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## 颅缝早闭的病因学机制和治疗靶标

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**摘要** 颅缝早闭是一种先天性颅面疾病, 其特征是一条或多条颅缝过早融合。重度颅缝早闭患者常见的并发症包括颅内压升高和神经认知功能障碍。颅缝早闭可单独发生或与多种综合征相关。不同类型的颅缝早闭与特定的基因突变有关。此外, 表观遗传改变和环境因素也被认为在颅缝早闭的病理生理过程中起着重要作用。该文综述了近年来关于颅缝早闭的类型、临床表现、病因及关键分子信号通路调控的研究进展, 并探讨了在动物模型中开发的治疗靶标, 为颅缝早闭的发生、发展及治疗提供全面且系统的认识。

**关键词** 颅缝早闭; 遗传变异; 信号通路; 治疗靶标

## Etiologic Mechanisms and Therapeutic Targets of Craniosynostosis

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**Abstract** Craniosynostosis is a congenital craniofacial disorder characterized by premature fusion of one or more cranial sutures. Common complications in patients with severe craniosynostosis include increased intracranial pressure and neurocognitive dysfunction. Craniosynostosis can occur alone or in association with multiple syndromes. Different types of craniosynostosis are associated with specific gene mutations. In addition, epigenetic alterations and environmental factors are also thought to play an important role in the pathophysiology of craniosynostosis. This article reviews the research progress on the types, clinical manifestations, etiology and key molecu-

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lar signaling pathways of craniosynostosis in recent years, and discusses the therapeutic targets developed in animal models, so as to provide a comprehensive and systematic understanding of the occurrence, development and treatment of craniosynostosis.

**Keywords** craniosynostosis; genetic variation; signaling pathways; therapeutic targets

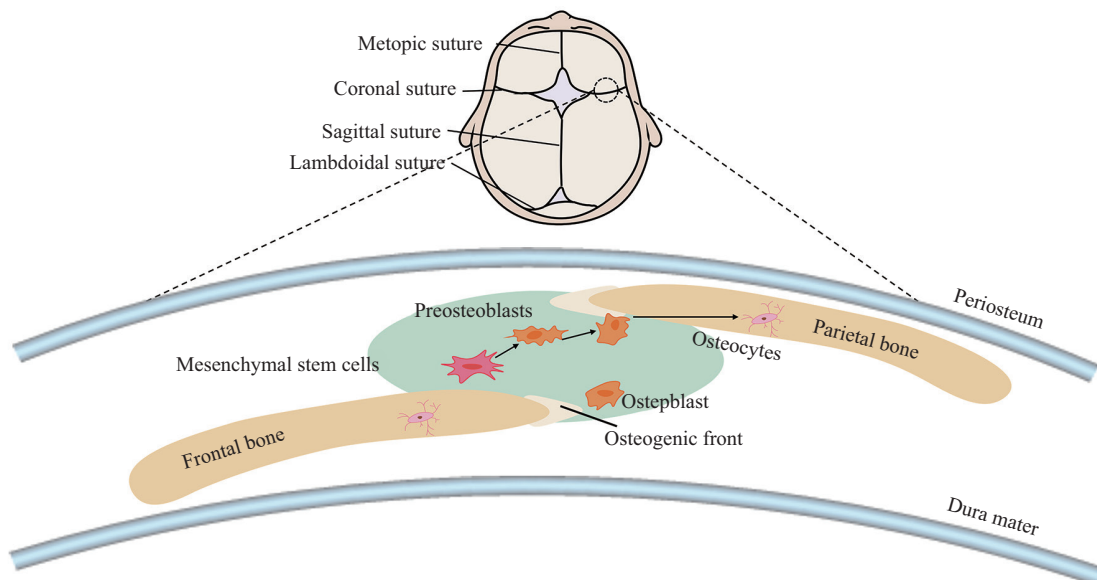
哺乳动物的颅骨由五块骨骼组成：前面成对的额骨、侧面成对的顶骨和后面孤立的枕骨。与软骨内成骨形成的长骨不同，颅骨是通过间充质细胞直接膜内骨化形成的<sup>[1]</sup>。颅骨中每块骨头相接处被称为颅缝，由带间充质的纤维组织、相邻骨板的两个成骨前沿、下方硬脑膜和上方骨膜组成<sup>[2]</sup>。相邻骨板的前沿由间充质组织隔开，其中含有促进颅骨持续生长的骨祖细胞。随着大脑和头部结构的成长，这些细胞在相邻颅骨前缘内通过膜内成骨，不断增殖并分化为成骨细胞，从而持续生成新的骨组织(图1)。颅缝主要由额缝(metopic suture)、冠状缝(coronal suture)、矢状缝(sagittal suture)和人字缝(lambdoidal suture)组成。颅缝的通畅对儿童时期颅骨生长及大脑的发育至关重要，其发育异常可导致各种先天性疾病，如颅缝早闭<sup>[3]</sup>。

颅缝早闭是一种颅缝过早融合导致的疾病，这限制了颅骨的正常生长和扩张，从而导致颅骨形状

异常<sup>[4]</sup>。在严重的情况下，可能导致颅内压升高和感觉、呼吸以及神经功能障碍<sup>[5-7]</sup>。近年来，随着基因组及外显子组测序的应用，逐渐鉴定出更多与颅缝早闭相关的基因。然而，由于只能在少数颅缝早闭患者中识别出明确的突变基因，越来越多的研究显示，环境因素对颅缝早闭发生发展起着重要的作用<sup>[8]</sup>。本文将对已知的颅缝早闭类型、病因、关键分子调控机制以及治疗靶标进行综合概述，为颅缝早闭的发生发展提供更加全面且系统的认识。

## 1 颅缝早闭的类型及临床表现

颅缝早闭的发病率约为1/2 500，在产前很少被诊断出来，该疾病通常是在婴儿出生后几个月通过体格检查来识别的。特定的头部形状和生长模式可提示存在产前综合征性颅缝早闭<sup>[9]</sup>。例如，特征性的三叶草头骨形态通常可通过超声检查识别。Pfeiffer综合征以及Apert综合征也可以根据双顶径和肢端



A: 颅缝主要包括额缝、冠状缝、矢状缝和人字缝。B: 颅缝间充质中存在颅缝细胞群，包括颅缝干细胞、前成骨细胞和成骨细胞，它们不断形成新骨以满足颅骨生长的要求，并最终分化为骨细胞。

A: the cranial sutures mainly include the sagittal suture, coronal suture, lambdoid suture, and squamosal suture. B: cranial suture cell populations exist in cranial suture mesenchyme, including cranial suture stem cells, pre-osteoblasts, and osteoblasts, which continuously form new bone to meet the requirements of skull growth and eventually differentiate into osteocytes.

图1 颅缝类型和冠状缝结构示意图

Fig.1 Schematic representation of cranial suture types and coronal suture structures

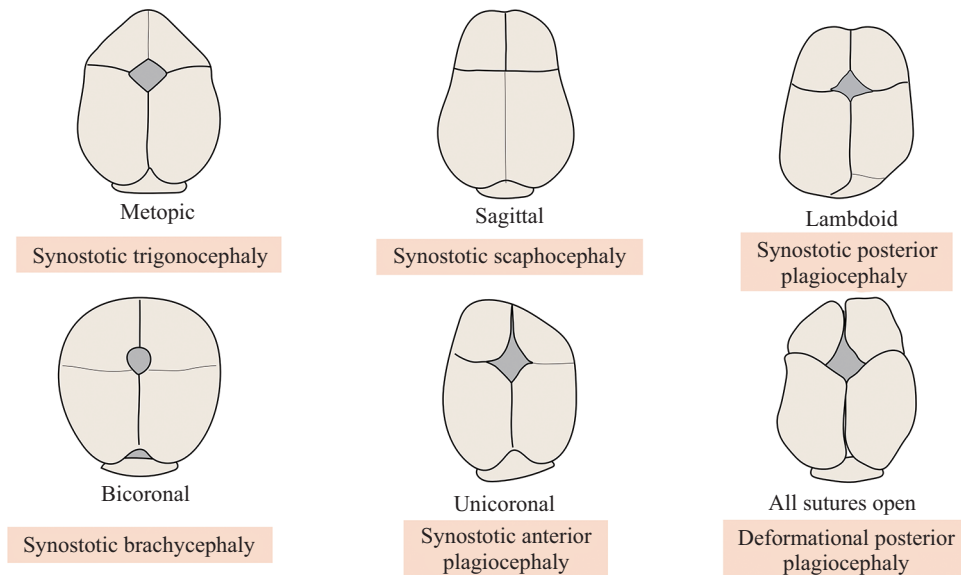


图2 不同形式的颅缝早闭引起的颅骨畸形

Fig.2 Skull deformities caused by different forms of craniosynostosis

畸形进行产前诊断<sup>[10]</sup>。颅缝早闭类型及其相应的表型如图2所示。颅缝早闭最常见的形式是矢状缝早闭, 占有颅缝早闭病例的45%, 主要呈现出舟状头畸形<sup>[11]</sup>。冠状缝早闭占20%~25%, 通常仅发生在一侧, 被称为单侧或单冠状缝早闭, 其特征为同侧前额扁平和中脸旋转(即“扭曲”或“偏转”)<sup>[12]</sup>。在双侧冠状缝早闭中, 前后生长由于代偿性颞叶扩张而受制, 导致短头畸形, 其中大部分病例可归因于已知的遗传原因<sup>[11]</sup>。额缝早闭占5%~15%, 可导致三角头畸形以及颞区变窄。人字缝早闭占不足5%病例, 单侧人字缝早闭通常表现为乳突膨大和颅底降低, 而双侧人字缝则导致枕部扁平 and 变宽, 耳朵位置下移或前移<sup>[13]</sup>。斜头畸形多见于人字缝, 应与变形性斜头畸形区分。后者的特征是由于位置成型导致后颅骨变平, 是枕骨不对称的更常见原因<sup>[14]</sup>。

颅缝早闭分为综合征型与非综合征型。非综合征型指的是单一的颅缝过早闭合, 不伴随其他异常。若颅缝早闭同时伴有如面部和四肢的畸形, 则归为综合征型<sup>[15]</sup>。患有颅缝早闭的婴儿可能出现除颅缝融合外的其他症状, 例如脑积水、听力缺陷、视力障碍、颅内压(intracranial pressure, ICP)升高或神经认知功能障碍相关的智力障碍(intellectual disability, ID)<sup>[15]</sup>。脑积水在12%~15%的综合征性颅缝早闭症患者中发生, 这可能源于脑脊液从异常狭小的后颅骨流出, 第四脑室收缩或脑脊液吸收障碍<sup>[16]</sup>。听力缺陷在颅缝早闭患者中较为常见, 表现为传导性听力

损失和中耳炎伴积液, 这两种情况都是颅底变窄及由此引起的咽鼓管狭窄导致<sup>[17-18]</sup>。在综合征患者中, 相比非综合征患者, 视力缺陷更为常见<sup>[19]</sup>。综合征性颅缝早闭症视力丧失的最常见原因是弱视和视神经病变, 后者通常是由于ICP升高引起的视水肿<sup>[20]</sup>。此外, 综合征患者更容易出现ID、社会问题和注意力缺陷, 并表现出退缩行为<sup>[20]</sup>。大多数研究显示, 非综合征颅缝早闭患者的智力通常长期维持在正常范围内, 尽管有些患者可能有ID。

## 2 颅缝早闭的病因

### 2.1 颅缝早闭的遗传学

先天性颅缝早闭的病理生理机制极其复杂, 目前仅有20%~30%的患者能够明确其遗传基础。在这些可识别的遗传原因中, 约86%归因于单基因突变, 其余是染色体异常, 这些突变基因及其下游影响的信号通路调控着颅缝内细胞的增殖与分化<sup>[21]</sup>。在一项关于颅缝早闭患者的10年前瞻性队列研究中, 21%的病例得到了遗传诊断。最常涉及的基因包括*FGFR2*(32%)、*FGFR3*(25%)、*TWIST1*(19%)和*EFNB1*(7%)<sup>[22]</sup>。表1展示了与颅缝早闭相关的常见基因变异。

### 2.2 颅缝早闭的表现遗传学

表现遗传学是指DNA序列无改变的情况下, 对基因表达进行各类修饰, 包括CpG二核苷酸的DNA甲基化、组蛋白修饰和非编码RNA<sup>[38]</sup>。这些修饰

表1 颅缝早闭部分致病基因

Table 1 Partial disease-causing mutated genes in craniosynostosis

基因 Gene	遗传模式 Inheritance	综合征 Syndrome	影响的颅缝 Suture(s) affected	主要表型特征 Major clinical characteristics	参考文献 Reference
<i>EFNB1</i>	XLD	Craniofrontonasal	Coronal	Frontonasal dysplasia, ocular hypertelorism, bifid nasal tip, nail splitting	[23]
<i>COLEC11</i>	AR	3MC syndrome 2	Metopic	Hypertelorism, blepharoptosis, arched eyebrows, cleft lip/palate	[24]
<i>CDC45</i>	AR	Philadelphia	Coronal	Thin eyebrows, small ears, variable short stature	[25]
<i>ERF</i>	AD	ERF-related craniosynostosis	Multi-suture	Midface hypoplasia, Chiari type I malformation, postnatal onset of craniosynostosis	[26]
<i>FGFR1</i>	AD	Pfeiffer	Multi-suture	Craniofacial deformations, syndactyly, digit/limb abnormalities	[23]
<i>FGFR2</i>	AD	Apert	Coronal, multi-suture	Dysmorphic facies, ocular anomalies, conductive hearing loss, cleft palate, syndactyly	[27]
<i>FGFR2</i>	AD	Crouzon	Multi-suture, coronal, sagittal	Crouzonoid facies, absence of major abnormalities of hands/feet, shallow orbits, normal limbs	[28]
<i>FGFR2</i>	AD	Pfeiffer	Multi-suture	Broad thumbs and halluces, cloverleaf skull, brain anomalies, fused elbows	[29]
<i>FGFR3</i>	AD	Muenke	Coronal	Low-frequency sensorineural hearing loss, normal to dysmorphic face	[30]
<i>HUWE1</i>	XLD	Crouzon	Multi-suture, metopic	Learning difficulties	[31]
<i>IL11RA</i>	AR	craniosynostosis and dental anomalies	Multi-suture	Craniosynostosis, delayed tooth eruption, some have supernumerary teeth and conductive hearing loss	[32]
<i>MSX2</i>	AD	Boston craniosynostosis	Sagittal, coronal, multi-suture	Highly variable craniosynostosis ranging from fronto-orbital recession to cloverleaf skull deformity	[33]
<i>RAB23</i>	AR	Carpenter syndrome 1	Multi-suture	Polysyndactyly, obesity, cardiac defects	[34]
<i>RUNX2</i>	AD	cranioclavicular dysplasia syndrome	Multi-suture	Delayed closure of fontanelles, dental abnormalities, hypoplastic clavicles	[35]
<i>TCF12</i>	AD	TCF12-related craniosynostosis	Coronal	Isolated uni- or bicoronal synostosis	[36]
<i>TWIST1</i>	AD	Saethre-Chotzen	Coronal	Abnormal extremities, facial asymmetry	[37]

AD: 常染色体显性遗传; AR: 常染色体隐性遗传; XLD: X连锁显性遗传。

AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; XLD: X-linked dominant inheritance.

对正常发育和生物学过程具有重要意义,参与了细胞分化,胚胎发育的过程<sup>[39-40]</sup>。对基因相同的双胞胎的研究表明,其中一个表现出颅缝早闭,而另一个则表现出正常的颅骨发育,这表明表观遗传在颅缝早闭的发生中起着重要作用<sup>[41]</sup>。赖氨酸特异性脱甲基酶6A(KDM6A)和KDM6B已被报道通过去除成骨基因启动子上的抑制标记组蛋白3的赖氨酸27位点的三甲基化(H3K27me3),从而调节与骨发育相关的基因表达<sup>[42]</sup>。PRIBADI等<sup>[43]</sup>研究发现,从Twist-1<sup>del/+</sup>小鼠中提取的颅骨细胞中Kdm6a和Kdm6b水平升高,抑制这些去甲基化酶可以抑制成骨分化,凸显了它

们作为颅缝早闭治疗靶点的潜力。增强子佐斯同源物2(enhancer of zeste homolog 2, EZH2)是一种关键的组蛋白甲基转移酶,主要负责H3K27me3的催化作用,从而在表观遗传层面上调控基因的表达<sup>[44]</sup>。特别地, EZH2在抑制成骨细胞分化中发挥着重要作用。研究表明, EZH2的功能缺失会引起颅缝发育相关基因失调,导致颅缝早闭的发生<sup>[45]</sup>。此外,不同的母体、父体、孕期相关和环境因素已被证实通过表观遗传机制影响颅缝早闭的形成<sup>[46-47]</sup>。BORKE等<sup>[48]</sup>在大鼠和小鼠动物模型中发现,在机械力诱导下, Tbx2基因在颅骨缝合线中的表达水平升高,导致骨形成

改变, 而 *Cx43* 基因表达水平下降。此外, 父亲年龄也与先天性颅面部和其他畸形的增加风险有关。由于精子随年龄增长而增加的新发突变率, 高龄有更高的单基因疾病风险, 这种情况被称为父亲年龄效应(paternal age effect, PAE)疾病<sup>[49]</sup>。PAE研究的主要模型之一是 Apert 综合征, 该症状在 99% 的病例中由两种特定的 DNA 序列变化(c.755C>G或c.758C>G)引起。其中, c.755C>G 突变在 66% 的病例中发生在 CpG 二核苷酸重复上, 而 c.758C>G 变化则出现在非 CpG 二核苷酸上。这种高频率的突变可能是由于逃避了 DNA 甲基化过程<sup>[50-51]</sup>。考虑到父亲高龄与出现的甲基化异常之间的联系, 精原细胞中高频率的新发突变可能是由表观遗传变化引起的。这种现象可能导致所谓的“自私精原细胞选择”, 从而增加先天性畸形的风险。此外, 颅缝早闭也与非编码 RNA 的调控有关。研究发现多种 miRNAs 与间充质干细胞(mesenchymal stem cells, MSCs)的分化调控有关。一些 miRNAs, 如 miR-133b, 尤其在 FGF 信号通路中发挥作用, 也可能调控颅缝的形成<sup>[52]</sup>。POTTER 等<sup>[53]</sup>研究发现, 与开放的颅缝相比, 在闭合的颅缝中发现了 31 个过表达的 miRNA 和 9 个低表达的 miRNA。另一项研究表明, 长链非编码 RNA LncRNA HOTAIR 通过 miR-152-CAMKII $\alpha$  轴, 在颅缝早闭中的破骨细胞分化过程中发挥调节作用<sup>[54]</sup>。

### 2.3 环境因素对颅缝早闭的影响

在颅缝早闭患者中, 仅有少数患者可以确定为遗传变异, 其余 70%~80% 患者的病因尚不清楚。这表明还需识别新的基因突变, 并考虑潜在的环境因素或基因与环境的相互作用<sup>[55]</sup>。因此, 探索环境危险因素对颅缝早闭病理生理的影响是具有意义的。一项对 173 687 名先天畸形儿童和 1 170 万对照儿童的大型回顾性研究显示, 怀孕期间吸烟的母亲所生儿童发生颅缝早闭的风险比不吸烟母亲的儿童高出 33% [OR(odds ratio): 1.33; 95% CI(confidence interval): 1.03~1.73], 另外一项病例对照研究发现, 母亲吸烟的孩子患颅缝早闭的可能性是前者的 1.7 倍 (95% CI: 1.2~2.7)<sup>[56]</sup>。ALDERMAN 等<sup>[57]</sup>研究发现, 母亲在怀孕期间每天吸烟超过一包, 其孩子患有颅缝早闭的可能性是不吸烟者的 3.5 倍。RASMUSSEN 等<sup>[58]</sup>利用国家出生缺陷预防研究的数据发现, 患有甲状腺疾病的母亲生下患有颅缝早闭的孩子风险较高 (OR: 2.47; 95% CI: 1.46~4.18)。母亲在怀孕

期间有某些亚硝基药物摄入史, 包括氯苯那敏、呋喃妥因, 也会导致后代患颅缝早闭的风险增加<sup>[59]</sup>。BOULET 等<sup>[60]</sup>提出父亲的职业, 如农业和林业工人、修理工、机械师等, 可能与其子女患颅缝早闭的风险增加相关。此外, 胎儿头部的约束也与颅缝早闭有关。SANCHEZ-LARA 等<sup>[61]</sup>评估了颅缝早闭与多胞胎、巨大儿、胚后胎龄之间的关联。结果表明, 在巨大儿病例中观察到冠状缝早闭的风险较高。此外, 胎头过早下降到子宫下段、母体子宫畸形、羊水过少也会对头部造成限制, 从而增加颅缝早闭的风险。我们课题组最近研究发现, 金属镍可能是颅缝早闭的一个危险因素, 子宫内暴露于氯化镍可增加后代小鼠颅缝早闭的发生率<sup>[62]</sup>。

## 3 颅缝早闭的发育机制

### 3.1 FGF/FGFR 信号通路

成纤维细胞生长因子 (fibroblast growth factor, FGF) 通路在胚胎发育和器官形成过程中发挥着重要作用。FGF 由 23 个配体组成, 研究显示至少有 18 个配体, 包括 FGF1~10 和 FGF16~23, 可以与 FGFR1~4 发生相互作用。FGFRs 的激活通过多种下游途径, 诱导级联信号, 进而调控细胞增殖、迁移、分化和血管生成等过程<sup>[63]</sup>。这些途径包括 PI3K/Akt、Ras/MAPK 和磷脂酶 C $\gamma$  信号通路。FGFRs 发生的突变大多为功能获得性的, 这些突变会过度激活下游信号, 干扰正常生理过程, 诱发颅缝早闭。动物实验表明, FGFR2IIIc<sup>S252W</sup> 能逆转 Apert 突变小鼠的颅缝早闭样变, 该变体可以竞争性地与 FGF 结合, 避免其与 FGFRs 结合, 从而在一定程度上缓解了包括颅缝早闭在内的综合征症状<sup>[64]</sup>。此外, ERK1/2 作为 FGF 下游信号通路, YIN 等<sup>[65]</sup>证实了 ERK1/2 抑制剂 PD98059 能挽救颅缝过早融合。上述基于分子机制的颅缝早闭治疗为颅缝早闭的药物治疗提供了潜在的策略和新的认识。

### 3.2 TGF- $\beta$ 信号通路

转化生长因子 (transforming growth factor, TGF) 超家族, 包括 TGF- $\beta$ 、活化素、抑制素等亚家族, 在多种组织的发育中起着至关重要的作用, 尤其是在颅颌面的发育中。TGF- $\beta$  激活调节基因转录的信号级联, 以控制细胞增殖、分化、凋亡和迁移等过程, 在组织和器官的发生和形成的生物过程中发挥重要的功能<sup>[66]</sup>。研究表明, TGF- $\beta$ 2 表达量的增加可能

促进颅缝早闭,而TGF- $\beta$ 3则表现出相反的作用<sup>[67]</sup>。OPPERMAN等<sup>[68]</sup>研究证明,一方面,在培养的颅顶骨添加TGF- $\beta$ 2可促进成骨祖细胞增殖,进而诱导颅缝过早融合,而应用中和抗体消除TGF- $\beta$ 2的表达虽不影响细胞增殖,但能抑制细胞分化,从而挽救颅缝早闭。另一方面,添加TGF- $\beta$ 3可以抑制细胞的增殖并阻止颅缝融合,而抑制TGF- $\beta$ 3的活性可诱导颅缝融合,这些发现表明不同的TGF- $\beta$ 超家族信号的异常表达可能影响颅缝的发育,导致颅缝过早融合。此外,研究表明,TGF- $\beta$ 2可能刺激Erk1/2的磷酸化,进而促进颅缝闭合。在闭合的颅缝中也观察到TGF信号下游介质,如磷酸化Smad2和Smad3水平的升高<sup>[69]</sup>。这些结果进一步强调了TGF信号在颅缝发育过程中起着至关重要的作用。

### 3.3 Wnt信号通路

Wnt信号通路是最保守的分子通路之一,在细胞增殖、分化、迁移等过程中发挥至关重要的作用<sup>[70]</sup>。特别是在神经嵴衍生间充质的增殖过程中,Wnt信号的转导显得尤为重要<sup>[71]</sup>。研究表明,低密度脂蛋白受体相关蛋白6(low density lipoprotein receptor-related protein 6, Lrp6)缺失或Wnt3/Wnt9拮抗剂突变导致Wnt信号转导不足,进而引起面部裂缝和面部中部发育异常<sup>[72]</sup>。Wnt信号传递有三条途径,一是典型的 $\beta$ -连环蛋白( $\beta$ -catenin)通路,另外两个则是非典型途径,分别为Wnt/Ca<sup>2+</sup>通路和平面细胞极性通路,这些途径都参与颅面发育。在颅缝早闭患者中,POTTER等<sup>[73]</sup>发现了与Wnt信号通路相关的遗传突变,特别是*SFRP2*和*DKK2*,这两个基因是Wnt信号的负向调节因子。此外,YILMAZ等<sup>[72]</sup>研究通过多重测序分析发现,AXIN2作为典型Wnt通路的负调控因子,能够磷酸化 $\beta$ -catenin并促进其降解。AXIN2基因第四外显子突变所导致的单倍体功能不足可能是矢状缝早闭的原因。值得注意的是,AXIN2主要在发育中的颅缝的成骨前沿和骨膜中表达,靶向破坏AXIN2可通过增强骨祖细胞分化诱导颅缝过早融合。这些研究成果不仅揭示了Wnt信号通路在颅面发育中的核心作用,也为颅缝早闭症的遗传学基础提供了新的见解。

### 3.4 BMP信号通路

骨形态发生蛋白(bone morphogenetic protein, BMP)是TGF- $\beta$ 超家族成员,其对于多组织的发育,尤其是在骨和软骨的发育过程中起着重要的作用<sup>[74]</sup>。BMP可

与跨膜受体结合,受体的激活可以使Smad1/5/8磷酸化,并与Smad4相互作用,活化的Smad复合物异位到细胞核后并刺激其调节的靶基因的转录<sup>[75]</sup>。BMP分子是颅缝和骨化中心最初形成所必需的分子之一。研究表明,通过激活BMP受体促进BMP信号转导表达会导致Smad1/5/8磷酸化水平上调,使颅缝过早融合<sup>[76]</sup>。除Smad1/5/8和Smad4外,Smad6是Smads的抑制性成员,被认为具有防止颅缝过早融合的功能<sup>[77]</sup>。Noggin是BMP的拮抗剂,与颅缝的通畅性有关。WANG等<sup>[78]</sup>研究发现,在冠状缝和矢状缝的发育过程中,可观察到Noggin的连续表达,但在闭合的颅缝中未观察到其表达,而BMP信号活性则呈现高水平。考虑到BMP信号在颅缝早闭中的作用,研究人员认为靶向干预BMP信号可能是颅缝早闭的潜在治疗方法。研究表明,Gremlin1,一种有吸引力的BMP拮抗剂,被封装在水凝胶中,用于预防手术后的颅缝再次融合<sup>[79]</sup>。虽然这种生物材料并未达到预防颅缝早闭的目的,但该方法为颅缝早闭的治疗提供了新的思路。由于BMP与其他分子之间的复杂相互作用,以及传递载体结构方面存在的诸多问题,因此对其分子机制需要进一步深入研究。

## 4 颅缝早闭的治疗

### 4.1 临床治疗

目前治疗颅缝早闭的主要手段是手术,辅以语言治疗和临床心理学等专业的支持,以减轻颅内压、改善颅骨畸形<sup>[80]</sup>。大多数非综合征形式的颅缝早闭可以选择性地治疗,而一些综合征形式的病例需要紧急干预。在严重病例中,重点是维持气道和营养支持以及正常ICP<sup>[7]</sup>。决定手术程度和手术方式的最重要因素是患者的年龄和临床表现<sup>[81]</sup>。体位性斜头畸形或轻微单侧畸形的患者可采用保守治疗。在某些情况下,可以使用微创方法,尤其是内窥镜带状颅骨切除术矫正位置畸形。对于6月龄以下的婴儿,重塑头盔可单独或联合颅缝切除术使用<sup>[82]</sup>。进行颅缝早闭手术的最佳时间窗口是6~12月龄,这段时间是大脑和头部发育最为活跃的阶段,因此是手术矫正头部形状和骨缺损再生的最佳时机<sup>[83]</sup>。手术治疗的并发症包括术后高热、脑膜炎、皮下及皮下血肿、硬脑膜破裂、脑脊液渗漏和失血等<sup>[84]</sup>。并发症的风险因手术类型而异。内窥镜辅助的颅缝切除术是并发症风险最低的干预措施,尽管其重塑效果有限<sup>[81]</sup>。

手术后的治疗并未结束,需要定期随访以监测头部生长和头围,观察颅内压增高的可能症状和其他潜在并发症。只有通过定期随访,才有可能及时发现颅缝过早融合,并及时为患者提供再次手术。

## 4.2 前瞻性治疗

鉴于目前手术治疗的复杂性和缺点,亟需开发替代方法来解决这一临床需求。一项早期研究在大鼠颅缝早闭手术(截骨术)矫正期间使用自体间充质干细胞和TGF- $\beta$ 3的受控释放成功减轻了颅缝再生后的骨化和继发性颅缝早闭症状。颅缝间充质中Gli1<sup>+</sup> MSC的过早丢失可能导致颅缝过早融合<sup>[85]</sup>。YU等<sup>[86]</sup>通过切除Twist1<sup>+/-</sup>颅缝早闭小鼠闭合的冠状缝,将Gli1<sup>+</sup> MSC植入可生物降解支架上可以恢复Twist1<sup>+/-</sup>颅缝早闭小鼠的缝合通畅性。重要的是,这种干预使Twist1<sup>+/-</sup>小鼠的头骨形状,神经认知功能和ICP正常化。这些结果凸显了未来颅缝早闭治疗方式的转变,为减轻颅缝早闭的并发症提供科学证据。最近一项针对治疗颅缝早闭的研究进一步支持了这种基于干细胞的治疗方法,在这项研究中,颅缝切除后移植骨干/祖细胞群(CD51<sup>+</sup>; CD200<sup>+</sup> MSCs)并使用Wnt3a处理可防止颅缝早闭<sup>[87]</sup>。此外,多种生物活性分子在颅缝早闭动物模型中的治疗潜力已经得到评估。在颅缝早闭的Twist1<sup>+/-</sup>小鼠模型中,PRIBADI等<sup>[43]</sup>发现使用Kdm6a和Kdm6b的药理学抑制剂GSK-J4能够降低Twist1<sup>+/-</sup>颅骨细胞的成骨分化,并减少骨矿化,从而阻止Twist1<sup>+/-</sup>小鼠的冠状缝合线融合。此外,SHIN等<sup>[88]</sup>将肽基脯氨酰顺-反异构酶1(peptidyl prolyl *cis-trans* isomerase 1, PIN1)抑制剂胡桃醌通过腹腔注射到怀孕的Fgfr2<sup>S252W/+</sup>小鼠中,防止其后代发生Apert综合征样表型。蛋白精氨酸甲基转移酶(protein arginine methyltransferases, PRMTs)是一组关键的酶类,它们在多种生物学过程中发挥重要作用<sup>[89]</sup>。在颅骨形成的分子机制中,PRMT1通过BMP信号调节SMADs甲基化,从而影响颅骨形成过程。针对PRMT1介导的BMP信号通路的靶向治疗可能成为降低颅缝早闭和其他相关颅面畸形风险的潜在方法<sup>[90]</sup>。

## 5 总结与展望

先前关于颅缝早闭的综述主要对颅缝早闭的关键调控因素包括分子生物学及遗传机制方面的研究进展进行了综述。与以往关于颅缝早闭的综述相

比,本文提供了一个更加全面和系统的视角,包括对近年来的研究进展的深入分析,特别关注于新近发现的基因突变、表观遗传学改变以及环境因素在颅缝早闭发病机制中的作用。此外,详细探讨了在动物模型中开发的新治疗靶标,为颅缝早闭的未来治疗和研究提供新的思路。本文提供一个更新、更全面的颅缝早闭知识框架,强调了该领域最新的科学发现和未来研究的潜在方向。

虽然目前对于颅缝早闭的遗传以及分子调控机制进行了大量的研究,新的分子调控理论和发病因素也逐渐被发现,但是复杂且相互作用的信号通路使得靶向调节特定分子以控制致病过程变得颇具挑战性。因此,预防策略和术后恢复的方法都是亟需进一步完善和发展的。此外,颅缝早闭是一种多因素和临床异质性疾病,需要多学科专家进行评估。同时,应持续监测新的致病基因和环境暴露因素,以便为产前筛选和咨询提供证据。目前,多数研究都集中在综合征颅缝早闭上,因其表现出更严重的表型和更强的遗传关联。然而,对于占有疾病70%~80%的非综合征病例的致病因素仍不清楚。深入了解颅缝早闭的病因及可能涉及的机理并进行充分的认识与探讨,将有助于为颅缝早闭的预防及治疗提供新的科学思路。

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