

干细胞在心房颤动基础研究与干预治疗中的研究进展

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摘 要: 心房颤动(AF)是临床上最常见的心律失常之一,然而其机制未完全阐明,治疗上存在复发率高、副作用大以及治疗效果不稳定等问题。近年来,干细胞因其多向分化潜能及间充质干细胞(MSC)分泌外泌体的功能,在心血管疾病研究与治疗领域具有极大的应用前景。本文综述了干细胞应用于AF机制研究及干预治疗的进展,涉及利用干细胞构建体外AF模型、基于此基础上开展药物筛选以及结合重编程或基因编辑技术开展AF遗传机制的探索,并回顾了MSC通过分泌外泌体改善心肌纤维化的作用,为未来AF的治疗提供新的方向。

关键词: 干细胞; 心房颤动; 诱导多能干细胞; 治疗; 疾病模型

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Research progress of stem cells in basic research and intervention therapy of atrial fibrillation

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Abstract: Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. However, its mechanism has not been fully elucidated, and there are many problems in the treatment of AF, such as high recurrence rate, large side effects and unstable therapeutic effect. In recent years, stem cells have shown great application prospects in the field of cardiovascular disease research and treatment because of their multi-directional differentiation potential and the function of mesenchymal stem cells (MSCs) to secrete exosomes. This article analyzes recent advancements of stem cells in the mechanism and intervention of AF, including the use of stem cells to construct an in vitro AF models, drug screening based on this models, and elucidates molecular mechanisms of AF combined with reprogramming or gene editing technologies. Furthermore, we explore the effect of mesenchymal stem cells on improving myocardial fibrosis by secreting exosomes. It provides a new direction for the treatment of AF in the future.

Key words: stem cells; atrial fibrillation; induced pluripotent stem cells; therapy; disease model

心房颤动(AF)是最常见的心律失常类型^[1]。近十年来,值得大家注意的是随着人口老龄化以及慢性基础病如冠心病、甲状腺功能亢进等的增加,AF的发病率呈现逐年上升的趋势^[2]。从全球健康数据交换数据库提取的AF相关流行病学资料提示全球AF的发病率不断上升^[2]。据估算,中国≥40岁人群的AF患病率约为2.3%,患者人数已超过1 000万^[3-4]。心房的无序颤动会导致心脏内血流速度变

慢,血液在左心房内滞留容易导致血栓形成从而引起脑血管栓塞、心力衰竭等严重并发症^[1,5]。目前主要通过抗凝、控制心率以及射频消融等控制AF的发作以及减少并发症的发生,然而这些方法存在高复发率、副作用大以及治疗效果不稳定等问题^[6]。例如,抗心律失常药物胺碘酮的长期应用会提高副作用如QT间期延长、室性心动过速、周围神经病变等的发生概率^[7]。而导管消融手术虽然可以终止AF的

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发生,但这种手术并不适用于所有患者,而且存在一定的风险和并发症^[8-10]。因此,探索更为安全、有效且能够解决个体差异问题成为AF研究的关键。

随着再生医学的发展,干细胞治疗逐渐吸引人们的注意力。干细胞的主要类型包括胚胎干细胞(ESC)、诱导多能干细胞(iPSC)以及成体干细胞^[11-12]。由于干细胞或其衍生物可以刺激身体自身的愈合并修复受损、患病组织的特性,广泛应用于许多领域及疾病研究,包括心血管系统、血液系统及自身免疫性疾病等^[12-14]。其中,间充质干细胞(MSC)依赖外泌体可以减少心肌细胞凋亡及心房纤维化,进而改善AF^[15];不仅如此,患者自身的体细胞重编程获得的iPSC可以分化为心肌细胞并用于疾病建模、药物筛选和个性化治疗^[16-18]。本文围绕干细胞特别是MSC以及iPSC在AF研究中的应用展开综述,探讨其在疾病模型构建、细胞分子机制研究、药物筛选和个性化治疗中的前景。

1 干细胞作为AF机制研究的工具

1.1 干细胞模型与AF病理生理学机制

AF发生的病理生理学机制主要包括心房电重构、结构重构、自主神经系统功能紊乱和炎症反应等^[19-21]。AF发生的电重构主要包括异位电活动和折返,表现为心房心肌细胞离子通道功能的改变。异位电活动通常起源于肺静脉,与早期和延迟后去极化相关;而折返主要是由于心房扩张和纤维化导致的传导速度改变和不应期变化^[21-22]。目前,AF的许多机制研究主要基于动物模型的实验,而由于物种差异及患者AF的复杂性,动物模型在AF诱导时的持续时间与动作电位特征方面差异很大^[23]。因此,动物模型的局限性也是显而易见的,这些显然限制了治疗干预从动物到人类的可转移性^[16,23]。而干细胞因其多向分化潜能,在AF模型研究中具有极大的潜能与应用价值。

1.1.1 ESC与AF模型 ESC具备在体外无限制增殖和向多种细胞类型分化的能力,这为再生医学与疾病模型开发提供了巨大的应用价值^[24]。这些细胞大部分是从早期胚胎的囊胚阶段提取,既在基础科学研究中占有一席之地,同时也在药物开发和疾病治疗的前期研究中发挥着重要作用^[25]。研究发现,人ESC及iPSC在激活素A和BMP4下可以诱导中胚层形成;然后,针对心脏特异性进行Wnt信号抑制;最后,添加视黄酸(RA)驱动向心房心肌细胞(CMs)分化^[17,26]。这些诱导分化的心房心肌细胞优

先表达心房特异性基因如NPPA(利钠肽A型)、KCNJ3(钾向内整流通道)和GJA5(连接蛋白40)等,并且与心室样CMs相比,动作电位(AP)持续时间更短^[26]。Laksman等^[26]发现在人ESC诱导融合的心房样CMs片中,AP传播均匀,并且可以模拟快速折返等AF特征性电活动,该模型对药物氟卡尼和多非利特的药理学反应与AF治疗效应一致,验证了其病理模拟能力。其建立的AF模型兼具电生理模拟和药物响应双重验证,为AF的机制研究开辟了新的技术路径。

1.1.2 iPSC与AF模型 iPSC是一种类似ESC的干细胞,因其来源广泛以及克服有关在研究以及临床中使用胚胎的各种伦理问题的优势,有可能取代ESC在疾病模型的应用^[27]。Ahmad等^[28]发现在传统方法的基础上使用Gremlin2(一种信号分子,随着心脏祖细胞的迁移,参与心脏发育和心房特异性分化)和视黄酸治疗的组合精准调控人诱导多能干细胞(hiPSC)向心房心肌细胞的分化,这种方法诱导分化的心房心肌细胞在形态学、电生理特性以及肾上腺能信号刺激上与成人心房心肌细胞特征相似,并且心房心肌细胞纯度更高。而Thorpe等^[29]通过在hiPSC向心房心肌细胞分化过程中优化添加视黄酸时间,产生的心房心肌细胞具有动作时程更短的电生理特性并可以响应突发起搏形成转子式心律失常,复现AF电活动特征。另外,有研究发现hiPSC诱导的心房心肌细胞与成纤维细胞以及胶原蛋白的混合物可以构建工程化心房(aEHM)模型,短时(24 h)快速的起搏可诱导与AF患者病理特征一致的AP时程缩短、L型钙电流减少及乙酰胆碱激活的钾电流反应减弱;在引入光敏感通道蛋白f-Chrimson实现连续7 d高频光学刺激后,观察到静息膜电位(RMP)超极化,表明电重塑的特定标志随时间依赖性发展^[16]。使用心房心肌细胞和aEHM替代传统动物模型,可以克服物种间电生理差异,更贴近人类病理机制,为靶向治疗开发提供了更精准、可扩展的实验体系,有望加速抗心律失常药物的临床转化。

1.2 干细胞与AF遗传学机制

AF的发生是由遗传因素和环境暴露的共同作用。近年,全基因组关联研究(GWAS)和遗传学研究寻找到了多个与AF相关的基因位点,涉及离子通道功能、细胞间连接和信号转导等^[30]。例如编码钠通道(如SCN5A)和钾通道(如KCNQ1、KCNH2)的基因突变可能导致心肌细胞的电活动异常^[30-31],

进而导致AF的发生。多项研究表明,基于hiPSC的疾病模型为研究AF的遗传学机制提供了新的平台^[18,32]。通过提取AF患者以及携带家族性变异基因AF患者外周血单核细胞或真皮成纤维细胞,可将其重编程为iPSC并诱导分化为心房心肌细胞,构建具有遗传背景特异性的病理模型^[18,33]。

Benzoni等^[18]发现,对患有家族性AF的3个兄妹提取真皮成纤维细胞并将其重编程为iPSC及诱导分化为心房心肌细胞后,获得的心肌细胞具有更高的跳动率、 I_f 和 I_{Ca-L} 的电流增加、显著延长的动作电位并在压力条件下振幅更大以及在异位搏动下的延迟后去极化更多,证明了hiPSC可以用作具有复杂遗传背景的人类心脏病理学的细胞模型^[18]。KCNA5基因[编码携带心房特异性超快速延迟整流器 K^+ 电流(I_{Kur})的 $K_v1.5$ 离子通道的 α 亚基]的功能缺失突变已被证明会导致遗传性AF, Marczenke等^[34]通过CRISPR/Cas9技术成功在hiPSC中实现KCNA5基因敲除,探索 $K_v1.5$ 通道在心房心肌细胞中的作用并证明了使用工程hiPSC进行心脏亚型特异性疾病建模是可行的。在对TTN截短变异(TTNtv)的研究中,Huang等^[35]对存在杂合TTNtv的早发性孤发性AF的患者中提取外周血单核细胞重编程为iPSC,并使用CRISPR/Cas9介导的同源定向修复将基因型WT/TTNtv校正为野生型WT/WT,产生一对同基因iPSC作为对照,同时生成aEHM,用以研究TTNtv对心房心肌细胞电生理学、肌节结构、收缩力以及细胞外基质相关基因表达的影响。此外,左心房特异性表达基因PITX2的降低与AF消融术后的复发有关。Reyat等^[36]使用PITX2缺陷的hiPSC定向分化为左心房心肌细胞,用于研究PITX2基因表达缺陷对心房线粒体功能障碍和代谢变化的影响。因此,干细胞特别是iPSC诱导的疾病模型为研究AF遗传原因提供了新的平台。

2 基于干细胞的AF治疗策略

AF的结构重构主要表现为心房成纤维细胞过度增殖及细胞外基质异常沉积,这是引起电传导紊乱及折返性心律失常的关键因素^[20,37]。AF的发生发展受炎症和氧化应激的影响,譬如M1型巨噬细胞的激活可以释放TNF- α 、IL-6等促炎因子促进AF发生;氧化应激可以损伤心房心肌细胞及促进其纤维化^[38]。干细胞在AF中的治疗研究与上述病理生理机制密切相关,MSC可以减少AF模型中的细胞凋亡、抑制纤维化以及炎症反应,达到改善结构重

构的目的。而基于干细胞模型提供的药物筛选为在靶向治疗的研究开发提供新方向。

2.1 MSC在AF治疗的多靶点干预策略

MSC是具有自我更新、免疫调节、抗炎等特性的成体干细胞,主要来源于脂肪组织(脂肪)^[39]、骨髓^[40]、脐带组织^[41]等。MSC的治疗潜力不仅源于直接分化为血管内皮细胞或心肌细胞的能力,更依赖于分泌外泌体(内体膜分泌的50~150 nm大小囊泡,主要包含蛋白质、mRNA和miRNA分子,是细胞间通讯的调节因子)介导的复杂调控机制^[42]。

Ramos等^[43]研究发现,MSC移植可以改善慢性阻塞性肺疾病小鼠的心房纤维化,预防心房重塑,这可能揭示了MSC在预防心房重塑,减少AF的发生和进展的潜能。外泌体作为载体被广泛应用,在体外将功能性microRNA(miRNA)递送到受体细胞^[44],而MSC亦是通过外泌体靶向干预AF的核心病理进程,如图1所示,骨髓来源的MSC外泌体通过分泌miR-148a降低HL-1(永生化的小鼠心房心肌细胞系)细胞中富含半胱氨酸的酸性分泌蛋白(SMOC2)的表达,减少心肌细胞凋亡^[42]。在大鼠开胸手术时将单剂量的细胞外囊泡直接输送到心房可能通过抑制炎症及成纤维细胞增殖达到减少心房纤维化的目的^[45]。与此同时,脂肪MSC经miR-320 d模拟物修饰后,其衍生外泌体中miR-320表达升高并通过调节靶标信号转导和转录激活因子3(STAT3),可以减少AF心肌细胞凋亡^[46]。核因子- κ B相关因子2(Nrf2)是细胞中必需的转录因子也是氧化稳态的关键调节因子,Xu等^[15]研究表明Nrf2过表达慢病毒转导的BMSC衍生的外泌体可以使AF大鼠的AF持续时间缩短,并通过减少炎症因子TNF- α 、IL-1 β 及纤维化蛋白 α -SMA的表达减少炎症、凋亡以及心肌纤维化。上述证据共同表明,MSC外泌体通过多靶点调控凋亡、炎症及纤维化信号,可为AF提供更精准的治疗策略。

2.2 基于干细胞模型的药物筛选

基于干细胞诱导的模型因其具有模拟人体心肌细胞的电生理特性,可以验证药物在AF的治疗效果。hESC诱导的心房CMs在左心房特异性钾离子通道阻滞剂的作用下,出现AP延长,而对于干细胞诱导的心室心肌细胞并没有影响,证明了hESC诱导的心房心肌细胞模型可用于评估新型抗心律失常药物的心房选择性^[25,47]。例如,利用干细胞诱导的AF模型,二甲双胍和达格列净通过对心房心肌细胞AF相关基因表达或电生理的改善验证其抗心律失常

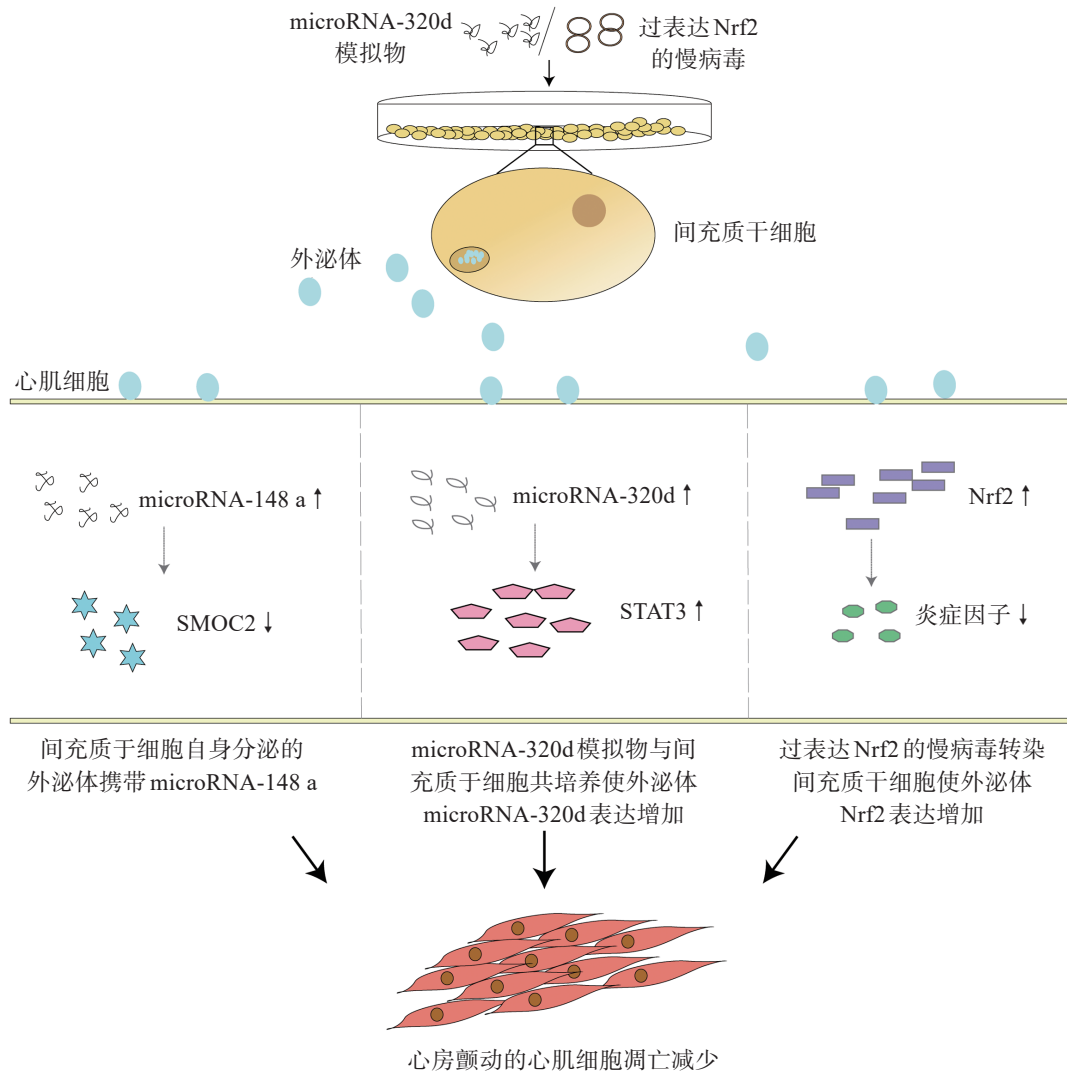


图1 间充质干细胞在治疗心房颤动的机制图

常作用^[48-49];另外,秋水仙碱改善炎症介导的心律失常、钙信号异常和细胞死亡^[50],也展示了干细胞模型在药物筛选中的独特价值:从分子机制解析到临床前疗效验证,为开发精准抗心律失常疗法提供了高效、可重复的研究平台。

3 干细胞在AF中的应用前景与局限性

3.1 应用前景

干细胞因其多向分化潜能AF研究中具有广阔前景,具体应用如图2所示,主要包括:(1)疾病模型构建:通过将ESC或者hiPSC诱导分化为心房心肌细胞以及在特定条件下构建aEHM,并予以适当频率及强度的电刺激构建AF模型,心肌细胞表现出与人AF相似的电生理特性,从而提供了与人心房电生理特性相似的AF模型^[16,26],有利于治疗干预研究向人的转移性。(2)药物筛选和个性化治疗:

iPSC衍生的心肌细胞可以用于药物筛选,为开发更有效的治疗药物提供新途径^[28,51]。另外,对于某些与基因突变相关的家族性或个体AF,通过提取患者自身细胞重编程为iPSC或者利用iPSC联合CRISPR/Cas9技术介导相关基因的缺失模拟遗传疾病^[18,34],有望针对个体患者的基因背景和疾病特征进行精准治疗的研究。(3)基于MSC外泌体的AF治疗:MSC作为外泌体的主要来源,通过自身分泌miRNA或工程化改造外泌体内容物,为AF提供精准治疗新途径^[46]。

3.2 局限性

干细胞在许多心血管疾病包括心肌梗死、心力衰竭以及心肌病中广泛研究^[52-54],但在治疗AF中的研究较少,仅局限于临床前研究阶段。虽然有文献报道1名84岁的慢性持续性AF患者,在予干细胞输注治疗心力衰竭过程中,意外发现20d后患者

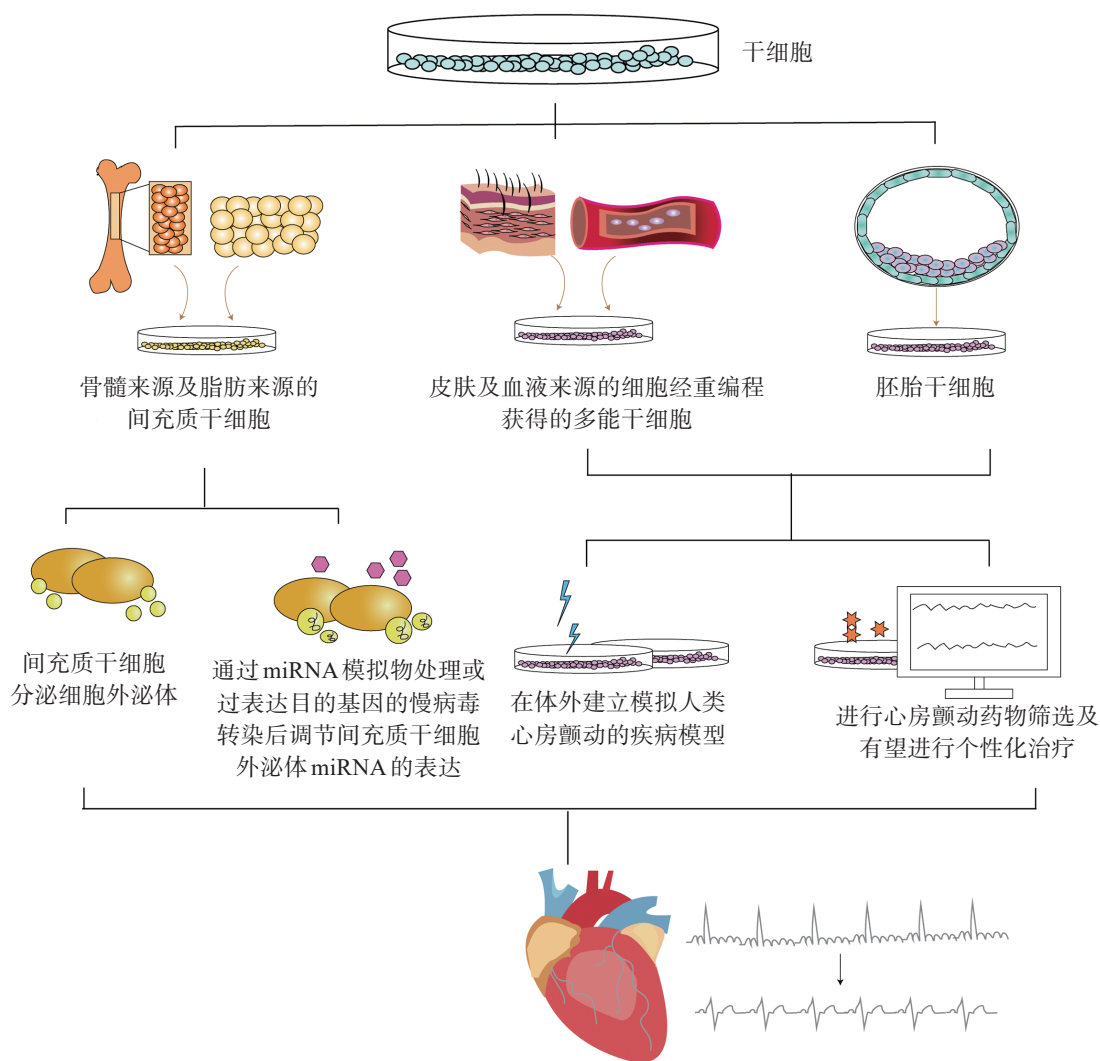


图2 干细胞应用于AF的研究进展图

恢复窦性心律,并在15个月后复查仍保持窦性心律^[55],但干细胞治疗因其机制复杂、技术瓶颈及安全性顾虑等原因在AF中缺乏相关的临床研究。另外,干细胞诱导分化的仅仅为心房心肌细胞,并非心房组织,可能存在以下问题:(1)不能模拟体内心房重构;(2)对药物、药效模拟与体内仍有区别。

4 小结及展望

本文主要回顾了干细胞技术在AF研究中的应用进展。多项基础研究表明,MSC通过分泌及调节细胞外泌体内的miRNA改善AF结构重塑^[46];经体细胞重编程获得的iPSC以及ESC可以诱导分化为心房心肌细胞并在相应频率的电刺激下在体外建立模拟人类AF的疾病模型,该模型可用于进行AF相关药物筛选^[26,49]。未来可依托患者体细胞重编程或结合CRISPR/Cas9基因编辑技术介导在iPSC实

现特定基因敲除,诱导分化及构建体外细胞甚至心房类器官模型,结合药物筛选,揭示药物在相应个体的药效及副作用,有望达到个性化治疗的目的。除此之外,基于AF病理分子机制,通过工程化改造MSC外泌体及提升外泌体的心肌归巢,有望实现精准靶向治疗。因此,利用干细胞技术以及相关的疾病模型研究有望推动治疗AF的进展。

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