieri P, Valero R, Raccah D, Vialettes B, Raoult D. Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii. *Int J Obes* (Lond) 2012; 36: 817-825 [PMID: 21829158 DOI: 10.1038/ijo.2011.153]
19 Poutahidis T, Kleinewietfeld M, Smillie C, Levkovich T, Perrotta A, Bhela S, Varian BJ, Ibrahim YM, Lakritz JR, Kearney SM, Chatzigiagkos A, Hafler DA, Alm EJ, Erdman SE. Microbial reprogramming inhibits Western diet-associated obesity. *PLoS One* 2013; 8: e68596 [PMID: 23874682 DOI: 10.1371/journal.pone.0068596]
20 Walker AW, Parkhill J. Microbiology. Fighting obesity with bacteria. *Science* 2013; 341: 1069-1070 [PMID: 24009379 DOI: 10.1126/science.1243787]
21 Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; 341: 1241214 [PMID: 24009397 DOI: 10.1126/science.1241214]
22 Spencer M, Yao-Borengasser A, Unal R, Rasouli N, Gurley CM, Zhu B, Peterson CA, Kern PA. Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation. *Am J Physiol Endocrinol Metab* 2010; 299: E1016-E1027 [PMID: 20841504 DOI: 10.1152/ajpendo.00329.2010]
23 Butler AA, Kozak LP. A recurring problem with the analysis of energy expenditure in genetic models expressing lean and obese phenotypes. *Diabetes* 2010; 59: 323-329 [PMID: 20103710 DOI: 10.2337/db09-1471]
24 卓鈵, 乐颖影. Toll样受体与代谢及代谢相关疾病. 生命科学 2013; 25: 158-168
25 秦会平, 王学红. 小肠菌群与肠道及代谢性疾病. 世界华人消化杂志 2016; 24: 375-381
26 Ilich JZ, Kelly OJ, Kim Y, Spicer MT. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. *Arh Hig Rada Toksikol* 2014; 65: 139-148 [PMID: 24945416 DOI: 10.2478/10004-1254-65-2014-2541]
27 Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; 9: 367-377 [PMID: 18401346 DOI: 10.1038/nrm2391]
28 Solinas G, Karin M. JNK1 and IKKbeta: molecular links between obesity and metabolic dysfunction. *FASEB J* 2010; 24: 2596-2611 [PMID: 20371626 DOI: 10.1096/fj.09-151340]
29 Lu JC, Chang YT, Wang CT, Lin YC, Lin CK, Wu ZS. Trichostatin A modulates thiazolidinedione-mediated suppression of tumor necrosis factor α-induced lipolysis in 3T3-L1 adipocytes. *PLoS One* 2013; 8: e71517 [PMID: 23951179 DOI: 10.1371//journal.pone.0071517]
30 Floyd ZE, Gawronska-Kozak B, Tam CS, Gimble JM. Mechanisms of metabolism, aging and obesity. *Biochimie* 2016; 124: 1-2 [PMID: 26995405 DOI: 10.1016/j.biochi.2016.03.005]
31 Basu S, Haghiac M, Surace P, Challier JC, Guerre-Millo M, Singh K, Waters T, Minium J, Presley L, Catalano PM, Hauguel-de Mouzon S. Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. *Obesity* (Silver Spring) 2011; 19: 476-482 [PMID: 20930711 DOI: 10.1038/oby.2010.215]
32 Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 2010; 11: 373-384 [PMID: 20404851 DOI: 10.1038/ni.1863]

应用要点

本文对肥胖-肠道菌群-TLRs三者关系做了深入的探讨，对进一步研究肥胖的治疗有重要意义，为搭建新的肥胖研究平台，新的治疗肥胖药物靶点的探究意义非凡，在接下来的肥胖研究中，这三者的关系不容忽视.

名词解释

TLRs: Toll样受体, 位于细胞膜表面或者细胞核内, 是进化中比较保守的一个受体家族, 至少包括10个成员, 能特异地识别病原相关的分子模式, 承担识别致病菌和启动防御机制的功能.

33 Lorenz G, Anders HJ. Neutrophils, Dendritic Cells, Toll-Like Receptors, and Interferon-α in Lupus Nephritis. *Semin Nephrol* 2015; 35: 410-426 [PMID: 26573544 DOI: 10.1016/j.semnephrol.2015.08.003]

34 Jang JH, Shin HW, Lee JM, Lee HW, Kim EC, Park SH. An Overview of Pathogen Recognition Receptors for Innate Immunity in Dental Pulp. *Mediators Inflamm* 2015; 2015: 794143 [PMID: 26576076 DOI: 10.1155/2015/794143]

35 Kabelitz D, Wesch D, Oberg HH. Regulation of regulatory T cells: role of dendritic cells and toll-like receptors. *Crit Rev Immunol* 2006; 26: 291-306 [PMID: 17073555 DOI: 10.1615/CritRevImmunol.v26.i4.10]

36 Husebye H, Doyle SL. Using Confocal Microscopy to Investigate Intracellular Trafficking of Toll-Like Receptors. *Methods Mol Biol* 2016; 1390: 65-77 [PMID: 26803622 DOI: 10.1007/978-1-4939-3335-8_4]

37 Keller JF, Carrouel F, Colomb E, Durand SH, Baudouin C, Msika P, Bleicher F, Vincent C, Staquet MJ, Farges JC. Toll-like receptor 2 activation by lipoteichoic acid induces differential production of pro-inflammatory cytokines in human odontoblasts, dental pulp fibroblasts and immature dendritic cells. *Immunobiology* 2010; 215: 53-59 [PMID: 19250704 DOI: 10.1016/j.imbio.2009.01.009]

38 Baik JE, Ryu YH, Han JY, Im J, Kum KY, Yun CH, Lee K, Han SH. Lipoteichoic acid partially contributes to the inflammatory responses to Enterococcus faecalis. *J Endod* 2008; 34: 975-982 [PMID: 18634930 DOI: 10.1016/j.joen.2008.05.005]

39 da Silva RA, Ferreira PD, De Rossi A, Nelson-Filho P, Silva LA. Toll-like receptor 2 knockout mice showed increased periapical lesion size and osteoclast number. *J Endod* 2012; 38: 803-813 [PMID: 22595116 DOI: 10.1016/j.joen.2012.03.017]

40 Woodman S, Gibson AJ, García AR, Contreras GS, Rossen JW, Werling D, Offord V. Structural characterisation of Toll-like receptor 1 (TLR1) and Toll-like receptor 6 (TLR6) in elephant and harbor seals. *Vet Immunol Immunopathol* 2016; 169: 10-14 [PMID: 26827833 DOI: 10.1016/j.vetimm.2015.11.006]

41 Patra S, Muthuraman MS, Meenu M, Priya P, Pemaiah B. Anti-inflammatory effects of royal poinciana through inhibition of toll-like receptor 4 signaling pathway. *Int Immunopharmacol* 2016; 34: 199-211 [PMID: 26971223 DOI: 10.1016/j.intimp.2016.02.027]

42 Zhang W, Hartmann R, Tun HM, Elson CO, Khafipour E, Garvey WT. Deletion of the Toll-Like Receptor 5 Gene Per Se Does Not Determine the Gut Microbiome Profile That Induces Metabolic Syndrome: Environment Trumps Genotype. *PLoS One* 2016; 11: e0150943 [PMID: 26950299 DOI: 10.1371/journal.pone.0150943]

43 Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011; 121: 2111-2117 [PMID: 21633179 DOI: 10.1172/JCI57132]

44 Maimaitiyiming H, Norman H, Zhou Q, Wang S. CD47 deficiency protects mice from diet-induced obesity and improves whole body glucose tolerance and insulin sensitivity. *Sci Rep* 2015; 5: 8846 [PMID: 25747123 DOI: 10.1038/srep08846]

45 Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; 444: 1027-1031 [PMID: 17183312 DOI: 10.1038/nature05414]

46 Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol* 2011; 11: 519-531 [PMID: 21785456 DOI: 10.1038/nri3024]

47 Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; 57: 1470-1481 [PMID: 18305141]

48 Lago R, Gómez R, Lago F, Gómez-Reino J, Gualillo O. Leptin beyond body weight regulation--current concepts concerning its role in immune function and inflammation. *Cell Immunol* 2008; 252: 139-145 [PMID: 18289518 DOI: 10.1016/j.cellimm.2007.09.004]

49 Halmos T, Suba I. [Physiological patterns of intestinal microbiota. The role of dysbacteriosis in obesity, insulin resistance, diabetes and metabolic syndrome]. *Orv Hetil* 2016; 157: 13-22 [PMID: 26708682 DOI: 10.1556/650.2015.30296]

50 Burcelin R, Luche E, Serino M, Amar J. The gut microbiota ecology: a new opportunity for the treatment of metabolic diseases? *Front Biosci* (Landmark Ed) 2009; 14: 5107-5117 [PMID: 19482607 DOI: 10.2741/3589]

51 Yamashita T, Kasahara K, Emoto T, Matsumoto T, Mizoguchi T, Kitano N, Sasaki N, Hirata K. Intestinal Immunity and Gut Microbiota as Therapeutic Targets for Preventing Atherosclerotic Cardiovascular Diseases. *Circ J* 2015; 79: 1882-1890 [PMID: 26212124 DOI: 10.1253/circj.CJ-15-0526]

52 Frosali S, Pagliari D, Gambassi G, Landolfi R, Pandolfi F, Cianci R. How the Intricate Interaction among Toll-Like Receptors, Microbiota, and Intestinal Immunity Can Influence Gastrointestinal Pathology. *J Immunol Res* 2015; 2015: 489821 [PMID: 26090491 DOI: 10.1155/2015/489821]

53 Corr SC, Gahan CC, Hill C. M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. *FEMS Immunol Med Microbiol* 2008; 52: 2-12 [PMID: 18081850 DOI: 10.1111/j.1574-695X.2007.00359.x]

54 Lundin A, Bok CM, Aronsson L, Björkholm B, Gustafsson JA, Pott S, Arulampalam V, Hibberd M, Rafter J, Pettersson S. Gut flora, Toll-like receptors and nuclear receptors: a tripartite communication that tunes innate immunity in large intestine. *Cell Microbiol* 2008; 10: 1093-1103 [PMID: 18088401 DOI: 10.1111/j.1462-5822.2007.01108.x]

55 Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is

required for intestinal homeostasis. *Cell* 2004; 118: 229-241 [PMID: 15260992 DOI: 10.1016/j.cell.2004.07.002]

56 He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, Shan M, Chadburn A, Villanacci V, Plebani A, Knowles DM, Rescigno M, Cerutti A. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. *Immunity* 2007; 26: 812-826 [PMID: 17570691 DOI: 10.1016/j.immuni.2007.04.014]

57 Fukata M, Abreu MT. TLR4 signalling in the intestine in health and disease. *Biochem Soc Trans* 2007; 35: 1473-1478 [PMID: 18031248 DOI: 10.1042/BST0351473]

58 Rosenstiel P, Derer S, Till A, Häsler R, Eberstein H, Bewig B, Nikolaus S, Nebel A, Schreiber S. Systematic expression profiling of innate immune genes defines a complex pattern of immunosenescence in peripheral and intestinal leukocytes. *Genes Immun* 2008; 9: 103-114 [PMID: 18216864 DOI: 10.1038/sj.gene.6364454]

同行评价

TLRs是介导肠道菌群与肥胖之间的关键信号蛋白, 本文将三者进行综述分析, 揭示肥胖形成的内在机制, 为肥胖症的深入研究有重要意义, 为肥胖的治疗搭建新的平台有着指导意义.

编辑: 于明茜 电编: 都珍珍

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

•消息•

《世界华人消化杂志》参考文献要求

本刊讯 本刊采用“顺序编码制”的著录方法, 即以文中出现顺序用阿拉伯数字编号排序. 提倡对国内同行近年已发表的相关研究论文给予充分的反映, 并在文内引用处右上角加方括号注明角码. 文中如列作者姓名, 则需在“Pang等”的右上角注角码号; 若正文中仅引用某文献中的论述, 则在该论述的句末右上角注码号. 如马连生[1]报告……, 研究[2-5]认为……; PCR方法敏感性高[6,7]. 文献序号作正文叙述时, 用与正文同号的数字并排, 如本实验方法见文献[8]. 所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准, 通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献, 包括世界华人消化杂志(http://www.wjgnet.com/1009-3079/index.jsp)和*World Journal of Gastroenterology*(http://www.wjgnet.com/1007-9327/index.jsp). 期刊: 序号, 作者(列出全体作者). 文题, 刊名, 年, 卷, 起页-止页, PMID编号 ; 书籍: 序号, 作者(列出全部), 书名, 卷次, 版次, 出版地, 出版社, 年, 起页-止页.

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton,
CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1009-3079