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· 综述 ·

近视中 Shh、PI3K/AKT、MMP-2 通路及关联性研究进展

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摘要:Shh、PI3K/AKT、MMP-2 是在机体中广泛表达的重要调控信号通路,与胚胎发育、细胞生长、增殖和分化密切相关。越来越多的研究发现 Shh、PI3K/AKT、MMP-2 信号通路在维持眼球的正常生长发育、眼部各组织再生和修复以及眼部多种疾病的发生发展过程中发挥着至关重要的作用。在近视的发生发展过程中均存在 Shh、PI3K/AKT、MMP-2 信号通路的异常表达,这表明 Shh、PI3K/AKT、MMP-2 信号通路对近视的发生发展尤为重要。寻找近视发病机制的相关信号通路也成为当下的热点话题,因此探索 Shh、PI3K/AKT、MMP-2 信号通路在近视发生发展中的表达变化以及关联性具有重要的意义。本文总结了 Shh、PI3K/AKT、MMP-2 信号通路在近视中的表达变化,并在此基础上对各通路之间的关联性进行探讨。

关键词:音猬因子;磷脂酰肌醇 3-激酶/蛋白激酶 B;基质金属蛋白酶-2;近视
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Advances in Shh, PI3K/AKT, and MMP-2 pathways and correlations in myopia

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Abstract: Shh, PI3K/AKT and MMP-2 are important regulatory signaling pathways widely expressed in the body, and are closely related to embryonic development, cell growth, proliferation and differentiation. More and more studies have found that Shh, PI3K/AKT and MMP-2 signaling pathways play a crucial role in maintaining the normal growth and development of the eye, the regeneration and repair of eye tissues, and the occurrence and development of various ocular diseases. It has been reported that there are abnormal expressions of Shh, PI3K/AKT and MMP-2 signaling pathways in the occurrence and development of myopia, which indicates that Shh, PI3K/AKT and MMP-2 signaling pathways are particularly important in the occurrence and development of myopia. In recent years, the search for signaling pathways related to the pathogenesis of myopia has become a hot topic at present. Therefore, it is of great significance to explore the expression changes and correlation of Shh, PI3K/AKT and MMP-2 signaling pathways in the occurrence and development of myopia. This paper focuses on the expression changes of Shh, PI3K/AKT and MMP-2 signaling pathways in myopia, and on this basis, the correlation between these pathways is discussed.

Key words: Sonic Hedgehog; Phosphatidylinositol 3-kinase/protein kinase B; Matrix metalloproteinase-2; Myopia

近视是指在不使用调节功能的状态下,平行光线经眼球屈光系统后聚焦于视网膜之前的病理性屈光状态,现已成为危害儿童和青少年身心健康发展最突出的问题之一。近年来,近视发病率呈现逐年上升和低龄化趋势[1]。研究发现,在新型冠状病毒肺炎大流行后,学龄期儿童的年近视进展为-0.35 D,发病率为 24.85%[2]。预计到 2050 年,中国儿童及青少年的近视发病率约为 84%[3],全球人口近视发病率约为 49.8%,其中 9.8%为高度近视[4]。近视及其并发症严重影响人们的学习、生活和身心健康,并且随着近视度数的增长,眼轴的增长,视网膜色素上皮和脉络膜厚度逐渐变薄,后续可能产生脉络膜新生血管及视网膜脱离等严重的并发症,导致不可逆的视力损害[5]。因此,深入探讨近视的潜在发病机

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制为近视防控提供理论支持尤为重要。

音猬因子(sonic hedgehog, Shh)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinose B, AKT)以及基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)是哺乳动物体内传导细胞内外信号的重要通路,在人和动物生长发育过程中发挥关键作用[6-8];已有研究表明,Shh、PI3K/AKT、MMP-2 信号通路在肿瘤[9-11]、神经系统疾病[12-14]、内分泌代谢疾病[15-17]、呼吸系统疾病[18-20]等发病机制中发挥着至关重要的作用,并且在以 Shh、PI3K/AKT、MMP-2 信号通路为靶点的疾病预防和治疗方面取得了重要的成果[21-24]。随着近视低龄化趋势的到来,关于近视发病机制的研究日益迫切,Shh、PI3K/AKT、MMP-2 信号通路与近视的相关性也成为当下研究热点。目前已有众多研究报道了 Shh、PI3K/AKT、MMP-2 信号通路异常表达与近视的发生发展密切相关,例如在豚鼠形觉剥夺性近视(form deprivation myopia, FDM)模型中,近视的诱导过程伴随着 Shh 表达水平的升高[25]。PI3K/AKT 信号通路的激活也促进了近视的发生发展[26]。也有研究发现缺氧诱导因子-2α(hypoxia-inducible factor-2α, HIF-2α)通过促进巩膜 MMP-2 表达和胶原降解介导缺氧性近视的发展[27]。本文主要以 Shh、PI3K/AKT 以及 MMP-2 信号通路为切入点,阐述三者在近视中的表达变化及探讨各通路之间的关联性,为日后近视发病机制的研究和探索精准防控近视新靶点提供理论依据。

1 音猬因子通路表达变化与近视

Shh 是 Hedgehog(HH)信号通路中的一类,与 Indian hedgehog(Ihh)和 Desert hedgehog(Dhh)共为 Hedgehog 同源基因,其中 Ihh 和 Dhh 表达较少,而 Shh 表达发挥主要作用,该通路是由分泌性糖蛋白配体(Shh)、跨膜蛋白受体 Ptched(Ptch)、Smoothened(Smo)、核转录因子(Gli)及下游目的基因组成,其中主要通过 Ptched1(Ptch 1)和 Smoothened(Smo)激活 Gli 转录因子发挥通路作用[28]。Shh 信号通路作为胞外配体信号通路,由多种器官分泌细胞产生,并且在哺乳动物中广泛表达,与机体胚胎发育及细胞增殖分化密切相关[29]。随着研究的不断深入,目前 Shh 信号通路已被认为是一把双刃剑,一方面 Shh 信号通路可以维持组织稳态和发育,另一方面该通路的异常表达又会引发机体发育异常[30]。

Shh 信号通路广泛存在于眼球组织中,其在脊椎动物眼球的视泡轴发育、视网膜的背腹侧分野以及视野形成等过程中发挥重要的调控作用,不仅可以维持眼球的正常生长发育,还参与眼部各组织再生和修复过程,同时也与眼部多种疾病的发生发展密切相关[31]。近视的发生是内在遗传基因和外界环境因素共同作用的结果,胚胎时期调控眼球发育的信号通路可能与近视的发病机制相关,目前,已有研究证实了近视发病机制中存在着 Shh 信号通路的激活,例如,Akamatsu 等[32]研究发现在雏鸡实验性近视 3、7 d 后视网膜组织中 Shh mRNA 的表达水平升高,第 7 天时表达最为显著,并且 Shh mRNA 的表达变化与近视的发展存在一致性。Escaño 等[33]通过半定量逆转录-聚合酶链反应检测 Shh 及其受体复合物和其它视网膜细胞基因的表达水平,结果显示 Shh mRNA 和蛋白在实验性近视眼中的表达显著增加。上述结论均提示我们 Shh 信号通路参与了近视的发生过程,并且该通路的过度激活与近视进展呈正相关。Qian 等[25]研究发现在 FDM 小鼠眼球中 Shh mRNA 表达水平及 Shh 信号通路活性均显著高于正常对照组,并且在玻璃体腔内注射 Shh 氨基末端肽(Shh-N)激活 Shh 信号通路后 FDM 眼球和正常眼球均出现眼轴正向增长和近视屈光度增加趋势,而玻璃体腔内注射环巴胺抑制 Shh 信号通路后则可以减缓 FDM 眼球的眼轴增长和近视屈光度增加从而抑制近视的进展,在正常眼球中抑制 Shh 信号通路可以促进眼球朝向远视方向发展。这种 Shh-N 的促近视作用和环巴胺的抗近视作用体现了 Shh 信号通路可以影响 FDM 和正常视觉输入眼的眼轴生长,并且参与屈光发育的调节。由此可见,Shh 信号通路可能参与调节导致近视眼轴延长和玻璃体腔延伸的信号级联反应,并且 Shh 信号通路的过表达可以诱导近视产生,抑制 Shh 信号通路反而阻碍了近视的进展,因此,以 Shh 信号通路为药物靶点对近视产生防控作用是未来临床实践中的一种可行方法。然而视网膜中 Shh 如何作用到巩膜,脉络膜及视网膜色素上皮上的信号分子是否参与其中,还需要更深入的研究。

2 PI3K/AKT 通路表达变化与近视

PI3K/AKT 信号通路是一条在传导细胞内外信号方面起着重要作用的中间通路,广泛存在于各种类型的细胞中,由关键分子 PI3K 和 AKT 组成,该通路可以在各类分子的刺激下,调节多个下游效应器,从而调控多种蛋白质,参与细胞的生长、增殖和分化[34]。

在眼科学方面,PI3K/AKT 信号通路对多种眼

部疾病例如白内障、青光眼、葡萄膜疾病以及视网膜疾病等有重要的调控作用[35]。在甲状腺相关性眼病中,由于 PI3K/AKT 信号通路的直接刺激,致使眼球部分纤维组织发生了增生性病理改变,从而导致眼球向外挤压,形成眼球突出[36]。这表明 PI3K/AKT 信号通路对眼部组织的生长和发育具有调控作用,而眼轴的延长是近视发生发展的重要原因,PI3K/AKT 信号通路的过度激活可能也是近视的发病机制之一。在近视方面的研究显示,miR-200a 在高度近视眼球的玻璃体中下调,而 PI3K/AKT 信号通路是下调的 miR-200a 的显著靶向通路[37]。胰岛素作为主要信号分子作用于视网膜色素上皮细胞,通过激活 PI3K/AKT 信号通路促使病理性近视相关蛋白如胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)和基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)的分泌增加,从而促进近视的发展,而这一过程在注射 PI3K 抑制剂 LY294002 后受到阻碍[38-39]。这进一步说明 PI3K/AKT 信号通路的过度表达与病理性近视的发生有关,而抑制该通路可能抑制近视的发展。然而,这种抑制作用仅在动物实验中得到验证,是否在人类近视眼的控制中也具有同样的作用,需要进一步探索。

3 基质金属蛋白酶-2 通路表达变化与近视

基质金属蛋白酶家族(matrix metalloproteinases, MMPs)是自然界进化中高度保守的一类锌依赖肽链内切酶,普遍存在于机体的多种器官和组织中[40]。MMP-2 为 MMPs 中的一类 IV 型胶原酶,在组织重塑和修复、胚胎生长发育、血管生成及炎症等生理方面起着重要的作用[41]。目前,人们认为巩膜细胞外基质(extracellularmatrix, ECM)合成与降解失衡是近视形成的原因之一,并且巩膜组织中 MMP-2 的异常表达也被认为是 ECM 重塑和近视发展的重要因素;在近视的有关报道中我们发现,MMP-2 信号通路表达的异常上调有效的降解了 ECM 中的 I、IV、V 型胶原,造成巩膜组织松解和眼轴延长,从而诱导近视的发生[42]。

一些动物模型的实验研究发现,MMPs 与近视的病变机制有关,并且在实验性近视研究中报道了 MMP-2 表达的增加,提示巩膜组织中 MMP-2 信号通路表达的上调对 ECM 重塑和近视的发生有重要贡献。例如在树鼩模型中,近视巩膜组织中活性 MMP-2 的数量明显高于对照组[43];在小鼠模型中,FDM 造模 2 周后与正常对照组相比,FDM 小鼠近视屈光度增加和眼轴伸长的同时伴随着巩膜组织中 MMP-2 的上调,而抑制巩膜巨噬细胞中 MMP-2 的表达可以使近视发生率降低 59%[44];FDM 豚鼠发生近视偏移的同时伴随着巩膜组织中 MMP-2 表达水平的升高,单眼剥夺组豚鼠巩膜中 MMP-2 mRNA 表达水平较对侧未剥夺眼升高 217%,较正常对照组豚鼠升高 222%,相反,抑制 MMP-2 的上调反而阻碍了近视的发展[45-46]。这说明 MMP-2 的表达变化与近视之间存在因果关系,并且近视的发生依赖于 MMP-2 表达的增加。除此之外,我们还发现透镜诱导性近视(lens-induced myopia, LIM)中 MMP-2 的变化趋势与 FDM 中变化趋势基本一致[47-48]。在人类近视患眼中,通过检测高度近视房水中炎症因子及 MMP-2 表达水平发现 MMP-2 表达水平的升高是导致患者出现高度近视的独立性危险因素,并且与眼轴长度密切相关[49-51]。后续相关研究以 MMP-2 为药物治疗靶点,抑制了 MMP-2 信号通路的表达,同时显著减缓了近视的进展[52-53]。这提示我们开发选择性 MMP-2 抑制剂可能是未来近视防控的重点研究方向。

4 Shh、PI3K/AKT、MMP-2 信号通路间的关联性

随着研究的不断深入,我们逐渐发现 Shh、PI3K/AKT 以及 MMP-2 信号通路之间具有密切关联性。Shh 信号通路已被发现在多种组织中与 PI3K/AKT 信号通路存在着交互通话,并且可以通过介导 PI3K/AKT 通路的表达来发挥生物学效应,例如在神经系统中,Shh 信号通路对 PI3K/AKT 信号通路的激活可以对神经元产生保护性作用[54-56]。在肿瘤中 Shh 信号通路通过调控 PI3K/AKT 信号通路导致肿瘤间质转化和癌细胞转移,两者具有协同作用[57-61]。与此同时,Shh 信号通路还可以通过激活 PI3K/AKT 信号通路促进血管内皮细胞生成和抗氧化酶的表达,从而促进组织修复和减弱细胞凋亡[62-63]。在视网膜母细胞瘤(retinoblastoma, RB)的细胞存活过程中 Shh 和 PI3K/AKT 信号通路之间也存在着明确的相互作用,抑制 PI3K/AKT 信号通路是抑制 Shh 信号通路的先决条件[64]。因此,PI3K/AKT 信号通路是 Shh 信号通路传导所必需的重要组成部分,两者协同作用对机体产生调控。

Shh 信号通路作为 MMP-2 的上游调控信号,两者间的异常表达共同诱导了近视的发生发展。在 FDM 豚鼠玻璃体腔内注射 Shh-N 后实验眼出现近视改变的同时伴随着巩膜组织中 MMP-2 表达的同步性上调,并且 MMP-2 的变化程度与注射药物浓

度之间呈现一定的梯度关系,而注射 Shh 特异性抑制剂 cyclopamine 后近视发展受到阻滞的同时伴有巩膜组织中 MMP-2 表达的明显下调[65]。在近视发生发展的过程中,Shh 信号通路介导的 ECM 降解、巩膜重塑以及眼轴延长是通过调控 MMP-2 的表达水平来实现的,因此,在未来的临床实践中,我们可以尝试通过调控 Shh 信号通路控制巩膜组织中 MMP-2 的表达水平来延缓近视的进展。然而,对于 Shh 信号通路是通过何种途径调控 MMP-2 的表达尚不明确,是否与 PI3K/AKT 信号通路有关,还需要更多的实验验证。

同时,有学者针对这一问题进行了实验研究,结果发现 FDM 豚鼠实验眼中 Shh、PI3K/AKT 以及 MMP-2 的表达水平具有一致性,在 Shh 信号通路激活、阻断后,实验眼屈光状态和 PI3K/AKT 通路的信号因子分别发生了相应的、且变化趋势一致的改变,Shh 表达水平在玻璃体腔内注射特异性 PI3K/AKT 通路阻滞剂后出现了明显的延缓和下降,并且这种表达下降趋势与 PI3K/AKT 阻滞剂呈现一定的浓度梯度关系,而阻断 PI3K/AKT 通路后,Shh 诱导近视的作用几乎被完全抑制[66]。这表明了 Shh 信号通路可以通过介导 PI3K/AKT 信号通路作用于下游的因子,调控近视的发生发展,并且 PI3K/AKT 信号通路对 Shh 信号通路具有负反馈调控作用,而 Shh 信号通路作为 MMP-2 的上游调控通路,PI3K/AKT 可能是其中间通路,即 Shh-PI3K/AKT-MMP-2 信号通路可能是近视发生发展过程中的一条完整通路。

5 小结与展望

综上所述,Shh、PI3K/AKT、MMP-2 信号通路在眼球生长发育中起着重要作用,近视的发病机制与这些通路密不可分,大部分实验结果支持 Shh、PI3K/AKT 及 MMP-2 信号通路的过度表达对实验性近视有促进作用,并且通过抑制这些通路的表达可以减缓近视的进展,因此,以 Shh、PI3K/AKT 及 MMP-2 作为近视防控的新型靶标或许有望解决近视进展的难题。虽然已知 Shh、PI3K/AKT 及 MMP-2 信号通路诱导近视发生发展的过程与 ECM 合成和降解失衡有关,但由于认识不足,进一步研究这些通路信号传递的具体机制、如何通过调控神经视网膜-色素上皮层-脉络膜-巩膜途径诱导近视产生以及是否与其他信号通路之间存在相互作用具有重要的意义和价值,同时,我们对于 Shh-PI3K/AKT-MMP-2 信号通路可能是近视中的一条完整通路已经有了初步的认识,但证据尚不充分,更有效和更具体地探讨 Shh、PI3K/AKT 及 MMP-2 信号通路之间的关联性也是进一步研究的关键。望本文可为后续近视潜在发病机制的探索提供新的研究方向,为精准防控近视开发新的候选靶点。

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(下转第 154 页)

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(编辑:李纬)

(上接第 148 页)

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