

· 综述 ·

心肌肌球蛋白结合蛋白C在儿童肥厚型心肌病中的研究进展

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[摘要] 儿童期肥厚型心肌病(hypertrophic cardiomyopathy, HCM)病情进展快, 猝死率高, 对儿童的生命健康有着极大的威胁。超声心动图或者磁共振可以进行辅助诊断, 但不能在疾病早期进行。研究发现心肌肌球蛋白结合蛋白C(cardiac myosin binding protein-C, cMyBP-C)基因突变与HCM密切相关, 探索cMyBP-C与HCM的关系, 可为儿童HCM的早期诊断与治疗提供指导, 改善预后。文章对cMyBP-C的分子结构与分子相互作用, 其与HCM的关系以及S-谷胱甘肽化cMyBP-C的诊断前景、心肌肌球蛋白ATP酶抑制剂的治疗前景和基因疗法进行综述。

[关键词] 肥厚型心肌病; cMyBP-C; 诊断; 治疗; 儿童

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Research progress of cardiac myosin binding protein - C in children with hypertrophic cardiomyopathy

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[Abstract] Hypertrophic cardiomyopathy(HCM) in children progresses faster and has a higher risk of sudden death, which is a great threat to children's life and health. Presently, echocardiography or magnetic resonance serve as auxiliary diagnosis, but these methods lack the capability to detect the disease at an early stage. Studies have found that mutations in cardiac myosin binding protein - C (cMyBP-C) gene are closely related to HCM. Exploring the relationship between cMyBP-C and HCM can provide guidance for early diagnosis and treatment of HCM in children, ultimately improving prognosis. This article presents a comprehensive overview of cMyBP-C, including its molecular structure, physiological functions, relationship with HCM, as well as the diagnostic potential of S - glutathionylated cMyBP-C, the therapeutic potential of myocardial myosin ATPase inhibitors, and the gene therapy.

[Key words] hypertrophic cardiomyopathy; cMyBP-C; diagnosis; treatment; child

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肥厚型心肌病(hypertrophic cardiomyopathy, HCM)是指由于肌小节蛋白编码基因或肌小节蛋白相关基因突变导致的一类心肌疾病^[1]。HCM既可表现为低风险的无症状, 也可表现为危险性较高的心源性猝死(sudden cardiac death, SCD)、左心室收缩功能障碍(left ventricular systolic dysfunction, LVSD)、心力衰竭等^[2-4]。在儿童中, HCM发病率为0.24/10万~

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0.47/10万^[5], 与成人HCM相比, 儿童HCM的特点是病因多样化, 包括先天性代谢错误、内分泌紊乱等^[6], 且更早发生LVSD^[7], 结局较差^[8], SCD是婴儿期后诊断的HCM患儿最常见的死亡原因^[9]。MYBPC3是HCM最重要的致病基因之一, 它编码的心肌肌球蛋白结合蛋白C(cardiac myosin binding protein-C, cMyBP-C)与肌动蛋白、肌球蛋白相互作用, 在调节肌节收缩中发挥重要作用^[10-11]。在2020年的一项报道中^[12], 研究人员评估了来自156个家庭的285例肌节蛋白基因突变携带者(中位年龄14.2岁, 男141例); 145例(50.9%)接受了心脏磁共振。其

中致病基因发生率为：MYBPC3 43.2%、MYH7 24.2%、TNNT3 13.7%、TNNT2 11.9%、TPM1 3.2%，可见MYBPC3突变发生率远高于MYH7及其他致病基因。另外，值得注意的是，在第1次阴性筛查后，大约50%的肌节蛋白基因突变携带者在15年的随访中发展为HCM，其中各致病基因外显率为：MYBPC3 43%、MYH7 66%、TNNT3 17%、TNNT2 50%、TPM1 42%、多种变异63%，可见MYBPC3外显率较低，因而较难从家族史的角度解释与预测后代患有HCM的风险，而应更加深入地解释MYBPC3与其控制的蛋白质功能之间的联系。由于MYBPC3的高突变率与家族史预测的不准确性，对于儿童早发的HCM，优先考虑研究MYBPC3突变所引起的cMyBP-C改变对儿童HCM诊断与治疗的指导意义，对cMyBP-C进行更加全面的探索可以为儿童HCM的诊断及预后评估提供更多、更新的方法。

1 cMyBP-C的分子结构与分子相互作用分析

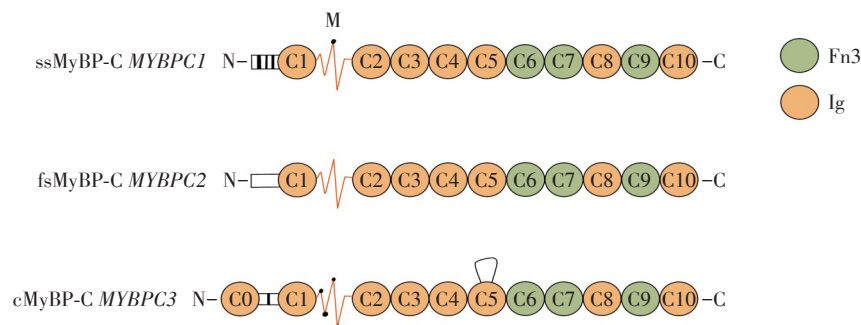
1.1 分子结构

肌球蛋白结合蛋白C(myosin binding protein-C, MyBP-C)有3种亚型，由不同染色体上的不同基因合成，它们具有相似的初级结构，都是由7~8个免疫球蛋白(immunoglobulin, Ig)以及3个纤维蛋白原-III(fibrinogen, Fn3)家族的球状结构域构成^[13-14]，同时还具有1个M结构域连接C1和C2，以及1个富含脯氨酸和丙氨酸的区域(proline/alanine, P/A)位于N端(图1)。其中cMyBP-C是心肌细胞特有的，在其他组织中检测不到，最初是在制备纯化肌球蛋白时发现，并被认为是一种杂质(称C蛋白)，但在随后被证明是肌节的组成部分，发挥重要作用。cMyBP-C分布于心肌肌节的A带，与肌球蛋白丝垂直连接，互相

间距约43 nm。该分子由1 274个氨基酸残基构成，分子量约为140 kDa，其在N端有额外的C0结构域，M结构域中有4个磷酸化位点^[13]，分别为Ser-273、Ser-282、Ser-302和Ser-307(小鼠，Uniprot ID O70468)，并且在C5结构域中有1个额外的28个氨基酸的环，该环有时被称为心脏特异性插入，有学者猜想与cMyBP-C的独特功能有关，但有待进一步研究^[15]。

1.2 cMyBP-C与肌球蛋白的相互作用

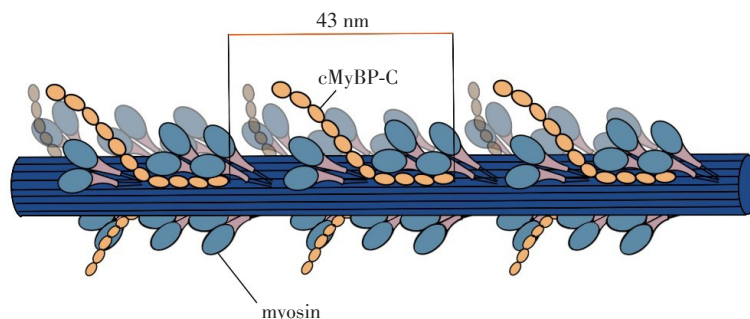
cMyBP-C在肌小节中的位置仅限于A带的C区，其通过C7和C10结构域与肌球蛋白轻链和肌联蛋白骨架之间的强结合作用锚定在粗肌丝上。C0结构域通过带正电的氨基酸与肌球蛋白轻链的1个短区域[氨基酸1554~1581(人类编号)]结合，同时C7~C9也是将结合亲和力最大化至0.5~3.5 μmol/L的必要条件^[14]。cMyBP-C调节肌丝的方式与其三维几何排列有关(图2)。目前cMyBP-C与粗肌丝的三维几何关系尚未彻底明确，不过存在许多假说，在其他文章中已经详细说明^[15]。其中值得关注的为3个cMyBP-C分子重复地围绕粗肌丝形成“三聚体”皇冠样的结构。cMyBP-C会影响肌球蛋白头部的包装，并影响3组肌球蛋白在包装和激活过程中的相互作用，这样只需要1个cMyBP-C分子就可以控制3个肌球蛋白^[16]。磷酸化与去磷酸化修饰对cMyBP-C的正常功能也有重要作用。目前已发现了至少17个磷酸化点位，研究表明cMyBP-C的去磷酸化加强其与肌球蛋白的作用，抑制肌动蛋白与肌球蛋白的结合^[17]；而其磷酸化又会导致相反效应——解除抑制、加强横桥循环^[17]，在HCM患者中也能发现cMyBP-C的磷酸化失调，这可能通过影响心肌的收缩特性而参与疾病的发病机制^[18]。



Schematic diagram of full length slow skeletal(ss), fast skeletal(fs)and cardiac(c)MyBPC paralogs. Each isoform comprises three Fn3 domains and seven or eight Ig domains. The known binding partners and positions are indicated by the horizontal stripes. The phosphorylation sites in the P/A and M domain of the ssMyBP-C and cMyBP-C paralogs are indicated by small black ellipses. The cMyBP-C has an additional 28 amino acid loop in the C5 domain.

图1 3种MyBP-C亚型示意图

Figure 1 Schematic diagram of three MyBP-C subtypes



With a total length of 43 nm, there are nine myosins, and three cMyBP-C proteins, divided into three groups. Three groups of myosin heads are arranged in a triple rotationally symmetric spiral array, protruding from the trunk at regular distances. Three cMyBP-Cs, with their C-terminal domains C7 to C10, bind to a series of myosin tails and extend to actin.

图2 cMyBP-C在粗肌丝中的三维几何排布

Figure 2 Schematic diagram of three-dimensional geometric arrangement of cMyBP-C in coarse myofilaments

1.3 cMyBP-C与肌动蛋白的相互作用

Ig样C0域是心脏同种型所特有的,而C0和C1之间的富含脯氨酸区域具有与肌动蛋白结合的序列^[19],这些序列已被证实不同的物种中存在差异^[20]。Risi等^[21]研究发现,C1结构域的215~218残基(Arg-Ala-Ser-Lys)构成了一带正电荷的环,并定位于原肌球蛋白带负电荷的结构旁,从而与原肌球蛋白相互作用,并可由C0结构域稳定。体外动力学实验、生物化学ATP酶测定和单分子研究表明,cMyBP-C诱导的细肌丝激活对Ca²⁺的敏感性增强^[22]。然而,在高钙条件下,cMyBP-C会降低肌动蛋白或细肌丝的滑动速度并降低肌球蛋白的ATP酶活性^[23],并且与肌球蛋白头部竞争细肌丝上的结合位点,抑制横桥形成。相反,在低Ca²⁺条件下,其N端结构域与肌动蛋白结合,激活原肌球蛋白,利于肌球蛋白与细肌丝结合^[11]。值得一提的是,在小鼠中,肌动蛋白丝的位移对cMyBP-C的特定结构域有很高的选择性。只有C0~C3片段导致位移并增加对Ca²⁺的敏感性,而较短的N端片段(C0~C1片段和含有前17个M结构域残基的C0~C1f片段)能与细肌丝结合,但对Ca²⁺敏感性和S1结合没有影响^[21]。这突出了需要明确cMyBP-C在肌动蛋白上的长期和瞬时结合位点。

2 HCM与cMyBP-C的联系

2.1 基因突变

研究显示,1500多个基因可能与HCM有关^[24],其中MYBPC3与HCM密切相关^[25]。cMyBP-C基因突变主要包括截短型突变和非截短型突变,其中截短型突变的比例超过75%^[26]。截短型突变(如无义突变)会导致HCM患者1个等位基因提前出现终止密

码子,从而使多肽链截短,触发无义介导的mRNA降解(nonsense-mediated RNA decay, NMD)和泛素-蛋白酶体系统(ubiquitin-proteasome system, UPS)的激活^[10],导致cMyBP-C的总体表达水平降低,是HCM的基本病理机制^[27]。MYBPC3非截短型的基因突变(如错义突变)的机制目前仍不确定,Spudich实验室提出mesa假说,阐明了与MYBPC3错义突变有关的超收缩性,被认为是一种可能的解释^[28]。mesa假说是将肌球蛋白的运动范围看作一个相对平坦的表面,参与cMyBP-C或肌球蛋白近端S2片段的静电相互作用,来稳定肌球蛋白头部结构。HCM突变体可能会影响这种结构的稳定性,破坏肌球蛋白头与肌动蛋白的相互作用,随后导致超收缩性^[11]。

MYBPC3突变引起的HCM临床表现多样,MYBPC3突变患者更常见心室功能障碍。MYBPC3 c.2149-1G>A突变与前间隔肥大、左心室射血分数保留和心房扩大相关^[29]。然而,携带MYBPC3-Q10961X的个体,无论是否有左心室肥厚,都表现出增高的间隔凸度^[30]。复合杂合子或纯合子MYBPC3截短突变可导致严重HCM表型,其特征是心室致密化不全和间隔缺损,这在儿童中是致命的^[31]。这些研究表明,对MYBPC3突变携带者,特别是特定突变类型的个体,需要深入研究来理解其表型差异和临床意义。

2.2 翻译后修饰

cMyBP-C的翻译后修饰包括磷酸化、S-谷胱甘肽化、乙酰化、瓜氨酸化和葡糖酰胺(O-linked β -N-acetylglucosamine, O-GlcNAc)化,其中磷酸化和S-谷胱甘肽化是现今研究比较多的翻译后修饰。在过去几年里,很多学者对cMyBP-C的磷酸化进行研究,因为cMyBP-C磷酸化与其他肌节的相互作用对

心脏收缩力有很大影响^[32-33]。蛋白激酶A、蛋白激酶C、钙调蛋白依赖性蛋白激酶II、蛋白激酶D和核糖体S6激酶作用于cMyBP-C的M结构域磷酸化位点,进而影响肌节的结构和功能。如蛋白激酶A的磷酸化抑制了cMyBP-C的N端区域结合肌动蛋白、肌球蛋白-S2或改变肌丝的Ca²⁺敏感性^[34]。cMyBP-C的N端区域,特别是通过M结构域,以Ca²⁺依赖的方式与钙调蛋白(calmodulin, CaM)相互作用^[35]。CaM是一种细胞内Ca²⁺受体,它在与Ca²⁺结合时可和几个目标蛋白结合并调节其活性,如Ca²⁺依赖性激酶。N端(C1-M-C2结构域)也与肌球蛋白的S2片段结合,靠近杠杆臂结构域。因此,可以通过cMyBP-C的磷酸化和去磷酸化来动态调节肌球蛋白和肌动蛋白间的相互作用。心肌肌联蛋白的构象可以影响半胱氨酸的S-谷胱甘肽化。生理条件下,谷胱甘肽与氧化型谷胱甘肽的比例约为100:1,但在氧化应激增加情况下可降至1:1。氧化型谷胱甘肽可使肌联蛋白折叠减弱,暴露出Ig结构域,使隐藏的半胱氨酸谷胱甘肽化,增加肌丝Ca²⁺敏感性,进而诱发保留射血分数的心肌舒张功能障碍,心肌重构、肥厚以及纤维化^[36-37]。尽管对cMyBP-C翻译后修饰的影响提出了多种假说,如蛋白质降解、蛋白质间相互作用的调节以及肌节收缩性和Ca²⁺敏感性的调节,但这些翻译后修饰在心脏病理生理学中的作用仍然有待进一步研究^[1]。

2.3 肌球蛋白构象的调节

在肌节中,可以找到3种不同的肌球蛋白构象,调节这些构象的比例可以调整心肌的能量消耗。在肌肉收缩的激活过程中,主要是肌球蛋白通过其两个头与肌动蛋白强结合。在肌肉松弛或舒张过程中,有两种不同的肌球蛋白构象,即超松弛(super-relaxed, SRX)和有序松弛(disordered-relaxed, DRX)构象,这两种构象处于动态平衡^[38-39]。SRX是一种肌球蛋白双失活状态,在这种状态下两种ATP酶均被抑制;DRX是一种肌球蛋白单失活状态,在这种状态下肌球蛋白能够水解ATP释放能量,增强肌节的收缩力。结构分析预测发现,这些构象会干扰肌球蛋白头间模体(interacting-heads motif, IHM)移动,放松成对的肌球蛋白分子^[28]。在肌球蛋白SRX状态下,ATP酶的速率非常慢,而ATP水解活动与DRX状态有关:cMyBP-C磷酸化促进DRX状态,肌球蛋白与cMyBP-C的相互作用稳定了SRX构型^[38-39]。Toepfer等^[40]构建了cMyBP-C缺陷小鼠模型,与野生型相比,Mybpc3^{fl}小鼠和Mybpc3^{fl}小鼠DRX状态

肌球蛋白分别增加了50%和94%。使用0.3 μmol/L MYK-461处理小鼠后,Mybpc3^{fl}小鼠和Mybpc3^{fl}小鼠SRX状态肌球蛋白分别增加了65%和70%,使DRX/SRX的比例正常化,证明了用MYK-461单一处理肌球蛋白可以改善由MYBPC3突变引起的肌节功能障碍,纠正HCM的典型表现——收缩性增强、舒张性减弱和ATP消耗过多。

3 cMyBP-C在儿童HCM中的临床应用前景

3.1 S-谷胱甘肽化cMyBP-C的诊断前景

目前,HCM是影响儿童和青少年的第2大常见心肌病^[41],主要表现为心肌过度收缩和舒张功能障碍。cMyBP-C的S-谷胱甘肽化可使氧化信号增强,从而引起Ca²⁺敏感性增加和横桥动力学减慢,是HCM舒张功能障碍的部分原因^[42]。Rosas等^[37]提出血清S-谷胱甘肽化cMyBP-C可能是一种心肌功能标志物。Zhou等^[43]研究发现有心肌舒张功能障碍的受试者血液中S-谷胱甘肽化cMyBP-C的含量是心肌舒张功能正常受试者的(1.46±0.13)倍。基于质谱的蛋白质组学已被证明是一种能够映射、定位和量化翻译后修饰的方法,识别与心血管疾病相关的翻译后修饰对临床至关重要^[44]。因此,未来有望通过检测循环血液中的S-谷胱甘肽化cMyBP-C含量来诊断HCM患儿,但此方法还有待进一步研究。

3.2 心肌肌球蛋白ATP酶抑制剂的治疗前景

cMyBP-C的基因相关位点突变可对ATP酶活性和Ca²⁺敏感性造成一定影响^[45],使得DRX/SRX比值异常,出现超收缩性。Mavacamten(即MYK-461)和Aficamten(即CK-274/CK-3773274)是心肌肌球蛋白ATP酶抑制剂,是现今研究的有潜力的HCM治疗药物^[46-47]。它们的作用机制相同,主要是降低肌球蛋白核苷酸结合口袋的基础Pi释放率,延迟肌球蛋白的机械化学循环,减少其ATP酶活性^[28]。Mavacamten和Aficamten稳定了SRX构型,可使DRX/SRX比值趋于正常,改善心肌功能。Mavacamten可显著降低HCM患者的左心室流出道峰值压差并升高静脉血氧分压^[48-49]。Aficamten可使梗阻性HCM患者的左心室流出道峰值压差显著降低,改善症状^[50]。Mavacamten半衰期较长,大约6周才能达到稳态浓度,而Aficamten的半衰期较短,2周内就能达到稳态^[51],更有利于对患者的治疗。现今,Mavacamten的成人3期临床试验(EXPLORE-HCM试验)已经完成^[52],并于2022年4月获得了美国食品和药物管理局的批准^[53],在中国,Mavacamten也已经由国家药

品监督管理局批准用于 HCM 患者。同时,对 Aficamten 的研究也在逐步深入^[54]。虽然心肌肌球蛋白 ATP 酶抑制剂在成年患者中的研究逐渐成熟,但是它在儿童患者中的研究仍相对匮乏。近期, Kinnear 等^[55]获取 HCM 患儿的诱导多能干细胞来源的心肌细胞,利用该心肌细胞对比 3 类不同药物的疗效,发现与传统药物维拉帕米和美托洛尔相比,靶向心肌肌球蛋白 ATP 酶抑制剂能够更完全地纠正存在 MYBPC3 基因突变的异常心肌细胞表型——收缩舒张功能障碍、Ca²⁺ 瞬态和 ATP 酶活性增强。药物治疗是控制儿童 HCM 临床症状的基本治疗方式^[56],研究心肌肌球蛋白 ATP 酶抑制剂在 HCM 患儿中的治疗效果和其安全性评估十分必要。

3.3 基因疗法前景

HCM 基因治疗的 3 个主要途径是基因替换疗法,即用正常蛋白补充缺陷蛋白;基因编辑疗法,纠正潜在的遗传缺陷(如错义突变);基因沉默疗法,即用小干扰 RNA (small interfering RNA, siRNA) 等分子抑制特定基因表达,使缺陷蛋白沉默。Argiro 等^[57]使用腺相关病毒 9 型的基因治疗证明了在纯合小鼠中靶向敲入 MYBPC3 具有长期疗效。Ma 等^[58]使用 CRISPR/Cas9 基因编辑技术来修复精子中 MYBPC3 基因的错误,如果 CRISPR 试剂与精子同时注射,72% 的胚胎最终出现纯合型 MYBPC3 基因,可以筛选胚胎,防止 HCM。微小 RNA (micro RNA, miRNA) 和 siRNA 都属于非编码小分子 RNA, miRNA 与心肌细胞肥大、纤维化和凋亡相关的调节途径有关,靶向沉默或上调 miRNA 可能对 HCM 患者的预后有作用。现今该技术仍处于实验阶段,其中 miRNA-133、miRNA-451、miRNA-21 等已开展研究。miRNA-451 在新生大鼠心肌细胞中过度表达,抑制 TSC1 表达, TSC1 是 miRNA-451 的直接靶点, miRNA-451 通过作用于此靶点来调节心脏肥大。miRNA-451 的上调可抑制 HCM 的发展,因此可借助 miRNA-451 治疗儿童 HCM^[59]。基因治疗是现今的研究热点,有基因缺陷的 HCM 患儿在未来通过基因治疗有望长期获益。

4 小 结

cMyBP-C 作为与肌动蛋白、肌球蛋白相互作用的重要分子,其发生基因突变、调节肌球蛋白构象、发生磷酸化等翻译后修饰都能影响心脏的收缩和舒张功能,与儿童 HCM 密切相关。儿童是 HCM 患者中的一个特殊人群,仍相对缺乏病因学基础和临

床结果等方面的数据^[60],但生物标志物 S-谷胱甘肽化 cMyBP-C、心肌肌球蛋白 ATP 酶抑制剂以及基因疗法为 HCM 患儿的早期诊断与治疗带来了更多可能,今后可以在 HCM 患儿中针对这些方面进行更多的临床探索研究。

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SHEN Tong was responsible for research plan progress, data analysis, paper writing and revision; HU Jing was responsible for data collection and analysis, paper writing and revision; ZHANG Haiyan was responsible for research direction guidance and paper revision.

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(上接第 97 页)

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