

1-磷酸鞘氨醇受体调节剂治疗炎症性肠病的研究进展[△]

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摘要 炎症性肠病(IBD)是一种胃肠道慢性炎症性疾病,目前其常规治疗药物存在特异性低、耐药性强等缺点。1-磷酸鞘氨醇受体(S1PR)调节剂是一种新型精准治疗药物,对IBD具有良好治疗效果。基于此,本文对S1PR调节剂的作用机制以及其在IBD治疗中的最新研究进展进行归纳,结果发现,S1PR调节剂可通过调节淋巴细胞迁移、降解受体、特异性调控S1PR,从而发挥抑制肠道炎症反应的作用。目前,Ozanimod与Etrasimod已获批用于治疗IBD,Amiselimod、KRP-203、Fingolimod、Ceralifimod虽未批准上市,但对IBD疾病展现出较大的潜力。

关键词 炎症性肠病;1-磷酸鞘氨醇受体调节剂;1-磷酸鞘氨醇;Ozanimod;Etrasimod

Research progress on the treatment of inflammatory bowel disease with sphingosine-1-phosphate receptor modulators

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ABSTRACT Inflammatory bowel disease (IBD), a chronic gastrointestinal inflammatory disorder, is currently limited by conventional therapies due to its lack of specificity and pronounced drug resistance. Sphingosine-1-phosphate receptor (S1PR) modulators, as novel precision therapeutic agents, demonstrate promising efficacy in IBD treatment. This review synthesizes the mechanistic insights and recent advances in the treatment of IBD with S1PR. Our analysis reveals that S1PR modulators suppress intestinal inflammatory responses through three core mechanisms: regulating lymphocyte migration, inducing receptor degradation, and exerting subtype-specific S1PR modulation. Currently, Ozanimod and Etrasimod have been approved for IBD treatment, while Amiselimod, KRP-203, Fingolimod and Ceralifimod are not approved for clinical use, but have shown great potential for IBD disease.

KEYWORDS inflammatory bowel disease; sphingosine-1-phosphate receptor modulators; sphingosine-1-phosphate; Ozanimod; Etrasimod

炎症性肠病(inflammatory bowel disease, IBD)是一种胃肠道慢性炎症性疾病,以胃肠道不同部位的慢性炎症为特征,包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC),其在临床常表现为腹痛、持续腹泻、血便、疲劳和体重减轻等。IBD的发病机制尚不明确,但研究发现,肠道细菌诱发的异常免疫反应可能与IBD相关。目前,IBD的常规治疗药物包括糖皮质激素、氨基水杨酸类药物和生物制剂,但这些药物的特异性低、耐药性强,其中生物制剂还易诱发过敏反应^[1]。

1-磷酸鞘氨醇受体(sphingosine-1-phosphate receptor, S1PR)调节剂是一类可减少淋巴细胞从淋巴器官向肠道迁移,从而特异性抑制肠道局部炎症反应,且不会广泛抑制全身免疫功能的新颖精准治疗药物^[2]。该调节剂不仅起效快速、疗效持久,还具有感染风险低、心血管风险可控的安全性优势,尤其适合需长期治疗的IBD患者^[2]。基于此,本文归纳了S1PR调节剂的作用机制,并对其在IBD治疗中的最新研究进展进行了综述,以期为其为IBD治疗药物开发和应用提供参考。

1 S1PR的分类及生理功能

细胞膜中的鞘磷脂经过鞘磷脂酶、神经酰胺酶及鞘氨醇激酶(sphingosine kinase, SphK)的催化生成1-磷酸鞘氨醇(sphingosine-1-phosphate, S1P), S1P通过与多种

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免疫细胞上的S1PR结合,参与调节免疫细胞的分化、迁移和增殖^[3]。S1P可促进免疫细胞向炎症部位迁移,抑制中性粒细胞凋亡,诱导M1巨噬细胞极化,促进树突状细胞成熟和活化,从而增强促炎细胞因子的产生^[4]。S1P/S1PR信号轴正在成为有效治疗IBD的新靶标^[5]。

S1PR有5种不同的亚型,其中S1PR1/2/3广泛表达,而S1PR4/5则主要在淋巴组织、造血组织和中枢神经系统中表达(表1)。S1PR1主要与G_i蛋白偶联,激活下游的磷脂酰肌醇3激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)和Rac1等信号通路,促进细胞存活、迁移和血管生成;S1PR2主要与G_q、G_i和G_{12/13}蛋白偶联,激活Rho、磷脂酶C(phospholipase C, PLC)和细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)等信号通路,调节细胞收缩、增殖和基因表达;S1PR3主要与G_i、G_q和G_{12/13}蛋白偶联,激活PI3K/Akt、PLC和Rho等信号通路,影响细胞生长、分化和心血管功能;S1PR4主要与G_i和G_{12/13}蛋白偶联,激活下游信号通路,参与免疫细胞的活化和迁移;S1PR5主要与G_i和G_{12/13}蛋白偶联,激活特定的信号通路,在神经系统中发挥作用^[6-7]。

表1 不同亚型S1PR的生理作用及在人体中表达的组织部位

S1PR的不同亚型	生理作用	在人体中表达的组织部位
S1PR1	调节淋巴细胞从淋巴器官逸出,并影响血管生成和淋巴细胞表达 ^[8]	淋巴细胞、血管内皮细胞等 ^[9]
S1PR2	调节巨噬细胞的活化,支持白细胞的滚动 ^[9]	心、肺、脑、肝、肾、脾和其他组织 ^[9]
S1PR3	调节免疫细胞趋化、募集和成熟,影响心血管系统 ^[10]	中枢神经系统、神经元、心脏、肺、平滑肌、内皮细胞 ^[11]
S1PR4	影响免疫调节、炎症反应 ^[12]	淋巴细胞、自然杀伤细胞
S1PR5	影响自然杀伤细胞迁移 ^[13]	自然杀伤细胞 ^[2]

2 S1PR调节剂的作用机制

肠道免疫系统的病理生理调控与S1PR调节剂的干预作用密切相关。在肠道相关淋巴组织(gut-associated lymphoid tissue, GALT)中,淋巴细胞可黏附到血管内皮上,并沿着血管内皮移动,受趋化因子的刺激后释放各种细胞因子^[14]。活化的淋巴细胞通过整合素介导进入肠道组织^[15]。IBD患者免疫应答异常主要是由于血管内皮上黏附的T细胞增多,从而导致向肠道迁移的T细胞数量增加^[16]。

肠道内不同类型细胞表达不同亚型的S1PR:肠上皮细胞表达除S1PR4以外的所有S1PR;骨髓来源的巨噬细胞主要表达S1PR1/2,少量表达S1PR3/4,不表达S1PR5;未成熟的树突状细胞和中性粒细胞表达所有S1PR;自然杀伤细胞表达除S1PR3以外的所有S1PR^[6-7]。S1PR调节剂可通过调节淋巴细胞迁移、降解

受体和特异性调控S1PR,从而发挥抑制肠道炎症反应的作用,具体机制如下。

2.1 调节淋巴细胞迁移、降解受体

S1P裂解酶在组织与体液中的差异性分布形成了明显的S1P浓度梯度(组织<淋巴<血液),这会驱动淋巴细胞从S1P低浓度区域向S1P高浓度区域迁移^[6,15]。S1PR1激动剂通过诱导受体内化,最终使受体被蛋白酶降解,阻断S1P信号感知^[17];S1PR1激动剂还可延长淋巴细胞在外周淋巴器官的滞留时间,从而有效阻断T细胞向肠道的异常迁移。这种双重调控可抑制结肠炎症浸润。

2.2 特异性调控S1PR

2.2.1 S1PR2激动剂

S1PR2激动剂具有特异性双向调控作用:在上皮微环境中,S1PR2激动剂通过激活S1PR2,进而激活SphK2-组蛋白去乙酰化酶1/2(histone deacetylase 1/2, HDAC1/2)-ERK1/2信号轴,促进上皮细胞增殖,增加细胞通透性,加剧肠屏障损伤^[18];而淋巴内皮特异性S1PR2激动剂则能抑制淋巴细胞跨内皮迁移,减少肠道淋巴细胞富集,从而减轻肠道炎症^[15]。

2.2.2 S1PR3/4拮抗剂

S1PR3/4拮抗剂可通过双重阻断机制,一方面阻断S1PR3,从而抑制血管平滑肌环氧化酶2(cyclooxygenase-2, COX-2)等炎症介质的产生^[19];另一方面阻断S1PR4,从而降低肠黏膜免疫球蛋白A(immunoglobulin A, IgA)水平^[20]。

2.2.3 S1PR5激动剂

S1PR5激动剂可通过激活S1PR5改变受体信号的空间定位,促使自然杀伤细胞从淋巴器官向外周血重新分布^[2],为改善肠道局部免疫失衡提供了新策略。

3 用于治疗IBD的S1PR调节剂

3.1 临床在研药物

3.1.1 Ozanimod

Ozanimod(RPC1063、Zeposia[®])是一种口服的S1PR1/5激动剂[半数效应浓度(median effect concentration, EC₅₀)为0.33 nmol/L],具有潜在的神经保护作用,其对S1PR1的选择性是对S1PR5选择性的27倍^[21]。Ozanimod于2021年在美国获批用于治疗中重度活动性UC成人患者;欧盟批准Ozanimod用于治疗对传统疗法或生物制剂反应不足、反应丧失或不耐受的中重度活动性UC成人患者^[22]。特别的是,Ozanimod对于不耐受UC患者的治疗效果尤为显著。

Ozanimod可诱导S1PR1持续性内化并促进其降

解,还可通过增强S1PR1偶联G蛋白与 γ -³⁵S标记的鸟苷三磷酸的结合能力抑制环磷酸腺苷的生成,从而抑制S1PR1介导的淋巴细胞向肠道迁移,减少促炎细胞因子释放,进而缓解肠道炎症并促进黏膜修复^[21]。研究发现,Ozanimod及其主要活性代谢物CC112273和CC1084037可以阻止淋巴细胞从淋巴组织排出,进而降低外周血中的绝对淋巴细胞计数,减轻淋巴细胞引起的炎症反应,从而发挥治疗UC的作用^[23]。Ozanimod的半衰期($t_{1/2}$)为20 h,其活性代谢物的 $t_{1/2}$ 均为10 d^[1],清除期约为55 d^[24]。

在Ⅱ期临床研究中,中重度活动性UC患者每天服用Ozanimod 1 mg可长期改善症状,71%患者的IBD生活质量问卷评分得到了有临床意义的改善^[25]。Ⅲ期临床试验显示,接受Ozanimod治疗的中重度活动性UC患者的临床反应、内镜改善和黏膜愈合这3个关键次要终点均有显著改善^[26]。接受Ozanimod治疗的患者,其直肠出血和大便次数的次级评分均有所下降^[27]。完成10周Ozanimod研究的患者中,有47.8%实现了临床应答,27.3%实现了内镜改善,12.6%实现了黏膜愈合(P 均小于0.001)^[28]。完成52周Ozanimod研究的患者中,服用Ozanimod的患者有37%得到了临床缓解,服用安慰剂的患者有18.5%得到了临床缓解^[29]。由此可知,Ozanimod对中重度活动性UC患者具有较好的疗效。

3.1.2 Etrasimod

Etrasimod是S1PR1的完全激动剂(EC_{50} 为0.57 nmol/L),也是S1PR4/5的部分激动剂^[30-31]。Etrasimod可抑制T细胞、中枢记忆T细胞、效应记忆T细胞、辅助型T细胞2(Th2)和Th17细胞以及B细胞的炎症反应并维持免疫监视,其 $t_{1/2}$ 约为33 h^[32], t_{max} 的中位值范围为3.5~7 h^[30]。Etrasimod在口服给药后吸收迅速,起效快,停药后淋巴细胞可以快速恢复到基线水平^[30]。2023年10月,美国FDA批准Etrasimod用于治疗成人中重度活动性UC。2024年2月欧洲药品管理局批准Etrasimod上市,用于治疗 ≥ 16 岁,对常规治疗或生物制剂反应不足、反应丧失或不耐受的中重度活动性UC患者。在临床前药理学研究中,Etrasimod对小鼠源(EC_{50} 为3.65 nmol/L)、犬源(EC_{50} 为4.19 nmol/L)和猴源(EC_{50} 为8.7 nmol/L)的S1PR1表现出完全激动活性,对人源S1PR4(EC_{50} 为147 nmol/L)和S1PR5(EC_{50} 为24.4 nmol/L)则表现出部分激动活性,对人源S1PR2、S1PR3未表现出激动或拮抗活性^[2]。

Ⅱ期临床试验显示,中重度UC成人患者口服

Etrasimod 2 mg可缓解临床症状、改善组织病理学损伤,且患者耐受性良好^[33-34]。接受Etrasimod治疗的大多数中度至重度活动性UC成人患者第12周出现临床缓解或内镜改善,并在经过52周治疗后仍能保持这种疗效,且未出现新的不良反应^[35]。另一项Ⅱ期临床试验显示,成人UC患者接受Etrasimod治疗34周后,生活质量明显改善^[36]。

Ⅲ期临床试验显示,接受Etrasimod治疗后,UC患者结肠组织中的活化免疫细胞特别是T细胞和B细胞亚群均显著减少,表明Etrasimod可以减轻UC患者的局部炎症^[37]。另一项Ⅲ期临床试验显示,接受Etrasimod治疗52周后,UC患者症状显著缓解、内镜结果显著改善($P < 0.05$)^[38]。

3.1.3 Amiselimod

Amiselimod对S1PR1/5的激动活性较强,对S1PR4的激动活性较小,对S1PR2/3几乎无激动活性^[39]。Amiselimod可调节淋巴细胞的转运,抑制结肠致病性Th1细胞和Th17细胞渗入结肠,从而抑制慢性结肠炎发生^[40]。

Ⅱ期临床试验显示,安慰剂组与Amiselimod组分别有54.1%和48.7%的患者的CD活动指数较基线下降100分,Amiselimod组患者的平均淋巴细胞计数随着时间的推移而减少;但Amiselimod在诱导临床缓解方面并不优于安慰剂,究其原因可能是Amiselimod不能减少CD炎症部位被异常激活的炎症性巨噬细胞^[41]。整体而言,CD患者对Amiselimod的耐受性良好,未报告Amiselimod新的安全性问题^[41]。

3.1.4 KRP-203

KRP-203是一种强效口服激动剂,对S1PR1/4/5具有较强激动活性,对S1PR3仅有部分激动活性^[42-43]。KRP-203能显著抑制结肠淋巴细胞产生干扰素 γ 、白细胞介素12(interleukin-12, IL-12)和肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α),但不影响IL-4的产生;此外,KRP-203还能阻断结肠黏膜中Th1细胞的产生,减少炎症部位淋巴细胞浸润,减少从血液中循环至胃肠道的活化淋巴细胞数量^[44]。

一项Ⅱ期临床试验显示,接受KRP-203治疗的中度活动性溃疡性UC成人患者中有14%出现临床缓解,接受安慰剂治疗的患者未出现临床缓解;尽管KRP-203未达到最低临床相关疗效阈值(20%),但KRP-203治疗效果仍优于安慰剂^[45]。

3.2 潜在治疗药物

3.2.1 Fingolimod

Fingolimod在体内可被SphK磷酸化生成有生理活性的磷酸酯,从而激活S1PR1/3/4/5,但对S1PR2基本无活性^[46]。动物实验表明,连续6 d腹腔注射Fingolimod(1 mg/kg)可显著改善小鼠结肠黏膜损伤,降低小鼠血清中TNF- α 、IL-6和干扰素 γ 水平^[47]。Fingolimod还可通过抑制巨噬细胞的M1极化,调节异常免疫反应,从而改善急性结肠炎^[47]。

研究发现,UC大鼠连续8 d灌胃Fingolimod(0.5 mg/kg),可减少腹泻、改善出血症状,还可减轻结肠组织炎症细胞浸润,改善黏膜出血和坏死;此外,Fingolimod可显著降低促炎细胞因子IL-9和Th17的表达,显著升高抗炎细胞因子IL-10的表达^[48]。

3.2.2 Ceralifimod

Ceralifimod是一种S1PR激动剂,对S1PR1和S1PR5的EC₅₀分别为0.027、0.334 nmol/L^[49]。Ceralifimod的前体药物为W-061,与传统S1PR激动剂(如Fingolimod)相比,W-061对淋巴细胞的特异性更高。研究发现,肠炎小鼠连续灌胃W-061(3 mg/kg)5 d后,可减少结肠固有层细胞浸润、黏蛋白耗竭及黏膜损伤;可抑制淋巴细胞向脾和黏膜固有层迁移,促进淋巴细胞归巢到次级淋巴组织;还可抑制Th17和Th1细胞向固有层迁移^[50]。

4 总结

S1PR调节剂正在成为治疗IBD的新型药物。S1PR调节剂可通过调节淋巴细胞迁移、降解受体、特异性调控S1PR,从而发挥抑制肠道炎症反应的作用。目前Ozanimod与Etrasimod在美国与欧盟已获批上市用于治疗IBD;临床上用于治疗IBD的S1PR调节剂还有Amiselimod与KRP-203。Amiselimod在诱导临床缓解方面疗效不佳,但未报告Amiselimod新的安全性问题;Amiselimod的临床研究验证了S1PR1/5双重激动策略在肠道淋巴细胞归巢调控中的可行性,同时揭示了黏膜巨噬细胞稳态在IBD治疗中的关键地位;其良好的耐受性特征为后续开发选择性更高的S1PR调节剂奠定了安全性基础,而疗效瓶颈则提示未来需结合巨噬细胞靶向策略或开发多靶点调节剂以突破现有治疗局限。KRP-203在临床试验中治疗效果优于安慰剂,但未达到最低临床相关疗效阈值(20%),且KRP-203对UC患者安全、耐受性良好;Fingolimod与W-061(Ceralifimod的前体药物)在动物实验中均能减轻小鼠的肠道炎症,减少结肠炎症细胞浸润及黏膜损伤,在治疗IBD疾病领域展现出较大的潜力。

S1PR调节剂作为新型口服靶向药物,具有精准靶向性、口服便利性与疗效持久性的优势,兼具疗效与安全性优势。未来S1PR调节剂的发展将聚焦于提升受体亚型选择性以降低副作用、拓展联合治疗方案等方面,从而为IBD治疗提供新参考。

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