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·专论与综述·

眼睛发育与骨形成蛋白信号通路的关系 *

赵 倩 刘 聪 朗元君 郑栋栋 周建峰△

（中国海洋大学医药学院 山东 青岛 266003）

摘要：在早期胚胎发育过程中，眼睛是由起源于不同胚层的几个部分经过一系列的诱导作用以及时间和空间上的相互协调作用形成的复杂而又具有精确功能的器官。在眼睛的形成发育过程中，许多信号通路及其相关的调控因子发挥着重要作用。本文主要关注眼睛发育过程与骨形成蛋白（BMP）信号通路的关系，BMP 信号的激活能够诱导晶状体的再生和 CLT（角膜到晶状体的分化转移）进程，维持睫状体的功能，促进视网膜的发生，影响巩膜的重塑和泪腺的发育。很多眼部疾病的发生与 BMP 信号通路的调节紊乱密切相关，因此可以将 BMP 信号通路作为一个潜在的药物靶点来探究治疗眼部疾病的方法。本文就 BMP 信号通路对眼睛发育的影响作一综述。

关键词：眼睛发育；CLT 进程；视网膜；巩膜重塑；BMP 信号通路

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Eye Development and BMP Signaling Pathway*

ZHAO Qian, LIU Cong, LANG Yuan-jun, ZHENG Dong-dong, ZHOU Jian-feng△

(School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong, 266003, China)

ABSTRACT: The eye is a complex organ with precise function. In early embryonic development, eye is composed of several parts which are from the different germ layers through a series of induction and interaction. Multiple signaling pathways and their associated regulatory factors play important roles in the development of eyes. This review focuses on the relationship between eye development and BMP signaling pathway. The activation of BMP signal can induce the regeneration of the lens and the process of cornea to lens trans-differentiation (CLT). The activation of BMP signal can also maintain the function of the ciliary body, promote the development of retina, affect scleral remodeling and the development of lacrimal gland. Many ocular diseases are closely related to the dysregulation of BMP signaling pathway. Therefore, the regulation of BMP signal pathway can serve as a potential target for therapies of ocular diseases.

Key words: Eye development; CLT process; Retina; Scleral remodeling; BMP signaling pathway

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在早期胚胎发育过程中，器官的形成和发生是一个精确而又复杂的过程，其中眼睛是由来源于不同胚层的细胞经过一系列的诱导及相互协调作用形成的复杂而又具有精确功能的器官[1]。这一过程中，任一环节出现问题，都可能诱发眼部疾病。常见的致盲性眼病主要分为三大类：高度近视、白内障、青光眼，这三类眼病严重威胁着人们的正常生活；它们的发生除了受环境的影响外，还与遗传因素密切相关，如 Crim1 基因移码突变会引起常染色体显性遗传的 MACOM 综合症，该综合症的临床表现为患者出现小角膜、高度近视、虹膜及视神经盘缺损[2]；Pax6 基因发生突变会诱发遗传性无虹膜症 [3]；Dicer 的功能缺失会引起睫状体发育缺陷，造成眼内压升高，出现原发性青光眼[4]。大量研究表明，在眼睛发育过程需要一系列信号通路的相互协调作用，其中 BMP 信号通路的调控至关重要[5]。

1 BMP 信号通路

骨形成蛋白（BMPs）是多功能生长因子，是一组结构类似功能高度保守的蛋白，是转化生长因子家族 β（transforming growth factor β，TGF-β）超家族的成员之一，因其能促进骨细胞的分化、诱导异位骨的形成而得名。BMPs 是由加州大学的 MarshallUist 教授于 1965 年在脱钙骨基质提取物中发现并命名的[6,7]。

在 BMP 信号通路中，BMP 配体与细胞膜上的受体结合，引起Ⅰ型受体激酶激活，使得Ⅰ型受体发生磷酸化，随后激活的Ⅰ型受体磷酸化下游的 Smad 效应器，磷酸化的 Smad 会和 co-Smad 形成异聚复合物，这个异聚复合物进入细胞核内在辅助调控因子的作用下调节下游靶基因的表达[8]。

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作者简介：赵倩（1991-），女，硕士研究生，主要研究方向：胚胎发育与信号通路的研究，电话：15684737661，E-mail: 1342329960@qq.com

△ 通讯作者：周建峰（1976-），男，博士，教授，主要研究方向：胚胎发育与信号通路研究，E-mail: jfzhou@ouc.edu.cn

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到目前为止,对于 BMP 信号转导通路的研究愈来愈多,很多研究证明了 BMP 信号转导通路在早期胚胎发育和组织稳态中发挥着关键作用[9,10],能够影响生物体的胚胎发育、器官形成、神经系统发育等[9,11];BMP 信号的浓度梯度还能影响生物体早期胚胎发育过程中背腹轴的正常形成[10,12];对 BMP 信号通路的调控能够影响肿瘤的发生与进展[13];此外,BMPs 在生物体眼睛发育过程中也发挥着不可或缺的功能,如调节晶状体和睫状体的再生、影响视网膜的发育及巩膜的重塑等。

2 眼睛发育与 BMP 信号通路的关系

2.1 BMP 信号通路影响角膜的正常发育

在角膜、晶状体、小梁网状结构和视网膜都有表达的 Chordin-like 1(CHRDL1)基因能够编码一种名为 Ventroptin 的蛋白,该蛋白是 BMP4 的拮抗剂[14,15]。临床研究发现 BMP4 发生功能缺失性突变时,病人会出现小眼或无眼症[16]。另有研究指出,伴 X- 染色体的巨角膜症与 CHRDL1 的突变相关,对爪蛙的 CHRDL1 进行敲降,会导致 CHRDL1-BMP4 相互制约的平衡被打破,BMP 信号通路处于持续激活状态,细胞生长分化加速,爪蛙出现巨角膜症[17],这表明 BMP 信号通路的稳定表达对维持角膜的正常发育至关重要。

2.2 BMP 信号通路的激活能够诱导晶状体的再生和 CLT 进程

处于幼期的非洲爪蛙,若晶状体被切除,将会诱导一个新的晶状体形成,这个新的晶状体源于外层的角膜,这一过程被称为角膜到晶状体的分化转移(CLT)[18,19]。当爪蛙晶状体被移除后,角膜细胞逐渐分化形成一种高表达 r-Crystallin(晶状体蛋白)的细胞,一段时间后新的晶状体形成,这一过程中 BMP 信号通路的靶基因 Nipsnap1 表达水平明显升高;当 BMP 信号通路的抑制剂 Noggin 过表达时,BMP 信号通路失活,角膜细胞的分化转移能力下降,多余的角膜细胞变得过度肥厚,进而死亡,无法形成新的晶状体[20]。

此外,BMP7 在发育的晶状体中有表达,它能够通过调节 Pax6 的表达影响晶状体蛋白的形成[21];在鼠胚胎中,BMP4 通过影响早期晶状体基板中 Sox2 的表达来调控晶状体的形成[22];BMP 信号通路 I 型受体 Bmpr1a 功能缺失时会抑制鼠的晶状体形成,但具体的作用机制还有待研究[23]。

2.3 BMP 信号通路的激活能够促进睫状体的形成

有研究表明,Noggin 诱导的转基因小鼠出现睫状体上皮发育缺陷是由 BMP 信号通路被抑制引起的,将该小鼠与 BMP7 过表达的转基因小鼠交配后,其后代双转基因小鼠的睫状体发育恢复正常,说明小鼠睫状体发育缺陷可以被过表达的 BMP7 营救;并且该研究还指出 BMP 信号对于维持睫状体上皮的细胞类型很重要,当 BMP 信号通路失活时,睫状体上皮细胞逐渐变成视网膜神经节细胞[24]。之后有研究报道,Notch2 能够通过参与 BMP 信号通路来调节鼠睫状体的形成,其作用机制为 Notch2 能够抑制 chrdl1 和 Nbl1(BMP 信号通路抑制剂)的表达水平,维持 BMP 信号的活性,进而影响睫状体的正常形成[25]。

2.4 BMP 信号通路影响视网膜的形成发育

BMP 信号通路对视网膜的发育十分重要,主要体现在以下两个方面。

其一,BMP 信号能够调节脊椎动物视网膜早期发育的几个进程,包括视杯和神经视网膜背腹轴的命运决定、视网膜祖细胞的延伸、视网膜细胞的程序性死亡等[26]。BMP 信号既可以通过建立相关基因背腹表达模式来控制视网膜神经节细胞和轴突投射细胞的分化[27],还可以通过影响视蛋白的表达水平调节圆锥体细胞的分化[28]。另有研究指出,NMDA(N- 甲基 -D- 天冬氨酸)能够诱导视网膜神经节细胞大量死亡,在该进程中 BMP 信号通路被激活,从而刺激视网膜神经节细胞的再生;同时过表达 BMP4 能够营救视网膜神经节细胞大量死亡的情况,表明在视网膜受损后 BMP 信号通路的激活能够保护视网膜神经节细胞,这提示 BMP 信号通路可以作为视网膜神经节细胞相关疾病(如青光眼)的潜在药物靶点[29]。

其二,早期研究较多关注 BMP 信号对视网膜早期发育的影响,而 2014 年 Kuribayashi 等人则指出 BMP 信号对视网膜后期的发育也很重要,研究表明 BMP 信号既能调节后期视网膜细胞类型(杆状感受器、muller 胶质细胞、双极细胞等)的分化,又可通过诱导 Hey2 的上调参与 muller 胶质细胞的成熟[30]。之后又有其他研究者在爪蛙中通过 noggin 的过表达以及功能缺失性实验验证了 Kuribayashi 等人的结论[31]。

2.5 BMP 信号通路参与巩膜的重塑过程

近视发生时,眼轴拉长,这一过程伴随着巩膜的重塑、细胞外基质(ECM)的改变,此过程会受到众多生长因子的调控[32,33],其中 BMP 信号通路中的 BMPs 发挥着重要作用。有研究指出外源的 BMP2 呈剂量依赖性地促进巩膜成纤维细胞的增生[34];张玉等人发现对 C57BL/6 小鼠进行形觉剥夺性近视实验后,BMP2 的表达水平明显下降且巩膜的形态学特征发生了变化[35];Guo 等通过实验发现巩膜中表达的 SLC39A5 功能缺失性突变与常染色体显性非综合症高度近视密切相关,其中 SLC39A5 能够抑制 BMP 信号通路下游因子 smad1 的表达,这很可能是此类高度近视发生的分子机制之一[34];这些研究充分证明了 BMP 信号通路与近视发生过程中巩膜的重塑密切相关。

2.6 BMP 信号通路参与泪腺的发育过程

泪腺是眼的附属器之一,对于维持眼表面微环境的稳定很重要,泪腺发育异常时易诱发干眼症。在泪腺的形成发育过程中,BMPs 蛋白发挥着重要作用,Dean 等通过实验发现 BMP7 是泪腺分枝形态发生的关键因子,它能够上调泪腺上皮细胞标志基因的表达[36];之后 Dean 再次提出在泪腺发育过程中,经典 WNT 信号能够负调控 BMP 和 FGF 信号对泪腺分枝的诱导作用,维持泪腺的正常形态和结构[37]。此外,Zoukhri 等人指出 BMP7 诱导的 BMP 信号上调能够参与泪腺受损后的修复过程[38]。

3 小结与展望

眼睛是一个非常精细的视觉器官,是人类最重要的感觉器官之一。虽然它所占的体表面积和体积比较小,但其功能对人类的生活至关重要。它是机体的一个重要组成部分,许多全身性疾病可在眼部有所表现。眼睛暴露于体表,易受到外伤和病原体的感染,最终出现眼部疾病,甚至失明。

目前已有大量与眼睛形成发育相关的研究,我们了解到许多信号通路通过调节相关转录因子控制着眼睛发育的各个方面,其中 BMP 信号通路就是研究的热点。临床研究表明晶状体病变易导致白内障;睫状体的形成异常会引起眼内压升高,出

现青光眼;高度近视的发生与角膜的重塑密切相关,而 BMP 信号通路能够诱导晶状体的再生,参与睫状体的形成发育,调控近视过程中巩膜的重塑。但目前多数眼科疾病主要还是通过手术进行治疗,尚未有将 BMP 信号通路作为药物靶点进行眼病治疗的相关研究,所以对 BMP 信号通路的深入研究不容懈怠,相关靶基因的鉴别仍需继续,这将会为临床上眼科疾病的治疗提供新途径。

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