·文献综述·

Rho 相关激酶抑制剂治疗 Fuchs 角膜内皮营养不良新进展

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摘要

Fuchs 角膜内皮营养不良(FECD)是以角膜内皮进行性损害,逐渐发展为角膜内皮失代偿为特征的一种营养不良性疾病,目前的标准疗法即角膜移植手术存在种种限制。最近的研究发现,Rho 相关激酶抑制剂可通过调节细胞周期蛋白 D 和 p27 信号传导通路促进细胞增殖,激活 Rac1 蛋白驱动肌动蛋白相关蛋白复合物(ARPC2)增加细胞黏附,调节膜出泡、核崩解和凋亡小体的形成抑制角膜内皮细胞的凋亡,有望治疗 FECD。文章主要对 Rho 相关激酶抑制剂治疗 FECD 的药理作用、基础研究、临床试验以及不良反应等相关进展进行综述,希望能尽早开发出疗效稳定且副作用少的化合物,为治疗 FECD 提供新方案。

关键词:Fuchs 角膜内皮营养不良;Rho 相关激酶抑制剂;治疗进展

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Advances in Rho - associated kinase inhibitors in the treatment of Fuchs endothelial corneal dystrophy

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Abstract

• Fuchs endothelial corneal dystrophy (FECD) is a progressive dystrophic disease characterized by gradual damage to the corneal endothelium, ultimately leading to endothelial decompensation. The current standard treatment, corneal transplantation, has several limitations. Recent studies have shown that Rho-associated kinase (ROCK) inhibitors can promote cell proliferation by modulating the cyclin D and p27 signaling pathways. Additionally, ROCK inhibitors activate Rac1, which drives the actin-related protein complex (ARPC2) to enhance cell adhesion, and regulate processes such as membrane blebbing, nuclear disintegration, and apoptotic body formation, thereby inhibiting the apoptosis of corneal endothelial cells. These findings suggest that ROCK inhibitors may be a promising therapeutic approach for FECD. This review provides an overview of the pharmacological effects, basic research, clinical trials, and potential adverse reactions associated with ROCK inhibitors in the treatment of FECD, with the aim of developing compounds with stable efficacy and minimal side effects for the treatment of FECD in the near future.

• KEYWORDS: Fuchs endothelial corneal dystrophy; Rho-associated kinase inhibitor; treatment progress

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0 引言

Fuchs 角膜内皮营养不良(Fuchs endothelial corneal dystrophy,FECD)是以角膜内皮细胞进行性减少、后弹力层增厚以及滴状赘疣为特征的一种营养不良性疾病[1]。当角膜内皮细胞丢失过多而致内皮功能失代偿时,角膜基质和上皮水肿引起视力下降、晨起视力不佳,随着时间的推移屈光发生变化,视力会有所改善[2],晚期逐渐发展为大泡性角膜病变,严重者可表现为失明[3]。FECD 在 50-60 岁的人群中发病更高,男女比例为 1:3-3.5[4-5]。目前 30 岁以上患有 FECD 的总人数接近 3 亿,预计 2050 年受 FECD 影响的患者人数将增加 41.7%[6]。在全球范围内,FECD 是角膜移植手术最常见的手术适应证之一[7]。在过去 10 a 中,后弹力层角膜内皮移植术(descements membrane endothelial keratoplasty,DMEK)已成为发达国家治疗 FECD 的标准疗法[8]。尽管 DMEK 术后视力显著提

升,视觉质量以及视力相关生活质量明显改善[9],但 DMEK 手术仍存在组织损伤以及植片脱离等并发症的概率。同时它也是一种技术难度高的手术,因此 DMEK 的开展受到制约[10]。全球范围内角膜供体缺乏更是从源头限制了 DMEK[11]。无内皮移植的后弹力层剥离手术,亦称为单纯后弹力层剥离术(descemet stripping only,DSO),似乎解决了供体紧缺以及移植物脱离等难题[12]。然而病例报告显示,DSO 预后并不稳定,需要苛刻的条件保证手术成功率,部分患者术后出现角膜水肿,尚需进一步手术干预[13]。近年来发现 Rho 相关激酶抑制剂治疗 FECD 取得令人雀跃的结果。本文将就其药理作用、基础实验研究、临床应用、不良反应等方面进行综述。

1 FECD 发病机制

角膜内皮层由角膜内皮细胞组成,健康成人内皮细胞密度范围为 2 000-4 000 cell/mm^2[14]。角膜内皮细胞在角膜基质层和房水之间充当选择性渗漏屏障,通过主动泵入离子维持渗透压,保持角膜处于相对脱水状态[1]。在氧化应激作用下,FECD 患者角膜内皮细胞内活性氧生成增多,核 DNA 和线粒体 DNA 遭到破坏,诱发细胞衰老及凋亡。角膜内皮细胞形态与大小改变,内皮细胞间充质转化,细胞外基质异常堆积形成滴状赘疣,角膜内皮细胞进行性减少[1]。由于角膜内皮细胞没有再生能力,只能通过相邻细胞迁移进行补偿[14]。当 FECD 内皮细胞密度降低至 500-1 000 cell/mm^{2}以下,内皮细胞泵和屏障功能受损,角膜内皮功能失代偿[14]。最新研究发现铁死亡[15]、雌激素代谢失调[16-17]、免疫调节串扰[18]等在 FECD 的发病机制中发挥作用(目前尚未发现这些机制中存在 Rho 相关激酶抑制剂作用位点,此处暂不详述)。

2 Rho 相关激酶抑制剂治疗 FECD

2.1 Rho 相关激酶抑制剂的药理作用 Rho 激酶(Rho kinase,ROCK)是一种丝氨酸/苏氨酸激酶[19],作为 Rho GTP 酶的下游效应蛋白参与趋化、基因表达、收缩平滑肌等生理过程[20]。在 GTP 酶激活蛋白和鸟嘌呤核苷酸解离抑制剂的调控下,鸟嘌呤核苷酸交换因子促使 Rho-A 蛋白与 GDP 结合的非活性构象转换为与 GTP 结合的活性构象[19]。激活的 Rho-A 蛋白触发 ROCK 级联信号传导通路,磷酸化靶蛋白发挥作用[21]。Rho/ROCK 信号通路在人体组织中广泛存在,是帕金森综合征、糖尿病心肌病、肺动脉高压、口腔癌等多种疾病的潜在治疗靶点[22-25]。眼部相关研究发现它可调节小梁网和角膜内皮的生理特性,增加视网膜血管通透性,诱发黄斑水肿[21]。

Rho 激酶有 ROCK1 和 ROCK2 两种异构体,不同的异构体作用略有不同[21]。Rho-A 蛋白及其效应器 ROCK2 主要在人角膜内皮细胞中表达[26]。角膜内皮细胞间存在接触抑制,细胞停滞在 G1 期无法增殖,通过调节细胞周期蛋白 D 和 p27 信号传导通路,Rho 相关激酶抑制剂促使这些细胞进入 S 期开始增殖[27]。Rho 相关激酶抑制剂还能诱导角膜内皮细胞迁移,促进内皮愈合,恢复内皮细胞泵和屏障功能[28]。功能分析显示,Rho 相关激酶抑制剂可增强线粒体呼吸作用,通过上调电子传递链 AMP 活化蛋白激酶途径诱导其过度表达,改变氧化磷酸化代谢途径,促使角膜内皮细胞迁移[29]。Rho 相关激酶抑制剂还激活 Rac1 蛋白,驱动肌动蛋白相关蛋白复合物(ARPC2),增加细胞黏附,促进内皮愈合[26,30]。此外,Rho 相关激酶抑制剂通过调节膜出泡、核崩解和凋亡小体的形成,从而抑制内皮细胞凋亡。角膜内皮细胞和角膜上皮细胞间的串扰似乎也发挥了一定作用,但机制尚不明确[31]。

2.2 Rho 相关激酶抑制剂治疗 FECD 的基础实验研究 体外实验结果表明,Rho 相关激酶抑制剂可逆转 FECD 表型。对 Rho 相关激酶抑制剂处理的猪离体角膜进行划痕试验后,Ki-67 阳性细胞数量增加,大部分角膜伤口愈合。这证明 Rho 相关激酶抑制剂不仅可以促进细胞增殖,还利于内皮愈合[32-33]。在牛角膜细胞模型中也得到了类似试验结果[29]。氧化应激诱发细胞凋亡是 FECD 发病机制之一[1]。角膜内皮细胞在紫外线照射后 Rho/ROCK/MLC 通路磷酸化,肌动蛋白收缩,细胞黏附减少,进而诱导细胞凋亡[29]。膜联蛋白 V 染色显示,紫外线照射 24 h 后应用 Rho 相关激酶抑制剂显著抑制猴角膜内皮细胞凋亡,兔样本中也观察到类似的抑制作用[29]。以上结果提示 Rho 相关激酶抑制剂能够抑制 MLC 磷酸化,通过增加黏附复合物的表达和抑制肌动蛋白收缩促进内皮细胞黏附,抑制内皮细胞凋亡[26]。

动物实验同样证实了 Rho 相关激酶抑制剂有希望治疗 FECD。在兔子模型中,局部施用 Rho 相关激酶抑制剂可以减轻角膜水肿[33]。手术损伤兔角膜内皮细胞,局部应用 Rho 相关激酶抑制剂 10 d[33]。前 3 d 每日 4 次,后 7 d每日 3 次,对侧眼应用生理盐水作为对照。每天通过裂隙灯检查、眼前段照相和角膜测厚仪监测角膜水肿、炎症和厚度来评估伤口愈合的进展[33]。眼前段照相记录结果显示,与对照组相比,应用 Rho 相关激酶抑制剂的兔子中 83.33%角膜水肿明显减轻[27]。角膜染色结果显示角膜出现封闭伤口区域以及多核的角膜内皮细胞,这些形态变化提示伤口愈合与 Rho 相关激酶抑制剂增迁移和增殖有关[33]。Rho 相关激酶抑制剂可延缓犬角膜水肿,62%患眼有所改善[34]。Rho 相关激酶抑制剂的两种剂型均有此作用,应用 ripasudil 的患犬病程进展明显慢于 netarsudil 组[35]。

2.3 Rho 相关激酶抑制剂的临床应用 ripasudil、netarsudil 和 fasudil 等三种 Rho 相关激酶抑制剂已投入临床使用。2014 年日本准许 ripasudil 用于治疗青光眼和高眼压症,最近英国也予以批准。2017 年底 netarsudil 在美国被批准用于青光眼治疗,2021 年于欧洲获批。fasudil 最初于 1995 年在日本获批用于治疗蛛网膜下腔出血引起的脑血管痉挛,最近有研究发现它对治疗糖尿病性黄斑水肿也有效[36-37]。此外还有一些 Rho 相关激酶抑制剂尚未获得临床应用许可。SNJ-1656 正在开展用于控制眼压的Ⅱ期试验[38]。Y-27632、AR-12286、sovesudil、PHP-0961 等仍处于体外实验等临床前阶段[32,39-40]。Koizumi 等首次在临床中证实 Rho 相关激酶抑制剂可用于治疗 FECD[41]。角膜内皮剥离术后患眼应用 Rho 相关激酶抑制剂 Y-27632,每日 6 次,连续应用 1 wk。2 wk 后随访发现角膜恢复透明,视力从 20/63 提高至 20/20,术后 12 a 随访预后良好[41]。然而在另一项实验中,DSO 术后 2 mo 未愈患者应用 Y-27632 无效,使用 ripasudil 2 wk 后患眼角膜方能恢复透明[42]。在 Macsai 等[43]的研究中,9 例参与者术后 1 d 即应用 0.4% ripasudil,每日 4 次,连续应用 2 mo,结果表明术

后立即接受 ripasudil 治疗的患者组视力恢复更快(4.6 wk *vs* 6.5 wk,$P<0.01$)。另一项研究显示 netarsudil 也有类似的效果[44]。以上这三种 Rho 相关激酶抑制剂中 ripasudil 的效果最为显著。这可能与 ripasudil 还抑制 TGF-β 诱导的 TGF-β 通路下游分子(SMAD2)和 Rho-ROCK 通路下游分子(MLC2)的表达和磷酸化有关。此外 ripasudil 进一步上调基质金属蛋白酶等蛋白水解酶(如 MMP1 和 MMP3)的基因表达也可能发挥了一定作用[45]。

局部应用 ripasudil 已通过局部和全身安全性分析实验,适用于特定的 FECD 患者[46]。这种治疗方案正在成为一种可靠的干预措施。目前 Kinoshita 等[47]正在计划进行一项临床试验,为 FECD 患者应用 ripasudil 滴眼液建立一级临床依据。最近一项随机研究调查了 netarsudil 治疗 FECD 相关角膜水肿的情况[48]。29 例参与者每天 1 次应用 0.02% netarsudil 或安慰剂 3 mo。与安慰剂相比,netarsudil 治疗后中央角膜厚度(平均差-26 μm)显著减低和最佳矫正视力(平均差+1.6 行)明显提升[48]。一项Ⅱ期实验结果表明 netarsudil 不仅减轻角膜水肿,提高视力,还改善了眩光等症状[49]。

2.4 Rho 相关激酶抑制剂的不良反应 研究表明,局部应用 ripasudil 与 netarsudil 不良反应的发生率分别为 3.3%和 18.7%,安全性可接受[21]。局部应用 Rho 相关激酶抑制剂的不良反应主要包括结膜充血、睑缘炎、蜂窝状/网状角膜上皮水肿等[21]。结膜充血最为常见且大多数为轻度,通常在 2 h 内消失[50]。睑缘炎是终止 ripasudil 治疗的最常见原因,在 netarsudil 治疗过程中并不显著[21]。蜂窝状/网状角膜上皮水肿是局部应用 Rho 相关激酶抑制剂最严重的不良反应之一[51-56]。这可能与内皮泵活性增加和上皮细胞间连接的改变导致液体转移到上皮层有关[51-52]。ripasudil 与 netarsudil 两种制剂都可观察到蜂窝状/网状角膜上皮水肿,netarsudil 更加多见。大多数病例停药后水肿完全消退,小部分患者需角膜移植[53]。内皮细胞计数减少、上皮缺陷或有穿透性角膜移植手术史的患者似乎更易发生角膜上皮水肿[54-55]。

3 小结

虽然目前 FECD 治疗方案较安全且有效,然而供体紧缺、免疫排斥等问题限制了 DMEK 的开展。因此,开发一些新型的治疗方式尤为重要。近年来发现 Rho 相关激酶抑制剂治疗 FECD 取得令人雀跃的成果,不仅从根源上解决了供体紧缺、免疫排斥等问题,还填补了 FECD 早期治疗的空白,更符合当下“早发现,早诊断,早治疗”的治疗理念。这种治疗方式也存在一些尚未解决问题,比如 Rho 相关激酶抑制剂的适应证较为局限,目前对轻中度患者治疗效果好,并不能真正取代手术治疗。部分学者并不看好单独应用 Rho 相关激酶抑制剂治疗 FECD,认为需要联合 DSO 才能达到预期疗效。相关Ⅲ期临床试验尚未进行,与真正投入临床使用尚有距离。总之,尽管 Rho 相关激酶抑制剂有希望成为治疗 FECD 的新方案,尚需开发出疗效稳定且副作用少的化合物并进行更大样本的多中心临床试验,进一步确定最佳适应证,方能真正应用于一线临床。

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