

Notch-mTOR信号介导的免疫反应与能量代谢轴: 中医药预防IBD复发的可能关键

刘端勇, 赵海梅

刘端勇, 赵海梅, 江西中医药大学生命科学院方剂教研室
江西省南昌市 330004

赵海梅, 副教授, 主要从事溃疡性结肠炎与中药免疫药理方面的研究.

基金项目: 国家自然科学基金资助项目, Nos. 81460679, 81260595; 2014年度国家留学基金委地方合作基金资助项目, Nos. 201408360106, 201408360110.

作者贡献分布: 刘端勇与赵海梅共同完成本文.

通讯作者: 赵海梅, 副教授, 330004, 江西省南昌市兴湾大道818号, 江西中医药大学生命科学院方剂教研室.
haimei79@163.com
电话: 0791-79118923

收稿日期: 2016-02-11
修回日期: 2016-02-27
接受日期: 2016-03-08
在线出版日期: 2016-06-18

Axis of immune response and energy metabolism mediated by Notch/mTOR signaling pathway: Pivotal mechanism of traditional Chinese medicine for preventing inflammatory bowel disease

Duan-Yong Liu, Hai-Mei Zhao

Duan-Yong Liu, Hai-Mei Zhao, Department of Prescription, School of Life Sciences, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, Jiangxi Province, China

Supported by: National Natural Science Foundation of China, Nos. 81460679 and 81260595; Fund for Visiting Scholars of Chinese Scholarship Council and Jiangxi Province, Nos. 201408360106 and 201408360110.

Correspondence to: Hai-Mei Zhao, Associate Professor,

Department of Prescription, School of Life Sciences, Jiangxi University of Traditional Chinese Medicine, 818 Xingwan Road, Nanchang 330004, Jiangxi Province, China. haimei79@163.com

Received: 2016-02-11
Revised: 2016-02-27
Accepted: 2016-03-08
Published online: 2016-06-18

Abstract

Inflammatory bowel disease (IBD) is a kind of worldwide refractory disease with a high recurrence rate. However, traditional Chinese medicine for IBD is associated with a better therapeutic effect and a lower recurrence rate, although the mechanism is still unclear. It is known that the Notch signaling pathway interacts with mTOR and regulates the body's immune level and cell energy, which is closely related with morbidity of IBD. These hint that axis of immune response and energy metabolism mediated by the Notch/mTOR signaling pathway is possibly a pivotal mechanism for traditional Chinese medicine to prevent IBD.

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Key Words: Notch; Mammalian target of rapamycin; Inflammatory bowel disease; Immune; Energy metabolism; Traditional Chinese medicine

Liu DY, Zhao HM. Axis of immune response and energy metabolism mediated by Notch/mTOR signaling pathway: Pivotal mechanism of traditional Chinese medicine for preventing inflammatory bowel disease. *Shijie Huaren Xiaohua Zazhi* 2016; 24(17): 2617-2624 URL: <http://www.wjgnet.com/1009-3079/full/v24/i17/2617.htm> DOI: <http://dx.doi.org/10.11569/wcjd.v24.i17.2617>

■背景资料

炎症性肠病 (inflammatory bowel disease, IBD) 是世界性难治疾病, 现代医学多采用氨基水杨酸类、糖皮质激素类、免疫抑制剂类等治疗, 存在复发率较高的困境, 中医药治疗效果好, 复发率低但发病机制不明.

■同行评议者

范一宏, 主任医师, 浙江省中医院消化科

■ 研究前沿

Notch-mTOR信号对免疫细胞的生存、发育、发展、成熟、分化、转输、功能及能量代谢的调节是该领域亟待研究的问题。

摘要

炎症性肠病(inflammatory bowel disease, IBD)是世界性难治性疾病, 其难治在于高复发率。中医药治疗IBD疗效高且复发率低, 但作用机制不明, 然Notch与mTOR信号间相互关联, 且通过各种途径调控机体免疫水平和细胞能量代谢变化, 并与IBD的发作密切相关, 提示调控Notch-mTOR信号介导免疫与能量轴变化可能是探索中医药预防和防止IBD复发的可能突破口和有效策略。

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

关键词: Notch; 哺乳动物雷帕霉素靶蛋白; 炎症性肠病; 免疫; 能量代谢; 中医药

核心提示: 炎症性肠病(inflammatory bowel disease, IBD)是慢性非特异性结肠炎症, 高复发率是其难治点之一, 中医药治疗疗效较高且复发率低, 但机制不明。Notch/mTOR信号关乎与IBD发病密切相关的免疫水平和能量代谢, 表明Notch-mTOR信号是探索中医药预防IBD复发的可能突破点和机会。

刘端勇, 赵海梅. Notch-mTOR信号介导的免疫反应与能量代谢轴: 中医药预防IBD复发的可能关键. 世界华人消化杂志 2016; 24(17): 2617-2624 URL: <http://www.wjgnet.com/1009-3079/full/v24/i17/2617.htm> DOI: <http://dx.doi.org/10.11569/wjcd.v24.i17.2617>

0 引言

炎症性肠病(inflammatory bowel disease, IBD)为世界性难治病之一, 包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD), 临床多表现为腹泻、黏液脓血便、腹痛、呈反复发作的慢性病程。治疗过程中溃疡愈合并不难, 难于在溃疡愈合之后, 极易复发, 因此高复发率是现代医学治疗UC的主要困境之一, 而传统中医学通过辨证论治不仅明显提高疗效, 而且复发率明显降低, 但其预防机制不明。

1 IBD治疗的难点与中医药优势

随着分子生物学和免疫学的研究进展, IBD的治疗方法不断更新, 其内科治疗药物主要有氨基水杨酸类、糖皮质激素类、免疫抑制剂类、抗菌药物类、微生态制剂、生物免疫制剂等等。作为IBD治疗的经典药物氨基水杨酸

类药物如柳氮磺吡啶、美沙拉嗪、4-氨基水杨酸等都是轻中度IBD和重症患者使用激素后缓解期的首选药物, 疗效也相对较好, 但据不完全统计IBD患者首次缓解后1-5年内仍然有30.6%-85.0%的复发率^[1]。也有研究表明, 即使联合给药同样存在较高的复发率, 如奥替溴安联合美沙拉嗪缓释片给药半年内复发率为34.4%^[2,3], 甚至包括生物免疫制剂也不例外^[4]。尽管治疗UC药物种类繁多, 总有效率较高, 但其复发率随着时间的推移不断提高、并且与剂量成反比, 使得现代医学治疗陷入了困境, 可谓举步维艰。而中医药则不同, 同等情况下比较发现, 复发率明显下降。如陆琳琳等^[5]采用多中心随机对照方法观察204例活动期UC患者, 经规范治疗后155例进入缓解期, 给予中医序贯疗法或美沙拉嗪维持治疗, 发现单纯中药治疗组半年内复发率为8.1%, 而美沙拉嗪对照组则高达23.3%; 同时付东亮^[6]用通过辨证论治采用中药内服联合灌肠治疗UC187例, 其复发率仅为10.6%, 明显低于柳氮磺吡啶治疗术20.4%的复发率, 且干丽红^[7]通过辨证论治采用中医序贯法治疗UC患者80例, 其复发率仅为5%, 同等采用柳氮磺吡啶治疗的复发率高达37.5%, 而齐相芬等^[8]采用自拟愈溃方治疗UC患者发现其复发率仅为10.0%明显低于美沙拉嗪治疗时的复发率28.6%, 从而提示中医药治疗UC可明显降低其复发率。

2 IBD发病的免疫学与能量代谢之间的关系

结肠上皮结构被破坏是IBD的共同病理特征之一。细胞间连接是结肠上皮屏障结构的重要组成部分, 上皮细胞的完整和充盈, 以及细胞间连接都是由actin细胞骨架支撑^[9], 而actin网络则由足够的ATP支持保持张力^[10,11]。ATP的耗竭将引起actin细胞骨架的萎缩、断裂、减少, 进而导致细胞萎缩或细胞间连接破坏, 最终导致细胞间隙加大, 结肠黏膜上皮间通透性增加, 细菌和抗原等致炎因素进入黏膜下层, 诱导炎症损伤^[12,13]。作为ATP的生产车间, 线粒体异常和ATP合成酶5B、抑制素PHB、磷酸冰糖异构酶等相关蛋白低表达, 都可导致ATP合成下降, 能量水平下降、actin解聚、紧密连接断裂、结肠上皮细胞凋亡加速, 进而破坏结肠上皮的完整性, 这一机制提示改善线粒体

功能, 补充能量成为治疗IBD的重要思路, 且Dashdorj等^[14]通过补充能量或使用线粒体靶向抗氧化剂, 保护或降低线粒体消耗, 提高ATP水平, 并明显抑制结肠黏膜损伤所证明^[15,16]。

同样, 能量代谢与机体免疫功能状态密切相关。ATP是最重要的代谢产物之一, 也是一种重要的信号分子, 一般情况下是在胞内由线粒体合成, 具有参与包括免疫细胞在内所有细胞的生存、黏附、增殖、分化及迁移等功能。而由细胞凋亡释放的ATP可诱导树突状细胞细胞表面的CD40、CD80、CD83及CD86分子表达上调, 从而促进树突状细胞的成熟^[17], 且不同浓度的胞外ATP可双向调节CD4⁺ T细胞和Treg细胞的功能, 浓度为250 nmol/L时刺激细胞增殖、细胞因子释放和黏附分子表达, 从而增强免疫效应, 但浓度在1 mmol/L时则诱导细胞凋亡并抑制CD4⁺ T细胞的活性, 也可显著活化Treg细胞, 从而产生免疫抑制作用^[18]。由此可见, ATP生成、释放和调控免疫系统形成一个复杂网络, 胞内的ATP有助于维持正常免疫细胞的功能, 胞外的ATP则可多角度兴奋或抑制免疫状态。

免疫因素在IBD发病过程扮演了重要角色, 虽纷繁复杂, 却也已为世人所公认^[19,20]。引起IBD发病的免疫学机制异常复杂, 但概而言之, 多为免疫系统内环境平衡被打破, 比如几种相互制约的免疫细胞水平或细胞因子水平平衡被打破, 或某些免疫细胞过度增殖或水平低下, 或某些致炎因素过度兴奋或抑炎因素过度抑制, 产生异常免疫反应, 免疫复合物在外周或局部聚集, 诱导炎症反应发生, 从而诱发黏膜损伤。常见有Th1/Th2细胞水平^[21,22]、Treg/Th17细胞^[23,24]、或DC^[25,26]、或自然杀伤细胞^[27]、或巨噬细胞^[28]等, 也有上皮细胞^[29]、M细胞^[30]等。无论凋亡或坏死细胞释放出的ATP, 还是线粒体合成ATP的途径及其作用是当前癌症和癌前疾病的免疫学治疗和研究的热点^[31]。而干预ATP水平和信号表达在IBD发病和治疗中的作用研究相对较少。

3 Notch-mTOR信号介导对免疫学与能量代谢轴之间的调控

3.1 Notch-mTOR通路 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR), 是一种丝氨酸-苏氨酸蛋白激酶, 属于磷脂酰肌

醇激酶相关激酶(PIKK)家族, 包括mTOR复合体1(mTOR complex 1, mTORC1)和mTORC2, 现代研究^[32,33]表明, 其不仅是细胞生长和营养的调节中心, 也是细胞能量感受调节分子。其通过感知能量状态, 调控下游信号通路, 影响能量水平, 从而调节细胞新陈代谢及细胞周期, 或促进代谢相关基因表达, 重组细胞骨架等, 进而调节细胞形态、生长、运动和功能发挥^[34]。

Notch基因是1917年Morgan等从果蝇体内发现, Notch信号广泛参与细胞增殖、分化和凋亡、免疫细胞的发育和部分组织器官的稳定运行等一系列生理病理过程, 是一条相对保守的信号通路^[35-37]。在哺乳动物Notch信号由4个Notch受体(Notch1-4)、5个配体(Delta-like1, 3, 4和Jagged1, 2)和细胞内效应器3部分组成。其与mTOR信号之间的调控关系十分复杂且不甚清楚, 但其网路结构中, 有人认为Notch信号位于PI3K/AKT/mTOR的上游可上调mTOR通路, 其下游靶基因Hes/可以抑制PTEN的表达, 或抑制MAPK, 从而正性调节PI3K/AKT/mTOR信号活化^[38,39]。

3.2 Notch-mTOR通路与能量代谢 mTOR信号调节细胞能量代谢涉及4个方面: (1)调节线粒体功能。mTORC1通过磷酸化其下游两个信号分子(4E-BPs和S6Ks), 能刺激mRNA的翻译, 促进脂质合成等代谢过程^[40-42], 或调控PGC-1 α 和HIF-1 α 等线粒体转录因子, 控制能量代谢^[43], 或直接磷酸化Bcl-xl等线粒体蛋白^[44], 或参与糖酵解通量和线粒体呼吸平衡^[45,46], 从而调控线粒体的活性, 提高ATP产量; (2)调节能量平衡, 主要通过mTORC2促进胰岛素分解脂质和葡萄糖转运^[47], 或通过内涵体/溶酶体蛋白复合体根据能量水平高低要求与AMPK交互作用调节能量平衡^[48,49]; (3)整合氨基酸和能量感应通路来实现, 亮氨酸等氨基酸可通过RagGTPase活化mTORC1, 或促进mTORC1转移到溶酶体并活化, 进而调节能量代谢^[50-52]。

Notch直接调节ATP的研究尚且鲜见, 但2014年*Nature medicine*杂志根据Bi等^[53]论文发表专门评述, 指出抑制Notch信号可诱导脂肪褐色变, 提高全身葡萄糖耐受和胰岛素敏感性, 进而抑制体质量增加, 提示调控Notch信号可以调节能量代谢^[54]。当然Notch信号调控能量代谢的确切机制和水平尚不清楚, 还有待于从

■ 相关报道

Bhonde等表明mTOR信号活化与IBD病密切相关, 同时Zheng等也表明通过Notch信号途径有效抑制Hatch1表达可致结肠杯状细胞损伤, 均提示mTOR-Notch信号是治疗炎症性肠病的有效途径。

■ 创新盘点

本文系统阐述了Notch-mTOR信号间的相互关系, 以及Notch-mTOR信号与免疫水平、细胞能量代谢以及分别与炎症性肠病IBD发病之间的相关性。调控Notch-mTOR信号介导免疫与能量轴变化可能是探索中医药预防和防止IBD复发的可能突破口和有效策略。

线粒体调控机制和胞内外ATP产生及信号等途径开展研究。

由此可见, 无论是单独mTOR信号还是Notch信号都可以从不同角度调节能量代谢, 鉴于Notch与mTOR信号之间的关系, Notch与mTOR形成信号转导通路关联已经被证实, 因此Notch-mTOR通路能量代谢之间, 极有可能形成Notch-mTOR-能量轴, 共同调节能量代谢, 进而影响细胞生长发育和组织稳定性。

3.3 Notch-mTOR通路免疫 Notch-mTOR通路对免疫系统的发育、成熟、功能分化和转运分布是十分复杂而灵活多变的, 其自身调节和外界干扰相互影响, 共同干预调节机体免疫状态。关键之处简述如下, mTOR能调节T细胞、B细胞、树突细胞、自然杀伤细胞等等免疫细胞, 是一种重要的免疫功能调节因子。淋巴细胞的活化需要大量的蛋白质、核苷酸和脂质等物质, 通过糖酵解氧化方式等方式完成, 而这一过程中需要大量的调节转录因子(KLF2和FOXOs)维持, 而这些转录因子都可以被mTOR信号所抑制, 从而调控淋巴细胞的新陈代谢, 影响淋巴细胞的分化、成熟和功能的实现^[55,56]。在T细胞运输方面, 趋化因子CD62L和CCR7的表达因子mTOR以及Akt的活化作用而减少, 究其原因主要在于mTORC2激活Akt导致FOXOs失活和KLF2的低表达, 进而使得在淋巴结中被活化的效应细胞转移到组织中^[57]。这一过程也受鞘氨醇1-磷酸盐受体1(sphingosine-1-phosphate, S1P1)调节, S1P1信号活化并激活mTOR, 促使Th1生成以及中和Treg分化^[58,59]。而B细胞的存活增殖、分化成熟也都与mTOR信号相关, mTOR信号可通过调节白介素(interleukin, IL)-7信号和PI3K/Akt信号干预, IL-7信号活化则促进前体B细胞的存活^[60], 而PI3K/Akt信号则通过活化B细胞信号受体, 促进B细胞活化, 或通过mTOR信号灭活FOXO1, 进而减少B细胞活化^[61]。当然mTOR信号更为熟悉的是通过其下游S6Ks以及4EBPs调节细胞周期蛋白, 调节免疫细胞分化和成熟^[62]。

而Notch对固有性和适应性免疫细胞的发育和功能均有调节作用, 其免疫调节多由其配体及其靶基因激活Notch信号参与完成, 如通过Deltalike1和Deltalike4诱导巨噬细胞产生和分泌IL-1 β 、IL-6等细胞因子^[63]; 通过活化其靶基因Hes1和Deltex激活巨噬细胞^[64,65], 通过

Jagged1激活Notch信号促进树突状细胞分化, 而Deltalike1激活Notch信号反而抑制树突状细胞分化^[66]。Notch信号也可通过Notch/RBP-J κ 信号促进CD4⁺ T细胞向Th1/Th2细胞的分化, 调节 $\gamma\delta^+$ T细胞的发生和迁移, 调节 $\alpha\beta^+$ T细胞和B细胞的成熟^[67,68], 并通过上调TGF- β 水平增强Treg细胞的抑制功能^[69]。尽管各自调控免疫系统的机制尚未完全明确, 但Notch-mTOR可从不同角度调控免疫细胞的生理状态和功能发挥是不争事实, 其激活与否、及激活程度可重塑免疫系统, 因而其与多种免疫性疾病如IBD、肿瘤、炎症感染等发病密切相关。

4 IBD发病与Notch-mTOR信号之间关联

Notch-mTOR信号调控免疫细胞发育成熟与分化转输的机制尚不明确, 其能否从能量转换角度干预免疫系统功能状态是当前研究热点, 其在IBD的发病机制研究中尚且不多。研究^[70]表明mTOR抑制剂可显著抑制葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导性结肠炎小鼠体质量下降, 出血指数和疾病指数升高, 结肠长度延长, 缓解病理性水肿、降低炎症细胞浸润程度, 同时显著降低和干扰素- γ 产量, 抑制mTOR蛋白及其下游p70S6K1和4E-BP1表达, 提示mTOR信号与实验性结肠炎发病密切相关, 且抑制mTOR信号有效治疗结肠炎。同时在DSS小鼠模型, 结肠黏膜Notch信号受体Jagged1 mRNA、Deltalike 1 mRNA和Deltalike 4 mRNA表达显著升高^[71]。Notch信号调节细胞命运, 其主要肠干细胞表达, 可上调转录抑制因子Hes-1表达、抑制Match-1表达, 研究^[72]表明在CD患者结肠黏膜表面Math-1、KLF4表达升高, 而Hes-1表达则下降, 表明通过Notch信号抑制Match-1的表达, Hes-1的升高是关键, 且是结肠杯状细胞损伤减少的关键因素所在。在UC的不同阶段, Hes1异常升高, 伴CDX2水平下降, 并通过Notch信号途径有效抑制Hatch1表达, 导致结肠杯状细胞损伤^[73]。尽管目前研究不多, 但也表明mTOR和Notch信号在以各自不同的方式参与IBD的发病, 并在其发病过程中发挥重要作用。

5 中医药调控Notch-mTOR信号关联免疫和能量轴的潜在价值

我们的前期基础已经发现, 在三硝基苯磺酸

(trinitro-benzenesulfonic acid, TNBS)/乙醇复合法诱导的结肠炎大鼠结肠黏膜中, ATP浓度显著下降、而ADP/ATP和AMP/ATP比值显著升高, 同时ATP5D蛋白和p-MAPK表达明显下降, 且F-actin分布明显减少, 细胞缝隙连接蛋白occludin表达下降, 伴结肠微循环障碍, 提示在TNBS诱导的结肠炎大鼠结肠上皮细胞中ATP水平显著下降, 导致F-actin细胞骨架支撑作用减弱, 细胞间缝隙加大, 结肠通透性增加, 致炎因子等进入黏膜上皮下层, 炎细胞渗出造成结肠黏膜炎性损伤。同时经黄芪建中丸给药治疗后, 上述变化趋势均造逆转, 同时结肠黏膜病理损伤明显缓解, 病理损伤分数、结肠上皮微循环障碍改善, 提示黄芪建中丸有效治疗TNBS诱导的结肠炎的可能途径是通过改善调节结肠上皮细胞能量代谢状态, 促进结肠上皮细胞修复、再生, 提高结肠上皮的屏障功能实现的^[74]。也有研究者采用该模型并用乌梅丸干预治疗发现, 结肠上皮杯状细胞大量丢失的同时, 结肠上皮细胞Notch-1、Hes-1 mRNA表达显著增强, Math-1 mRNA表达明显降低, 而经不同剂量的乌梅丸治疗后, 结肠上皮细胞Notch-1、Hes-1 mRNA表达明显降低, Math-1 mRNA表达显著增高, 提示乌梅丸可通过抑制Notch-1信号的过度活化, 调节Hath-1和Math-1基因之间的平衡, 促进结肠黏膜屏障的修复和肠上皮的再生而治疗IBD^[75]。

Notch-mTOR信号通路调控免疫状态和介导细胞能量代谢, 尽管干预Notch-mTOR信号治疗IBD鲜见报道, 但其与IBD发病密切相关性, 提示调控Notch-mTOR信号途径是预防和阻止IBD反复发作及其新药研发的有效策略和思路。但Notch-mTOR信号与IBD发病间的暗箱机制还有于进一步揭示, 因此从Notch-mTOR信号调控免疫-能量轴探索IBD发病机制, 势必成为将来IBD机制研究和新药开发的研究热点。尤其是中医药对IBD复发具有良好地预防临床效果, 但其作用机制不明, 因此, Notch-mTOR信号是探索中医药预防IBD复发的可能突破点和机会。

6 参考文献

- 1 Park SH, Kim YM, Yang SK, Kim SH, Byeon JS, Myung SJ, Cho YK, Yu CS, Choi KS, Chung JW, Kim B, Choi KD, Kim JH. Clinical features and natural history of ulcerative colitis in Korea. *Inflamm*

- 2 *Bowel Dis* 2007; 13: 278-283 [PMID: 17206722 DOI: 10.1002/ibd.20015]
- 3 戴禄寿, 谢军培, 江拥军. 奥替溴安联合美沙拉秦缓释片治疗溃疡性结肠炎临床研究. *临床军医杂志* 2012; 40: 791-792
- 4 苏伟明. 奥硝唑联合美沙拉秦治疗溃疡性结肠炎的疗效观察. *临床合理用药* 2011; 5: 20-21
- 5 纪桂贤. 溃疡性结肠炎治疗进展. *中国误诊学杂志* 2011; 5: 3048-3050
- 6 陆珮琳, 沈洪, 张声生, 王垂杰, 赵文霞. 中医序贯疗法对溃疡性结肠炎维持缓解的疗效观察. *南京中医药大学学报* 2011; 27: 118-120
- 7 付东亮. 中药内服联合灌肠治疗溃疡性结肠炎187例临床研究. *中国实用医药* 2012; 7: 27-28
- 8 干丽红. 中医序贯疗法维持治疗溃疡性结肠炎效果观察. *辽宁中医药大学学报* 2014; 16: 202-204
- 9 齐相芬, 张仁诚, 胡文平, 刘俊丽, 高文艳, 王长洪, 林一帆, 吴卓霖. 自拟愈溃方维持缓解脾肾阳虚型溃疡性结肠炎的临床疗效观察. *中国中西医结合消化杂志* 2015; 23: 885-887
- 10 Lie PP, Cheng CY, Mruk DD. The biology of interleukin-1: emerging concepts in the regulation of the actin cytoskeleton and cell junction dynamics. *Cell Mol Life Sci* 2012; 69: 487-500 [PMID: 21744066 DOI: 10.1007/s00018-011-0760-0]
- 11 Buelto D, Duncan MC. Cellular energetics: actin and myosin abstain from ATP during starvation. *Curr Biol* 2014; 24: R1004-R1006 [PMID: 25442847 DOI: 10.1016/j.cub.2014.09.004]
- 12 McCullagh M, Saunders MG, Voth GA. Unraveling the mystery of ATP hydrolysis in actin filaments. *J Am Chem Soc* 2014; 136: 13053-13058 [PMID: 25181471 DOI: 10.1021/ja507169f]
- 13 Rodgers LS, Fanning AS. Regulation of epithelial permeability by the actin cytoskeleton. *Cytoskeleton (Hoboken)* 2011; 68: 653-660 [PMID: 22083950 DOI: 10.1002/cm.20547]
- 14 姜旭光, 姜明霞, 王枫. 干扰上皮细胞能量代谢对炎症性肠病发病的影响. *世界华人消化杂志* 2015; 23: 4393-4398
- 15 Dashdorj A, Jyothi KR, Lim S, Jo A, Nguyen MN, Ha J, Yoon KS, Kim HJ, Park JH, Murphy MP, Kim SS. Mitochondria-targeted antioxidant MitoQ ameliorates experimental mouse colitis by suppressing NLRP3 inflammasome-mediated inflammatory cytokines. *BMC Med* 2013; 11: 178 [PMID: 23915129 DOI: 10.1186/17]
- 16 Wang A, Keita ÅV, Phan V, McKay CM, Schoultz I, Lee J, Murphy MP, Fernando M, Ronaghan N, Balce D, Yates R, Dicay M, Beck PL, MacNaughton WK, Söderholm JD, McKay DM. Targeting mitochondria-derived reactive oxygen species to reduce epithelial barrier dysfunction and colitis. *Am J Pathol* 2014; 184: 2516-2527 [PMID: 25034594 DOI: 10.1016/j.ajpath.2014.05.019]
- 17 Guo W, Liu W, Jin B, Geng J, Li J, Ding H, Wu X, Xu Q, Sun Y, Gao J. Asiatic acid ameliorates dextran sulfate sodium-induced murine experimental colitis via suppressing mitochondria-mediated NLRP3 inflammasome activation. *Int Immunopharmacol* 2015; 24: 232-238 [PMID: 25523461 DOI: 10.1016/j.intimp.2014.12.009]
- 18 Ma Y, Adjemian S, Yang H, Catani JP, Hannani D, Martins I, Michaud M, Kepp O, Sukkurwala AQ, Vacchelli E, Galluzzi L, Zitvogel L, Kroemer

■名词解释

哺乳动物雷帕霉素靶蛋白: 是一种丝氨酸-苏氨酸蛋白激酶, 其不仅是细胞生长和营养的调节中心, 也是细胞能量感受调节分子。

■同行评价

本文可能为中医药治疗IBD机制阐明了方向。本文的科学性、创新性和可读性能较好地反映国内外胃肠病学临床和基础研究的先进水平。

- G. ATP-dependent recruitment, survival and differentiation of dendritic cell precursors in the tumor bed after anticancer chemotherapy. *Oncoimmunology* 2013; 2: e24568 [PMID: 23894718 DOI: 10.4161/onci.24568]
- 18 TrabANELLI S, OcAdlíková D, Gulinelli S, Curti A, Salvestrini V, Vieira RP, Idzko M, Di Virgilio F, Ferrari D, Lemoli RM. Extracellular ATP exerts opposite effects on activated and regulatory CD4+ T cells via purinergic P2 receptor activation. *J Immunol* 2012; 189: 1303-1310 [PMID: 22753942 DOI: 10.4049/jimmunol.1103800]
- 19 姜雨薇, 金丹. 炎症性肠病免疫学发病机制研究进展. *延边大学医学学报* 2014; 37: 76-78
- 20 章丽雅, 杨芬, 刘伟, 许春娣, 夏振炜, 周同. 炎症性肠病与固有免疫调节. *现代免疫学* 2013; 33: 157-163
- 21 Heilmann RM, Suchodolski JS. Is inflammatory bowel disease in dogs and cats associated with a Th1 or Th2 polarization? *Vet Immunol Immunopathol* 2015; 168: 131-134 [PMID: 26672910 DOI: 10.1016/j.vetimm.2015.10.008]
- 22 Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, Stallhofer J, Beigel F, Bedynek A, Wetzke M, Maier H, Koburger M, Wagner J, Glas J, Diegelmann J, Koglin S, Dombrowski Y, Schaubert J, Wollenberg A, Brand S. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon- γ -expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut* 2014; 63: 567-577 [PMID: 23468464]
- 23 Lee SY, Lee SH, Yang EJ, Kim EK, Kim JK, Shin DY, Cho ML. Metformin Ameliorates Inflammatory Bowel Disease by Suppression of the STAT3 Signaling Pathway and Regulation of the between Th17/Treg Balance. *PLoS One* 2015; 10: e0135858 [PMID: 26360050 DOI: 10.1371/journal.pone.0135858]
- 24 Shin JY, Yoon IH, Lim JH, Shin JS, Nam HY, Kim YH, Cho HS, Hong SH, Kim JS, Lee WW, Park CG. CD4+VEGFR1(HIGH) T cell as a novel Treg subset regulates inflammatory bowel disease in lymphopenic mice. *Cell Mol Immunol* 2015; 12: 592-603 [PMID: 26211666 DOI: 10.1038/cmi.2015.71]
- 25 Wu W, He C, Liu C, Cao AT, Xue X, Evans-Marin HL, Sun M, Fang L, Yao S, Pinchuk IV, Powell DW, Liu Z, Cong Y. miR-10a inhibits dendritic cell activation and Th1/Th17 cell immune responses in IBD. *Gut* 2015; 64: 1755-1764 [PMID: 25281418 DOI: 10.1136/gutjnl-2014-307980]
- 26 Zeng JQ, Xu CD, Zhou T, Wu J, Lin K, Liu W, Wang XQ. Enterocyte dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin expression in inflammatory bowel disease. *World J Gastroenterol* 2015; 21: 187-195 [PMID: 25574091 DOI: 10.3748/wjg.v21.i1.187]
- 27 Yadav PK, Chen C, Liu Z. Potential role of NK cells in the pathogenesis of inflammatory bowel disease. *J Biomed Biotechnol* 2011; 2011: 348530 [PMID: 21687547 DOI: 10.1155/2011/348530]
- 28 Spaeth GL. Eastern European tumult: lessons for physicians. *Ophthalmic Surg* 1989; 20: 845 [PMID: 2630962]
- 29 Luo K, Cao SS. Endoplasmic reticulum stress in intestinal epithelial cell function and inflammatory bowel disease. *Gastroenterol Res Pract* 2015; 2015: 328791 [PMID: 25755668 DOI: 10.1155/2015/328791]
- 30 Hamilton MJ, Frei SM, Stevens RL. The multifaceted mast cell in inflammatory bowel disease. *Inflamm Bowel Dis* 2014; 20: 2364-2378 [PMID: 25401721 DOI: 10.1097/MIB.0000000000000142]
- 31 吴红艳, 王艳林. 细胞外ATP与肿瘤免疫. *生命的化学* 2013; 33: 644-647
- 32 Schmelzle T, Hall MN. TOR, a central controller of cell growth. *Cell* 2000; 103: 253-262 [PMID: 11057898 DOI: 10.1016/S0092-8674(00)00117-3]
- 33 Sarbassov DD, Ali SM, Sabatini DM. Growing roles for the mTOR pathway. *Curr Opin Cell Biol* 2005; 17: 596-603 [PMID: 16226444 DOI: 10.1016/j.ceb.2005.09.009]
- 34 肖昊, 谭碧娥, 吴苗苗, 邵方元, 印遇龙. mTOR信号通路调节细胞能量代谢的机制. *中国科学: 生命科学* 2015; 45: 1124-1131
- 35 Radtke F, Fasnacht N, Macdonald HR. Notch signaling in the immune system. *Immunity* 2010; 32: 14-27 [PMID: 20152168 DOI: 10.1016/j.immuni.2010.01.004]
- 36 Bassil R, Orent W, Elyaman W. Notch signaling and T-helper cells in EAE/MS. *Clin Dev Immunol* 2013; 2013: 570731 [PMID: 24324509 DOI: 10.1155/2013/570731]
- 37 Espinoza I, Pochampally R, Xing F, Watabe K, Miele L. Notch signaling: targeting cancer stem cells and epithelial-to-mesenchymal transition. *Onco Targets Ther* 2013; 6: 1249-1259 [PMID: 24043949 DOI: 10.2147/OTT.S36162]
- 38 Mungamuri SK, Yang X, Thor AD, Somasundaram K. Survival signaling by Notch1: mammalian target of rapamycin (mTOR)-dependent inhibition of p53. *Cancer Res* 2006; 66: 4715-4724 [PMID: 16651424 DOI: 10.1158/0008-5472]
- 39 Palomero T, Sulis ML, Cortina M, Real PJ, Barnes K, Ciofani M, Caparros E, Buteau J, Brown K, Perkins SL, Bhagat G, Agarwal AM, Basso G, Castillo M, Nagase S, Cordon-Cardo C, Parsons R, Zúñiga-Pflücker JC, Dominguez M, Ferrando AA. Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. *Nat Med* 2007; 13: 1203-1210 [PMID: 17873882 DOI: 10.1038/nm1636]
- 40 Morita M, Gravel SP, Chénard V, Sikström K, Zheng L, Alain T, Gandin V, Avizonis D, Arguello M, Zakaria C, McLaughlan S, Nouet Y, Pause A, Pollak M, Gottlieb E, Larsson O, St-Pierre J, Topisirovic I, Sonenberg N. mTORC1 controls mitochondrial activity and biogenesis through 4E-BP-dependent translational regulation. *Cell Metab* 2013; 18: 698-711 [PMID: 24206664 DOI: 10.1016/j.cmet.2013.10.001]
- 41 Roux PP, Topisirovic I. Regulation of mRNA translation by signaling pathways. *Cold Spring Harb Perspect Biol* 2012; 4: a012252 [PMID: 22888049 DOI: 10.1101/cshperspect.a012252]
- 42 Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, Vander Heiden MG, MacKeigan JP, Finan PM, Clish CB, Murphy LO, Manning BD.

- Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell* 2010; 39: 171-183 [PMID: 20670887 DOI: 10.1016/j.molcel.2010.06.022]
- 43 Porstmann T, Santos CR, Griffiths B, Cully M, Wu M, Leevers S, Griffiths JR, Chung YL, Schulze A. SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. *Cell Metab* 2008; 8: 224-236 [PMID: 18762023 DOI: 10.1016/j.cmet.2008.07.007]
 - 44 Ramanathan A, Schreiber SL. Direct control of mitochondrial function by mTOR. *Proc Natl Acad Sci U S A* 2009; 106: 22229-22232 [PMID: 20080789 DOI: 10.1073/pnas.0912074106]
 - 45 Durán RV, Oppliger W, Robitaille AM, Heiserich L, Skendaj R, Gottlieb E, Hall MN. Glutaminolysis activates Rag-mTORC1 signaling. *Mol Cell* 2012; 47: 349-358 [PMID: 22749528 DOI: 10.1016/j.molcel.2012.05.043]
 - 46 Lorin S, Tol MJ, Bauvy C, Strijland A, Poüs C, Verhoeven AJ, Codogno P, Meijer AJ. Glutamate dehydrogenase contributes to leucine sensing in the regulation of autophagy. *Autophagy* 2013; 9: 850-860 [PMID: 23575388 DOI: 10.4161/auto.24083]
 - 47 Kocalis HE, Hagan SL, George L, Turney MK, Siuta MA, Laryea GN, Morris LC, Muglia LJ, Printz RL, Stanwood GD, Niswender KD. Rictor/mTORC2 facilitates central regulation of energy and glucose homeostasis. *Mol Metab* 2014; 3: 394-407 [PMID: 24944899 DOI: 10.1016/j.molmet.2014.01.014]
 - 48 Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 2011; 13: 132-141 [PMID: 21258367 DOI: 10.1038/ncb2152]
 - 49 Dunlop EA, Tee AR. The kinase triad, AMPK, mTORC1 and ULK1, maintains energy and nutrient homeostasis. *Biochem Soc Trans* 2013; 41: 939-943 [PMID: 23863160 DOI: 10.1042/BST20130030]
 - 50 Jewell JL, Kim YC, Russell RC, Yu FX, Park HW, Plouffe SW, Tagliabracchi VS, Guan KL. Metabolism. Differential regulation of mTORC1 by leucine and glutamine. *Science* 2015; 347: 194-198 [PMID: 25567907 DOI: 10.1126/science.1259472]
 - 51 Rebsamen M, Pochini L, Stasyk T, de Araújo ME, Galluccio M, Kandasamy RK, Snijder B, Fauster A, Rudashevskaya EL, Bruckner M, Scorzoni S, Filipek PA, Huber KV, Bigenzahn JW, Heinz LX, Kraft C, Bennett KL, Indiveri C, Huber LA, Superti-Furga G. SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. *Nature* 2015; 519: 477-481 [PMID: 25561175 DOI: 10.1038/nature14107]
 - 52 Wang S, Tsun ZY, Wolfson RL, Shen K, Wyant GA, Plovnick ME, Yuan ED, Jones TD, Chanturanpong L, Comb W, Wang T, Bar-Peled L, Zoncu R, Straub C, Kim C, Park J, Sabatini BL, Sabatini DM. Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science* 2015; 347: 188-194 [PMID: 25567906 DOI: 10.1126/science.1257132]
 - 53 Bi P, Shan T, Liu W, Yue F, Yang X, Liang XR, Wang J, Li J, Carlesso N, Liu X, Kuang S. Inhibition of Notch signaling promotes browning of white adipose tissue and ameliorates obesity. *Nat Med* 2014; 20: 911-918 [PMID: 25038826 DOI: 10.1038/nm.3615]
 - 54 Gridley T, Kajimura S. Lightening up a notch: Notch regulation of energy metabolism. *Nat Med* 2014; 20: 811-812 [PMID: 25100522 DOI: 10.1038/nm.3650]
 - 55 Reinitz DM, Mansfield JM. Independent regulation of B cell responses to surface and subsurface epitopes of African trypanosome variable surface glycoproteins. *J Immunol* 1988; 141: 620-626 [PMID: 2454998 DOI: 10.1002/eji.201343920]
 - 56 Buckley AF, Kuo CT, Leiden JM. Transcription factor LKLF is sufficient to program T cell quiescence via a c-Myc-dependent pathway. *Nat Immunol* 2001; 2: 698-704 [PMID: 11477405 DOI: 10.1038/90633]
 - 57 Kerdiles YM, Beisner DR, Tinoco R, Dejean AS, Castrillon DH, DePinho RA, Hedrick SM. Foxo1 links homing and survival of naive T cells by regulating L-selectin, CCR7 and interleukin 7 receptor. *Nat Immunol* 2009; 10: 176-184 [PMID: 19136962 DOI: 10.1038/ni.1689]
 - 58 Carlson CM, Endrizzi BT, Wu J, Ding X, Weinreich MA, Walsh ER, Wani MA, Lingrel JB, Hogquist KA, Jameson SC. Kruppel-like factor 2 regulates thymocyte and T-cell migration. *Nature* 2006; 442: 299-302 [PMID: 16855590 DOI: 10.1038/nature04882]
 - 59 Liu G, Yang K, Burns S, Shrestha S, Chi H. The S1P(1)-mTOR axis directs the reciprocal differentiation of T(H)1 and T(reg) cells. *Nat Immunol* 2010; 11: 1047-1056 [PMID: 20852647 DOI: 10.1038/ni.1939]
 - 60 Lazorchak AS, Liu D, Facchinetti V, Di Lorenzo A, Sessa WC, Schatz DG, Su B. Sin1-mTORC2 suppresses rag and il7r gene expression through Akt2 in B cells. *Mol Cell* 2010; 39: 433-443 [PMID: 20705244 DOI: 10.1016/j.molcel.2010.07.031]
 - 61 Limon JJ, Fruman DA. Akt and mTOR in B Cell Activation and Differentiation. *Front Immunol* 2012; 3: 228 [PMID: 22888331 DOI: 10.3389/fimmu.2012.00228]
 - 62 Benhamron S, Tirosh B. Direct activation of mTOR in B lymphocytes confers impairment in B-cell maturation and loss of marginal zone B cells. *Eur J Immunol* 2011; 41: 2390-2396 [PMID: 21674478 DOI: 10.1002/eji.201041336]
 - 63 Tsao PN, Wei SC, Huang MT, Lee MC, Chou HC, Chen CY, Hsieh WS. Lipopolysaccharide-induced Notch signaling activation through JNK-dependent pathway regulates inflammatory response. *J Biomed Sci* 2011; 18: 56 [PMID: 21843347 DOI: 10.1186/1423-0127-18-56]
 - 64 Camelo S, Raoul W, Lavalette S, Calippe B, Cristofaro B, Levy O, Houssier M, Sulpice E, Jonet L, Klein C, Devedre E, Thuret G, Duarte A, Eichmann A, Leconte L, Guillonnet X, Sennlaub F. Delta-like 4 inhibits choroidal neovascularization despite opposing effects on vascular endothelium and macrophages. *Angiogenesis* 2012; 15: 609-622 [PMID: 22869002 DOI: 10.1007/s10456-012-9290-0]
 - 65 Wang YC, He F, Feng F, Liu XW, Dong GY, Qin HY, Hu XB, Zheng MH, Liang L, Feng L, Liang YM, Han H. Notch signaling determines the M1 versus M2 polarization of macrophages in antitumor immune responses. *Cancer Res* 2010; 70: 4840-4849 [PMID: 20501839 DOI: 10.1158/0008-5472.CCR-09-4000]

- 10.1158/0008-5472.CAN-10-0269]
- 66 Lewis KL, Caton ML, Bogunovic M, Greter M, Grajkowska LT, Ng D, Klinakis A, Charo IF, Jung S, Gommerman JL, Ivanov II, Liu K, Merad M, Reizis B. Notch2 receptor signaling controls functional differentiation of dendritic cells in the spleen and intestine. *Immunity* 2011; 35: 780-791 [PMID: 22018469 DOI: 10.1016/j.immuni.2011.08.013]
- 67 Caton ML, Smith-Raska MR, Reizis B. Notch-RBP-J signaling controls the homeostasis of CD8-dendritic cells in the spleen. *J Exp Med* 2007; 204: 1653-1664 [PMID: 17591855 DOI: 10.1084/jem.20062648]
- 68 Iwahashi S, Maekawa Y, Nishida J, Ishifune C, Kitamura A, Arimochi H, Kataoka K, Chiba S, Shimada M, Yasutomo K. Notch2 regulates the development of marginal zone B cells through Fos. *Biochem Biophys Res Commun* 2012; 418: 701-707 [PMID: 22293205 DOI: 10.1016/j.bbrc.2012.01.082]
- 69 Hue S, Kared H, Mehwish Y, Mouhamad S, Balbo M, Levy Y. Notch activation on effector T cells increases their sensitivity to Treg cell-mediated suppression through upregulation of TGF- β RII expression. *Eur J Immunol* 2012; 42: 1796-1803 [PMID: 22585622 DOI: 10.1002/eji.201142330]
- 70 Bhonde MR, Gupte RD, Dadarkar SD, Jadhav MG, Tannu AA, Bhatt P, Bhatia DR, Desai NK, Deore V, Yewalkar N, Vishwakarma RA, Sharma S, Kumar S, Dagia NM. A novel mTOR inhibitor is efficacious in a murine model of colitis. *Am J Physiol Gastrointest Liver Physiol* 2008; 295: G1237-G1245 [PMID: 18927209 DOI: 10.1152/ajpgi.90537]
- 71 Imaeda H, Andoh A, Aomatsu T, Uchiyama K, Bamba S, Tsujikawa T, Naito Y, Fujiyama Y. Interleukin-33 suppresses Notch ligand expression and prevents goblet cell depletion in dextran sulfate sodium-induced colitis. *Int J Mol Med* 2011; 28: 573-578 [PMID: 21667014 DOI: 10.3892/ijmm.2011.718]
- 72 Laitman LE, Dahan S. Taking inflammatory bowel disease up a Notch. *Immunol Res* 2012; 54: 69-74 [PMID: 22427015 DOI: 10.1007/s12026-012-8314-6]
- 73 Zheng X, Tsuchiya K, Okamoto R, Iwasaki M, Kano Y, Sakamoto N, Nakamura T, Watanabe M. Suppression of *hath1* gene expression directly regulated by *hes1* via notch signaling is associated with goblet cell depletion in ulcerative colitis. *Inflamm Bowel Dis* 2011; 17: 2251-2260 [PMID: 21987298 DOI: 10.1002/ibd.2161]
- 74 Liu DY, Pan CS, Liu YY, Wei XH, Zhou CM, Sun K, He K, Li C, Yan L, Fan JY, Wang CS, Hibi T, Liu HN, Han JY. Huang Qi Jian Zhong Pellet Attenuates TNBS-Induced Colitis in Rats via Mechanisms Involving Improvement of Energy Metabolism. *Evid Based Complement Alternat Med* 2013; 2013: 574629 [PMID: 23840258 DOI: 10.1155/2013/574629]
- 75 闫曙光, 惠毅. 乌梅丸对溃疡性结肠炎大鼠结肠上皮细胞Notch信号通路的影响. *时珍国医国药* 2015; 26: 320-322

编辑: 于明茜 电编: 都珍珍





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

