·文献综述·

Hippo 通路及其在眼科领域的研究进展

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摘要

Hippo 通路是一个进化上保守的信号通路,它受细胞内外多种因素的调控,通过效应分子 YAP/TAZ,参与调节细胞的增殖、分化、迁移和再生等多种重要生理活动,其在组织发育、器官再生以及肿瘤发生等方面均有广泛的研究。近年来的研究显示,Hippo 通路与眼部组织的发育、再生和眼部疾病联系密切。阐明 Hippo 通路在眼部组织中的作用有助于揭示眼科疾病发生发展的机制,对完善眼科基础研究,指导眼科临床工作都具有深远的意义。本文从 Hippo 通路的核心组分、生物学作用以及近年来 Hippo 通路在眼部组织如角膜、小梁网、晶状体、视网膜和葡萄膜中的研究进展进行了详细综述。
关键词:Hippo 通路;发育;再生;晶状体;视网膜
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Hippo pathway and its research progress in ophthalmology

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Abstract

• The Hippo pathway, regulated by multiple intracellular and extracellular signals, is an evolutionarily conserved signaling pathway. Through YAP/TAZ, the effector molecule, Hippo pathway participates in a variety of important physiological activities such as regulating the proliferation, differentiation, migration and regeneration of cells. Extensive studies have revealed that the Hippo pathway involves in tissue development, organ regeneration and tumorigenesis. Recent studies have shown that the Hippo pathway is closely related to the development and regeneration of ocular tissues and development of ocular diseases. Elucidating the role of Hippo pathway in ocular tissues will help to reveal the mechanism of occurrence and development of ophthalmic diseases, and it has far-reaching significance for improving the basic research and guiding the clinical work of ophthalmology. In this manuscript, the components and functions of the Hippo pathway and the recent research progress of Hippo pathway in ocular tissues such as cornea, trabecular meshwork, lens, retina and uvea were reviewed.
• KEYWORDS: Hippo pathway; development; regeneration; lens; retina

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0 引言

Hippo 通路是一个进化上保守的信号通路,它最初在黑腹果蝇中发现[1],调控许多生物过程,包括调节细胞生长和分化,控制器官大小和再生。哺乳动物 Hippo 通路的核心组分包括一个激酶级联——MST1/2、SAV1、MOB1 和 LATS1/2,以及下游效应因子——转录共激活因子 YAP 和 TAZ[2]。这些 Hippo 通路的核心组分通过调控下游靶基因的转录,参与细胞增殖、分化、迁移和维持干细胞活性等生理活动[3-5]。目前的研究发现,Hippo 通路可能与很多眼部组织的发育再生和眼科疾病存在密切联系,本文从 Hippo 通路的核心组分、生物学作用及其在眼科领域的研究进展进行了综述。

1 Hippo 通路的核心组分和调控机制

在果蝇体内,Hippo 通路核心组分包括由蛋白激酶 Wart(Wts)、Salvador(Sav)、Hippo(Hpo)和 Mob(Mats)[2]形成的激酶级联,以及下游效应因子 Yorkie(Yki)。Hpo 在果蝇中发生突变可导致器官过度生长,形成类似河马(Hippopotamus)的外观,故称为 Hippo 通路。

从果蝇到哺乳动物,Hippo 通路是高度保守的。Wts、Sav、Hpo 和 Mats 在哺乳动物中的同源蛋白分别为 LATS1/2、SAV1、MST1/2 和 MOB1。MST1/2 与 SAV1 形成异二聚体,使 SAV1、MOB1 和 LATS1/2 激酶磷酸化[6-8]。LATS1/2直接磷酸化 Yki 同源蛋白 YAP(yes-associated protein)和 TAZ(transcriptional activator with PDZ-binding domain),从而抑制其进入细胞核[9-10]。YAP/TAZ 是不含

DNA 结合域的转录调控因子,主要与 TEAD(TEA/ATTS domain)家族转录因子结合[11-12]。Hippo 通路的活性受到多种信号如机械应力、细胞间接触、细胞极性、代谢状态和生长因子的严格调控,进而控制着 YAP/TAZ 在细胞核和细胞质之间的定位变化。Hippo 通路关闭时(图 1A),未磷酸化的 YAP/TAZ 进入细胞核中,与 TEADs 和其他转录因子结合,启动对细胞增殖、分化和迁移至关重要的转录程序。Hippo 通路开启时(图 1B),活化的 LATS 激酶磷酸化 YAP/TAZ,导致其与蛋白 14-3-3 结合并停留细胞质中,最终被降解[13-14]。在核内没有 YAP/TAZ 的情况下,TEAD 通过与转录调控因子 VGLL4 结合[15-16],抑制靶基因如结缔组织生长因子(connective tissue growth factor, CTGF)和 Cyr61[17] 的表达,从而限制组织生长和细胞增殖。

2 Hippo 通路的生物学作用

2.1 控制器官大小 控制器官大小是 Hippo 通路最常见的生理功能。在果蝇体内,Hippo 通路激酶或上游调节因子的突变导致眼、翅膀等器官的过度生长[18]。在小鼠体内,特异性激活 *Yap*1 或敲除 *Mst*1/2、*Sav*1 可导致心脏可逆性增大[19],并且心肌细胞的增殖和凋亡对 YAP 的调控敏感[20-21]。Hippo 通路还可通过响应拉伸和压缩等机械信号来控制器官大小。在体外培养的哺乳动物细胞中,当细胞被拉伸时,YAP 和 TAZ 活性升高,当细胞被压缩时活性降低[22]。

2.2 调控胚胎期细胞分化和器官发育 Hippo 通路在胚胎细胞分化过程中的部分作用已得到证实。敲除 *Tead*4 的小鼠胚胎不能分化出滋养外胚层细胞。敲除 *Lats*1/2、*Nf*2 等基因后,所有细胞无法分化成内细胞团来源的组织[23-24]。此外,组织特异性的 YAP 缺失会导致小鼠心脏、骨骼和肾脏的发育异常[21,25-26]。人体内 YAP 转录活性缺失也会导致眼部组织的发育异常,例如,*TEAD*1 突变可导致 Sveinsson 脉络膜视网膜萎缩和 Aicardi 综合征[27-28],在视神经裂闭合缺陷中也发现了 *YAP* 缺失突变[29]。由此可见,Hippo 通路在早期胚胎细胞分化和器官正常发育中起关键作用。

2.3 维持干细胞活性和调控组织再生 Hippo 通路的效应分子 YAP/TAZ 可调控不同干细胞的功能,YAP 能促进胚胎干细胞的多能性[30],TAZ 可调节间充质干细胞的分化[31-32]。小鼠干细胞的基因表达谱显示,YAP 和 TEAD 在多种组织的干细胞中富集[33],如肠、肝、皮肤和神经的干细胞或祖细胞中均观察到 *Yap/Taz* 的高表达[34-35]。*Yap/Taz* 条件性敲除小鼠的肠道再生能力受阻[36]。肝部分切除术后数天内,YAP 活性被诱导,可能是肝脏完全再生所必需的[37-38]。成人心肌的再生非常有限,然而,*YAP* 特异性激活可使心肌的再生能力得到一定程度的恢复[39-40]。相反,心脏特异性的 *YAP* 缺失会抑制心肌的再生[41]。

2.4 在细胞间黏附和接触抑制中的作用 接触抑制是贴壁细胞与相邻细胞进行物理接触时停止增殖的现象。细胞之间的相互接触可通过 YAP 和 TAZ 来调控细胞的增殖和存活[42]。一种可能的机制是:当细胞接触时,黏附连接蛋白如 Crumbs、PATJ、PALS 和 E-钙黏蛋白可以与 YAP 和 TAZ 结合[43],将 YAP/TAZ 隔离在细胞连接处,阻止它们进入细胞核,还可通过阻止 YAP/TAZ 去磷酸化[43],从而抑制细胞增殖。

3 Hippo 通路在眼部组织的研究进展

3.1 Hippo 通路在晶状体中的研究

3.1.1 维持晶状体上皮细胞极性 晶状体的透明性依赖于晶状体上皮细胞的有序排列,即顶端朝向晶状体纤维,基底部朝向前囊膜,称为晶状体上皮细胞的顶端-基底极性。Song 等[44]的研究发现,野生型小鼠晶状体中,YAP 蛋白与极性复合体蛋白 Crb 在晶状体上皮细胞(lens epithelial cell, LEC)的顶端连接处共定位,在小鼠晶状体中特异性敲除 *Yap* 可导致 LEC 形态由正常的立方型变扁平,并且 Par 和 Crb 极性复合体的顶端定位被破坏,上皮细胞极性紊乱,从而导致小鼠出现白内障。因此,YAP 可能通过与极性复合体 Par 和 Crb 相互作用,调控它们的定位[22,45],从而维持正常 LEC 的极性。

3.1.2 调节晶状体细胞增殖和纤维分化 正常生理状态下,LEC 终身保持增殖和分化。LEC 在持续增殖的同时,逐渐迁移至赤道部的过渡区并退出细胞周期,分化为晶状体纤维(lens fibers, LF)细胞。Kumar 等[46]发现,晶状体受到的外力牵拉可作为调节 Hippo 通路的机械信号,改变 YAP 在 LEC 中的定位从而调节 LEC 增殖。YAP 的上游负调节因子 NF2 很可能直接调节赤道部的 LEC 退出细胞周期[47],并激活分化为 LF 细胞的基因如 β-晶状体蛋白。但是 NF2 是直接作用于 YAP 还是通过经典的 Hippo 上游激酶(如 MST1/2 和 LATS1/2)作用仍然未知。Dawes 等[48]发现,在低浓度成纤维细胞生长因子(fibroblast growth factors, FGF)的刺激下,FGF 与受体结合激活 MEK-ERK1/2,促进 YAP 进入细胞核,与 TEAD 结合促进 LEC 增殖的基因转录;而在高浓度 FGF 刺激下,Hippo 信号通路被激活,YAP 被 MST1/2-LATS1 激酶级联磷酸化后与 14-3-3 蛋白结合,并留在细胞质中,最终导致 LEC 退出细胞周期,开始纤维分化。

3.1.3 Hippo 通路与白内障 白内障即晶状体混浊,是全球第一位的致盲眼病[49],其确切的发病机制尚不清楚,近年研究发现,Hippo 通路可能参与白内障的发生发展。He 等[50]观察到 *Yap* 敲除小鼠在出生后 1.5mo 出现核性白内障,表现为 LEC 数量减少、纤维细胞脱核异常和 Morgagian 小球积聚,且晶状体比野生型小。YAP 缺失引起白内障的病理过程分为两个方面——主要影响和次要影响。主要影响是 YAP 缺失会下调与晶状体增殖和发育相关基因如 Sox2、Pax6 和 Dnase2b[51-52] 的表达,导致 LEC 增殖减少。次要影响是 YAP 缺失加速晶状体细胞衰老并导致晶状体结构蛋白水平降低以及炎症因子水平增加,最终促进白内障的形成。此外,Lu 等[53]的研究发现小鼠中 *Yap*1 的杂合缺失可导致成年期白内障,大多数 *Yap*1 杂合小鼠在出生后 6mo 时出现了白内障,且晶状体存在多种形态缺陷,包括囊膜破裂、皮质内空泡和纤维断裂。可能的机制是:*Yap*1 基因的杂合缺失导致其靶基因 *Crim*1 无法维持足够的表达,使 LEC 不能持续增殖,从而造成晶状体发育异常和混浊[54]。总而言之,Hippo 通路在晶状体上皮的增殖、分化中具有不可或缺的作用,Hippo 通路核心成分有望作为研究晶状体发育的重要分子,并且可能有助于某些先天性白内障的诊断和预测。

3.2 Hippo 通路在视网膜中的研究

3.2.1 调节视网膜发育 在视泡发育过程中,神经视网膜(neural retina, NR)和视网膜色素上皮(retinal pigment epithelium, RPE)来自共同的祖细胞[55-56]。在斑马鱼

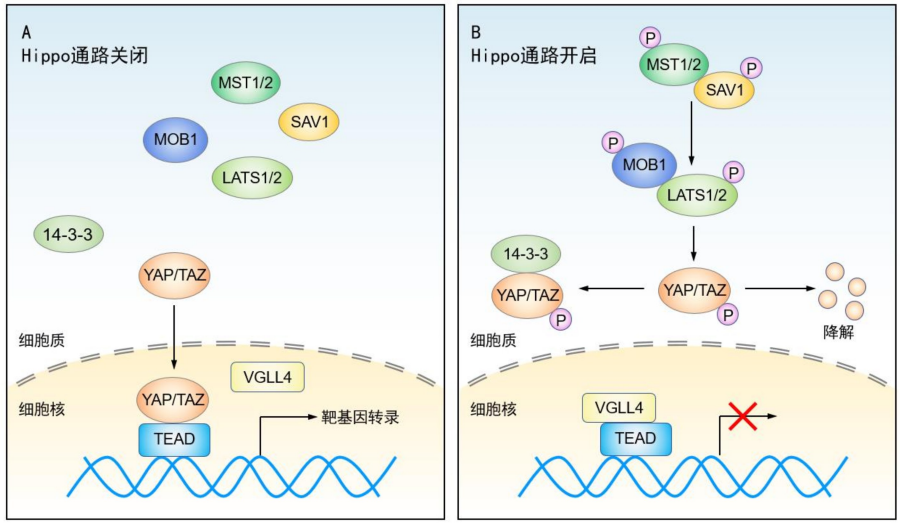

图 1 Hippo 通路的核心组分 A:当 Hippo 通路关闭时,YAP/TAZ 去磷酸化并进入细胞核,在核内与 TEAD 等转录因子结合,诱导靶基因转录;B:当 Hippo 通路开启时,活化的 LATS 激酶使 YAP/TAZ 磷酸化,与 14-3-3 结合,停留在胞质中并被降解,此时 TEAD 与 VGLL4 结合,抑制靶基因转录。

中[57],YAP/TAZ-TEAD 信号在视杯发生过程中处于活跃状态,而 *yap*$^{-/-}$突变体表现出 RPE 缺陷,说明 YAP 和 TAZ 可调节 RPE 细胞命运,潜在机制是 YAP/TAZ 通过与转录因子 TEAD 结合,从而调节 RPE 细胞分化。在非洲爪蟾胚胎中,YAP 和参与许多发育过程的蛋白 PKNOX1[58]相互作用,控制视网膜干细胞中 S 期的进程并维持基因组稳定。Kim 等[59]的研究发现,YAP 可能通过促进视网膜祖细胞从 G1 期过渡到 S 期,以及加快 S 期和 G2 期的进程,从而维持视网膜祖细胞的增殖活性。

3.2.2 调节视网膜 Müller 细胞重编程和纤维分化 视网膜 Müller 细胞在视网膜损伤时能够重新进入细胞周期并产生多能祖细胞,参与视网膜再生[60],还可以转化为肌成纤维样细胞促进视网膜纤维化[61]。Rueda 等[62]的研究发现,YAP 可促进 Müller 细胞表达 cyclin D1,重编程为视网膜祖细胞,而 Hippo 通路激活可通过抑制 YAP 的活性阻止视网膜再生。在糖尿病小鼠模型的研究中发现[63],高血糖条件下视网膜 Müller 细胞中的 YAP 被激活,从而使 Müller 细胞发生纤维分化和收缩,并产生细胞外基质(extracellular matrix, ECM)和释放促纤维化因子,增加的 ECM 又反过来激活 YAP,形成促进视网膜纤维化的循环,最终导致糖尿病牵拉性视网膜脱离。因此,Hippo 通路有助于视网膜再生疗法的研究,如何调控 Hippo 通路来促进视网膜再生并减少视网膜纤维化是一个值得探讨的问题。

3.2.3 参与视网膜微血管生成 信号转导和转录因子激活因子 3(STAT3)是一种转录因子,调节细胞增殖、分化、凋亡[64]并促进缺血视网膜中的新生血管形成[65]。YAP 与 STAT3 相互作用以促进 STAT3 的磷酸化激活、核易位和血管内皮生长因子(vascular endothelial growth factor, VEGF)转录,从而上调人视网膜微血管内皮细胞的增殖、迁移和血管形成[66]。此外,STAT3 通过降低紧密连接蛋白 ZO-1 和 Occludin[67]的表达增加小鼠视网膜血管内皮通透性,从而促进糖尿病视网膜病变的进展。STAT3 与 YAP 的相互作用为视网膜新生血管形成提供了新的治疗靶点。

3.3 Hippo 通路在角膜中的研究

3.3.1 调节角膜上皮细胞增殖 角膜上皮在受到损伤后,通过局部角膜上皮细胞的增殖和迁移来覆盖缺损并重建屏障功能,从而修复损伤。YAP 的上游调节剂溶血磷脂酸(lysophosphatidic acid, LPA)被证明可通过表皮生长因子受体(epidermal growth factor receptor, EGFR)通路调节角膜上皮细胞增殖,并通过 PI3K/AKT 途径促进角膜伤口愈合[68]。此外,Lee 等[69]的研究表明,应激反应蛋白 Sesn2 的缺乏会增加角膜上皮细胞中活性氧的产生并激活 YAP,从而促进角膜上皮细胞增殖。因此,对角膜上皮细胞中的 YAP 活性进行调节有助于促进损伤修复,而 LPA 和 Sesn2 可作为潜在的治疗靶点。

3.3.2 调节角膜缘干细胞增殖 角膜缘干细胞(limbal stem cells, LSCs)有助于维持角膜上皮的稳态[70-71],是角膜上皮再生的来源,当角膜损伤后增殖活跃以加速修复损伤[71-72]。Hippo 通路的效应分子 YAP 在调控 LSCs 增殖分化中具有重要作用。在直径大于 4mm 的伤口中,YAP 激活介导 LSCs 的活化和增殖,随后迁移以封闭缺损的上皮[73]。Gouveia 等[74]提出,角膜伤口愈合过程中基质变硬,诱导 YAP 激活以抑制 ABCG2 的表达[75],从而促进 LSCs 分化[76-77]。因此,调控 YAP 的活性可促进 LSCs 介导的角膜上皮修复。Hou 等[78]的研究证明 Agrin 可以抑制 YAP1 的磷酸化并调节下游 cyclin D1 的表达,从而促进 LSCs 的增殖。

3.3.3 Hippo 通路与角膜疾病 除了调控角膜上皮细胞和 LSCs 的增殖分化外,Hippo 通路在某些角膜疾病中也发挥着重要作用。转录组测序结果显示,在圆锥角膜中,Hippo 通路(FAT4、LATS2、TEAD2、TEAD4)的 mRNA 表达水平与非圆锥角膜相比显著下调[79]。Zhang 等[80]发现,在小鼠角膜真菌感染期间,差异基因在 Wnt、cGMP-PKG 和 Hippo 通路显著富集。以上研究结果提示 Hippo 通路可能在圆锥角膜和真菌性角膜炎的发病机制中起重要作用,靶向调控该通路和关键因子可能有助于这些疾病的防治。

综上,Hippo 通路有望成为角膜修复和再生疗法的重要靶点,Hippo 通路中的某些分子可能成为角膜感染性疾病或遗传性疾病诊断和预后的分子靶标。

3.4 Hippo 通路在小梁网中的研究 既往研究证明,YAP 和 TAZ 在青光眼中随着小梁网(trabecular meshwork, TM)

的弹性硬度的增加而上调[81]。最近的研究发现,在人类小梁网(hTM)细胞中,LPA 及其受体可通过调节细胞收缩张力来刺激 YAP/TAZ 的转录活性,并增加 CTGF 的表达,进而导致 ECM 的产生增加[82],也可通过 IL-6 反式信号转导与 YAP、TAZ 和 STAT3 通路相互作用[83],引起 ECM 异常重塑从而导致眼内压升高[84-85]。而交联的 ECM 又会使 β-连环蛋白和 YAP/TAZ 功能失调导致 TM 变硬[86]。因此,抑制 YAP 活性可改善 hTM 细胞中 LPA 和/或 IL-6 反式信号转导介导的高眼压。miR-137 可通过直接靶向 Src 来阻断 YAP/TAZ 的激活,促进细胞生长并抑制 hTM 细胞中的 ECM 蛋白表达[87],因此可能被用作治疗青光眼的新靶点。

3.5 Hippo 通路在葡萄膜中的研究 研究表明,YAP/TEAD 可通过结合 CD44 启动子激活 CD44 基因转录,或者通过激活靶基因转谷氨酰胺酶 2[88],促进脉络膜新生血管(choroidal neovascularization, CNV)形成[89]。用 YAP-siRNA 处理显著降低了小鼠模型中激光诱导的 CNV 的程度[90],表明 YAP 可能是治疗 CNV 的重要分子靶标。超过 80%的葡萄膜黑色素瘤(uveal melanoma, UM)携带 *GNAQ* 或 *GNA*11 的激活突变[91-92],其编码蛋白 Gq/11 可能通过激活 YAP 促进葡萄膜黑色素瘤的发生[93],在 *GNAQ* 和 *GNA*11 突变的脉络膜痣中也观察到下游 YAP 激活[94]。而 YAP 抑制剂维替泊芬能选择性抑制 Gq/11 突变的葡萄膜黑色素瘤发生,因此有望成为治疗葡萄膜黑色素瘤的分子靶向药物。

4 讨论与展望

综上所述,Hippo 通路在眼组织中主要通过激酶级联传递信号,作用于效应分子 YAP/TAZ,从而调控细胞增殖与分化,在角膜、晶状体、视网膜等组织的发育、再生中具有重要作用,Hippo 通路的异常激活或失活可引起白内障、青光眼、角膜和视网膜病变等,但具体致病机制尚不清楚。Hippo 通路如何受到眼内特有环境如房水、玻璃体中的因子的调控?Hippo 通路如何与其他信号通路相互作用,调控眼部组织的生理功能?YAP 与何种下游分子相互作用,从而调控眼部组织特异的基因表达?以上问题有待进一步的研究。阐明 Hippo 通路在眼部组织中的作用机制,不仅能够完善现有研究的理论体系,而且有望在眼科临床中应用,例如,Hippo 通路中的基因可为某些遗传性眼部疾病诊断提供预测,Hippo 通路激酶(如 LATS、MST)和效应分子(YAP/TAZ)可作为某些眼部肿瘤的治疗靶点,或成为监测某些眼部疾病预后的指标。因此,Hippo 通路在眼科疾病的防治中具有广阔的应用前景。

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