· 综述 ·

姜黄素对肠道屏障的作用及机制*

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[关键词] 姜黄素;肠道屏障;靶点;慢性炎症;作用机制
DOI:10.3969/j.issn.1671-038X.2021.02.14
[中图分类号] R285.6 [文献标志码] A

Effects and mechanisms of curcumin on intestinal barrier function

Summary Curcumin is the main effective ingredient of Traditional Chinese herbs turmeric. It has a variety of functions, such as anti-inflammatory, anti-oxidation and anti-tumor. However, its efficacy is controversial due to its low bioavailability. In this paper, we demonstrated that curcumin could repair the intestinal barrier function through enhancing the activity of intestinal alkaline phosphatase, maintaining the homeostasis of gut flora, promoting the secretion of mucus, increasing the level of antibacterial peptides, as well as maintaining the integrity of intestinal epithelium and tight junctions. Consequently, curcumin could reduce the harmful bacteria/bacterial products into the systemic circulation, so as to inhibit the inflammatory response and show its beneficial effects.

Key words curcumin; intestinal barrier function; target; chronic inflammation; mechanism

姜黄素是一种从姜科植物的根茎中提取而得的橙黄色多酚类化学物质,是中药姜黄、郁金等的主要有效成分,被广泛用于食品添加、化妆品、染料等。近些年大量研究表明姜黄素还存在较高的医疗价值,具有抗炎、抗氧化、抗肿瘤、抗凋亡、抗纤维化、免疫调节等作用,可用于多种疾病[1],已逐渐成为国内外的一个研究热点。

虽然多项临床研究证实了姜黄素的有益作用,但因姜黄素难吸收、血液中几乎检测不到、生物利用度极低等因素,阻碍了两者间因果关系的建立。有学者从化学药物角度否定了姜黄素药物开发的可能性,称其为"无效的万能药"[2]。但是,姜黄素的临床疗效是不容忽视的,因此,本文推测其可能存在独特的非常规起效机制。

1 姜黄素的作用靶点及机制

肠道可能是姜黄素的作用靶点。系统总结既往研究,我们发现姜黄素具有以下特点:①肠腔中存在较高浓度的姜黄素,因此肠道可能是姜黄素发挥作用的一个重要部位;②研究证实姜黄素可抑制葡聚糖硫酸钠(dextran sulfate sodium,DSS)诱导的肠炎模型小鼠炎症[3],在结肠癌的预防和辅助治疗中具有一定作用[4-5],表明姜黄素对肠道有益;③姜黄素经肠道菌群代谢,通过还原、脱甲氧基化、脱甲基化和羟基化等生物转化产生新的代谢产物,并发挥局部或全身作用[6]。因此,我们推测姜黄素可能通过靶向肠道而发挥其有益作用。

对肠道屏障功能的调节是姜黄素潜在的起效机制。胃肠道是人体内外环境间最大的管腔相互作用区域之一,在调节免疫系统,进而影响健康方面起着关键作用[7]。肠道的屏障功能在其中扮演重要角色,许多疾病的病理生理学与功能受损的肠道屏障有关(包括炎症性肠病、结直肠癌等肠道疾病,以及慢性肝病、糖尿病、肥胖等肠外疾病)[8]。对于这些疾病,目前认为受损的肠道屏障导致肠道通透性增加,引起大量抗原跨过肠上皮,激活易感人群的免疫系统,随之而来的是肠道局部或远端器官炎症机制的激活[9]。慢性炎症是诸多疾病的病理基础。以肠道屏障为作用位点,姜黄素不再受其低吸收、低利用度的限制,并为我们提供了研究姜黄素作用机制的新方向。

2 肠道屏障的分层及姜黄素对其的作用

肠道屏障包含以下 5 层:肠内碱性磷酸酶(intestinal alkaline phosphatase,IAP)、肠道菌群、肠上皮的黏液层、潘氏细胞分泌的抗菌肽和上皮细胞之间的紧密连接,见图 1。

2.1 第 1 层:IAP

IAP 是一种由肠上皮细胞分泌的具有脱磷酸作用的金属酶,可对脂多糖(lipopolysaccharide,LPS)进行解毒,是肠腔第一道防线[10]。LPS 与其结合蛋白结合形成复合物,并能与细胞膜上 Toll 样受体(toll-like receptors,TLRs)作用,激活

*基金项目:国家自然科学基金(No:82004333);浙江省自然科学基金(No:LQ21H290002);"十三五"浙江省中医药重点学科建设计划(No:2017-XK-A24)
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TLR-4，启动级联信号，进而释放促炎细胞因子[11]，最终形成与慢性炎症疾病相关的慢性炎症反应。IAP 通过对脂质 A 部分脱磷酸作用，使 LPS 解毒并生成单磷酰 LPS，降低 TLR-4 信号的激活，还能抑制核因子 κB(Nuclear factor kappa-B，NF-κB)的活化[12]，抑制 LPS 介导的炎性级联反应。因此，IAP 在维持宿主和肠腔内微生物环境之间的稳态方面发挥着核心作用。

增加 IAP 含量在炎症性肠病、坏死性肠炎、抗生素相关性腹泻、败血症及代谢综合征等疾病中具有一定的治疗前景[13]。姜黄素可通过刺激内源性 IAP 合成，从而有效改善 IBD[14]。Ghosh 等[15]发现姜黄素可逆转高脂饮食引起的 IAP 活性减低及 LPS 移位入血，改善动脉粥样硬化及糖耐量异常；此外，姜黄素亦可通过增加内源性 IAP 含量，减少 LPS 入血，减轻慢性肾脏病[16]。上述证据表明姜黄素可修复肠道屏障的第 1 层。

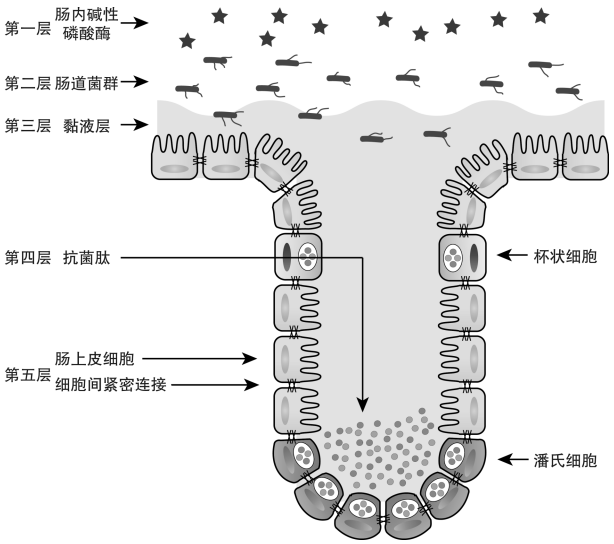

图 1 肠道屏障的分层示意图

2.2 第 2 层：肠道菌群

人类的肠道中含 10^{13} 个细菌细胞，相当于人体真核细胞的数量。正常的肠道菌群可维持肠道稳态，是肠道屏障的重要组成部分。肠道菌群的紊乱，可导致：肠道通透性改变，细菌移位；短链脂肪酸(short-chain fatty acids，SCFAs)合成减少，肠上皮能量代谢异常；变形菌门等 G-菌增加，引起 LPS 相关的持续低度炎症等。以上的菌群改变均参与了肥胖、非酒精性脂肪性肝病、炎症性肠病等诸多疾病的形成[18]。

多项研究表明姜黄素可作用于肠道菌群。小样本前瞻性研究表明姜黄和姜黄素分别增加受试者粪便 7%和 69%的菌群种数[19]。Saeed 等[20]发现表明姜黄素可改善非酒精性脂肪性肝病患者肠道菌群的代谢，降低患者血清甲胺、三甲胺、硫酸吲哚氧基和马尿酸浓度。Yazdi 等[21]报道姜黄素可被鼠李糖乳杆菌 GG 和双歧杆菌 BB12 利用，并促进该菌的生长，进而抑制 LPS 诱导促炎因子 IL-8 的释放。Gan 等[22]证明姜黄素可减少大肠杆菌的数量，降低肠道 TLR-4、IL-1、TNF-α 表达水平，改善肠道炎症。此外，Tariful 等[23]还发现姜黄素可增加高脂饮食小鼠梭状芽孢杆菌属细菌数量，使 SCFAs 合成增加。而 SCFAs(尤其是丁酸)可促进肠上皮细胞代谢，增加 O_2 的消耗，使得缺氧诱导因子(Hypoxia-inducible factor，HIF)稳定，而 HIF 具有很强的肠道屏障保护作用[24]。同时，姜黄素可被菌群代谢成 23 种已知的活性物质，发挥重要生理作用，形成双向调节作用[25]。上述证据表明，姜黄素可靶向肠道菌群，改善肠道屏障功能。

2.3 第 3 层：肠上皮黏液层

肠上皮黏液层是肠腔内容物与上皮细胞之间的主要防御壁，它可避免肠内容物与肠上皮间的直接接触，防止致病菌入侵，避免肠道炎症的发生[26]。黏蛋白在黏液层的构建中扮演重要角色，高度糖基化的黏蛋白 Muc2 是肠内最为丰富的黏蛋白，研究表明，$Muc2^{-/-}$ 小鼠肠黏蛋白合成障碍，上皮细菌黏附增多，引起肠道屏障功能异常，可自发形成结肠炎[27]。

高脂、低纤维素饮食可破坏黏液层，使得肠上皮细胞直接暴露，引起损伤，而该损伤作用可被姜黄素所逆转[28]；此外，Junior 等[29]发现姜黄素可增加肠内酸性黏蛋白数量；Cucolas 等[30]报道姜黄素可提高肠道缺血/再灌注损伤后黏蛋白 1 的水平，修复肠道黏液屏障；姜黄素可通过清除超氧阴离子和脂质过氧化物，恢复线粒体功能，以减少的肠炎模型小鼠黏蛋白的降解[31]。以上证据表明姜黄素可维持肠道屏障黏液层的完整性。

2.4 第 4 层：抗菌肽

肠道上皮细胞除了构建一个单细胞层的物理屏障外，其中一些特殊的分泌细胞——潘氏细胞还可分泌抗菌肽[32]，这些多肽构成了肠道屏障的第 4 层，并在宿主对抗肠道细菌中扮演重要角色。抗菌肽分泌的异常，可增加肠道感染性疾病的易感性。Guo 等[33]报道姜黄素可通过维生素 D 受体上调肠道抗菌肽基因表达的水平。Ming 等[34]报道姜黄素可增加抗菌肽 hepcidin 和 β-防御素，拮抗炎症反应。在肠道感染性疾病模型中姜黄素可促进抗菌肽的表达，以抑制免疫和炎症反应[34]。表明姜黄素可保护肠道屏障第 4 层。

2.5 第 5 层：肠上皮

肠上皮屏障是由上皮细胞和细胞间连接(桥粒、粘着连接和紧密连接)组成，它作为一个高度选择性的屏障，阻止腔内抗原、微生物及其毒素的易位，同时允许必要的膳食营养素、电解质的通过。

其中紧密连接负责封闭细胞间空间和调节选择性的细胞旁路转运，是上皮通透性调控阀。因此，完整的肠上皮及紧密连接是肠道屏障的重要组成部分。

姜黄素可通过 AMPL-TFEB 信号通路促进线粒体自噬，改善线粒体功能，对抗氧化应激导致的肠上皮损伤[37]。此外，紧密连接的异常可导致细胞旁路转运的通透性改变。Ghosh 等[38]发现姜黄素可增加人类结肠 Caco-2 肠上皮细胞 ZO-1 和 Claudin-1 的含量，降低细胞旁路通透性、改善肠道屏障功能。Wang 等[39]报道姜黄素可降低细菌源性内毒素 LPS 及 IL-1β，进而减少 ZO-1、Claudin-1、Claudin-7 和肌动蛋白丝的降解，从而维持肠道屏障完整。此外，Tian 等[40]亦证明姜黄素可通过促进 ZO-1 蛋白表达，修复肠上皮结构，恢复肠上皮通透性，进而保护肠道缺血/再灌注损伤。从以上数据不难看出，姜黄素具有保护第 5 层肠道屏障的作用。

3　总结

因生物利用度较差，传统药效学无法解释姜黄素的有益作用，而本文靶向肠道，系统阐述了姜黄素通过强 IAP 活性，维持肠道菌群稳态，促进黏液分泌，增加抗菌肽含量，维持肠上皮及紧密连接的完整，从而维持肠道屏障功能，减少内毒素、细菌等有害物质易位入血，进而抑制免疫系统的激活，减轻局部或全身慢性炎症，发挥其有益作用的具体机制。这一新机制的建立，为我们研究药物作用机制提供了一种全新的思路。而将来更进一步的研究可能聚焦于肠上皮细胞如何利用姜黄素以及阐明具体胞内作用机制。

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(收稿日期: 2020-07-28)