·特约综述·

hiPSC在心血管疾病机制和转化应用中的研究进展

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摘　要：心血管疾病是全球范围内致死率最高的一类疾病，其致病机制和功能修复仍有待阐明。人类诱导多能干细胞(hiPSC)的出现和发展，为心血管疾病研究提供了新的契机，极大地加深了人类对于心血管疾病的认识。本文总结了hiPSC来源的心血管细胞和心脏类器官的最新研究进展并介绍本团队在该领域的相关研究成果，重点讨论了hiPSC来源心肌细胞和非心肌细胞的诱导分化，及其在疾病建模、功能修复、药物筛选及机制解析中的作用。此外，本文还简要概述了hiPSC来源心脏类器官在心脏疾病研究中的应用现状。

关键词：人诱导多能干细胞；心血管疾病；心肌细胞；非心肌细胞；心脏类器官
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Human Induced Pluripotent Stem Cells in Cardiovascular Disease: Mechanisms and Translational Applications

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Abstract: Cardiovascular diseases are the leading cause of mortality worldwide, yet their pathogenic mechanisms and functional repair remain incompletely understood. The emergence and development of human induced pluripotent stem cells (hiPSC) have provided unprecedented opportunities for cardiovascular disease research, and markedly enhanced our understanding of cardiovascular disease mechanisms. This review summarizes recent advances in cardiovascular cells and

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cardiac organoids derived from hiPSC, and presents our team's related research findings in this field. It highlights the induction and differentiation of hiPSC-derived cardiomyocytes and non-myocytes, as well as their roles in disease modeling, functional repair, drug screening, and mechanistic investigation. Furthermore, the current applications of hiPSC-derived cardiac organoids in cardiovascular disease research are also discussed.

Key words: human induced pluripotent stem cell; cardiovascular diseases; cardiomyocytes; non-myocytes; cardiac organoids

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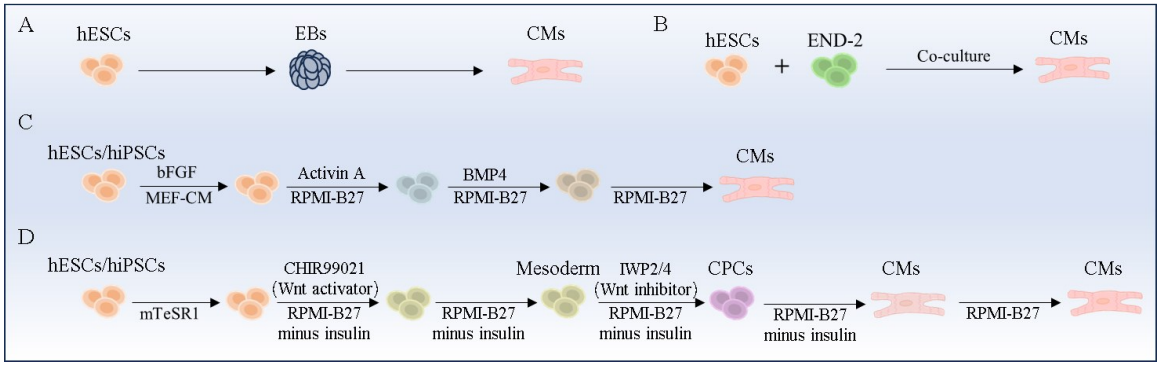
心血管疾病是导致全球死亡的首要原因,严重威胁人类健康[1-3]。人诱导多能干细胞(human-induced pluripotent stem cell, hiPSC)的出现,为心血管疾病致病机制的研究和治疗策略的开发提供理想的细胞来源。2006年,Yamanaka团队[4]通过逆转录病毒将编码四种转录因子八聚体结合转录因子3/4(octamer-binding transcription factor 3/4, Oct3/4)、SRY盒-2(SRY-box 2, Sox2)、Kruppel样转录因子4(kruppel-like transcription factor 4, Klf4)和骨髓细胞瘤癌基因(myelocytomatosis oncogene, c-Myc)的基因导入小鼠胚胎和成体的成纤维细胞中,获得与胚胎干细胞(embryonic stem cell, ESCs)特性相似的细胞,即诱导多能干细胞(induced pluripotent stem cells, iPSCs)。2007年,Yamanaka团队[5]成功将人真皮成纤维细胞重编程为hiPSC。同年,Thomson团队[6]也报道了使用不同的因子组合,将人成纤维细胞重编程为hiPSC。迄今为止,hiPSC可由多种来源的体细胞重编程而来,包括皮肤[5-6]、尿液[7-8]、血液[9]、牙髓[10]和毛囊[11]等。在特定的诱导条件下,hiPSC可以分化为包括内、中、外胚层来源的不同细胞类型,例如内胚层来源的肝星状细胞[12]和胰腺β细胞[13],中胚层来源的心肌细胞[5]和成骨细胞[14],以及外胚层来源的星形胶质细胞[15]和神经元[16-17]等,广泛用于糖尿病、心脏病、神经退行性病变等多种疾病的机制研究和转化应用。本文重点讨论hiPSC来源的心肌细胞(hiPSC-derived cardiomyocytes, hiPSC-CMs)、心脏成纤维细胞(hiPSC-derived cardiac fibroblasts, hiPSC-CFs)、内皮祖细胞(hiPSC-derived endothelial progenitor cells, hiPSC-EPCs)、内皮细胞(hiPSC-derived endothelial cells, hiPSC-ECs)、间充质基质/干细胞(hiPSC-derived mesenchymal stromal/stem cells, hiPSC-MSCs)、平滑肌细胞(hiPSC-derived smooth muscle cells, hiPSC-SMCs),以及心脏类器官在心血管疾病研究中的最新进展。

1 hiPSC来源的心肌细胞

心脏是一个由心肌细胞和非心肌细胞组成并具有瓣膜结构的空腔器官[18]。心脏的主要功能是泵血。心脏泵血功能的实现取决于心肌细胞的生物电活动和收缩特性。成体心肌细胞是终末分化的细胞,增殖能力极低,损伤后难以自我修复和再生。外源性心肌细胞为其修复再生提供了新的细胞来源,它可通过多种方法由人多能干细胞诱导分化获得(图1)。早期采用悬滴法诱导人ESCs形成拟胚体,进而分化为心肌细胞[19]。随后开发了将人ESCs与小鼠内脏内胚层样细胞共培养的方法,以提高心肌细胞的诱导效率[20]。之后研发了单层细胞诱导法,通过在分化过程中精确调控生长因子和小分子的添加,实现对心肌分化的高效诱导。2007年,Murry实验室[21]最先利用单层培养的人ESCs进行心肌诱导,通过添加激活素A和骨形态发生蛋白4(bone morphogenetic protein 4, BMP4),使心肌细胞分化效率达到30%以上。同年,Yamanaka团队[5]首次构建hiPSC时,采用单层细胞诱导法获得hiPSC-CMs。2012年,Lian团队[22]通过使用Wnt信号通路激动剂CHIR99021,诱导hiPSC向中胚层细胞分化,随后应用Wnt信号抑制剂IWP2/4,将其定向分化为心脏祖细胞,并进一步生成心肌细胞,最终获得纯度接近90%的心肌细胞。2013年,Fukuda团队[23]使用葡萄糖缺乏但富含乳酸的培养基培养纯化心肌细胞,成功将细胞纯度提升至99%以上。本团队的研究发现,Lin28-TNFR2信号在hiPSC向心肌细胞分化过程中发挥关键调控作用[24]。随着诱导分化方案的不断优化,目前可以获得高纯度的hiPSC-CMs,为心脏疾病建模、修复研究和药物筛选提供理想的细胞来源。



A：hESCs differentiate into CMs through the formation of EBs[19]. B：hESCs differentiate into CMs through co-culture with visceral endoderm-like cells (END-2)[20]. C：hESCs/hiPSC differentiate into CMs under monolayer culture by supplementing activin A and BMP4[21]. D：hESCs/hiPSC differentiate into CMs under monolayer culture via temporal modulation of Wnt signaling[22]. hESCs: human embryonic stem cells; EBs: embryoid bodies; CMs: cardiomyocytes; END-2: visceral endoderm-like cells; hiPSC: human-induced pluripotent stem cells; bFGF: basic fibroblast growth factor; MEF-CM: mouse embryonic fibroblast conditioned medium; BMP4: bone morphogenetic protein 4; CHIR99021: glycogen synthase kinase 3 inhibitor or Wnt/β-catenin signaling pathway activator; IWP2/4: Wnt signaling pathway inhibitor; CPCs: cardiac progenitor cells.

图1　人多能干细胞分化为心肌细胞的示意图

Fig. 1　Schematic diagram of the differentiation of human pluripotent stem cells into cardiomyocytes

1.1　疾病建模

hiPSC-CMs作为一种优良的体外细胞模型，在遗传性和非遗传性心脏疾病建模与机制研究中发挥重要作用（附表1和附表2）。迄今为止，hiPSC-CMs已被证明可以在体外模拟多种遗传性心脏疾病表型，例如扩张型心肌病（dilated cardiomyopathy，DCM）[25-26]、肥厚型心肌病（hypertrophic cardiomyopathy，HCM）[27-28]、长QT综合征[29-31]、致心律失常性右室心肌病[32-34]、心房颤动[35-36]、Brugada综合征[37-38]及杜氏肌营养不良症心肌病[39-40]等。DCM和HCM是常见的遗传性心肌病。Ito团队[41]利用患者体细胞和CRISPR/Cas9技术，构建携带层粘连蛋白A/C（lamin A/C，LMNA）（Q353R）突变及同基因型修复的hiPSC，诱导分化为hiPSC-CMs后成功建立DCM体外疾病模型，并发现该突变导致DNA损伤积累和维生素D信号传导受损。Hu团队[42]利用DCM患者特异性hiPSC来源的心肌细胞和类器官模型，揭示了心肌肌钙蛋白T（cardiac troponin I，cTnT）（p.K185E）序列变异通过减弱cTnT与14-3-3蛋白之间的相互作用，破坏肌节-线粒体通讯，进而过度激活14-3-3蛋白介导的RAS/丝裂原活化蛋白激酶激酶1（Raf-1 proto-oncogene，serine/threonine kinase，RAF1）-p44/42-动力相关蛋白1（dynamin-related protein 1，DRP1）/线粒体分裂因子（mitochondrial fission factor，MFF）信号轴，加速患者来源hiPSC-CMs线粒体的碎片化。此外，Ramachandra等[43]利用HCM患者来源的hiPSC-CMs模型，发现抑制髓过氧化物酶（myeloperoxidase，MPO）可以提高肌球蛋白结合蛋白C3（myosin binding protein C3，MYBPC3）的磷酸化水平，有效缓解心肌细胞的舒张缺陷。本团队前期已运用仙台病毒成功将*TNNT2*（c.229C > T）突变HCM患者外周血中分离出的单核细胞重编程为hiPSC[44]。近期，我们进一步获得了*MYBPC3*（c.194C > T）突变DCM患者特异性hiPSC-CMs，发现该突变促进钙网蛋白2（calsequestrin 2，CASQ2）表达，干扰兰尼碱受体2（ryanodine receptor 2，RyR2）介导的钙释放，导致hiPSC-CMs中钙离子调控失衡，RyR2抑制剂可有效缓解失衡。此外，该突变也会破坏hiPSC-CMs线粒体动力学平衡。

另一方面，利用hiPSC-CMs对非遗传性心脏病进行建模也取得显著的进展。hiPSC-CMs已被成功应用于病理性心脏肥大[45]、糖尿病心肌病[46]、缺血性心力衰竭[47]、铁过载心肌病[48]、围产期心肌病[49]以及心房颤动[50]等多种非遗传因素引发的心脏疾病研究。Wang等[45]运用血管紧张素II（angiotensin II，Ang II）处理健康hiPSC-CMs，建立心脏肥大的体外模型，并发现环状RNA sirtuin 1（circ-SIRT1）通过激活沉默信息调节因子1（sirtuin 1，SIRT1）促进细胞自噬，抑制Ang II诱导的心脏肥大。Jin等[46]使用棕榈酸处理hiPSC-CMs，以模拟毒性脂质诱导的线粒体功能障碍，构建了糖尿病心

肌病的体外细胞模型,并发现成纤维细胞生长因子21(fibroblast growth factor 21, FGF21)通过激活AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)/叉头框O3(forkhead box O3, FOXO3)/沉默信息调节因子3(sirtuin 3, SIRT3)信号轴,有效抑制毒性脂质引发的心肌细胞线粒体功能障碍和氧化应激反应。Davis等[47]将hiPSC分化为功能性hiPSC-CMs,再运用模拟缺血环境的培养基(葡萄糖缺乏但富含乳酸)对心肌细胞进行纯化,建立了缺血性心力衰竭的体外模型。

1.2 功能修复

心肌损伤后的心脏修复要补充足量的心肌细胞,成年心肌细胞难以再生,而诱导获得的外源性心肌细胞hiPSC-CMs可为心脏修复提供充足的细胞来源。迄今为止,hiPSC-CMs已被成功移植至多种动物模型,包括小鼠[51-53]、大鼠[54-55]、猪[56-57]以及非人灵长类动物[58]。研究表明,移植的hiPSC-CMs可以在动物心脏受损区域中存活,并且能够与宿主的心肌细胞整合,从而改善受损心脏的收缩功能。Kawamura等[56]将hiPSC-CMs贴片移植至猪梗死的心脏中,结果显示hiPSC-CMs贴片可以显著改善梗死心脏功能并减弱左心室重塑。Ong等[59]将hiPSC-CMs移植至急性心肌梗死的小鼠心脏中,并发现hiPSC-CMs通过释放促血管生成因子和抗凋亡因子促进血管生成并减少细胞凋亡,从而改善小鼠心脏功能。2024年,Kobayashi等[58]将hiPSC-CMs来源的心球体(cardiac spheroids)移植至食蟹猴心脏的梗死区域,结果显示心球体可显著改善左心室射血分数和缩短分数,有效恢复受损心脏的收缩功能。尽管如此,目前利用hiPSC-CMs修复受损心脏仍面临诸多挑战,主要包括细胞移植后的滞留率与存活率低,以及存在诱发心律失常和免疫排斥反应等风险。

hiPSC-CMs移植后的低滞留率与存活率是制约心脏修复的主要因素之一。研究发现,提升移植细胞的增殖能力或成熟度、使用生物材料改善移植部位的微环境等优化策略可以提高hiPSC-CMs移植后的滞留和存活。一方面,将具有增殖能力的hiPSC-CMs移植至受损心肌区域,能够更有效地促进心脏修复与再生。Zhao等[60]报道,细胞周期蛋白D2(cyclin D2, CCND2)过表达不仅能促进移植hiPSC-CMs的增殖,也能促进MI猪模型中移植物附近宿主心肌细胞的增殖。Tanaka等[61]发现,在大鼠梗死心脏中移植成熟度高的hiPSC-CMs,可以促进细胞在梗死区域的植入和成熟,并且在移植后的12周内持续促进微血管的形成。另一方面,hiPSC-CMs与生物材料的联合使用可以有效促进受损心脏的修复。Munarin等[62]将hiPSC-CMs与负载血管生成因子的海藻酸盐微球结合构建三维工程心肌组织,用于治疗大鼠MI,该微球在植入部位局部微环境中持续释放血管内皮生长因子(vascular endothelial growth factor, VEGF)和bFGF,促进缺血心脏的血管再生。此外,明胶水凝胶已被证实可以显著提高移植细胞在梗死区域的数量,并且还可以通过增加内源性血管生成因子的释放,促进梗死区域的血管生成[63]。Kawaguchi等[64]将经过纯化的hiPSC-CMs心球体与明胶水凝胶共移植至心衰大鼠及猪模型的心脏中,显著恢复受损心脏降低的射血分数,促进血管生成,从而改善动物的心脏功能。

1.3 药物筛选

在疾病建模的同时,利用hiPSC-CMs开展药物筛选与安全性评估,对于新药的研发及上市后监测具有重要意义。在临床前药物开发与安全性评估过程中,不良心脏事件是导致研究中止的主要原因。hiPSC-CMs为预测此类事件提供可靠且有效的体外研究平台。McKeithan等[29]利用携带导致电生理紊乱(长QT综合征3型)突变的患者hiPSC-CMs进行大规模功能筛选,以指导抗心律失常药物美西律(mexiletine)的化学结构优化,成功发现四种新的类似化合物(MexA2-5),其药效更强且致心律失常风险更低。此外,患者特异性hiPSC-CMs是发现遗传性心肌病新治疗靶点的强大模型,有效助力精准医学的发展。Perea-gil等[65]采用基于化学遗传学的表型筛选策略,利用肌钙蛋白T2(troponin T2, *TNNT2*)(c.547C > T)突变DCM患者来源的hiPSC-CMs,发现丝氨酸生物合成途径可能是DCM新的治疗靶点。

hiPSC-CMs还可应用于大规模药物的心脏毒性研究。肿瘤治疗药物通常与心脏毒性有关,利用hiPSC-CMs可以评估不同抗癌药物所引起的心脏毒性。目前已有关于阿霉素(doxorubicin)、普纳替尼(ponatinib)、美法仑(melphalan)、卡非佐米(carfilzomib)等药物心脏毒性的研究。Huang等[66]建立了基于人群的hiPSC-CMs药物毒性筛选平台,用于研究药物研发应用中不同人群间的药物毒性

及不良药物反应差异，发现阿霉素、地戊曲酯、拉帕替尼和柔红霉素等9种药物可显著诱导心脏毒性。Liu等[67]提出一套药物筛选流程，该流程结合hiPSC-CMs、CRISPR干扰和激活（CRISPRi/a）双向筛选以及小分子筛选，成功锁定碳酸酐酶12，并发现其遗传抑制可以保护hiPSC-CMs免受阿霉素诱导的心脏毒性侵害。

2　hiPSC来源的非心肌细胞

心脏是一个具有高度异质性的器官，除心肌细胞外，还包含多种类型的非心肌细胞，如成纤维细胞、内皮细胞、周细胞、平滑肌细胞、脂肪细胞以及免疫细胞等[18]。血管系统由内皮细胞、周细胞和平滑肌细胞构成多层结构网络，形成血液与组织环境之间的重要界面[68]。近年来，非心肌细胞在心血管疾病研究中引起关注。越来越多的研究表明，非心肌细胞在心力衰竭[69]、心脏纤维化[70-71]、心律失常[72-73]、肢体缺血[74-75]和高血压[76-77]等多种心血管疾病的发生、发展及治疗中发挥重要作用。来源于hiPSC的非心肌细胞是心血管疾病体外建模和药物筛选研究的理想细胞模型。此外，因其具备良好的可扩增性和旁分泌功能以及较低的免疫排斥风险，被认为是细胞治疗中具有潜力的种子细胞来源，在心血管疾病治疗中展现出良好的应用前景。本节重点介绍hiPSC-CFs、hiPSC-EPCs、hiPSC-ECs、hiPSC-SMCs以及hiPSC-MSCs的最新研究进展与应用情况（附表3）。

2.1　hiPSC来源的心脏成纤维细胞

心脏纤维化是许多不同心脏疾病的共同特征，表现为病理刺激下的细胞外基质沉积[78]。成纤维细胞是心脏纤维化的核心参与者，当心脏成纤维细胞因损伤或炎症而被激活时，其胶原蛋白的生成会显著增加，最初有助于维持心脏结构，但过度纤维化会损害心脏功能，最终导致心力衰竭[79]。hiPSC-CFs为在体外模拟心脏纤维化过程及进行药物筛选提供了可靠的实验平台。目前，已有多种获得hiPSC-CFs的分化方法[80-81]。例如，Zhang[80]等建立了一种从hiPSC稳定诱导生成心外膜来源心脏成纤维细胞的方法：经CHIR99021诱导中胚层分化后，通过IWR-1转化为心脏祖细胞；随后在CHIR99021与视黄酸协同作用下分化为心外膜细胞；最终经FGF及转化生长因子-β（transforming growth factor-β，TGF-β）抑制剂调控实现成纤维细胞定向分化。Wu团队[82]利用hiPSC-CFs对抗纤维化药物进行高通量筛选，并利用hiPSC-CMs和hiPSC-ECs对初筛药物进行反向筛选以避免心脏毒性，最终确定青蒿琥酯（artesunate）为先导化合物。此外，利用hiPSC-CFs模型研究心脏纤维化的发病机制，极大地加深了人们对该疾病的认识。Wang等[83]利用hiPSC-CFs研究Bcl2相关抗凋亡基因3（BAG cochaperone 3，BAG3）与DCM纤维化之间的关系，发现BAG3的缺失通过上调TGFBR2的表达水平，激活TGF-β信号通路，驱动心脏纤维化。Chen等[84]研究发现，泛素样蛋白HLA-F邻近转录本10（HLA-F adjacent transcript 10，FAT10）是一种针对MI后心脏纤维化的新型调节剂，在hiPSC-CFs中过表达FAT10，可缓解TGF-β1诱导的纤维化反应。

2.2　hiPSC来源的内皮祖细胞

内皮祖细胞是存在于骨髓和外周血中的血管前体细胞，可以直接分化为内皮细胞和平滑肌细胞，也可以通过释放血管活性因子，发挥旁分泌和自分泌效应，促进血管修复[85]。hiPSC-EPCs的诱导分化方法从建立到不断改良，近年来已取得突破性进展[86-92]。2014年，Lian等[86]开发了一种利用小分子化合物CHIR99021和生长因子VEGF诱导hiPSC分化为内皮祖细胞的方法，并发现WNT/β-catenin信号通路在这一过程中起关键的调节作用。之后，Farkas等[88]结合细胞因子、小分子化合物及无血清培养基，改良了hiPSC-EPCs的诱导分化方案，使其纯度提升至接近90%。本团队通过利用尿液中的脱落肾上皮细胞重编程获得hiPSC，随后在多种因子的作用下将其分化，建立无创来源的hiPSC-EPCs诱导方法[93]。进一步研究发现，Gremlin1（GREM1）重组蛋白能提高hiPSC-EPCs诱导效率，该项发现已获得国家发明专利授权[94]。hiPSC-EPCs可为心血管疾病治疗提供充足和优质的细胞来源，是极具应用潜力的种子细胞。Yoo等[95]将牙髓细胞来源的hiPSC诱导为内皮祖细胞，并证实其通过促进新生血管生成，减轻后肢缺血小鼠的肢体坏死程度，改善MI小鼠的心功能障碍。Shen等[96]使用hiPSC-EPCs治疗小鼠缺血性急性肾损伤和心脏功能异常，发现其通过修复内皮细胞和减弱心肌细胞凋亡，对急性肾损伤和心功能障碍亦具有保护作用。本团队将hiPSC-EPCs与二氧化锰

杂化水凝胶结合,用于治疗小鼠严重肢体缺血,展现出良好的治疗效果。另外,我们将hiPSC-EPCs作为种子细胞种植在小口径人工血管的内表面,促使其内皮化,改善了比格犬股动脉-人工血管置换术后的远期通畅性能。近年来,国内企业研发的hiPSC-EPCs药物已顺利进入临床试验阶段,用于治疗严重下肢缺血和急性缺血性卒中。

2.3 hiPSC来源的内皮细胞

血管内皮细胞位于血管壁的最内层,构成通透性屏障,负责管壁内外两侧的液体、气体和大分子物质的进出[97]。此外,内皮细胞具有内分泌功能,能合成和分泌多种生物活性物质[98-99]。hiPSC-ECs已成为心血管研究中不可或缺的细胞来源,有助于缓解供体细胞短缺的问题,提高疾病的治疗效果。hiPSC-ECs的分化策略包括基质细胞共培养、拟胚体分化和2D单层培养[100]。2009年,Choi团队[101]通过将hiPSC与OP9基质细胞共培养,成功诱导其向内皮细胞分化,首次获得$CD31^{+}CD43^{-}$的hiPSC-ECs。2015年,Patsch团队[102]通过抑制糖原合酶激酶-3(glycogen synthase kinase-3, GSK3)并添加BMP4处理,促使hiPSC快速向中胚层定向分化,随后给予VEGF-A刺激,可在6 d内高效诱导约80%的内皮细胞生成。hiPSC-ECs具有强大的促血管生成能力,已有许多研究证明其在心血管疾病中的治疗潜力[103-106]。例如,在小鼠下肢缺血模型中,移植的hiPSC-ECs表现出强大的血运重建能力,显著恢复缺血部位的血液灌注[107]。在小鼠和非人灵长类动物恒河猴MI模型中,hiPSC-ECs与hiPSC-CMs的联合治疗显著提高动物梗死心肌的修复效率,并发现hiPSC-ECs可以增强新生血管形成并促进心肌细胞成熟[108]。另外,hiPSC-ECs也具有良好的抗血栓形成能力。Park等[109]将hiPSC-ECs接种于脱细胞人脐动脉内表面,构建出组织工程血管导管,该导管在移植至大鼠下腔静脉后表现出良好的通畅性,此通畅性主要归因于hiPSC-ECs优异的抗血栓形成能力。此外,hiPSC-ECs来源的外泌体亦表现出良好的治疗效果。Ye等[110]研究发现,hiPSC-ECs来源外泌体中的miR-199b-5p可以促进小鼠缺血肢体的血管生成。Li等[111]发现hiPSC-ECs来源的外泌体可有效改善MI小鼠的心肌收缩功能,缓解不良的左心室重塑。

2.4 hiPSC来源的平滑肌细胞

血管平滑肌细胞是构成血管壁中膜层的主要细胞类型,具有维持血管张力、调节血流和血压等功能[102-112]。平滑肌细胞功能障碍与心血管疾病密切相关。目前,基于hiPSC技术构建的平滑肌细胞模型已成为心血管疾病研究的重要工具。许多研究发现,hiPSC-SMCs可用于心血管疾病建模和治疗。Liu等[113]通过RepSox和血小板源生长因子BB(platelet-derived growth factor, PDGF-BB)+TGF-β两种方案产生收缩型和合成型的不同表型hiPSC-SMCs,用于不同类型动脉疾病的体外细胞建模。Liu等[114]构建了hiPSC来源谱系特异性平滑肌细胞器官芯片,可用于识别不同节段主动脉的异质性特征,并在药物测试中表现出对环丙沙星的差异性反应。在疾病治疗方面,hiPSC-SMCs移植通过促进VEGF介导的血管生成作用,改善小鼠后肢缺血[115]。

2.5 hiPSC来源的间充质基质/干细胞

基于间充质基质/干细胞的细胞治疗展现出强大的治疗效果,全球已有多种间充质干细胞药物(如美国的Ryoncil和中国的艾米迈拓赛注射液等)获批上市。hiPSC-MSCs较普通hMSCs具有更好的均质性和稳定性[116-118],在心血管疾病的临床前模型中表现出良好的治疗前景。研究发现,hiPSC-MSCs治疗可以减小大鼠MI模型中心脏梗死区域的瘢痕大小和细胞凋亡程度,从而改善心脏功能[119]。在小鼠下肢缺血模型中,静脉注射hiPSC-MSCs可以促进脾调节性T细胞的活化,降低脾自然杀伤细胞表达,促进缺血区M2巨噬细胞极化,从而改善缺血肢体的血流灌注[120]。此外,hiPSC-MSCs外泌体来源的miR-9-5p可以通过调控血管过氧化物酶1(vascular peroxidase 1, VPO1)/细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)信号通路、抑制小鼠心肌细胞线粒体碎片化,从而缓解阿霉素诱导的心肌细胞衰老[121]。相似地,hiPSC-MSCs外泌体也能通过miR-202-5p介导的TRAF3结合蛋白2(TRAF3 interacting protein 2, TRAF3IP2)/c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)信号轴、抑制细胞焦亡,从而对MI发挥保护作用[122]。本团队研究发现,hiPSC-MSCs可显著降低自发性高血压大鼠的血压及其终末靶器官的炎症[116]。进一步解析机制,发现hiPSC-MSCs通过激活脾神经,促进脾脏胆碱乙酰转移酶阳性(ChAT+)细胞释放乙酰胆碱,从而发挥降压作用[116]。该研究为高血压患者提供了潜在的细胞治疗新策略。

3　心脏类器官

心脏类器官（cardiac organoids，COs）是具有三维自组织结构、多细胞成分且能自发搏动的体外模型，能够模拟心脏的生理功能[123]。COs为心脏发育、疾病研究和药物研发提供强大的工具。COs常见的构建方法有两种：一种方式是将hiPSC诱导为拟胚体，随后进一步分化为心脏中的多种细胞类型；另一种方式则是将预先分化的心脏不同细胞类型进行体外组装。近些年，构建包含多细胞成分的COs研究取得一系列突破性进展。2020年，Giacomelli等[124]通过将预先分化的hiPSC-CMs、hiPSC-ECs和hiPSC-CFs进行组装，成功构建无支架的三维COs，该模型可用于致心律失常性心肌病和其它类型心脏病的研究。2023年，Schmidt等[125]建立人类多腔室COs，成功模拟包括左、右心室、心房、流出道及房室管在内的所有主要胚胎心腔的发育过程，可用于评估基因突变、致畸因子及药物对心脏发育的潜在不良影响。2024年，Song等[126]利用hiPSC生成包含心肌细胞、内皮细胞和心脏成纤维细胞的自组织COs，并用该模型对MI和心脏纤维化进行建模。2025年，Zhang等[127]开发了一种心室COs（包含hiPSC-CMs、hiPSC-ECs和hiPSC-CFs），并通过缺氧/复氧诱导来模拟心肌缺血/再灌注损伤。最近，Abilez等[128]通过筛选34种不同的分化条件，确定最优的血管诱导因子的组合，进而成功构建具有空间组织和分支血管网络的心脏血管化类器官，该类器官包含心肌、血管、心内膜、心外膜和神经元细胞类型，可用于心脏发育的研究。以上研究表明，hiPSC来源的COs能够高度模拟人类心脏的生理与病理表型，也为药物研发提供了一个更为安全和高效的体外实验平台。然而，这些模型仍存在一定的缺陷与不足。例如，目前的COs在成熟度方面尚不理想，多数仅能模拟早期心脏的生理特征，具体表现为细胞类型不够全面、缺乏有效的血液灌注系统和神经调控机制，难以完整再现成人心脏的复杂生理状态，亟待进一步探索和完善。

4　总结与展望

综上所述，hiPSC来源的不同类型心血管细胞和COs在心血管疾病机制研究、药物筛选及治疗中已经取得了重要进展。随着全球心血管疾病负担的增加，hiPSC在心血管疾病中应用必将进一步加深。然而，hiPSC来源心血管细胞与COs在结构和功能方面仍表现出一定的局限性。当前，该领域仍面临以下核心挑战：①hiPSC来源心血管细胞成熟度不足，类器官缺乏完整血管与神经支配，影响功能模拟准确性；②hiPSC来源心血管细胞的诱导分化过程与规模化生产缺乏统一标准，批次间质量差异较大；③移植后细胞的存活率低及与宿主组织的功能性整合困难，制约了其临床转化进程。针对上述挑战，可以从以下方面推进：①优化培养方案或创新培养体系，提升细胞与类器官的成熟度和功能性；②建立标准化的质量控制与生产工艺，结合跨学科技术手段提高细胞均质性并降低制备成本；③利用新型生物材料与先进递送技术，增强移植后细胞的定植效率与治疗效果。未来，借助多学科交叉融合与技术创新，hiPSC技术将突破现有瓶颈，在心血管疾病的精准预防与治疗中发挥更加重要的作用，为疾病机制解析和个性化医疗策略的开发提供有力的支撑。

附表
Appendix table

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