

微量营养素锌促进肠上皮发育及再生机制的研究进展

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摘要:必需微量元素锌是多种酶的重要组分,能作为辅助因子参与蛋白质的激活、折叠及功能调节。锌主要在小肠被吸收,而锌稳态受锌转运体、渗透通道和金属硫蛋白的影响,其稳态异常会引起肠道结构和屏障功能紊乱,导致机体生长发育受阻。此外,锌能够识别细胞信号,通过调节干细胞微环境中 Wnt/ β -连环蛋白(Wnt/ β -catenin)和哺乳动物雷帕霉素靶蛋白复合物 1(mTORC1)信号通路增加肠道干细胞活性,促进肠上皮发育及损伤后修复。本文综述了锌在肠道中的转运系统,及其促进肠道黏膜更新和再生的调控机制,旨在为锌制剂的研发和应用提供新思路。

关键词: 锌;锌转运蛋白;肠道干细胞;发育;再生

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微量元素锌(zinc, Zn)被称为“生命元素”,含量在人体内仅次于“铁”。Zn 参与哺乳动物基因组中 10%蛋白质的合成,它的缺乏会导致机体生长发育受阻、皮肤角质化以及软骨细胞增生等^[1-2];相反,Zn 的过量摄入会造成“Zn 中毒”,抑制机体免疫功能^[3-4]。Zn 存在有机 Zn 和无机 Zn 2 种形式^[5],其中无机 Zn 的摄入是通过在肠腔中转换成 Zn^{2+} ,并与胰腺分泌的 Zn 配体形成络合物进入小肠上皮细胞,再通过基底膜进入门静脉与血清白蛋白形成血清白蛋白 Zn 复合物,随血液循环到达全身各个器官组织;而有机 Zn 多以氨基酸螯合物的形态存在,其吸收存在 2 种可能:其一,氨基酸螯合物解离后进入肠道参与物质代谢,通过肠系膜入血,进入器官组织;其二,Zn 直接以氨基酸螯合物的形式,借助氨基酸转运载体穿过肠细胞膜进入血液循环^[6]。

1 Zn 的转运载体及其转运机制

机体内 Zn 平衡主要通过小肠摄取、肾脏重吸收和粪便排出维持。肠细胞主要通过 Zn 转运载体摄入 Zn,且摄入量与吸收效率成反比^[7-8]。哺乳动物的 Zn 转运载体分为 2 种:Zn 调控转运蛋白家族(zinc-regulated transporter-like proteins, ZIP)和阳离子扩散辅助蛋白家族(cation diffusion facilitator family, CDF),二者均具有跨膜结构域^[9-10]。ZIP 也称 SLC39A,编码 14 种蛋白,即 ZIP1 ~ ZIP14,促进 Zn 进入胞浆;CDF 又称 SLC30A,编码 10 种转运蛋白,即 ZnT1 ~ ZnT10,促进 Zn 从胞浆流向胞外或核内(图 1)^[11-13]。

研究表明,ZIP3 位于细胞顶膜上,通过介导胞浆 Zn 的跨膜转运过程,构造囊泡“Zn 池”^[14-15]。当 Zn 浓度降低时,肠细胞转运载体蛋白 ZIP4 活性上升,并被募集到细胞的表面,促进 Zn 的吸收;ZIP4 基因敲除会导致肠道结构完整性被破坏、隐

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窝凋亡和肠道干细胞微环境稳态紊乱,而外源补充 Zn 可逆转这一现象^[16]。ZIP5 定位在肠上皮细胞、胰腺腺泡细胞和肾细胞的基底外侧膜上,通过促进细胞吸收膳食 Zn 和“囊泡池”释放 Zn 2 种方式来维持细胞 Zn 水平^[17]。ZIP6 又称 LIV-1 (SLC39A6),其主要功能是将 Zn²⁺转运到细胞质基质中^[18]。ZIP7 定位于内质网和高尔基体,作为细胞内 Zn 进出的“看门人”,具有与 ZIP5 相似的作用,此外还参与预防 Zn 在高尔基体中的过度积累造成的“Zn 中毒”^[19]。而 ZnT1 位于细胞的基底外侧膜上,通过调节自身活性降低过高的 Zn²⁺浓度^[20-21]。ZnT5~ZnT7 可将胞浆内 Zn 转运至高尔基体内,参与蛋白质的加工、分拣和运输。除上述 2 类转运载体外,二价金属离子转运蛋白 1 (divalent metal transporter 1, DMT1)、金属硫蛋白 1 (metallothionein, MT1) 和锌转运蛋白 LIV-1 亚家族 (LIV-1 subfamily of zinc transporters, LZT) 等也参与了 Zn 的吸收。DMT1 主要参与二价金属离子的吸收过程,通过影响锌转运蛋白的功能和表达,在 Zn 吸收过程中发挥着重要作用^[22];MT1 可通过增加 ZnT1 诱导内源性 Zn 的组织分布,决定了各组织 Zn 含量的不同^[23];LZT 则有一个独特的基序 (HEXPHEGD),具有将 Zn 跨膜运输的功能^[24]。总之,Zn 浓度变化需要 Zn 转运载体 ZIP、CDF、MT1 和 DMT1 等协同调节以维持 Zn 在体内的稳态^[25-26]。

2 Zn 促进肠道发育

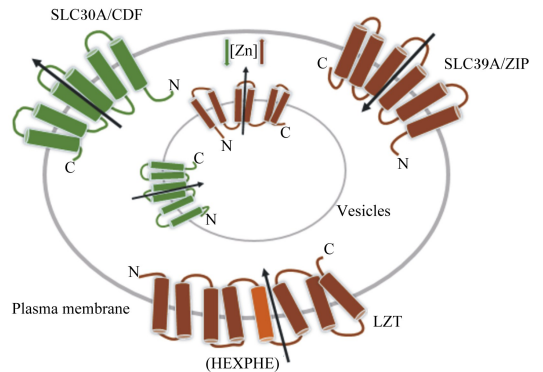
2.1 Zn 制剂

目前,动物生产中运用到的 Zn 饲料添加剂主要有 2 种类型:无机 Zn 和 Zn 氨基酸螯合物。因为蛋氨酸锌 (Zn-Met)、赖氨酸锌 (Zn-Lys)、天冬氨酸锌 (Zn-Asp) 和甘氨酸锌 (Zn-Gly) 等 Zn 氨基酸螯合物在动物体内具有比无机 Zn 更好的生物利用度,所以逐渐被人们认识和接受^[27-30]。Huang 等^[31]证实,相较于硫酸锌 (ZnSO₄),添加 Zn-Met 和 Zn-Gly 处理肠上皮细胞更能提高细胞活力,改善细胞状态;并且 Zn 转运体 MT1 和 ZnT1 mRNA 丰度显著增高,这可能是促进有机 Zn 有效吸收的机制之一。

2.2 Zn 促进肠道发育

肠上皮每 3~5 d 会更新 1 次,其动力是位于隐窝底部的肠道干细胞 (intestinal stem cell, ISC)

的扩增(包括增殖、迁移和分化)。隐窝中存在的多种生长因子、细胞因子和细胞外基质分子构成了“干细胞微环境”,其对 ISC 增殖和分化过程提供必要的支持,以维持肠道上皮稳态^[32]。Amcheslavsky 等^[33]报道,锌指蛋白 (zinc finger protein, ZFP) 能促进果蝇肠道干细胞分化,其被敲除后干细胞分化功能丧失,干细胞微环境平衡被破坏。Ohashi 等^[34]研究表明,肠道隐窝中高度表达的 ZIP7 被敲除后,潘氏细胞功能严重衰弱,肠道干细胞发生凋亡。补充 Zn 能够增强肠道干细胞增殖能力,增加肠吸收细胞、杯状细胞和肠内分泌细胞数量,改善肠上皮形态结构^[35-36]。上述研究提示 Zn 是肠道干细胞及分化细胞维持正常功能的关键因子。



Zn: 锌 zinc; SLC30A/CDF: 阳离子扩散辅助蛋白家族 cation diffusion facilitator family; SLC39A/ZIP: Zn 调控转运蛋白家族 zinc-regulated transporter-like proteins; LZT: 锌转运蛋白的 LIV-1 亚家族 LIV-1 subfamily of zinc transporters; HEXPHE: LZT 中脯氨酸和谷氨酸残基 proline and glutamate residues in LZT; plasma membrane: 浆膜; vesicles: 囊泡。

图 1 Zn 的跨膜转运

Fig.1 Transmembrane transport of Zn^[13]

小肠黏膜刷状缘膜 (brush-border membrane, BBM) 可增加小肠表面积和肠内膜阻力,促进营养物质的消化吸收。研究表明,Zn-Met 能通过增加转运蛋白质和 BBM 酶的活性,改善肠道形态结构,促进鸡肠绒毛的发育^[27]。同时,Zn-Met 或 Zn-Gly 还可显著增加肉仔鸡小肠金属硫蛋白 mRNA 丰度,促进自身被肠细胞吸收^[37]。此外,Zn 制剂能调节肠道屏障功能。Zhang 等^[38]发现,饲料添加氧化锌 (ZnO) 可以上调断奶仔猪的闭合蛋

白(occludin)和紧密连接蛋白-1(zonula occludens protein-1,ZO-1)的表达,降低肠道通透性,提高肠道机械屏障功能;这与 Shao 等^[39]在 Caco-2 细胞上开展的 Zn 对肠上皮细胞屏障影响的试验结果一致。ZnSO₄ 则被报道可通过促进乳酸菌在肠道定植并分泌酸性物质抑制有害菌生长,从而增加肠道微生物屏障功能^[40]。

肠道黏膜抗氧化及免疫功能是维持肠上皮稳态的 2 项重要指标。早在 2000 年,Cario 等^[41]就发现,补充 Zn 能提高肠黏膜的抗氧化能力,加快肠上皮细胞更新代谢,改善缺 Zn 诱导的肠炎。同时,血清中的抗氧化指标,包括超氧化物歧化酶(superoxide dismutase,SOD)和谷胱甘肽过氧化物酶(glutathione peroxidase,GSH-Px)的活性在添加 Zn-Gly 后显著增加^[30]。此外,Han 等^[42]研究表明,壳聚糖 Zn 可显著提高仔猪黏膜免疫力,减少肠上皮凋亡细胞数,促进肠道黏膜发育。

3 Zn 驱动肠上皮损伤后修复

肠上皮易受到毒素和病原体等外源有毒有害物的攻击,肠道损伤后的快速修复是维持肠道结构和功能完整性的关键。研究表明,Zn 口服液或饲料中添加 Zn 可降低肠黏膜的通透性,改善腹泻引起的肠道损伤^[43-45]。Tran 等^[46]研究发现,乳清来源的生长因子提取物(whey growth factor extract,WGFE)可改善甲氨蝶呤(methotrexate,MTX)引起的肠道损伤,而 Zn 和 WGFE 结合使用对 MTX 引起的肠黏膜炎的治疗效果更好。Zhou 等^[29]在小鼠和小鼠类肠团上的研究表明,L-天冬氨酸锌能提高肠道干细胞的增殖和分化活性,加速呕吐毒素暴露下肠上皮再生。此外,Cario 等^[41]通过细胞划痕试验发现,培养基中添加 ZnSO₄ 可以提高肠上皮细胞的迁移能力,并促进伤口愈合。

在畜牧生产实践中,仔猪的高腹泻率是影响我国养猪生产效率的关键因素。其中细菌性腹泻的机理很大程度上是因为包括肠毒素在内的一系列细菌分泌的毒素或 5-羟色胺(5-hydroxytryptamine,5-HT)激活了肠上皮细胞膜上相关受体,诱导氯离子(Cl⁻)过量分泌,进一步引起水的分泌,导致仔猪分泌性腹泻。而缺 Zn 使机体对有害菌更敏感^[47],因此补充 Zn 对预防和治疗仔猪腹泻具有重要意义^[12,48]。研究表明,饲料中添加高水平 Zn(2 500 mg/kg)会减少断奶仔猪肠

道样品中 5-HT 的含量,降低腹泻发生率^[49-50]。而 Ou 等^[51]则证明,ZnO 通过下调肠道肥大细胞中干细胞因子(stem cell factor,SCF)基因 mRNA 和蛋白质表达水平,抑制其释放组胺,从而降低仔猪腹泻。此外,有研究报道,Zn 以抵御肠道病原菌的侵害和激活免疫系统等形式预防和治疗急性和慢性腹泻疾病^[52]。尽管目前相关研究已揭示了 Zn 抑制腹泻的部分机理,但是其中还存在一些疑点等待研究人员的进一步解答,如 Zn 如何影响肠道微生物代谢,以及 Zn 通过什么途径影响肠道免疫系统。对这些问题的回答,有助于深入认识 Zn 缓解仔猪腹泻的机制,为 Zn 的精准调控指明方向。

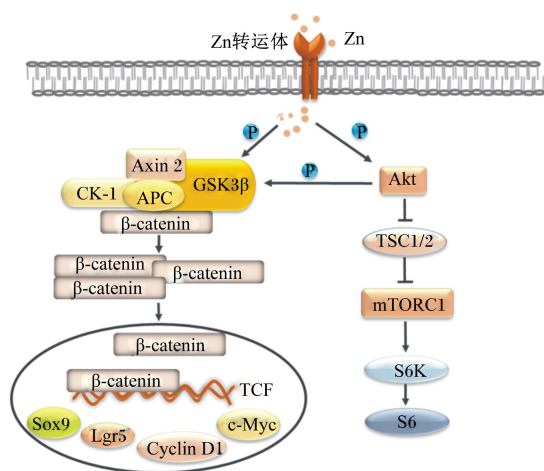
4 Zn 对肠道干细胞调控机制研究

ISC 的增殖分化受到 Wnt/ β -连环蛋白(Wnt/ β -catenin)和哺乳动物雷帕霉素靶蛋白复合物 1(mammalian target of rapamycin complex 1,mTORC1)信号通路等信号通路的调控^[53-54]。Wnt/ β -catenin 通路是维护肠道干细胞增殖分化所必需的^[55-57],mTORC1 信号通路通过调节肠道蛋白质代谢,增强肠道干细胞活性^[58-60]。它们参与了 Zn 促进肠道干细胞自更新和再生过程(图 2)。

4.1 Zn 参与 Wnt/ β -catenin 信号通路调节 ISC 增殖

肠道中 Wnt 信号梯度沿隐窝-绒毛轴逐渐减弱^[61-62]。当存在 Wnt 配体时,它会与细胞膜上的受体结合,引起 β -catenin 去磷酸化,使得 β -catenin 在细胞质中富集并转移至细胞核内,与 T 细胞特异性转录因子(T cell-specific transcription factor,TCF)结合,调控 *c-Myc* 基因、细胞周期蛋白 D1(cell-cycle protein cyclin D1,Cyclin D1)和亮氨酸重复单位的 G 蛋白偶联受体 5(leucinerich-repeat-containing G-protein-coupled receptor 5,Lgr5)等关键靶基因转录,从而促进细胞增殖^[63]。研究表明,Zn 能够提高糖原合酶激酶 3 β (glycogen synthase kinase 3 β ,GSK3 β)磷酸化水平,诱导 β -catenin 上游的负调控因子 GSK3 β 、肌酸激酶-1(creatine kinase-1,CK-1)、轴抑制蛋白 2(axis inhibition protein 2,Axin 2)和结肠腺瘤性息肉病蛋白(adenomatous polyposis coli protein,APC)等组成的降解复合物失活,从而激活 Wnt/ β -catenin 信号通路^[55]。Zhou 等^[29]发现,口服 Zn-Asp 可激活小鼠肠道中 Wnt/ β -catenin 信号通路,上调肠道干细胞标志 *Lgr5* 的

表达,促进小鼠干细胞体外扩增为类肠团。有趣的是,在干细胞培养基中缺乏 Wnt 配体的情况下,补充 ZFP 转录因子——多形性腺瘤基因样蛋白 2 (pleiomorphic adenoma gene-like protein 2, *PLAGL2*) 同样能激活 Wnt/ β -catenin 信号通路,提高类肠团的出芽率^[61]。



Zn: 锌 zinc; GSK3 β : 糖原合酶激酶 3 β glycogen synthase kinase 3 β ; APC: 结肠腺瘤性息肉肉蛋白 adenomatous polyposis coli protein; CK-1: 肌酸激酶-1 creatine kinase-1; Axin 2: 轴抑制蛋白 2 axis inhibition protein 2; S6K: 核糖体蛋白 S6 激酶 ribosomal protein S6 kinase; S6: S6 核糖体蛋白 S6 ribosomal protein; TCF: T 细胞特异性转录因子 T cell-specific transcription factor; Cyclin D1: 细胞周期蛋白 D1 cell-cycle protein cyclin D1; Lgr5: 亮氨酸重复单位的 G 蛋白偶联受体 5 leucinerich-repeat-containing G-protein-coupled receptor 5; TSC1/2: 结节性硬化 1/2 tuberous sclerosis 1/2; mTORC1: 哺乳动物雷帕霉素靶蛋白复合体 1 mammalian target of rapamycin complex 1; Sox9: 性别决定区 Y 框蛋白质 9 sex determining region Y-box 9; Akt: 蛋白激酶 B protein kinase B; β -catenin: β -连环蛋白。

图 2 Zn 介导 Wnt/ β -catenin 和 mTORC1 信号转导机制

Fig.2 Regulatory mechanisms of Wnt/ β -catenin and mTORC1 signaling pathways by Zn^[55,64]

4.2 Zn 参与 mTORC1 信号通路调节肠道发育

蛋白质代谢主要受到 mTORC1 信号通路的调节^[60]。mTORC1 是磷脂酰肌醇 3-激酶相关激酶家族的成员,其通过磷酸化翻译起始因子 eIF4 和核糖体蛋白 S6 激酶 1 调控 mRNA 的翻译,进而调节细胞增殖。p70S6 激酶是 mTORC1 信号通路下游重要的靶标之一, Lynch 等^[65]发现, Zn 可通过激活 mTORC1 信号通路,上调 p70S6 激酶的表达,

促进细胞蛋白质的合成。Nimmanon 等^[64]进一步研究证实, Zn 通过提高蛋白激酶 B (protein kinase B, PKB/Akt) 磷酸化水平促进 mTORC1 信号通路的激活,同时抑制了 *GSK3 β* 的表达。此外, Geiser 等^[16]敲除小鼠肠道中的 *ZIP4* 基因后, mTORC1 活性也随之降低,导致蛋白质代谢紊乱,潘氏细胞分泌溶菌酶和 α -防御素的功能发生障碍,肠道干细胞增殖分化异常,肠上皮功能性细胞数量显著降低。

5 小结

综上所述, Zn 不仅作为微量元素维持机体正常需要,也是肠上皮发育和再生的控制因子;其可通过增强肠道干细胞增殖分化能力,提高肠道屏障和抗氧化功能,进而促进肠道损伤后修复,这些过程依赖于 Wnt/ β -catenin 和 mTORC1 等信号通路的调控作用。从目前的研究来看, *GSK3 β* 可能是联系 Zn 与 Wnt/ β -catenin 和 mTORC1 之间桥梁,然而, Zn 与它们之间是否还存在其他直接或间接的作用仍不清楚。未来在分子生物学的基础上,结合分子动力学,可能有助于揭示胞外 Zn 和胞内 Zn 调节肠道干细胞活性的机制,为畜牧生产中 Zn 制剂调控动物肠道发育的生产应用以及其在药理学方面对肠炎和腹泻等疾病的治疗提供理论依据。

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Research Progress on Mechanism of Micronutrient Zinc Promoting Development and Regeneration of Intestinal Epithelium

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Abstract: Zinc, an essential trace element, is an important component of many enzymes, which, as a cofactor, participates in protein activation, folding and functional regulation. Zinc is mainly absorbed in the small intestine, and zinc homeostasis is regulated by zinc transporters, osmotic channels and metallothionein. The abnormality of zinc homeostasis leads to the dysfunction of intestinal structure and barrier, and hinders the growth and development of the body. In addition, zinc can recognize cellular signals, increase intestinal stem cell activity by regulating the Wnt/ β -catenin and mammalian target of rapamycin complex 1 (mTORC1) signaling pathways, and promote intestinal epithelial development and repair after injury. This paper reviewed the transport system of zinc in the intestine and its regulatory mechanism for intestinal renewal and regeneration, in order to provide new ideas for the development and application of zinc preparations. [*Chinese Journal of Animal Nutrition*, 2020, 32(11):5038-5045]

Key words: zinc; zinc transporter protein; intestinal stem cells; development; regeneration