·学术前沿:肠道菌群与屏障功能专题·

高原环境致肠道屏障损伤的研究进展

彭 元,朱敏侠
(西藏民族大学医学院高原低氧环境与生命健康实验室,陕西 咸阳 712082)

摘 要:肠道屏障的完整性是肠道发挥生理功能的基础,对维持机体营养吸收、抗原阻隔和免疫稳态至关重要。高原环境以低压低氧为核心特征,常叠加寒冷、强紫外线、运动负荷增加、脱水及饮食改变等复合应激,可导致肠道机械、化学、免疫及生物这4层屏障协同失衡,从而诱发局部乃至全身炎症反应。现有研究显示,高原相关肠道屏障损伤并非由单一通路驱动,而是缺氧诱导因子-1α(HIF-1α)、核因子-κB(NF-κB)等低氧—炎症信号异常激活,Notch与Wnt/β-catenin信号通路异常增强协同导致杯状细胞减少与黏蛋白2(MUC2)分泌不足,辅助性T细胞17/调节性T细胞(Th17/Treg)失衡与NOD样受体热蛋白结构域相关蛋白3(NLRP3)炎性小体活化,以及肠道菌群失调与短链脂肪酸(SCFAs)保护作用减弱等多环节共同介导。本文系统梳理了高原环境致肠道屏障损伤的分子机制,并在此基础上提出"适应—失代偿"转化下的多机制协同模型,并结合急进高原场景,总结了改善肠道屏障损伤的相关干预策略的证据进展与局限性,以期为高原相关肠道损伤的预防与干预提供理论依据与实践参考。

关键词:肠道屏障;高原环境;肠道菌群;损伤机制;多机制协同模型;干预策略
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Research Progress on Intestinal Barrier Injury in High-altitude Environments

PENG Yuan, ZHU Minxia
(Key Laboratory of High Altitude Hypoxia Environment and Life Health, School of Medicine, Xizang Minzu University, Xianyang 712082, China)
Correspondence to: ZHU Minxia; E-mail: mxzhu@xzmu.edu.cn

Abstract: The integrity of the intestinal barrier is the basis of physiological function of the intestine, which is essential for maintaining nutrient absorption, antigen exclusion, and immune homeostasis. High-altitude environments are characterized by hypobaric hypoxia and are often complicated by combined stresses such as cold, intense ultraviolet radiation, increased physical exertion, dehydration, and dietary changes. These factors may lead to synergistic dysfunction of the mechanical, chemical, immune, and biological barriers of the intestine, thereby inducing local or systemic inflammatory responses. Current evidence indicates that high-altitude-related intestinal barrier injury is not driven by a single pathway but is co-mediated by multiple factors: aberrant activation of hypoxia-inflammation signaling pathways, including hypoxia-inducible factor-1α (HIF-1α) and nuclear factor-κB (NF-κB); synergistic enhancement of Notch and Wnt/β-catenin signaling pathways leading to goblet cell reduction and insufficient mucin 2 (MUC2) secretion; imbalance of T helper 17/regulatory T cells (Th17/Treg) and activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome; as well as gut microbiota dysbiosis and weakened protective effects of short-chain fatty acids (SCFAs). This article systematically reviews the molecular mechanisms underlying high-altitude-induced intestinal barrier injury, and proposes a multi-mechanism synergistic model under the "adaptation-decompensation"

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作者简介:彭元,第一作者,研究方向:高原病发病机制与干预研究,E-mail: 19861658972@163.com;朱敏侠,通信作者,教授,研究方向:高原病发病机制与干预研究,E-mail: mxzhu@xzmu.edu.cn

framework on this basis. Combined with scenarios of acute high-altitude exposure, it summarizes the evidence progress and limitations of intervention strategies of ameliorating intestinal barrier injury, aiming to provide a theoretical basis and practical reference for the prevention and intervention of high-altitude-related intestinal injury.

Key words: intestinal barrier; high-altitude environment; gut microbiota; injury mechanisms; multi-mechanism synergistic model; intervention strategies

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高原地区以低压低氧为主要环境应激特征,常伴低温、强紫外线等环境暴露[1]。现有研究提示,高原暴露,尤其是急性低压低氧暴露,可通过氧化应激增强、肠道菌群失衡及黏膜受损等途径增加肠道屏障功能发生风险,并进一步诱发局部乃至全身炎症反应[1-4]。对于短时间由平原进入高原地区的人群,急性高原病的发生风险显著升高[5]。除头痛、乏力、头晕、睡眠障碍及恶心等典型临床表现外[6],部分个体还可出现腹胀、腹部不适、腹泻等胃肠道症状[7],严重时甚至可发生胃肠道黏膜损伤及消化道出血[8]。这些临床现象提示,肠道可能是高原应激中的易损靶器官之一。

目前,高原医学相关研究多聚焦于急性高原病及高原脑水肿及高原肺水肿等方面,针对高原环境所致肠道屏障损伤的系统研究相对匮乏。基于此,本文围绕高原环境诱导肠道屏障损伤的分子机制及干预策略研究进展进行综述,分析现有研究的局限性,并对未来研究方向加以展望,以期为高原环境所致肠道损伤的防治提供理论依据与研究思路。

1 肠道屏障组成与肠道屏障损伤的病理学改变

1.1 肠道屏障组成

肠道屏障由机械屏障、化学屏障、免疫屏障及生物屏障共同构成[9],其完整性对于维持机体营养吸收、抗原阻隔及免疫稳态至关重要[10-11]。机械屏障主要由肠道上皮细胞(intestinal epithelial cells, IECs)及其细胞间连接复合体构成[9]。相邻IECs通过紧密连接(tight junction, TJ)、黏着连接和桥粒形成顶端连接复合体,其中TJ位于细胞顶端侧,是调控旁细胞通透性、维持上皮极性和屏障选择性的关键结构[12]。化学屏障主要由覆盖肠上皮表面的黏液层及其所含黏蛋白(mucin, MUC)、消化液成分、溶菌酶和其他抗菌分子构成,可通过阻隔、灭活或抑制病原菌黏附与侵袭,减少腔内有害成分与上皮直接接触[9]。免疫屏障以肠相关淋巴组织为核心[13],联合固有层及上皮内免疫细胞、分泌型IgA(secretory IgA, sIgA)以及抗菌肽等,共同介导病原清除与免疫排斥[9, 14]。生物屏障主要由共生菌群及其代谢产物构成[9]。稳态菌群可通过定植抗力抑制致病菌过度增殖[9],并借助短链脂肪酸(short chain fatty acids, SCFAs)等代谢物维持IECs能量代谢与TJ稳态,同时调节局部免疫反应[15]。上述各类屏障并非彼此孤立,而是通过上皮、黏液、免疫、菌群之间的双向调控共同维持肠道内环境稳态,任一层面受损均可能引发其余屏障的继发性失衡,进而导致肠黏膜稳态破坏[16]。

1.2 高原环境致肠道屏障损伤的病理学改变

高原环境致肠道屏障损伤的主要环境应激因素为低压低氧,且常伴寒冷、强紫外线及体力负荷增加等复合应激[1],其病理学改变以多层屏障同步受损为主要特征。机械屏障方面,急性或持续低压低氧暴露可导致IECs脱落,并伴随claudin-1、occludin和ZO-1等TJ蛋白表达下调,进而导致TJ复合体破坏、上皮通透性升高[2, 17]。化学屏障主要表现为杯状细胞(goblet cell, GC)减少、黏液层变薄及MUC2表达与分泌减少[18],进而削弱黏膜表面的物理隔离作用,使脂多糖(lipopolysaccharide, LPS)等微生物相关分子及其他炎症刺激更易接近上皮表面,从而进一步放大局部炎症反应并加剧肠道屏障破坏[19]。免疫屏障呈现“炎症放大”与“防御失衡”并存的异常现象,表现为促炎细胞因子上调[17],以及黏膜免疫稳态紊乱,包括sIgA异常改变和肠道相关免疫细胞群重塑,进而增加病原及其产物易位和继发感染风险[20]。生物屏障的病理学改变主要为肠道菌群结构失调,包括*Faecalibacterium*等SCFAs相关有益菌减少,以及*Enterobacteriaceae*等机会致病菌相关群类增多[4, 21]。上述改变可通

过促进肠道通透性升高和炎症反应放大，进一步加剧肠道屏障损伤，形成菌群失衡—炎症激活—屏障破坏的恶性循环[22]。综上，高原环境下肠道屏障损伤表现为多层屏障协同失衡，而非单一结构的局部破坏。

2　高原环境下肠道屏障损伤的机制

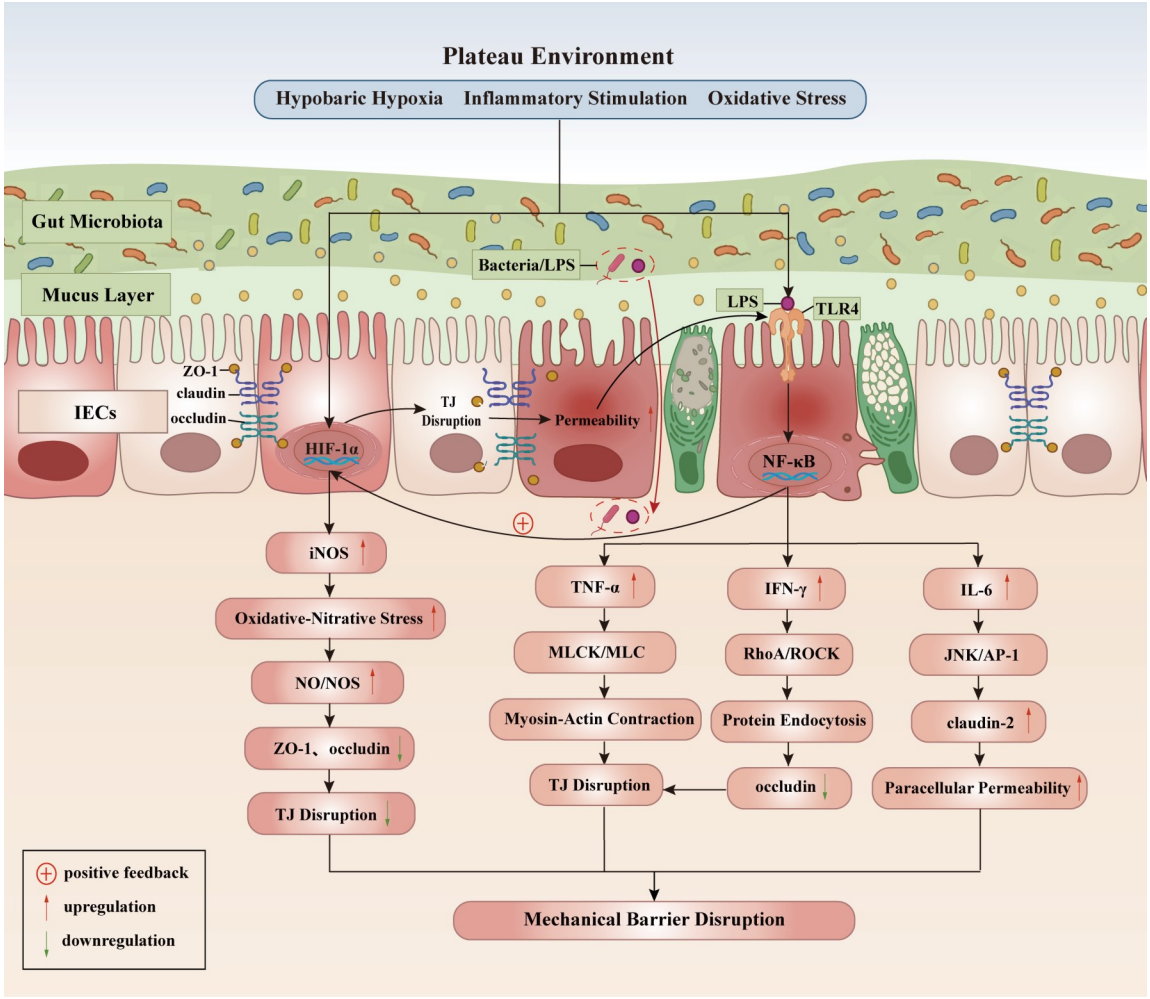
2.1　机械屏障与肠道屏障损伤

在高原环境下，机械屏障的破坏是由缺氧诱导因子-1α（hypoxia-inducible factor-1α，HIF-1α）与核因子-κB（nuclear factor kappa-B，NF-κB）构成的“低氧-炎症”交互信号轴协同介导的病理过程。HIF-1α作为肠道低氧应答的核心转录因子，其功能具有明显的环境依赖性，在生理性低氧微环境中有助于维持上皮稳态[23]。高原低氧环境首先由细胞内的氧感受器感知，并进一步激活缺氧诱导因子信号通路。在常氧条件下，HIF-1α经脯氨酰羟化酶羟基化后迅速被VHL E3泛素连接酶识别并降解[24]；低氧时，脯氨酰羟化酶活性受抑，HIF-1α稳定化并转位入核，与组成型表达的HIF-1β形成异源二聚体，启动缺氧反应元件依赖的基因转录程序[24]。其中，HIF依赖性信号可通过与claudin-1启动子区域低氧应答元件的结合直接增强其转录表达，从而维持TJ完整性与机械屏障功能[25]。然而，在高原急性或持续低压低氧暴露条件下，由于组织氧分压急剧下降且难以恢复至常氧水平，HIF-1α可由生理或早期适应性应答逐渐转为异常激活，并参与机械屏障损伤过程[26]。一方面，IECs内氧分压急剧下降可导致HIF-1α持续高表达并发生核转位[16, 27]，其异常激活与occludin、ZO-1等TJ蛋白表达下降受损密切相关[16]，进而引起TJ破坏、肠道通透性升高[27]。LPS等细菌产物易位随之增加，激活Toll样受体4（Toll-like receptor 4，TLR4）通路并促进NF-κB核转位[28]，诱导肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白介素-6（interleukin-6，IL-6）等炎症介质大量释放[29]。这些炎症介质可通过不同分子通路破坏TJ稳态。TNF-α可通过NF-κB依赖的肌球蛋白轻链激酶（myosin light chain kinase，MLCK）转录激活及肌球蛋白轻链（myosin light chain，MLC）磷酸化，诱导肌动蛋白-肌球蛋白收缩并破坏TJ复合体[30]；干扰素-γ（interferon-γ，IFN-γ）则可通过Ras同源基因家族成员A/Rho相关卷曲螺旋形成蛋白激酶依赖的TJ蛋白内吞促使occludin从膜表面移位[31-32]；IL-6则可通过c-Jun氨基末端激酶/激活蛋白1（c-Jun N-terminal kinase/activator protein 1，JNK/AP-1）通路上调成孔型紧TJ蛋白claudin-2表达，进一步增加旁细胞通透性[33-34]。这3条通路在高原低氧背景下被同步激活，共同导致TJ蛋白表达下调、定位异常，最终造成机械屏障完整性下降。另一方面，NF-κB还可在转录水平反向增强HIF-1α表达，二者形成正反馈环路，使低氧-炎症耦联效应持续放大，加重机械屏障损伤[35]。此外，HIF-1α的异常升高常伴随诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）上调，引发黏膜局部氧化-硝化应激增强[36-37]。过量一氧化氮（nitric oxide，NO）及其衍生的活性氮（reactive nitrogen species，RNS）可能通过诱导TJ蛋白发生硝化修饰、错位或降解，从而削弱TJ复合体稳定性[38]；同时，RNS还可干扰肠上皮氧化还原稳态与细胞骨架重构[39]，并诱导DNA损伤和线粒体功能障碍，进而触发IECs凋亡[38]，最终导致机械屏障完整性下降。

综上，HIF-1α并非单纯的保护或损伤因子，而是机械屏障低氧应答网络中的中枢调控节点。高原环境下，HIF-1α异常激活与NF-κB炎症通路的交互串扰，共同构成了驱动机械屏障失稳、通透性升高的核心分子机制（图1）。

2.2　化学屏障与肠道屏障损伤

化学屏障是阻止肠腔内病原菌及其有害产物直接接触上皮表面的第一道防线[40]。在高原低氧环境下，Notch信号通路的异常激活可显著损伤化学屏障功能，其核心机制可能与抑制GC分化、下调MUC2表达有关[41]。生理状态下，肠道干细胞的分化受微环境中Notch等信号通路精密调控，以维持吸收型细胞与分泌型细胞之间的平衡[42]。然而，低氧应激可促进Notch通路激活，促进Notch胞内域入核并与CBF1/无毛基因抑制因子/Lag-1蛋白转录复合物结合[43]，进而上调发状分裂相关增强子1（hairy and enhancer of split 1，Hes1）表达[41]。Hes1的高表达可通过转录抑制无刚毛同源物1[42]，抑制GC及潘氏细胞等分泌谱系细胞的分化，使肠干细胞分化偏向吸收型肠上皮细胞。最终，GC数量减少、MUC2合成与分泌能力下降，导致黏液层变薄，黏膜表面的物理隔离作用减弱，从而损伤肠道屏障功能[41]。



IECs: intestinal epithelial cells; TJ: tight junction; LPS: lipopolysaccharide; MUC2: mucin2; DAO: diamine oxidase; D-LA: d-lactate; Th17/Treg: T helper 17/regulatory T cells; sIgA: secretory IgA; SCFAs: short chain fatty acids; TLR4: Toll-like receptor 4; HIF-1α: hypoxia-inducible factor 1α; iNOS: inducible nitric oxide synthase; NO: nitric oxide; NOS: nitric oxide synthase; ZO-1: zonula occludens-1; NF-κB: nuclear factor kappa-B; TNF-α: tumor necrosis factor-α; IFN-γ: Interferon-γ; IL-6: interleukin-6; MLCK: myosin light chain kinase; MLC: myosin light chain; RhoA: ras homolog family member A; ROCK: rho-associated coiled-coil containing protein kinase. This figure was drawn by Adobe Illustrator.

图1 肠道机械屏障损伤机制图

Fig. 1 Mechanisms of intestinal mechanical barrier injury

除Notch通路外，Wnt/β-catenin信号通路同样参与高原低氧环境下的肠道屏障损伤。在生理条件下，Wnt/β-catenin通路对肠干细胞的增殖、更新及隐窝稳态维持至关重要[44]，其适度活化是隐窝基底干细胞池维持所必需的[45]。然而，在低氧条件下，Wnt信号可出现异常增强，且近年研究提示这一过程可能受到表观遗传调控因子含溴结构域蛋白4(bromodomain-containing protein 4, BRD4)的介导[46]。高原低氧暴露可显著上调BRD4表达，而BRD4作为溴结构域和超末端结构域家族成员，可识别乙酰化组蛋白并招募转录延伸复合物[47]，从而促进Wnt/β-catenin通路核心组分及其下游靶基因的转录激活，进而诱导干细胞异常增殖、分化程序受扰及炎症反应增强[46]。与此同时，异常增强的Wnt/β-catenin信号还可能与Notch信号共同破坏吸收谱系与分泌谱系之间的平衡，减少GC生成并下调MUC2表达，最终导致化学屏障受损并加重肠道屏障功能障碍[41, 46]。

综上，高原低氧环境下，Notch信号通路的异常激活与Wnt/β-catenin信号通路的异常增强协同抑制GC分化及MUC2表达，导致黏液层变薄，从而损伤肠道化学屏障(图2)。

2.3 免疫屏障与肠道屏障损伤

肠道免疫屏障是维持黏膜耐受与病原清除平

衡的关键环节[48]，而高原低氧可破坏这一平衡[49]。持续低氧及其继发的氧化应激和微生物相关分子易位可激活TLR4/NF-κB炎症轴，促使TNF-α、IL-6等介质持续释放，从而加重上皮损伤[50]，并为后续NOD样受体热蛋白结构域相关蛋白3（NOD-like receptor family pyrin domain containing 3，NLRP3）炎性小体激活提供促炎微环境[51]。与此同时，活性氧（reactive oxygen species，ROS）等第二信使可进一步促进NLRP3炎性小体的组装与激活，继而募集并活化半胱氨酸天冬氨酸蛋白酶-1，促进IL-1β和IL-18的成熟与释放，并诱导焦亡，从而加剧黏膜炎症反应并削弱肠道免疫屏障功能[52-53]。另一方面，HIF-1α可促进维甲酸相关孤儿受体γt（retinoic acid-related orphan receptor γt，RORγt）介导的辅助性T细胞17（T helper 17 cells，Th17）分化，并抑制叉头框蛋白P3阳性调节性T细胞（forkhead box p3$^+$ regulatory T cells，Foxp3$^+$Treg）的表达及稳定性，从而推动免疫反应向促炎方向偏移[54-55]。在低氧和炎症信号共同作用下，IL-6、IL-1β、IL-23等促炎细胞因子可进一步加剧Th17/Treg失衡，促进黏膜免疫稳态破坏[56]。除T细胞亚群失衡外，低压低氧还可进一步引起肠道相关淋巴组织细胞构成及黏膜体液免疫功能的异常。低压低氧可造成派尔集合淋巴结中初始T细胞数量下降，同时伴随自然杀伤细胞和树突状细胞增加，以及sIgA水平或功能的异常改变[57]。现有研究表明，低氧暴露联合体力负荷可导致sIgA水平下降，并在持续暴露或训练期间维持于较低水平[58]，说明低氧应激可能削弱黏膜免疫球蛋白介导的防御功能，为细菌黏附、定植和侵袭创造条件。

综上，高原低氧对肠道免疫屏障的影响并非单纯表现为炎症增强，而是通过促炎激活与防御削弱并存的方式共同重塑肠黏膜免疫微环境，最终加剧肠道屏障损伤（图2）。

2.4　生物屏障与肠道屏障损伤

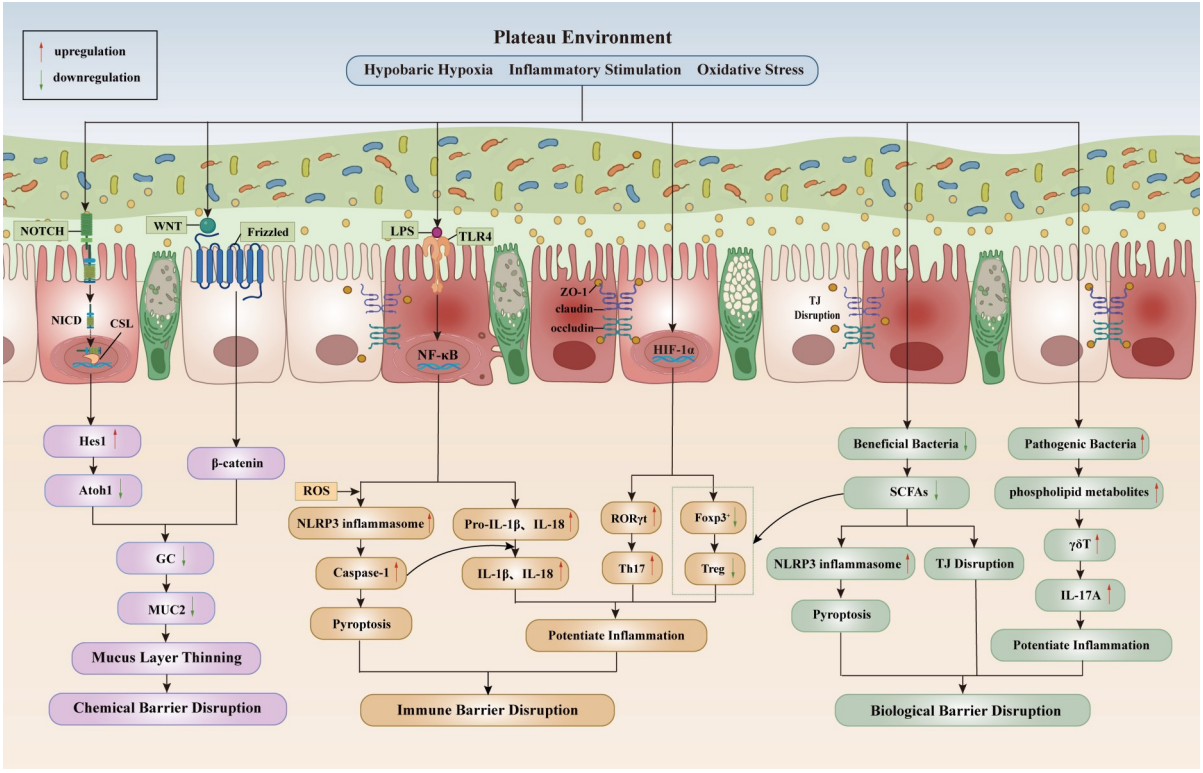
肠道共生菌群通过与肠道屏障及黏膜免疫系统相互作用，参与维持肠道内环境稳态和肠道屏障功能，是肠道稳态的重要调控因素之一[59]。现有研究表明，在不同人群和动物模型中，高原低氧诱导的菌群变化具有一定异质性，但总体趋势表现为与SCFAs生成相关的有益菌减少，而部分机会致病菌或促炎相关菌群增加[22, 60]。菌群失调引发的代谢异常是肠道屏障损伤的重要机制之一。SCFAs中，丁酸盐是IECs的重要能量底物[61]，当菌群失衡导致丁酸供给不足或丁酸代谢受损时，肠上皮细胞可由氧化磷酸化转向糖酵解[62]，并伴随黏膜修复与更新能力下降[62]。丁酸盐还可通过激活G蛋白偶联受体并抑制组蛋白去乙酰化酶，促进TJ蛋白的表达与装配，从而增强肠道屏障功能[63]。此外，SCFAs，还可通过促进Foxp3$^+$Treg分化[64]，并在多数肠道炎症模型中抑制NLRP3炎症小体的异常活化[65]，从而维持免疫稳态。因此，高原低氧环境下与SCFAs生成相关菌群的减少及其保护作用减弱，可能削弱肠道屏障稳态维持和黏膜免疫调节能力，从而导致肠道通透性升高并放大炎症反应[22]。除SCFAs减少外，特定促炎菌群的异常扩增也通过其代谢产物加剧肠道屏障损伤。低氧性肠损伤模型中，脱硫弧菌属丰度升高，其磷脂代谢物可通过分化簇1d分子依赖性途径进行抗原递呈，诱导产IL-17A的γδT细胞大量扩增，进而加重肠道炎症与肠道屏障损伤[66]。

此外，菌群失调导致的肠源性LPS等内毒素负荷增加，可通过激活TLR4/NF-κB炎症通路，破坏紧密连接并损伤机械屏障[67]；同时，机械屏障受损后肠腔菌群组分更易接触黏膜免疫系统，继而削弱化学与免疫屏障功能，进一步放大局部乃至全身炎症反应，形成菌群失调—屏障破坏—炎症加重的恶性循环[68]。粪菌移植实验进一步支持了菌群在高原肠道屏障损伤中的中介作用。研究发现，将高原暴露小鼠的肠道菌群移植至常氧环境下受体小鼠后，受体小鼠同样出现肠黏膜结构损伤和肠道屏障破坏，提示肠道菌群失衡并非单纯伴随现象，而是高原环境诱导肠道屏障损伤的重要机制环节[4]。

综上，高原低氧通过诱导菌群结构失调、削弱SCFAs的保护性代谢、激活促炎菌群及其代谢产物、增强细菌产物易位等多重途径，协同破坏肠道屏障结构与功能（图2）。

2.5　高原环境下肠道屏障损伤的多机制协同调控网络

综合现有研究可见，高原环境致肠道屏障损伤并非由单一通路驱动，而是以低压低氧为核心起点[35]、以高原特异复合应激为放大背景的多层屏障协同失衡过程[49]。高原暴露初期，低压低氧抑制脯氨酰羟化酶活性，使HIF-1α稳定并转位入核，启动



NOTCH: notch signaling pathway; WNT: wnt signaling pathway; LPS: lipopolysaccharide; TLR4: Toll-like receptor 4; NICD: notch intracellular domain; CSL: cbf1/suppressor of hairless/lag-1; NF-κB: nuclear factor kappa-B; ZO-1: zonula occludens-1; HIF-1α: hypoxia-inducible factor-1 alpha; TJ: tight junction; Hes1: hairy and enhancer of split 1; Atoh1: Atonal homolog 1; GC: goblet cell; MUC2: mucin 2; ROS: reactive oxygen species; NLRP3: NOD-like receptor family pyrin domain containing 3; IL-1β: interleukin-1 beta; IL-18: interleukin-18; RORγT: retinoic acid-related orphan receptor gamma t; FOXP3: forkhead box p3; TH17: T helper 17 cells; Treg: regulatory T cells; SCFAS: short-chain fatty acids; γδT: gamma delta T cells; IL-17A: interleukin-17a. This figure was drawn by Adobe Illustrator.

图2 肠道化学、免疫及生物屏障损伤机制图

Fig. 2 Mechanisms of intestinal chemical, immune, and biological barrier injury

生理性适应程序[25]。而当低氧暴露持续、海拔跃升过快或叠加寒冷、运动负荷这些高原特异复合应激时,可通过上皮缺氧及ROS/RNS蓄积[17],推动HIF-1α及NF-κB信号异常激活,从而诱导TNF-α、IL-6等炎症因子大量释放,并下调occludin、ZO-1等TJ蛋白表达,进而导致TJ复合体破坏、肠道通透性升高,最终破坏机械屏障[9]。

机械屏障破坏后,肠腔内LPS等微生物相关分子易位增加,通过激活TLR4/NF-κB通路进一步释放促炎因子。与此同时,GC减少和MUC2分泌不足又进一步削弱化学屏障黏膜表面防御,使腔内LPS及其他有害刺激更易接触上皮并进入固有层,为炎症反应持续升级提供结构基础[18]。在此基础上,菌群失衡和免疫重塑进一步构成损伤的放大环路。一方面,高原低氧可导致肠道菌群组成与代谢谱重塑,部分SCFAs生成相关有益菌减少,促炎相关菌群及其代谢产物增加,进而削弱上皮能量供给、损害TJ稳态并增强炎症反应[22, 60];另一方面,促炎细胞因子持续释放、Th17/Treg失衡、NLRP3炎性小体异常激活及sIgA防御功能减弱[56-57],又会进一步降低黏膜免疫稳态并增加微生物相关分子易位。因此,机械屏障、化学屏障、免疫屏障和生物屏障之间并非彼此孤立,而是在高原环境中形成了屏障破坏—菌群失衡—炎症放大—屏障损伤加剧的正反馈网络。

综上,高原相关肠道屏障损伤可概括为一个适应—失代偿转化下的多机制协同模型。在暴露早期,机体可通过一过性低氧应答、局部免疫调节及有限度的微生态重塑维持相对稳态;而当低氧暴露持续、海拔跃升过快,或叠加寒冷、运动负荷及其他炎症诱因作用于机体时,超过机体代偿能力,促使原本具有适应意义的低氧应答和菌群重塑转化为致损过程,最终导致4层屏障协同失衡并推动肠道屏障损伤进展。

3　高原环境下肠道屏障损伤的干预

高原环境下肠道屏障损伤的干预应强调高原特异性、证据层级和转化可行性这3条主线。对急进高原人群而言，控制登高速度、设置适应期并限制初期体力负荷，是最具场景针对性的基础措施[69-70]，其核心在于减轻急性低压低氧、内脏低灌注及运动负荷叠加所致的缺氧和炎症放大[35]。在主动干预中，微生态靶向策略最接近临床转化方向。益生菌可发酵膳食纤维等可通过调节菌群结构、改善代谢、稳定TJ并减轻炎症反应发挥保护作用[71-72]。部分小样本随机研究已显示，其对低压低氧相关肠通透性升高或高原适应指标具有改善效果[72]。相比之下，硝酸盐、色氨酸、柑橘果络提取物等膳食营养干预以及吡咯烷二硫代氨基甲酸酯、硒纳米颗粒等药物或候选制剂，虽在动物实验中显示出抗炎、抗氧化和维持肠道屏障稳定的潜力，但整体仍以前临床证据为主[27, 50, 73-75]（表1）。

表1　高原环境下肠道屏障损伤的主要干预策略及证据概况

Table 1　Intervention strategies and evidence profile for intestinal barrier injury at high altitude

Category	Key measures	Main mechanisms	Evidence/limitations
Exposure and acclimatization	Graded ascent, pre-acclimatization, and no strenuous activity in the first 48 h[69]	Reduce acute hypobaric hypoxia, splanchnic hypoperfusion, and inflammatory amplification at the source[35]	Highly applicable, but randomized human trials with intestinal barrier endpoints are lacking
Microbiota-targeted	Probiotics[71] and fermentable dietary fiber[72]	Modulate gut microbiota and metabolism, stabilize TJs, and attenuate inflammation and oxidative stress[71-72]	Closest to clinical translation, but studies remain limited by small sample size, short exposure, and endpoints partly focused on oxygenation or altitude acclimatization
Dietary interventions	Nitrate[27], tryptophan[73], and citrus tangerine pith extract[74]	Exert anti-inflammatory and antioxidant effects, improve the microbiota-metabolite axis, and maintain barrier homeostasis[27,73-74]	Evidence derives largely from animal studies, with few clinical trials using intestinal barrier outcomes as primary endpoints
Drugs and candidates	PDTC[50] and selenium nanoparticles[75]	Inhibit inflammatory amplification pathways such as TLR4/NF-κB, alleviate oxidative stress, and maintain TJ stability[50, 75]	Still mainly limited to preclinical studies; evidence on dose window, safety, and altitude-specific applicability remains insufficient

TJs: tight junction proteins; TLR4/NF-κB: Toll-like receptor 4/nuclear factor kappa-B; PDTC: pyrrolidine dithiocarbamate.

4　总结与展望

综上，高原相关肠道屏障损伤并非由单一通路所致，而是由低压低氧触发、并在寒冷、快速海拔跃迁、运动负荷等复合应激放大下形成的4层屏障协同失衡的病理过程。未来，随着多组学整合分析技术的快速发展，应进一步深入阐明高原低氧环境所致肠道屏障损伤的核心机制。同时，围绕急进高原人群系统开展纵向队列研究，挖掘基于血清外泌体、微小RNA及粪便代谢物的高灵敏度早期预警标志物。在此基础上，积极开发具有肠道保护作用的天然药物，并优化益生菌、营养支持与靶向药物的联合干预策略。通过上述研究，有望为高原世居人群及急进高原人群的肠道健康维护提供更坚实的理论依据与可行的实践路径。

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