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聚焦基因治疗的扩张型心肌病模型构建及进展

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【摘要】 扩张型心肌病是引起心力衰竭的主要疾病之一,存在病因学异质性。近 1/4 扩张型心肌病患者与遗传相关,心室扩大和心肌收缩功能障碍是该病的主要特征。核纤层蛋白 A(Lamin A,LMNA)基因突变是遗传性扩张型心肌病的重要病因,心律失常是 LMNA 突变遗传性扩张型心肌病的重要临床表征。近年来基于 C57/B6 遗传背景小鼠聚焦基因治疗的啮齿类动物扩张型心肌病模型构建及其干预是研究的热点,对犬和猪等大动物模型构建也有一定的研究。大动物尤其是非人灵长类动物是更贴近人的理想模型,但目前对于非人灵长类动物的心脏疾病模型并未涉及扩张型心肌病,故本文综述了基因层面的扩张型心肌病啮齿类动物及大动物模型的研究,提出可进行基于当前研究基础上的非人灵长类扩张型心肌病模型的理念,为今后有针对性地研究致病机制以及临床治疗提供新思路。

【关键词】 扩张型心肌病;LMNA 突变;基因治疗;动物模型
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Model establishment and progress of focused gene therapy for dilated cardiomyopathy

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【**Abstract**】 Dilated cardiomyopathy is a main disease that causes heart failure and exhibits etiological heterogeneity. Nearly a quarter of dilated cardiomyopathy in patients is related to genetics, and ventricular dilation and myocardial systolic dysfunction are the main characteristics of the disease. LMNA mutation is a major cause of hereditary dilated cardiomyopathy, and arrhythmia is a major clinical manifestation of hereditary dilated cardiomyopathy with LMNA mutation. In recent years, establishment of a dilated cardiomyopathy model in C57/B6 mice and its treatment by focused gene therapy has been a research focus, and some important conclusion have been drawn from the establishment of large animal models in dogs and pigs. However, large animals, especially non-human primates, are closer to humans. At present, dilated cardiomyopathy is not involved in the heart disease model of non-human primates. Therefore, this article reviews studies on rodent and large animal models of dilated cardiomyopathy at the genetic level and proposes the idea of developing a dilated cardiomyopathy model in a non-human primate. It also provides new ideas to study the pathogenesis and clinical treatment.

【**Keywords**】 dilated cardiomyopathy; LMNA mutation; gene therapy; animal model
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扩张型心肌病(dilated cardiomyopathy, DCM)是在没有异常负荷条件或冠状动脉疾病能够引起左心室收缩功能障碍的情况下存在左心室(left ventricle, LV)扩张和收缩功能障碍[1]。DCM 存在病因学异质性,非遗传性占 75%。DCM 的患病率约为 1/250 ~ 1/2500,在成人中发病率每年可达 7/100 000,在儿童中发病率每年可达 0.57/100 000,男性高于女性,且 66%的儿童患有特发性疾病[2]。人 DCM 遗传背景特定致病突变仍未明确,其研究也是当前热点。心肌病的遗传复杂性挑战了传统“单基因疾病”理念,目前研究集中于“力传导缺陷”假说,未来研究希望发现遗传突变组合,理解心肌病的分子亚型[3]。基因突变是 DCM 的重要病因,核纤层蛋白 A(Lamin A, LMNA)突变是导致 DCM 的常见突变之一。

1　LMNA 突变是遗传性 DCM 的重要病因

LMNA 突变是遗传性 DCM 的重要病因。在包含 2032 名 DCM 患者的研究中,导致家族及散发性 DCM 病例的合并频率为 5%;152 名患者中有 105 名(69%)为男性;LMNA 突变携带者 DCM 诊断的平均年龄为 40 岁。LMNA 突变 DCM 患者的平均 LVEF 为 35%,受损程度稍低;心脏移植(heart transplantation, HTx)的平均年龄为 41 岁;26%的 LMNA 突变 DCM 患者中进行了植入式心律转复除颤器(Implantable cardioverter-defibrillator, ICD)的植入来干预临床心律失常问题[4-7]。LMNA 突变导致心脏损伤机制有结构假说:LMNA 突变相关层粘连蛋白结构缺陷导致细胞核结构软化和形态异常;机械转导假说:A 型层粘连蛋白突变导致收缩组织的结构调节失常,机械应力抵抗力降低;基因转录假说:Lamin A/C 能够直接结合染色质,调节其空间组织,影响转录和基因定位;线粒体功能破坏:LMNA 突变导致异染色质结构和表观遗传标志物(H3K9me2/3)增加,并破坏线粒体超微结构[4,7]。LMNA 突变通过影响细胞核机械结构和基因转录导致心肌病的发生。

2　心律失常是 LMNA-DCM 的重要临床表征

心律失常是 LMNA-DCM 的重要临床表征。其中包括房室传导阻滞、束支传导阻滞、窦房结功能异常的传导系统疾病占 73%;心房颤动、心房扑动、室上性心动过速占 61%;室性心律失常占 50%;另外还有心源性猝死[8]。

3　LMNA-DCM 的突变发生率及突变类型

在一项关于 LMNA 突变的临床研究中发现 66

名心脏移植受者或转诊心脏移植患者中有 5 个突变(7.6%),另外一项研究中 44 名扩张型心肌病患者中有 4 个突变(9.1%)(LMNA 突变的类型及表型如表 1)。所有 LMNA-DCM 都伴有不同程度的心律失常。LMNA 突变的类型有 *p. Arg*541*Cys*、*p.Arg*541*Gly*、*p. Arg*89*Leu*、*p. Val*256*Gly*、*p. Gly*400*Argfs* * 11、*p. Thr*510*Tyrfs* * 42、*p. Gln*246 *、*p. Ser*431 *、*p. Tyr*481 *,其中 *p. Arg*89*Leu*、*p. Val*256*Gly*、*p. Gly*400*Argfs* * 11、*p. Thr*510*Tyrfs* * 42、*p. Gln*246 *、*p. Ser*431 *、*p. Tyr*481 * 突变伴有房室传导阻滞,*p. Gly*400*Argfs* * 11 突变伴有病态窦房结综合征[9]。

表 1 LMNA 突变的类型及表型

Table 1 Types and phenotypes of LMNA mutations

突变类型 Mutation type	N(外显) N(exon)	DCM	AVB	SSS	CD + SWMA	HF	CPK	ICD	OHT
*p.Arg*541*Cys*	1(1)	+	−	−	+ (LBBB)	+	0	1	1
*p.Arg*541*Gly*	3(2)	+	−	−	+ (NBBB)	−	0	0	−
*p.Arg*89*Leu*	1(1)	+	+	−	−	−	0	0	1
*p.Val*256*Gly*	1(1)	+	+	−	−	−	0	0	−
*p.Gly*400*Argfs* * 11	3(2)	+	+	+	−	+	2	0	0
*p.Thr*510*Tyrfs* * 42	5(4)	+	+	−	−	−	3	2	1
*p.Gln*246 *	2(1)	+	+	−	−	+	0	0	−
*p.Ser*431 *	5(4)	+	+	−	−	−	0	1	1
*p.Tyr*481 *	4(4)	+	+	−	−	+	2	0	2

注:DCM:扩张型心肌病;AVB:房室传导阻滞;HF:心力衰竭;SWMA:节段性壁运动异常;SSS:病态窦房结综合征;CD:传导性疾病;CPK:磷酸肌酸激酶;ICD:植入型心律转复除颤器;OHT:心脏移植;LBBB:左束支传导阻滞;NBBB:非特异性束支传导阻滞;+:患有;−:不患有。

Note. DCM. Dilated cardiomyopathy. AVB. AV block. HF. Heart failure. SWMA. Segmental wall motion abnormalities. SSS. Morbid sinus syndrome. CD. Conductive disease. CPK. Phosphocreatine kinase. ICD. Implantable cardioverter defibrillator. OHT. Heart transplant. LBBB. Left bundle branch block. NBBB. Non-specific bundle branch block. + . With. −. No.

4 聚焦基因治疗的啮齿类动物 DCM 模型

近年来基于 C57/B6 遗传背景小鼠聚焦基因治疗的啮齿类动物 DCM 模型构建及其干预也是研究的热点(总结如表 2)。

对含 p. H222P LMNA 突变的小鼠模型中 $Lmna^{H222P/H222P}$ 突变导致小鼠胚胎体内心脏缺陷,赖

表 2 聚焦基因治疗啮齿类动物 DCM 模型

Table 2 A rodent DCM model that is focused on gene therapy

基因靶点及突变类型 Gene targets and the type of mutations	是否基于临床样本 Is it based on a clinical sample	研究内容 Research contents	干预措施 Intervention study	文献来源 Literature reference
*SDHAF*4-CM-KO	是 Yes	揭示了线粒体复合体Ⅱ在扩张型心肌病发生发展中的重要作用 Evealed the important role of mitochondrial complex Ⅱ in the development and progression of dilated cardiomyopathy	补充富马酸靶向线粒体或抑制线粒体分裂改善线粒体动力学,部分恢复心功能并延长突变小鼠的寿命 Fumarate supplementation for targeting to mitochondria or inhibition of mitochondrial fission improves mitochondrial dynamics, partially restores cardiac function and extends the lifespan of mutant mice	[10]
*Atat*1-KO	是 Yes	证明了由 cofilin-1 和 MRTF-A/SRF 介导的肌动蛋白-微管细胞骨架相互作用,促进了 LMNA 突变引起的扩张型心肌病 Demonstrated that the actin-microtubule cytoskeleton interactions mediated by cofilin-1 and MRTF-A/SRF promoted a dilated cardiomyopathy caused by LMNA mutations	调节 α-微管蛋白乙酰化水平 Regulation of α-tubulin ETC levels	[11]
*BAG*3-CM-KO	是 Yes	抑制 HDAC6 保护心脏功能 HDAC6 inhibition protected the cardiac function	iPSC-CMs 与表型筛选和深度学相结合具有加速药物发现的能力 iPSC-CMs combined with phenotypic screening and depth science have the ability to accelerate drug discovery	[12]

续表 2

基因靶点及突变类型 Gene targets and the type of mutations	是否基于临床样本 Is it based on a clinical sample	研究内容 Research contents	干预措施 Intervention study	文献来源 Literature reference
*PLN-R*14-KO	是 Yes	PLN-R14del 相关心肌病的首发表现中蛋白质稳态和 PLN 蛋白聚集的改变 Altered protein homeostasis and PLN protein aggregation in the first manifestation of PLN-R14del-associated cardiomyopathy	对 PLN 蛋白聚集的干预可能作为新的靶点 Proprognosis for PLN protein aggregation may serve as new targets	[13]
*BRD*4-CM-KO	是 Yes	BRD4 调节心肌细胞线粒体稳态有重要作用 BRD4 has an important role in regulating mitochondrial homeostasis in cardiomyocytes	临床前模型中小分子 BET 蛋白抑制剂(如 JQ1)已显示出逆转心肌肥厚和心力衰竭的疗效 Small-molecule BET protein inhibitors such as (such as JQ1) in preclinical models have shown efficacy to reverse cardiac hypertrophy and heart failure	[11]
*TAB*2-CM-KO	是 Yes	TAB2 是心肌稳态和重构的关键调节因子,通过抑制 ripk1 依赖的细胞凋亡和坏死性凋亡 TAB2 is a key regulator of cardiac homeostasis and remodeling by inhibiting ripk1 dependent and necrotising apoptosis	靶向 ripk1 为可能的治疗靶点 Targeting ripk1 as a possible therapeutic target	[14]
*LEMD*2-CM-KI	是 Yes	LEMD2 对基因组稳定性和心脏功能的重要性 Importance of LEMD2 for genome stability and cardiac function	心肌细胞特异性 LEMD2 基因治疗 Cardiomyocyte-specific LEMD2 gene therapy	[15]
*Tnnt*2-KI	是 Yes	心脏驻留与噬细胞通过 TRPV4 依赖的机制感知机械刺激,协调适应性重塑和衰竭心脏的存活 Heart residence and phages sense mechanical stimulation through a TRPV4 dependent mechanism, coordinating adaptive remodeling and survival of the failing heart	TRPV4 通道活性调节 DCM 的适应性重构和冠状动脉血管生成,机械感知是心脏巨噬细胞活化的机制 TRPV4 channel activity regulates adaptive remodeling of the DCM and coronary angiogenesis, and mechanoception is the mechanism of cardiac macrophage activation	[16]
OGT/OGA-CM-KI	是 Yes	过度的 o-glcnac 化可导致心肌病,部分由于能量缺陷 Excessive o-glcnac comorylation can cause cardiomyopathy, partly due to energetics defects	减少过度的 o-glcnac 糖基化 To reduce the excessive o-glcnac idiorylation	[17]
*Bag*5-KI	是 Yes	BAG5 的失活突变可导致 DCM,BAG5 可能是 DCM 病例的基因检测靶点 Inactivating mutations in BAG5 can cause DCM, and BAG5 may be a target for genetic testing in DCM cases	基因治疗 Gene therapy	[18]
*RLC/MYL*2-KI	是 Yes	突变诱导的肌球蛋白能量状态的重新分布是导致人类 DCM-D94A 突变相关机制之一,影响 SRX-DRX 平衡 Mutation-induced redistribution of myosin energy states is one of the associated mechanisms leading to DCM-D94A mutations in humans, affecting the SRX-DRX balance	DCM-d94a 突变降低了肌球蛋白运动功能,导致小鼠发生收缩功能低下和 DCM,未来可从此机制开展工作 DCM-d94a mutation reduced the automotor function of myoidal eggs, leading to the contractile hypofunctional phenotype and DCM in mice, which can be developed in this mechanism in the future	[19]
*NR4A*2-CM-KI	否 No	NR4A2 过表达导致细胞周期再进入和 DNA 复制增加,但不导致心肌细胞分裂导致 DCM NR4A2 overexpression leads to cell cycle re-entry and increased DNA replication, but does not cause cardiomyocyte division leading to DCM	核受体作为一个新的重要的调节因子调节心肌细胞自我更新和心脏重生 Nuclear receptors as a new important regulator regulating cardiomyocyte self-renewal and cardiac rebirth	[20]

续表 2

基因靶点及突变类型 Gene targets and the type of mutations	是否基于临床样本 Is it based on a clinical sample	研究内容 Research contents	干预措施 Intervention study	文献来源 Literature reference
*ADAR*1-CM-KO	否 No	具有酶活性的 ADAR1 可预防由内源性非编辑 RNA 触发的 irf7 导致的心脏自身炎症反应引起的 DCM Enzymatically active ADAR1 prevents DCM resulting from the cardiac autoinflammatory response of the irf7 guides triggered by the endogenous non-edited RNA	ADAR1 在心肌细胞中具有不依赖 RNA 编辑的功能,预防心衰发生 ADAR1 has the function of nonisis RNA editing in cardiomyocytes to prevent the occurrence of heart failure	[21]
LMNA-CM-KO	否 No	SUN1 微蛋白的心肌细胞特异性表达可预防心肌病进展 Cardiomyocyte-specific expression of the SUN1 microprotein prevents cardiomyopathy progression	可能避免了开发针对每种不同 LMNA 心肌病诱发突变(有超过 450 种突变)的特异性疗法 Development of specific therapies for each different LMNA cardiomyopathy-induced mutations (with more than 450 mutations) may be avoided	[22]
*HDAC*6-KO	否 No	去乙酰化酶在控制肌原纤维功能和心肌被动僵硬中的作用,提示可逆的乙酰化改变了肌联蛋白的顺应性 Role of deacetinase in controlling myofibrillar function and passive stiffness of myocarmuscle suggests that reversible acetinchanges the compliance of myxin	靶向 HDAC6 来操纵心脏弹性特性 To the HDAC6 to manipulate the cardiac elastic properties	[23]
Rev-erbα/β-CM-KO	否 No	生物钟介导的预测和营养诱导的反应在心肌代谢中的时间协调,心脏分子睡眠类型可能参与了人类 DCM 的发生 Temportemporal coordination of clock-mediated predictions and nutrient-induced responses in myocardial metabolism, cardiac molecular sleep types may be involved in the development of DCM in humans	Rev-erb 下游的心肌生物学为治疗靶点 Cardiac muscle biology downstream of Rev-erb is a therapeutic target	[24]
*CU*1/2-KO	否 No	ULK1 和 ULK2 在发育中的心脏中功能冗余,而 ULK1 在成人心脏中具有更独特、更突出的作用 ULK1 and ULK2 have several functions in the developing heart, while ULK1 has a more distinct and prominent role in the adult heart	提高 ULK1 活性可能代表了部分心肌疾病的潜在治疗方法 Improving ULK1 activity may represent a potential therapeutic approach for several myocardial disorders	[25]
*Tmem*65-KD	否 No	Imem65 功能异常导致闰盘(ICD)结构受损,心脏电生理异常,最终导致心肌病 Imem65 abnormal function leads to boudoir disc (ICD) structure damage, cardiac electrophysiological abnormalities, and eventually leads to cardiomyopathy	未来需了解 Tmem65 水平降低时发生死亡的原因 Future future needed to understand the causes of Tmem65 reduction	[26]
*MTFP*1-CM-KO	否 No	揭示了 MTFP1 在控制生物能量效率和细胞死亡敏感性方面的新功能,并确定了其在预防致病性心脏重构中的重要性 Revcovers a novel function of MTFP1 in controlling bioenergetic efficiency and cell-death plant sensitivity and identifies its importance in preventing pathogenic cardiac remodeling	MTFP1 有望成为减轻心脏病理事件和心脏疾病代谢重构的靶点 MTFP1 is expected to be a target for attenuated cardiac pathology events and metabolic remodeling in cardiac diseases	[27]
*Mst*1-CM-KI	否 No	Hippo 信号激活通过抑制线粒体基因介导线粒体损伤,从而促进 DCM 的发生发展 Hippo signaling activation mediates mitochondrial damage by inhibiting mitochondrial genes, thus contributing to the development of DCM	Hippo 通路是治疗心肌病线粒体功能障碍的重要靶点 Hippo pathway is a target for the treatment of mitochondrial dysfunction in cardiomyopathy	[28]

注:CM:心肌细胞;KO:基因敲除;KI:基因敲入;KD:基因过表达。
Note. CM. Cardiomyocyte. KO. Gene knockout. KI. Gene knock-in. KD. Gene overexpression.

氨酸特异性去甲基化酶 1 抑制剂(lysine-specific demethylase 1, LSD1) GSK-LSD1 挽救了 $Lmna^{H222P/H222P}$ 胚胎的心脏发育,且可预防小鼠的纤维化和心力衰竭,靶向组蛋白去甲基化酶 LSD1 可在核纤层蛋白病小鼠模型中预防心肌病[29];对相同遗传背景的两个独立的大鼠品系,建立近端和远端 TTNtv 模型(TTNtvA:A 带变异;TTNtvZ: Z 盘变异;纯合突变的大鼠无法存活,杂合突变的大鼠以正常的孟德尔比率出生)实验发现核糖体分析确定了 titin 的截短变异体的翻译足迹,TTN 的近端和远端 TTNtv 改变亚型加工并触发 NMD,大鼠和人类的 TTNtv 对心脏几何形状和功能产生不利影响,未来的研究聚焦于确定在 TTNtv 和遗传或环境的二次触发相互作用中风险最大[30];对 Rbm20R636Q-KO 小鼠模型,纯合子突变小鼠的短轴缩短分数显著降低表现出与 DCM 一致的形态学特征[31-32]。实验发现心脏基因的异常剪接(如 TTN 突变)是 RBM20 相关心肌病的主要原因,通过 AAV9 对这些小鼠进行包含 ABEmax-VRQR-SpCas9 和单向导 RNA 的 ABE 成分的全身递送,心功能恢复且寿命延长[33]。RNA-seq 显示,ABE 校正挽救了 R636Q/R636Q 小鼠的心脏转录谱,全身校正 ABE 减少了 CMs 中存在的毒性 RNP 颗粒,并挽救了小鼠的心功能障碍[34]。

5　扩张型心肌病大动物模型研究

大动物构建模型有着绝对优势,包括生理、认知能力、神经解剖学、社会复杂性、繁殖和发育等方面非人灵长类与人类具有高度相似性。神经系统相似性:研究脑脊髓接口的可植入组件,为脊髓损伤患者的概念验证研究提供了一条实用的转化途径[35];器官解剖学相似性:基于基因编辑技术,NHPs 被用于开发模拟人类疾病(如癌症)的高效转化医学平台[36];生殖系统相似性:自体鞘膜干细胞移植可以改善 NHPs 激素水平以及早发性卵巢功能不全的症状[37]。非人灵长类动物(non-human primates, NHPs)的大型的单细胞转录组图谱已构建,包含了来自成年 NHPs 食蟹猴 45 个组织、113 个细胞群的超过 100 万个细胞,提供了一个巨大的注释资源[38-39]。基于超灵敏序贯荧光原位杂交(USeqFISH)的空间转录组学已开发,可用于非人灵长类动物中原位 AAV 分析和多模态单细胞分析[40-41]。在蛋白层面,反义寡核苷酸(anti-sense oligonucleotides, ASO)在 NHPs 肌肉中的效力的探究:调节与血浆蛋白的结合可以以物种依赖性的方式影响 ASO 活性和在肝外组织的分布,为确定增强 ASO 在肌肉组织中的效力的其他策略奠定了基础[42];分泌蛋白 PCSK9(LDL 受体的拮抗剂)失活对治疗高胆固醇血症的探究[43-44]:在 6 只非人灵长类动物中单次输入表达靶向 PCSK9 的工程巨核酸酶的 AAV 载体可导致肝中 PCSK9 的剂量依赖性破坏,以及循环 PCSK9 和血清胆固醇的稳定减少,证明了在非人灵长类动物中具有生理学意义的高效体内编辑[45]。

大动物犬模型目前存在犬类天然 DCM 模型及突变基因,易患天然 DCM 的犬类有纽芬兰犬、圣伯纳犬、杜宾猎犬、大丹犬、爱尔兰猎狼犬、拳师犬、英国可卡犬,其中与人 DCM 相关的基因有 ACTC1、ACTN2、CSRP3[46]。犬类模型构建方式为小剂量(0.7 mg/kg)阿霉素经 5F Judkins 导管注入左冠状动脉主干,每周重复输注,持续 5 周。模型实验结果显示肌纤维萎缩和细胞质空泡化,并伴有间质纤维化,主要见于左心室;证明反复冠状动脉内灌注阿霉素是一种简单可靠的制备犬扩张型心肌病模型的方法[47]。

在关于基因突变相关的模型上,2019 年,家系研究揭示位于 1 号染色体长臂的 RBM20 基因第九个外显子错义突变可导致 DCM[48]。正常 RBM20 存在于细胞核,突变 RBM20 在胞质异常聚集,突变 RBM20 导致 TTN、CAMK2D 等重要功能基因转录的 pre-mRNA 异常剪切[49-51]。RBM20 存在多种突变,其中位于 RS 区域的最常见[50],人 R636S 突变被用于 DCM 猪模型,通过具有高度精确性和可控性的 TALEN 基因编辑里的同源定向修复技术(HDR)引入错义突变序列(R636S)及一个防再次被切割的 BglⅡ序列[51],超声显示纯合突变猪 EF 值明显下降,杂合子无明显改变,MRI 也显示纯合突变猪心脏扩大,EF 下降。新生纯合突变猪出生时心脏即明显改变:心脏体积增大,心室扩张,室壁更薄,更柔软和脆弱,心脏重量明显增加;杂合突变胞质少量聚集 RBM20,纯合突变大量聚集;电镜显示肌节缩短且结构受损,心肌细胞排列紊乱。另外参照文献[52],在 iPCS 中验证了碱基编辑和先导编辑在 RBM20 基因突变的效果,并进一步在其 DCM 小鼠模型中得到证实,由此提出在大动物模型中是否可以有此效果,需进一步验证。纯合突变猪生存率明显降低;猪血浆 ANP 和 BNP 明显增加;RBM20 纯合

突变猪心肌纤维化、心肌肥大、心肌受损等相关基因上调,细胞周期、DNA 合成相关基因下调。

6 总结与展望

非人灵长类依然是更贴近人类的模型,猴在免疫相关基因表达模式和细胞通讯方面与人类的相似程度显著高于小鼠[52],目前对于非人类灵长类动物的心脏疾病模型并未涉及 DCM,而猴模型是很好的大动物心脏疾病模型,但目前并未从基因层面创建 DCM 模型。目前对于 DCM 的治疗集中于心衰层面,暂未发现可治疗因基因突变导致 DCM 的药物,有研究利用 iPSCs 表明洛伐他汀改善 LMNA 心肌病的内皮功能障碍,他汀类药物可能为新的药物选择。最新研究利用碱基编辑和先导编辑等方式修正基因突变,在小动物模型中已取得了成果,不仅在 iPSC 中验证了碱基编辑和先导编辑在修正 RBM20 突变的效果,还在其 DCM 小鼠模型中证实了 ABE 可有效修正基因突变,恢复其心脏功能并延长寿命[53]。在今后的研究中基于基因治疗的大动物及非人灵长类模型的发展,借助高层次平台和科研团队可以从基因层面治疗 DCM 实现更大的突破。

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