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文献综述 REVIEW

肠黏膜细胞的紧密连接与肠壁通透性的研究进展

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■背景资料
肠黏膜机械屏障主要由肠上皮细胞和相邻细胞间的连接构成, 位于肠上皮细胞间的连接方式有紧密连接、黏附连接、桥粒等, 其中紧密连接在维持肠壁通透性中作用最大. 紧密连接结构的破坏, 可导致肠壁通透性增高, 进而引起一系列病理生理变化.

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Advances in research of intestinal epithelial tight junctions and intestinal permeability

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Abstract
Intestinal epithelial tight junctions are a structural basis for the intestinal barrier and play an important role in the regulation of intestinal permeability. Increased intestinal permeability caused by the destruction of tight junctions may result in bacterial translocation, systemic inflammatory response, and multiple organ dysfunction syndrome. In this paper, we review the structure and function of tight junctions, factors affecting intestinal permeability, and measures for improving the dysfunction in intestinal permeability.

Key Words: Tight junction; Intestinal permeability; Cytokine

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摘要
肠黏膜细胞的紧密连接是构成肠黏膜屏障的重要结构基础, 在调节肠黏膜通透性中发挥着重要的作用. 其结构的破坏, 可导致肠壁通透性增高, 引起细菌移位、全身炎症反应及多器官功能受损. 本文就肠黏膜紧密连接的结构和功能、与通透性的影响因素及改善措施进行了综述.

关键词: 紧密连接; 肠壁通透性; 细胞因子

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0 引言
肠黏膜机械屏障主要由肠上皮细胞和相邻细胞间的连接构成, 位于肠上皮细胞间的连接方式有紧密连接、黏附连接、桥粒等, 其中紧密连接在维持肠壁通透性中作用最大[1,2]. 近年来, 有关紧密连接与肠壁通透性的研究已成为热点. 下面就国内外有关的研究进展作一综述.

1 肠黏膜细胞紧密连接的构成与生理功能
1.1 紧密连接的构成 肠黏膜紧密连接存在于黏膜细胞膜的边缘和顶部, 控制着细胞间通道开放, 是细胞旁路途径的第一道防线[3,4]. 在正常生理情况下, 紧密连接是完整的. 但在病理情况下, 其结构和功能则被破坏, 如氧化应激、NO等均可损伤紧密连接, 引起肠壁通透性增高, 导致肠道细菌的移位[5,6]. 紧密连接是由超过50种蛋白质组成的复合体, 结构十分复杂. 他不同于黏附连接和桥粒(黏膜细胞间存在15-20 nm的间隔), 是通过吻合点封闭细胞间隙[7]. 紧密连接主要由4种跨膜蛋白组成: occludin、claudins、junctional adhesion molecules (JAMs)和tricellulin. 他们与连接复合物蛋白(ZO-1、ZO-2、ZO-3、p130、7H6、Symplekin)、细胞骨架结构(微管、中丝、微丝)共同构成紧密连接复合物[8]. 跨膜蛋白通过连接复合物蛋白与细胞骨架连接在一起.

occludin蛋白是紧密连接中最早发现的蛋白, 大小为60 000-82 000 Da, 作为膜蛋白的必要成分, 细胞外有两个环, 细胞内有一个短的N端

和一个长的C端[9,10]. occludin蛋白在紧密连接中的定位主要是由磷酸化水平决定的[11]. 研究显示, occludin蛋白的胞外环型结构及跨膜结构主要参与肠壁通透性的调节[12]. Der p1的变应原能够水解occludin蛋白, 导致紧密连接结构破坏, 细胞旁路通透性增高[13].

JAMs属于免疫球蛋白超家族, 可表达于许多细胞[14,15]. 与其细胞外区域相连的配体, 可调节细胞旁路通透性[16]. JAM-A在紧密连接中的作用至关重要, Laukoetter等[17]对JAM-A缺失大鼠的肠黏膜分析, 发现白细胞渗透及淋巴细胞聚集增多, 肠壁通透增高.

诸多紧密连接蛋白中, claudin蛋白尤为重要[18]. 至今已发现有24种异构体[19]. claudin蛋白之间的链锁连接形成了细胞旁路途径, 是影响紧密连接通透性的主要因素. 最近研究发现, 在相邻细胞间, claudin-claudin连接方式可以发生在同源蛋白之间, 也可以发生在非同源蛋白之间. 这些连接方式成为肠黏膜屏障组织特异性的基础[20,21]. 除claudin-2、5、6表达增加能降低肠壁屏障功能外, 其他claudin蛋白的缺失能增加肠壁的通透性, 如claudin16蛋白突变可引起肾脏高镁血症[22]. claudin3, 4缺失导致细菌性毒素的产生[23]. 最近研究发现, claudin蛋白可以根据物质的大小、电荷调节通透性[24]. 大多数claudin蛋白是通过羧基端与ZO-1、ZO-2、ZO-3的C端连接在一起的[25]. 在连接复合体下方是肌动蛋白环, 肌动蛋白丝将连接复合体与肌动蛋白环相连, 他的收缩可以调节肠壁的通透性[26].

最重要的紧密连接调节通路是zonulin通路, 许多实验证实, zonulin的增加可致肠壁通透性增加[27,28]. Drago等[29]观察肠黏膜暴露于gliadin后, Caco-2细胞将zonulin释放于细胞表面. Zonulin通过与细胞表面的特殊受体结合, 活化了磷脂酶C, 然后水解磷脂酰纤维醇并释放纤维醇1、4、5磷酸盐以及甘油二酯. 细胞内Ca^{2+}离子释放, PKCα被激活, 活化的PKCα靶蛋白的磷酸化, 随后聚合肌动蛋白G和肌动蛋白F. 这种聚合作用促使肌动蛋白丝重排, 细胞骨架被调整, 包括ZO-1在内的蛋白从连接复合体移位, 肠黏膜紧密连接松弛, 黏膜通透性增加[29]. 一旦zonulin信号通路结束, 紧密连接又重新稳固[8].

1.2 紧密连接的生理功能

1.2.1 *通透性屏障功能*: 紧密连接调节着离子和大分子物质的跨细胞旁路的被动转运(允许离子及小分子可溶性物质通过, 而不允许毒性大分子及微生物通过).

1.2.2 *维持细胞极性功能*: 上皮细胞的顶部和基膜之间由于蛋白质和脂质的构成不同, 紧密连接结构可将细胞顶部和基底部分为不同的液性空间. 在相邻细胞的外侧浆膜可见连续的融合点, 即紧密连接线, 这些融合点可限制细胞的不同液性空间脂质和完整膜蛋白的自由扩散. 有研究学者认为, occludin参与该功能的形成与调控, Ebnet等[30]认为, 细胞极性的形成与JAM及极性蛋白PAR-3有关.

■*研发前沿*
为了防治肠黏膜细胞紧密连接所导致的肠壁通透性的增加, 国内外学者从多方面研究, 正致力于找到更有效、更全面的治疗措施, 这已成为近几年肠壁通透性研究的一大热点.

2 肠黏膜细胞的紧密连接与肠壁通透性

紧密连接与肠上皮细胞共同构成肠道的选择性屏障, 紧密连接一旦受损, 肠上皮细胞间隙通透性就会增加, 细菌或毒素借此进入体循环, 引起肠道感染, 甚至SIRS而危及生命. 以下就影响紧密连接及肠壁通透性的因素分别讨论.

2.1 *细菌及毒素* 大肠杆菌的致病性与肠上皮细胞间紧密连接结构的破坏有关. 国外学者通过实验发现, 致病性大肠杆菌(enteropathogenic *E. coli*, EPEC)可作用于紧密连接, 减少ZO-1、occludin和claudin-1蛋白的表达[31,32]. 产气荚膜杆菌通过与claudin-3、4的胞外成分结合, 形成的复合物使得黏膜形成孔道, Ca^{2+}内流, 触发宿主黏膜细胞凋亡, 导致通透性增高[33]. 还可通过其肠毒素改变claudin蛋白的再分布, 调节紧密连接的结构, 从而影响紧密连接通透性. 霍乱弧菌通过释放毒素HA/P, 破坏occludin与ZO-1的连接, 导致细胞骨架结构的瓦解, 紧密连接破坏, 引起肠壁通透性增高[34].

2.2 *细胞因子和炎症介质* 肠黏膜受损时, 可激发上皮细胞、巨噬细胞等产生大量炎性细胞因子作用于细胞间的紧密连接结构, 导致肠道屏障的破坏, 肠黏膜通透性升高. 如TNF-α、INF-γ可降低紧密连接蛋白ZO-1和occludin的表达, 导致紧密连接的瓦解, 增加黏膜通透性[35,36]. 爆发性肝脏疾病时, TNF-α增多, 通过下调occludin启动子表达, 从而使occludin蛋白表达下降, 致使肠壁通透性增加[37]. IFN-γ通过微胞饮的方式重新排列紧密连接蛋白, 使occludin表达失控, 引起通透性的增加[38]. 体外研究还发现, TNF-α、INF-γ在破坏紧密连接方面具有协同作用[39]. IL-4和IL-13可导致细胞凋亡并破坏claudin-2从而增加黏膜通透性. 有研究学者通过实验证实了这点[40,41]. 内毒素可使诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)合成增加, 导致NO产生过

■相关报道
杨俊等报道乳酸菌可改善EIEC感染后Caco-2的细胞骨架结构, 增加紧密连接相关蛋白表达, 从而起到降低肠壁通透性, 保护肠屏障的作用.

量, NO与过氧化物反应, 形成过氧化亚硝酸盐, 可通过氧化铁-硫中心、蛋白质羟基、破坏细胞肌动蛋白骨架、松解肠上皮细胞间的紧密连接等方式破坏肠上皮细胞屏障功能, 增加肠壁通透性[42].

2.3 其他因素 生冷食物和多脂饮食通过抑制紧密连接蛋白occludin、claudin-1、claudin-3以及JAM-1的表达增加肠壁的通透性[43,44]. 最近研究表明, 辣椒素也可以影响肠黏膜通透性, Tsukura等[45]通过实验证实, 分子大小在(100-200 μm)的辣椒素对Caco-2细胞结构和功能有破坏作用, 导致肠壁通透性增加. Lammers等[46]在探索gliadin与肠黏膜作用后引起肠壁功能障碍的机制时, 发现gliadin与CXCR-3结合形成复合物并将其与MyD88联系在一起, 增加zonulin的释放从而增加肠壁的通透性. 热休克蛋白可改善温度增高对肠壁通透性的影响, 其可能的机制是热休克蛋白对occludin蛋白的表达调控作用[47]. 另外, 用乙醛干预的细胞增殖后, 肠壁通透性增加, 可能与ZO-1络氨酸磷酸化有关[48].

3 改善肠黏膜细胞的紧密连接与肠壁通透性的措施

近些年来, 关于防治紧密连接破坏所致的肠壁通透性增加方法学的研究包括营养支持、抗氧化剂、益生菌、中草药等.

3.1 营养支持 谷氨酰胺(Gln)是肠道黏膜细胞代谢所必须的物质, 对维持肠道黏膜上皮结构的完整性起着重要的作用[49]. Gln可直接或间接地影响肠道上皮细胞内的介质, 如cAMP和Ca^{2+}, 以增加细胞间紧密连接程度、改变紧密连接对流动物质的选择性和降低乳糖跨紧密连接的弥散率. 动物实验及临床研究均证实, Gln可有效维持肠道黏膜结构, 防止肠道通透性改变[50,51]. 但是van den Berg等[52]在对极低体质量出生新生儿的实验中应用谷氨酸盐并不能改善肠壁通透性的增高, 其机制还未清楚. 另有研究发现, 精氨酸也可降低肠梗阻鼠血浆中内毒素含量, 减少肠道屏障紧密连接破坏和降低通透性, 减少内毒素对机体免疫功能的损害[53-55].

3.2 抗氧自由基、细胞因子、炎症介质的治疗 一些细胞因子抗体可抑制iNOS表达, 减少NO生成. Francés等[56]就报道TNF-α抗体可明显减少自由基生成, 一定程度上缓解了肠壁通透性. Akyürek等[57]还试图应用血小板激活因子的拮抗剂-BN52021修复损伤肠黏膜, 以缓解肠上皮增高的通透性. 胰岛素样生长因子-1(insulin-like growth factor 1, IGF-1)是体内普遍存在的多肽, IGF-1改善肠壁通透性的机制可能是抑制了TNF-α及COX-2等细胞因子表达释放, 从而避免了NO增加. 体内研究已发现给肝硬化大鼠补充IGF-1可以保护肠壁黏膜细胞、减少细菌易位[58,59]. Hadjiyanni等[60]通过对1-型糖尿病大鼠研究, 观察得出胰高血糖素样肽-2虽不能改变1-型糖尿病的发生但他可却降低肠壁通透性. 研究显示前列腺素可以保护肠黏膜细胞之间紧密连接复合体, 阻挡肠道中有害物质穿透肠黏膜, 从而保护肠黏膜通透性[61].

3.3 益生菌 补充益生菌可恢复肠道微生物平衡, 抑制外源性致病菌过度增长, 促进肠上皮细胞黏蛋白及sIgA的分泌, 修复肠道黏膜屏障等作用. Resta-Lenert等[62]研究发现, 乳酸菌和双歧杆菌通过维护细胞骨架和ZO-1蛋白及occludin表达, 对表皮生长因子刺激作用增强. 修复EPEC引起的破坏作用. Puthenedam等[63]也证实了这点. 国内学者杨俊等[64]报道, 乳酸菌应用于侵袭性大肠杆菌(enteroinvasive *E.coli*, EIEC)感染后的肠上皮细胞, 表现为细胞骨架表达增多, 紧密连接相关蛋白(claudin, occludin, JAM-1, ZO-1)表达亦增加, 肠壁通透性较感染后明显改善. White等[65]报道乳酸杆菌属(LP299)在防止肠壁通透性的发展中也起到了重要的作用, 但其机制尚不十分清楚. Anderson等[66]最新研究发现, 乳酸菌MB452能够保护肠屏障, 其机制可能是提高了紧密连接相关基因的表达.

3.4 中草药 大黄、参附注射液、四君子汤等对内毒素的生物活性有一定的拮抗作用, 能消除氧自由基、减少TNF-α、IL-6、NO等细胞因子和炎性介质的合成与释放、阻止细菌及毒素进入血循环、维持跨膜电位差等保护黏膜屏障, 降低肠壁通透性[67].

3.5 锌、钙 Zhang等[68]通过对断奶后仔猪应用锌后, 发现肠通透性降低, 且occludin和ZO-1表达增加, 说明锌降低肠壁通透性的主要机制可能是增加了occludin和ZO-1的表达, 从而能够解释在临床上应用锌可起到对腹泻的改善作用. Schepens等[69]对炎症性肠病大鼠应用钙可改善肠黏膜屏障, 降低通透性. 其机制可能与减少黏膜刺激有关.

3.6 其他途径 Temmesfeld-Wollbrück等[70]通过实验证实肾上腺髓质素(adrenomedullin, AM)能够改善肠壁屏障功能和全身炎症反应, 其主要是

通过增加cAMP来保护肠屏障, 但是AM并不能引起Caco-2细胞cAMP的增加. PDE可降低cAMP的含量, 应用PDE抑制物也不能使AM引起的cAMP增加, 说明AM是通过独立的途径作用于Caco-2细胞的cAMP, 从而起到保护肠黏膜的作用的. Park等[71]对神经节苷脂(ganglioside, GGS)研究显示, GGS饮食能够增加IL-10的含量, 减少NO及肠紧密连接蛋白的下降, 进而降低肠壁通透性. Suzuki等[72]通过实验证实Kaempferol能促使肌动蛋白骨架与紧密连接蛋白结合, 从而提高肠屏障功能.

4 结论

肠上皮细胞的紧密连接在肠壁通透性中发挥着重要的作用, 许多因素影响紧密连接的结构, 导致肠壁通透性的增加, 从而引起细菌移位, 全身炎症反应等. 因而可从改善紧密连接的角度出发, 寻求改善肠壁通透性的方法, 为临床治疗提供新思路.

5 参考文献

1 Schneeberger EE, Lynch RD. The tight junction: a multifunctional complex. *Am J Physiol Cell Physiol* 2004; 286: C1213-C1228
2 Förster C. Tight junctions and the modulation of barrier function in disease. *Histochem Cell Biol* 2008; 130: 55-70
3 Terry S, Nie M, Matter K, Balda MS. Rho signaling and tight junction functions. *Physiology* (Bethesda) 2010; 25: 16-26
4 白爱平. 炎症性肠病肠黏膜屏障损伤机制. 世界华人消化杂志 2008; 16: 3187-3191
5 Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; 49: 1877-1887
6 Assimakopoulos SF, Tsamandas AC, Louvros E, Vagianos CE, Nikolopoulou VN, Thomopoulos KC, Charonis A, Scopa CD. Intestinal epithelial cell proliferation, apoptosis and expression of tight junction proteins in patients with obstructive jaundice. *Eur J Clin Invest* 2011; 41: 117-125
7 Tsukita S, Furuse M, Itoh M. Multifunctional strands in tight junctions. *Nat Rev Mol Cell Biol* 2001; 2: 285-293
8 Visser J, Rozing J, Sapone A, Lammers K, Fasano A. Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms. *Ann N Y Acad Sci* 2009; 1165: 195-205
9 Hartsock A, Nelson WJ. Adherens and tight junctions: structure, function and connections to the actin cytoskeleton. *Biochim Biophys Acta* 2008; 1778: 660-669
10 Harhaj NS, Antonetti DA. Regulation of tight junctions and loss of barrier function in pathophysiology. *Int J Biochem Cell Biol* 2004; 36: 1206-1237
11 Suzuki T, Elias BC, Seth A, Shen L, Turner JR, Giorgianni F, Desiderio D, Guntaka R, Rao R. PKC eta regulates occludin phosphorylation and epithelial tight junction integrity. *Proc Natl Acad Sci U S A* 2009; 106: 61-66
12 Mitic LL, Van Itallie CM, Anderson JM. Molecular physiology and pathophysiology of tight junctions I. Tight junction structure and function: lessons from mutant animals and proteins. *Am J Physiol Gastrointest Liver Physiol* 2000; 279: G250-G254
13 Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ, Stewart GA, Taylor GW, Garrod DR, Cannell MB, Robinson C. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. *J Clin Invest* 1999; 104: 123-133
14 Ebnet K, Suzuki A, Ohno S, Vestweber D. Junctional adhesion molecules (JAMs): more molecules with dual functions? *J Cell Sci* 2004; 117: 19-29
15 Liu Y, Nusrat A, Schnell FJ, Reaves TA, Walsh S, Pochet M, Parkos CA. Human junction adhesion molecule regulates tight junction resealing in epithelia. *J Cell Sci* 2000; 113 (Pt 13): 2363-2374
16 Bazzoni G. The JAM family of junctional adhesion molecules. *Curr Opin Cell Biol* 2003; 15: 525-530
17 Laukoetter MG, Nava P, Lee WY, Severson EA, Capaldo CT, Babbin BA, Williams IR, Koval M, Peatman E, Campbell JA, Dermody TS, Nusrat A, Parkos CA. JAM-A regulates permeability and inflammation in the intestine in vivo. *J Exp Med* 2007; 204: 3067-3076
18 Koval M. Claudins--key pieces in the tight junction puzzle. *Cell Commun Adhes* 2006; 13: 127-138
19 Amasheh S, Fromm M, Günzel D. Claudins of intestine and nephron - a correlation of molecular tight junction structure and barrier function. *Acta Physiol* (Oxf) 2011; 201: 133-140
20 Turksen K, Troy TC. Barriers built on claudins. *J Cell Sci* 2004; 117: 2435-2447
21 Krause G, Winkler L, Mueller SL, Haseloff RF, Piontek J, Blasig IE. Structure and function of claudins. *Biochim Biophys Acta* 2008; 1778: 631-645
22 Cereijido M, Contreras RG, Flores-Benítez D, Flores-Maldonado C, Larre I, Ruiz A, Shoshani L. New diseases derived or associated with the tight junction. *Arch Med Res* 2007; 38: 465-478
23 Sonoda N, Furuse M, Sasaki H, Yonemura S, Katahira J, Horiguchi Y, Tsukita S. Clostridium perfringens enterotoxin fragment removes specific claudins from tight junction strands: Evidence for direct involvement of claudins in tight junction barrier. *J Cell Biol* 1999; 147: 195-204
24 Gupta IR, Ryan AK. Claudins: unlocking the code to tight junction function during embryogenesis and in disease. *Clin Genet* 2010; 77: 314-325
25 Itoh M, Furuse M, Morita K, Kubota K, Saitou M, Tsukita S. Direct binding of three tight junction-associated MAGUKs, ZO-1, ZO-2, and ZO-3, with the COOH termini of claudins. *J Cell Biol* 1999; 147: 1351-1363
26 Anderson JM. Molecular structure of tight junctions and their role in epithelial transport. *News Physiol Sci* 2001; 16: 126-130
27 Wang W, Uzzau S, Goldblum SE, Fasano A. Human zonulin, a potential modulator of intestinal tight junctions. *J Cell Sci* 2000; 113 Pt 24: 4435-4440
28 Smecuol E, Sugai E, Niveloni S, Vázquez H, Pedreira S, Mazure R, Moreno ML, Label M, Mauriño E, Fasano A, Meddings J, Bai JC. Permeability,

■创新盘点
改善肠屏障功能的措施已有很多学者总结报道, 但从改善紧密连接的角度出发, 改善肠壁通透性的报道比较少, 本文就这方面结合近几年的研究进行了总结.

■**应用要点**
通过本文可以了解目前紧密连接与肠壁通透性的研究进展, 为广大学者今后深入的研究提供帮助, 为临床治疗提供新的思路.

zonulin production, and enteropathy in dermatitis herpetiformis. *Clin Gastroenterol Hepatol* 2005; 3: 335-341
29 Drago S, El Asmar R, Di Pierro M, Grazia Clemente M, Tripathi A, Sapone A, Thakar M, Iacono G, Carroccio A, D'Agate C, Not T, Zampini L, Catassi C, Fasano A. Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. *Scand J Gastroenterol* 2006; 41: 408-419
30 Ebnet K, Iden S, Gerke V, Suzuki A. Regulation of epithelial and endothelial junctions by PAR proteins. *Front Biosci* 2008; 13: 6520-6536
31 Muza-Moons MM, Schneeberger EE, Hecht GA. Enteropathogenic Escherichia coli infection leads to appearance of aberrant tight junctions strands in the lateral membrane of intestinal epithelial cells. *Cell Microbiol* 2004; 6: 783-793
32 Shifflett DE, Clayburgh DR, Koutsouris A, Turner JR, Hecht GA. Enteropathogenic E. coli disrupts tight junction barrier function and structure in vivo. *Lab Invest* 2005; 85: 1308-1324
33 Chakrabarti G, McClane BA. The importance of calcium influx, calpain and calmodulin for the activation of CaCo-2 cell death pathways by Clostridium perfringens enterotoxin. *Cell Microbiol* 2005; 7: 129-146
34 Wu Z, Nybom P, Magnusson KE. Distinct effects of Vibrio cholerae haemagglutinin/protease on the structure and localization of the tight junction-associated proteins occludin and ZO-1. *Cell Microbiol* 2000; 2: 11-17
35 Patrick DM, Leone AK, Shellenberger JJ, Dudowicz KA, King JM. Proinflammatory cytokines tumor necrosis factor-alpha and interferon-gamma modulate epithelial barrier function in Madin-Darby canine kidney cells through mitogen activated protein kinase signaling. *BMC Physiol* 2006; 6: 2
36 崔巍, 刘沛. 肿瘤坏死因子受体1在暴发性肝衰竭肠黏膜屏障功能损害中的作用. 中华肝脏病杂志 2007; 15: 542-543
37 崔巍, 马力, 闻颖, 刘沛. 暴发性肝衰竭时肠上皮细胞间紧密连接蛋白occludin表达下降. 世界华人消化杂志 2006; 14: 3008-3012
38 Utech M, Ivanov AI, Samarin SN, Bruewer M, Turner JR, Mrsny RJ, Parkos CA, Nusrat A. Mechanism of IFN-gamma-induced endocytosis of tight junction proteins: myosin II-dependent vacuolarization of the apical plasma membrane. *Mol Biol Cell* 2005; 16: 5040-5052
39 张强, 李秋荣, 王萌, 马健, 黎介寿. 肿瘤坏死因子和干扰素对肠上皮紧密连接的破坏作用. 肠内与肠内营养 2006; 13: 335-337
40 Ceponis PJ, Botelho F, Richards CD, McKay DM. Interleukins 4 and 13 increase intestinal epithelial permeability by a phosphatidylinositol 3-kinase pathway. Lack of evidence for STAT 6 involvement. *J Biol Chem* 2000; 275: 29132-29137
41 Madden KB, Whitman L, Sullivan C, Gause WC, Urban JF Jr, Katona IM, Finkelman FD, Shea-Donohue T. Role of STAT6 and mast cells in IL-4- and IL-13-induced alterations in murine intestinal epithelial cell function. *J Immunol* 2002; 169: 4417-4422
42 Han X, Fink MP, Yang R, Delude RL. Increased iNOS activity is essential for intestinal epithelial tight junction dysfunction in endotoxemic mice. *Shock* 2004; 21: 261-270
43 Polimeno L, Loiacono M, Pesetti B, Mallamaci R, Mastrodonato M, Azzarone A, Annoscia E, Gatti F, Amoruso A, Ventura MT. Anisakiasis, an underestimated infection: effect on intestinal permeability of Anisakis simplex-sensitized patients. *Foodborne Pathog Dis* 2010; 7: 809-814
44 Suzuki T, Hara H. Dietary fat and bile juice, but not obesity, are responsible for the increase in small intestinal permeability induced through the suppression of tight junction protein expression in LETO and OLETF rats. *Nutr Metab* (Lond) 2010; 7: 19
45 Tsukura Y, Mori M, Hirotani Y, Ikeda K, Amano F, Kato R, Ijiri Y, Tanaka K. Effects of capsaicin on cellular damage and monolayer permeability in human intestinal Caco-2 cells. *Biol Pharm Bull* 2007; 30: 1982-1986
46 Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, Rallabhandi P, Shea-Donohue T, Tamiz A, Alkan S, Netzel-Arnett S, Antalis T, Vogel SN, Fasano A. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology* 2008; 135: 194-204.e3
47 Dokladny K, Moseley PL, Ma TY. Physiologically relevant increase in temperature causes an increase in intestinal epithelial tight junction permeability. *Am J Physiol Gastrointest Liver Physiol* 2006; 290: G204-G212
48 Hamada K, Shitara Y, Sekine S, Horie T. Zonula Occludens-1 alterations and enhanced intestinal permeability in methotrexate-treated rats. *Cancer Chemother Pharmacol* 2010; 66: 1031-1038
49 宋怀宇, 杨建荣. 肝病患者肠黏膜屏障功能的变化及谷氨酰胺干预的研究进展. 世界华人消化杂志 2009; 17: 2798-2802
50 邓志云, 郭光华, 杨毅. 早期肠内谷氨酰胺补给对烫伤大鼠肠黏膜细胞紧密连接的影响. 世界华人消化杂志 2009; 17: 2031-2036
51 Fukatsu K, Kudsk KA, Zarzaur BL, Wu Y, Hanna MK, DeWitt RC. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. *Shock* 2001; 15: 318-322
52 van den Berg A, Fetter WP, Westerbeek EA, van der Vegt IM, van der Molen HR, van Elburg RM. The effect of glutamine-enriched enteral nutrition on intestinal permeability in very-low-birth-weight infants: a randomized controlled trial. *JPEN J Parenter Enteral Nutr* 2006; 30: 408-414
53 Fan J, Meng Q, Guo G, Xie Y, Li X, Xiu Y, Li T, Ma L. Effects of early enteral nutrition supplemented with arginine on intestinal mucosal immunity in severely burned mice. *Clin Nutr* 2010; 29: 124-130
54 Tan B, Yin Y, Kong X, Li P, Li X, Gao H, Li X, Huang R, Wu G. L-Arginine stimulates proliferation and prevents endotoxin-induced death of intestinal cells. *Amino Acids* 2010; 38: 1227-1235
55 Viana ML, Santos RG, Generoso SV, Arantes RM, Correia MI, Cardoso VN. Pretreatment with arginine preserves intestinal barrier integrity and reduces bacterial translocation in mice. *Nutrition* 2010; 26: 218-223
56 Francés R, Chiva M, Sánchez E, González-Navajas JM, Llovet T, Zapater P, Soriano G, Muñoz C, Balanzó J, Pérez-Mateo M, Song XY, Guarner C, Such J. Bacterial translocation is downregulated by anti-

TNF-alpha monoclonal antibody administration in rats with cirrhosis and ascites. *J Hepatol* 2007; 46: 797-803
57 Akyürek N, Salman B, Irkörücü O, Tezcaner T, Azili C, Erdem O, Akca G, Akin O, Tatlicioglu E. The effect of platelet activating factor antagonist BN 52021 on bacterial translocation and ICAM-I expression in experimental obstructive jaundice. *J Invest Surg* 2005; 18: 247-256
58 Lorenzo-Zúñiga V, Rodríguez-Ortigosa CM, Bartolí R, Martínez-Chantar ML, Martínez-Peralta L, Pardo A, Ojanguren I, Quiroga J, Planas R, Prieto J. Insulin-like growth factor I improves intestinal barrier function in cirrhotic rats. *Gut* 2006; 55: 1306-1312
59 Conchillo M, de Knegt RJ, Payeras M, Quiroga J, Sangro B, Herrero JI, Castilla-Cortazar I, Frystyk J, Flyvbjerg A, Yoshizawa C, Jansen PL, Scharschmidt B, Prieto J. Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: results of a pilot randomized controlled clinical trial. *J Hepatol* 2005; 43: 630-636
60 Hadjiyanni I, Li KK, Drucker DJ. Glucagon-like peptide-2 reduces intestinal permeability but does not modify the onset of type 1 diabetes in the nonobese diabetic mouse. *Endocrinology* 2009; 150: 592-599
61 Flores-Benitez D, Rincon-Heredia R, Razgado LF, Larre I, Cereijido M, Contreras RG. Control of tight junctional sealing: roles of epidermal growth factor and prostaglandin E2. *Am J Physiol Cell Physiol* 2009; 297: C611-C620
62 Resta-Lenert S, Smitham J, Barrett KE. Epithelial dysfunction associated with the development of colitis in conventionally housed mdr1a-/- mice. *Am J Physiol Gastrointest Liver Physiol* 2005; 289: G153-G162
63 Puthenedam M, Williams PH, Lakshmi BS, Balakrishnan A. Modulation of tight junction barrier function by outer membrane proteins of enteropathogenic Escherichia coli: role of F-actin and junctional adhesion molecule-1. *Cell Biol Int* 2007; 31: 836-844
64 杨俊, 张中伟, 秦环龙. 乳酸菌对肠上皮细胞侵袭性大肠杆菌损伤的保护作用. 世界华人消化杂志 2008; 16: 3394-3399
65 White JS, Hoper M, Parks RW, Clements WD, Diamond T, Bengmark S. The probiotic bacterium Lactobacillus plantarum species 299 reduces intestinal permeability in experimental biliary obstruction. *Lett Appl Microbiol* 2006; 42: 19-23
66 Anderson RC, Cookson AL, McNabb WC, Park Z, McCann MJ, Kelly WJ, Roy NC. Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC Microbiol* 2010; 10: 316
67 张英谦, 刘建华, 李佃贵, 孙波. 大黄对脓毒症幼猪肠屏障保护作用及机制研究. 中华中医药杂志 2007; 22: 843-847
68 Zhang B, Guo Y. Supplemental zinc reduced intestinal permeability by enhancing occludin and zonula occludens protein-1 (ZO-1) expression in weaning piglets. *Br J Nutr* 2009; 102: 687-693
69 Schepens MA, Schonewille AJ, Vink C, van Schothorst EM, Kramer E, Hendriks T, Brummer RJ, Keijer J, van der Meer R, Bovee-Oudenhoven IM. Supplemental calcium attenuates the colitis-related increase in diarrhea, intestinal permeability, and extracellular matrix breakdown in HLA-B27 transgenic rats. *J Nutr* 2009; 139: 1525-1533
70 Temmesfeld-Wollbrück B, Brell B, zu Dohna C, Dorenberg M, Hocke AC, Martens H, Klar J, Suttorp N, Hippenstiel S. Adrenomedullin reduces intestinal epithelial permeability in vivo and in vitro. *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G43-G51
71 Park EJ, Thomson AB, Clandinin MT. Protection of intestinal occludin tight junction protein by dietary gangliosides in lipopolysaccharide-induced acute inflammation. *J Pediatr Gastroenterol Nutr* 2010; 50: 321-328
72 Suzuki T, Tanabe S, Hara H. Kaempferol enhances intestinal barrier function through the cytoskeletal association and expression of tight junction proteins in Caco-2 cells. *J Nutr* 2011; 141: 87-94

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■同行评价
本文科学性和可读性较好, 能较好的反映目前领域的水平, 具有很好的参考价值.

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• 消息 •

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