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紧密连接调节剂 Zonulin 的研究进展

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［摘要］紧密连接作为肠上皮细胞间重要的连接方式，在维持肠道通透性中发挥着关键的作用，而 Zonulin 作为目前唯一已知的紧密连接生理调节剂，当其表达上调可促使紧密连接开放，从而导致肠道通透性增加，发一系列肠内及肠外疾病。在这篇综述中，介绍了 Zonulin 的作用机制以及它与相关疾病的关系，同时也总结了肠道微生物群对 Zonulin 表达的影响以及 Zonulin 拮抗剂醋酸拉唑肽的一些临床研究，旨在探寻 Zonulin 在临床诊疗中的潜在价值。

［关键词］Zonulin；紧密连接；肠通透性；综述
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Research Progress on the Tight Junction Regulator Zonulin

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［**Abstract**］Tight junctions，as an important way of connecting intestinal epithelial cells，play a crucial role in maintaining intestinal permeability. As the only known physiological regulator of tight junctions，Zonulin upregulates its expression and promotes the opening of tight junctions，leading to increased intestinal permeability and a series of intestinal and extraintestinal diseases. This review aims to introduce the mechanism of action of Zonulin and its relationship with related diseases and at the same time to summarize the influence of gut microbiota on Zonulin expression and some clinical studies on the antagonist of Zonulin，paclitaxel acetate，with a purpose to explore the potential value of Zonulin in clinical diagnosis and treatment.

［**Key words**］Zonulin；Tight connection；Intestinal permeability；Summarize

肠上皮细胞和细胞间连接所构成的肠上皮屏障作为一个选择性渗透屏障，不仅可以保障营养物质的吸收，同时还能防止肠腔内抗原、细菌等有害物质穿过肠上皮进入人体循环[1]。紧密连接(tight junction，TJ)做为细胞间最重要的连接方式，在维持肠道通透性中发挥着关键的作用，当其结构破坏时，会导致肠道通透性增加[2]。Zonulin 是迄今为止唯一发现的细胞间紧密连接的生理调节剂[3]，在调节肠道通透性中发挥着关键的作用。目前研究发现，通过 Zonulin 所介导的肠道通透性，不仅涉及消化系统性疾病，还与中枢神经系统、自身免疫系统以及内分泌系统等多个系统的疾病的发生发展密切相关。因此，本文就拟 Zonulin 的作用机制以及它所介导的肠道通透性与临床疾病的研究进展作一综述，以期待为未来诊断与治疗相关疾病提供全面的认识。

1　Zonulin 及其作用机制

1.1　Zonulin 的发现

1991 年，Fasano 及其团队在开发霍乱弧菌疫苗时发现了 1 种由霍乱弧菌分泌并能可逆性调节

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细胞间紧密连接的蛋白-封闭带毒素(zonula occludens toxins，Zot)[4]。该蛋白可通过一系列信号级联反应激活蛋白激酶C(protein kinase C，PKC)引起靶细胞肌动蛋白的聚合，导致细胞间紧密连接复合物的分解，从而导致细胞间通透性增高，并通过结合免疫荧光技术证实了Zot能够与胃肠道上皮细胞相互作用，在空肠和回肠远端具有很高的结合，并沿绒毛至隐窝逐渐减少[5]。基于上述研究，Fasano及其团队推测Zot的对肠道的这种作用机制可能模仿了人体内某种或多种内源性调节蛋白，经过近10 a的研究，终于在2000年从成人和胎儿肠道中提取出1种分子量约为47 kDa的蛋白质，将其命名为Zonulin，通过动物离体实验(恒河猴)证明了Zonulin能可逆地调节肠道的通透性[6]，与此同时对乳糜泻急性期患者的肠组织及血清进行检测，发现其表达增加[7]。

1.2 Zonulin的分泌

为了解Zonulin是否也存在于其他组织中，Fasano及其团队对人的脑组织及心脏组织进行了分离提纯后发现在人大脑组织中也含有Zonulin的表达[8]，这也为血脑屏障及脑肠轴的研究提供了新的方向。为了解Zonulin是如何释放的，Fasano等用醇溶蛋白刺激(正常小鼠组与敲除CXCR3基因小鼠组)对比发现，正常小鼠的肠段跨上皮电阻显著下降30%，肠组织中的Zonulin表达增加，而敲除CXCR3基因小鼠组的跨上皮电阻以及肠组织中的Zonulin表达无改变，证明了Zonulin的释放依赖于与C-X-C基序趋化因子受体3(C-X-C-motif chemokine receptor type3，CXCR3)结合，随后通过体外细胞实验证明了Zonulin的释放还需要髓样分化因子88(myeloid differentiation primary response 88，MyD88)的介导，即抗原及醇溶蛋白等先通过与肠道上皮细胞上的CXCR3结合，然后经MyD88介导将信号传递至下游，从而使得Zonulin释放[9]。

1.3 Zonulin的蛋白特性及基因

2009年Tripathi及Fasano等利用蛋白组学对人血清进行分析确定了Zonulin的蛋白特性，该研究证实了Zonulin与结合珠蛋2的前体-前结合珠蛋白2(pre-haptoglobin2，preHP2)相同，同时通过实验经证明了Zonulin不参与结合珠蛋白2的合成，也不是由成熟的结合珠蛋白2水解而成，它们有各自有不同的生物学效应，Zonulin不能够对红细胞释放的游离血红蛋白进行清除，结合珠蛋白也不参与肠道通透性的调节，血清中Zonulin的水平较低，与结合珠蛋白2有千倍之差，该研究还发现了Zonulin对肠道通透性的影响有时间及剂量的依赖性，随着时间的延长和剂量的增大，Zonulin对肠道通透性的影响越大[10]。人类结合珠蛋白(haptoglobin，HP)基因2种类型(HP1和HP2)，由于每个人都有2个HP等位基因，因此人类有3种可能基因型(HP1-1、HP1-2、HP2-2)；并且研究发现，拥有HP2等位基因(HP1-2或HP2-2)的人可以检测产生活性的Zonulin，而拥有HP1-1基因型的人检测不到的Zonulin[11-12]。与普通人相比，在患有乳糜泻[11]、炎症性肠病[13]以及1型糖尿病的患者中，HP2基因型的携带率增高，研究人员推测，高Zonulin生成基因型具有一定程度的炎症遗传风险，可能与preHP2、Zonulin的产生以及其对肠屏障的影响有关[12]。

1.4 Zonulin的信号传导通路

研究发现，Zonulin表面含有表皮生长因子样物质和蛋白酶激活受体2(proteinase-activated receptor 2，PAR2)激活肽样片段，Zonulin可直接激活细胞上的表皮生长因子受体(epidermal growth factor receptor，EGFR)，同时还可以通过PAR2途径激活EGFR从而发挥生物活性[10]，其中PAR2对EGFR的激活起着关键的作用，其下游可通过多条途径作用于EGFR[14]，Tripathi等[10]研究发现当敲降小鼠或细胞中PAR2基因时，Zonulin对肠道通透性增强效果大大较低(通过跨上皮电阻测量)，当利用EGFR选择性抑制剂AG1478预处理时可消除因Zonulin引起的TEER降低。EGFR受体跟配体结合后可以激活其下游通道的磷脂酶C，激活的磷脂酶C可将磷脂酰肌醇(phosphatidylinositol，PPI)水解为三磷酸肌醇(inositol 1，4，5-trishosphate，IP-3)和二酰甘油(diacylglycerol，DAG)，使得蛋白激酶C磷酸化和促进细胞内Ca^{2+}释放，然后引起肌动蛋白聚合使细胞骨架重排，并导致(zonula occludens-1，ZO-1)等紧密连接蛋白磷酸化从连接复合体中分离，使得细胞的紧密连接疏松，肠道通透性增加[14-15]。

2 Zonulin与人类疾病

2.1 消化系统疾病

2.1.1 乳糜泻(celiac disease，CD) 做为1种自身免疫性肠病，它与HLA基因遗传有密切关系，当人体摄入含醇溶蛋白或麦谷蛋白的食物(如小麦、

大麦、燕麦等），不仅能引起腹胀、腹泻等一系列胃肠道症状，长时间还可能导致营养不良等肠外症状，在主要存在于欧美地区[16-17]。目前对 Zonulin 的了解大部分都源于对 CD 患者的研究所展开的，CD 已被用研究 Zonulin 的一种模型疾病[3]，Zonulin 驱动的乳糜泻中紧密连接结构破坏对疾病的发展起着关键的作用[2]，研究表明 Zonulin 在 CD 患者人群的组织及血清中呈高水平状态，随着 Zonulin 水平的增高，患者的临床症状也随之加重[7, 18]。最近 1 项 Meta 分析显示，利用 Zonulin 抑制剂醋酸拉唑肽对 CD 患者进行治疗，胃肠道症状有明显改善[19]，目前对醋酸拉唑肽治疗 CD 的研究已经进入到 III 期临床试验[20]。

2.1.2　炎症性肠病（inflammatory bowel disease，IBD）　包括克罗恩病（Crohn's disease，CD）和溃疡性结肠炎（ulcerative colitis，UC）2 种亚型[21]，目前对其发病机制仍不明确，一系列研究表明表明肠道通透性改变在 IBD 的发病机制中起着重要作用，其症状加重与肠上皮屏障的破坏密切相关[22]，IBD 患者血清及粪便中 Zonulin 的水平明显升高，并在活动期增加，患者肠道通透性与 Zonulin 的水平呈明显的正相关关系，并且 CD 患者血清 Zonulin 的水平高于 UC 患者[23-24]。对 IBD 患者进行治疗后，患者血清中的 Zonulin 水平下降[25]，这些研究为诊断及治疗 IBD 提供了新的方向。

2.1.3　腹泻型肠易激综合征（irritable bowel syndrome，IBS）　作为 1 种常见的功能性胃肠道疾病，主要分 4 种类型：腹泻型、便秘型、交替混合型以及未分类型[26]。其发病与人的心理症状（抑郁、焦虑、紧张等）有关，IBS 的病理生理学已被证明与肠通透性的改变以及肠道相关慢性炎症密切相关[27]。对此，一些学者通过检测 IBS 患者血清及粪便中的 Zonulin 水平发现，其浓度与健康人群对比升高，与腹泻的程度呈正相关[28-29]。研究人员通过采用，通过醋酸拉唑肽、瑞巴派特[30]、益生菌[28, 31]、合生元[32] 等干预后，症状改善的同时也伴随着 Zonulin 水平的下降，再次验证了 Zonulin 所介导的肠道通透性以及肠道微生物群与肠道慢性疾病密切相关。

2.1.4　消化系统其他疾病　一些学者在对坏死性小肠结肠炎、新生儿胃肠道损伤和环境肠道功能障碍等疾病研究时发现，通过监测 Zonulin 的水平变化可以对病情的严重程度及疗效进行提供一定程度的价值[33-35]。Ling 等通过体外细胞实验证实了 Zonulin 通过调节肠道通透性参与坏死性小肠结肠炎疾病的发生，双歧杆菌治疗可减弱肠通透性的，降低了血清 Zonulin 的水平[36]。Diana 等[37] 研究发现在新生儿中 Zonulin 的水平升高与脂多糖水平升高呈明显的正相关[37]。

在各种肝病中，包括非酒精性脂肪性肝病、肝炎、肝硬化和肝细胞癌，都伴随着 Zonulin 水平升高[38-40]，并且肝细胞癌患者血清 Zonulin 的水平明显高于其他肝脏疾病患者[40]。相关研究分析，Zonulin 水平升高可能导致病原体、抗原和有毒物质从肠道释放到肝脏，从而引发炎症反应和随后的肝组织损伤[15, 41]。

同时相关研究表明[42-43]，胃肠道手术后会造成肠道屏障功能，导致 Zonulin 水平表达上升，术前及术后口服益生菌可以降低血清 Zonulin 浓度、术后发热持续时间、抗生素治疗持续时间以及术后感染并发症发生率，并且术后败血症的发生与术后血清 Zonulin 浓度升高有关，通过检测血清 Zonulin 浓度变化可以为我们术后评估胃肠道功能提供了一定的价值。

2.2　中枢神经系统性疾病

2.2.1　精神障碍性疾病　目前随着对微生物群–肠–脑轴的研究发现，肠微生物群可能利用肠道中的细菌毒素其他抗原浸润肠道上皮细胞并改变细胞间骨架蛋白的相互作用[44]。随着肠道通透性的增加，肠道细菌进入血液，然后通过血脑屏障进入大脑，进而引发神经炎症反应，导致神经系统器质病变及功能障碍[45]。目前研究表明，Zonulin 作为上皮细胞间紧密连接的调节剂[14]，可以通过破坏肠上皮屏障及血脑屏障介导精神障碍性疾病发生发展[46]，如自闭症[47]、精神分裂症[48-49]、多动症[50]、抑郁症[50] 等都伴随着患者 Zonulin 水平的上调，一些学者[45, 51-52] 通过系统综述得出，Zonulin 所介导的肠道通透性与上述病情的严重程度呈正相关，Zonulin 上调的同时伴随着也伴随着脂多糖、I-FABP、claudin-5 等肠道通透性标志物的增加。有学者[53] 认为这些疾病发生可能是肠道通透性改变以及血脑屏障的破坏，菌群移位，导致大脑长期慢性炎症，使得星形胶质细胞和小胶质细胞功能障碍，也使得多巴胺能神经元的数量减少、色氨酸代谢紊乱以及 GABA 和谷氨酸量改变，从而影响脑功能，但具体机制尚不清楚。

2.2.2　神经系统疾病　在阿尔茨海默病[54-55]、帕金森病[56-57] 及多发性硬化[58] 等神经系统疾病中，也都伴随血清 Zonulin 的升高，阿尔茨海默病患者中 Zonulin 水平升高与简易精神状态检查评分

降低显着相关[54]，同时与姿势功能障碍相关[55]，帕金森病人的Zonulin水平与患者的震颤程度以及睡眠质量相关[56-57]，多发性硬化患者的进展情况相关[58]。Alba等[59]利用Zonulin转基因小鼠株证明了Zonulin途径在中枢神经系统疾病中的关键作用，研究表明，高水平Zonulin导致小鼠肠道通透性增加和生物失调，此外，Zonulin转基因小鼠血脑屏障完整性受损并伴有神经炎症和行为改变，通过抗生素治疗减少肠道微生物群可以使上述症状得到适度改善，证明Zonulin依赖性的肠道通透性增加与促进大脑功能和行为改变的促炎性肠道微生物群协同作用可能导致神经系统炎症性疾病。

2.2.3 神经系统肿瘤 在神经系统肿瘤方面，Zonulin也发挥着重要作用，Roberta等[60]在最近1项研究发现胶质母细胞瘤中Zonulin的高表达与患者的不良愈后相关，患者血清及肿瘤组织中Zonulin水平升高时，患者的无进展生存期降低，通过结合影像学分析，血清及肿瘤细胞中Zonulin的高表达与术前核磁共振扫描肿瘤的增强强度以及脑水肿的程度呈正相关；在此次研究中，为了证实肿瘤组织中的Zonulin不是来自于外周血，Roberta等通过对3种胶质母细胞瘤细胞系(U87MG、U118MG和A172)在无血清肿瘤细胞培养基中体外培养发现，所以肿瘤细胞系中Zonulin的表达都显著增加，通过分析得出，Zonulin在肿瘤细胞中的高表达可能通过破坏血脑屏障加重脑组织水肿，同时促进肿瘤的生长及浸润。

2.3 自身免疫性疾病

自身免疫性疾病是1组以免疫稳态失衡和产生异常自身抗体为特征的慢性炎症性疾病，如类风湿性关节炎、系统性红斑狼疮、强直性脊柱炎等，大量研究表明免疫耐受的破坏是促进自身免疫性疾病发病和进展的关键机制之一，但免疫耐受受损的具体机制尚不清楚[61-62]。肠粘膜屏障的完整对于维持免疫稳态至关重要，当肠粘膜屏障受损，外部抗原就会通过受损的肠粘膜屏障侵入体内，诱导和加剧全身炎症反应，导致自身免疫耐受性破坏和免疫稳态失衡，加剧自身免疫性疾病的进展[63]。Zonulin作为肠上皮细胞紧密连接的调节剂，在类风湿性关节炎[64]、系统性红斑狼疮[65]、强直性脊柱炎[66]、桥本甲状腺炎[67]等自身免疫系统中，也都伴随着Zonulin的改变，这些研究这些发现为笔者提供了方向-通过恢复肠道屏障功能来解决从自身免疫到炎症的转变，从而预防自身免疫性疾病的发病。

2.4 其他疾病

此外，在内分泌系统疾病(1型糖尿病[12]、2型糖尿病[68])，呼吸系统疾病(哮喘[69]、慢性阻塞性肺疾病[70]、社区获得性肺炎[71])，心血管系统疾病(慢性心力衰竭[72]、冠心病[73])，泌尿系统疾病(儿童肾病综合征[74]、IgA肾病[75]、糖尿病肾病[76])，妊娠并发症(妊娠糖尿病[77]、妊娠高血压[78]、肝内胆汁淤积症[79]、不良围生结局[80])，肥胖[70, 81]以及病毒感染[82-84]等疾病中，都发现Zonulin水平的改变，说明Zonulin通过改变肠道通透性直接或间接地参与了这些疾病的发病机制。

3 Zonulin与肠道微生物群

肠道微生物群在维持肠道稳态和功能方面发挥着重要作用，一方面肠道共生微生物通过直接和间接机制增强肠道屏障，在一定程度上促进健康[85]；另一方面当肠道菌群失调、代谢活动紊乱或肠道内细菌多样性的变化，上皮细胞通透性增加，可能导致毒素、抗原和细菌从内腔进入血流，引发肠内肠外各种疾病[27]。许多研究证明，微生物群改变可通过影响Zonulin的表达，从而导致肠道通透性改变，在乳糜泻[86]、炎症性肠病[87]、肠易激综合征[88]、糖尿病[89]、肥胖[90]、以及结直肠癌手术[42-43]患者中，通过补充益生菌、益生元或合生元可以降低Zonulin的表达从而降低肠道通透性，促进患者健康。

4 Zonulin途径相关药物

4.1 Zonulin的拮抗剂

醋酸拉唑肽(larazotide acetate，LA)，又称AT-1001，作为Zonulin的拮抗剂，AT-1001是1种可以人工合成含有8个氨基酸的短肽，可通过竞争性与Zonulin PA受体(PAR2以及EGFR)结合从而加强细胞间紧密连接，降低肠道通透性，从而预防疾病的发生发展[91]，研究表明它对乳糜泻、克罗恩病、肠易激综合征、类风湿性关节炎等疾病有一定的治疗作用[64, 92]。近期李志学等[93]已对该药物作了系统综述。

4.2 Zonulin的激动剂

AT-1002也是1种合成肽衍生物，它是Zot的1个片段，能够通过激活蛋白激酶C，引发细胞骨架重排以及紧密连接蛋白磷酸化后从连接复合

体中分离，从而使得细胞的紧密连接破坏，从而调节细胞间的通透性[94]。目前一些研究表明，AT-1002 是可以在鼻腔、皮肤增加药物的渗透，从而提高其生物利用度[95-96]。

4.3 其他

由于 Zonulin 需直接或通过 PAR2 及其下游可通过多条途径来激活 EGFR，从而发挥生物活性作用，所以相关受体的拮抗剂也能减缓肌动蛋白重排和紧密连接破坏，降低细胞间的通透性，从而达到治疗相关疾病的作用[97]。

5 小结

Zonulin 作为上皮细胞间紧密连接的调节蛋白，在维持人体健康与疾病发展中起着关键作用。虽然目前对它的具体病理生理作用知之甚少，但通过先前研究可以看出，由于它表达升高从而导致肠道通透性增加是一个必要的步骤。笔者相信对 Zonulin 更深入的研究能在未来为疾病的诊断及治疗提供帮助。

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