·综　述·

线粒体离子通道在心血管疾病中的研究进展

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[摘　要]　线粒体功能障碍是心血管疾病发生发展的重要机制之一,随着对线粒体功能的深入研究,人们发现线粒体离子通道的功能对线粒体至关重要。本综述旨在总结与心血管疾病相关的线粒体离子通道,并分别阐述它们在不同的心血管疾病(如缺血再灌注损伤、心律失常、心力衰竭、糖尿病性心肌病和肺动脉高压)中发挥的病理生理学作用。近年来,线粒体靶向药物的研发成为医学发展中不可或缺的领域,因此本文总结了广泛使用、具有较高特异性以及能够调节心血管功能的线粒体离子通道激活剂或抑制剂,为心血管疾病的治疗和预防提供新思路。

[关键词]　线粒体;线粒体离子通道;心血管疾病

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Research progress on mitochondrial ion channels in cardiovascular disease

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[**Abstract**]　Mitochondrial dysfunction is one of the most important mechanisms in developing cardiovascular diseases. With the deep study of mitochondrial function, it has been found that the function of mitochondrial ion channels are crucial to mitochondria. This review aims to illustrate the mitochondrial ion channels associated with cardiovascular disease, and to elucidate their pathophysiological roles in different cardiovascular diseases, such as ischemia-reperfusion injury, arrhythmia, heart failure, diabetic cardiomyopathy, and pulmonary hypertension. In recent years, the research and development of mitochondria targeting drugs has become an indispensable field in medical pharmacology. Therefore, we summarized widely used mitochondrial ion channel activators or inhibitors with high specificity that can regulate cardiovascular function, providing new ideas for the treatment and prevention of cardiovascular diseases.

[**Key words**]　mitochondrial; mitochondrial ion channels; cardiovascular diseases

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线粒体是心肌细胞的能量代谢中枢,是维持正常心肌收缩力和心脏电活动所必需的细胞结构,因而心血管疾病的发生发展通常伴随线粒体功能障碍[1],而目前研究表明线粒体离子通道功能异常所致的线粒体和细胞内离子稳态失衡是线粒体功能障碍的重要机制之一[2]。目前,大量证据表明线粒体离子通道功能异常影响许多病理生理过程,如线粒体氧化磷酸化和三磷酸腺苷(adenosine triphosphate,ATP)生成的效率,线粒体结构和体积的维持,细胞内酶活性和信号转导的调节,以及细胞的增殖和凋亡等[3]。

线粒体由线粒体基质、线粒体内膜、膜间隙和线粒体外膜组成[4]。线粒体外膜的选择性较低,允许多种代谢产物和离子自由进出,而线粒体内膜具有较高的离子选择性,其通透性对调节ATP合成至关重要[2]。目前研究表明,心肌细胞线粒体对钙离子(Ca^{2+})、钾离子(K^{+})、钠离子(Na^{+})以及某些阴离子

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高效且精密的调节与线粒体离子通道的良好功能紧密相关[5-6],而这些离子在线粒体内外的水平异常与缺血再灌注损伤、心力衰竭、糖尿病心肌病、肺动脉高压和心律失常等心血管疾病的发生发展密切相关,调节离子通道的表达和功能将改善上述疾病的进展[3]。

因此,本文旨在介绍各线粒体离子通道在心血管系统中的主要功能,总结线粒体离子通道与各种心血管疾病发生发展的研究进展,为心血管疾病的防治提供新思路。

1 线粒体膜上的主要离子通道

1.1 钙离子转运通道

线粒体钙离子转运通道是调控线粒体钙稳态的主要结构,对调节心肌细胞的能量供应、信号转导以及细胞凋亡至关重要[7],从而直接影响心脏电活动和心脏收缩功能。线粒体钙摄取对线粒体功能起双向调节作用,一方面,线粒体内游离钙离子浓度($[Ca^{2+}]_m$)升高增加线粒体呼吸链复合体的活性及其氧化磷酸化生成ATP的能力,此外,还能有效提高三羧酸循环中关键酶的活性[8-9];另一方面,$[Ca^{2+}]_m$过度升高将诱导线粒体通透性转换孔(mitochondrial permeablity transition pore,mPTP)开放,介导Ca^{2+}和其他<1.5 kDa的溶质迅速从线粒体中释放,导致线粒体破裂、氧化磷酸化解耦联和促凋亡因子释放,促进细胞死亡和凋亡[10]。

线粒体钙内流主要由电压依赖性阴离子选择性通道(voltage dependent anion channel,VDAC)、线粒体钙离子单向转运蛋白复合物(mitochondrial calcium uniporter complex,MCUC)和线粒体兰尼碱受体(mitochondrial ryanodine receptor,mRYR)转运蛋白介导,而线粒体钙外流由线粒体Ca^{2+}/H^+逆向转运体(leucine zipper-EF-hand containing transmembrane protein 1,Letm1)、线粒体钠钙交换蛋白(mitochondrial Na^+/Ca^{2+} exchanger,mNCLX)和mPTP介导[11]。除外非选择性的VDAC定位于线粒体外膜,其余离子通道均位于线粒体内膜上,其中MCUC是调控线粒体钙离子稳态的最重要通道,主要由线粒体钙离子单向转运蛋白(mitochondrial calcium uniporter,MCU)亚单位、线粒体钙摄取蛋白1和2(mitochondrial calcium uptake,MICU1/2)、MCU显性负β亚单位(MCUb)、MCU调节器1(MCUR1)和溶质载体25A23(SLC25A23)组成。生理情况下,线粒体钙外流主要由Letm1和mNCLX介导[12-13],而在心肌细胞缺血再灌注等病理情况下,主要由mPTP非选择性开放大量释放Ca^{2+},进而导致线粒体膜电位降低、ATP合成和呼吸链功能抑制、线粒体基质肿胀和外膜破裂、以及促凋亡蛋白释放[14]。

1.2 钾离子转运通道

线粒体K^+稳态的重要作用包括调节线粒体氧化呼吸链效率、维持线粒体膜电位、调节活性氧(reactive oxygen species,ROS)生成以及维持线粒体体积等[15]。

线粒体内流钾通道均位于线粒体内膜,包括线粒体ATP敏感性K^+通道($mitoK_{ATP}$)、钙激活K^+通道($mitoK_{Ca}$)、电压门控K^+通道($mitoK_V$),串联孔结构域酸敏K^+通道3型(mitoTASK-3)和SLO2通道(mitoSLO2),而钾外流主要由K^+/H^+逆向转运蛋白(K^+/H^+ exchanger,KHE)介导[16-18]。目前,研究$mitoK_{ATP}$通道和$mitoK_{Ca}$通道在心脏中的作用相对较多[2],缺血预处理和缺血后处理是二者发挥心脏保护作用的关键机制[19-20]。其中$mitoK_{Ca}$通道根据激活通道的电导度不同被分为$mitoBK_{Ca}$通道、$mitoIK_{Ca}$通道和$mitoSK_{Ca}$通道,目前仅$mitoBK_{Ca}$通道和$mitoSK_{Ca}$通道在心肌线粒体中有报道[21],并且在成年心肌细胞中,BK_{Ca}通道仅存在于线粒体的内膜中[2,22]。线粒体K^+通道的状态是调节心功能、心率、血管张力和血压的关键因素之一[23-26]。

1.3 钠离子转运通道

Na^+是心肌细胞中除外Ca^{2+}的另一个重要的第二信使,主要通过调节线粒体内膜的流动性来调节线粒体氧化磷酸化功能和活性氧的产生[27]。正常情况下,线粒体钠离子浓度($[Na^+]_m$)通常比细胞内($[Na^+]_i$)低,该浓度差有利于促进线粒体钙外流,维持线粒体内外钙稳态和质子梯度,同时调节心肌细胞兴奋性、收缩性、自律性和能量代谢[28]。

线粒体钠内流和外流分别由mNCLX和线粒体钠氢泵(Na^+-H^+ exchange,NHE)介导[2]。值得注意的是,正常情况下mNCLX是Na^+内流和Ca^{2+}外流的主要通道,由mNCLX形成的Na^+梯度和线粒体膜电位共同构成促进线粒体Ca^{2+}外流的驱动力[7,29],但是在心肌细胞缺血时mNCLX介导钙内流,在再灌注时恢复其正常功能[30]。与MCUC在心肌线粒体和肌浆网连接处高度表达不同的是,mNCLX主要存在于非肌浆网相关的其他线粒体结构域中,这有助于离子的高效转运和减少线粒体钙超载[31]。心肌细胞的肌膜下线粒体具有较高水平的mNCLX[32],抑制mNCLX还将抑制内质网摄取细胞中的Ca^{2+}[33]。

1.4　阴离子转运通道和其他离子转运通道

线粒体阴离子通道对调节线粒体内外Cl^-、Br^-、I^-、SCN^-、NO_3^-、PO_4^-、HCO_3^-和SO_4^{2-}等阴离子稳态至关重要[2]，其广泛参与调节线粒体基质pH、线粒体体积以及细胞死亡等病理生理学反应，在缺血再灌注损伤和心律失常等疾病中发挥心脏保护作用[34-35]。

目前已发现位于心肌细胞线粒体中的阴离子通道主要包括VDAC、内膜负离子通道（inner membrane anion channels，IMAC）和细胞内氯离子通道（chloride intracellular channel，CLIC）[2,35]，此外还发现一种Ca^{2+}激活的氯离子（Cl^-）通道ANO1在肺血管内皮线粒体中表达[36]。VDAC和IMAC分别是离子和代谢物（ATP、超氧化物和细胞色素C等）通过线粒体外膜和内膜的主要通道，而CLIC是较为专一的Cl^-转运通道，具有调节内皮细胞血管生成[37]、细胞周期[38]和细胞分化[39]等重要作用，其主要分为6个亚型，其中心肌细胞中CLIC4和CLIC5分别定位于线粒体外膜和内膜[40]，已知Cl^-电流与心肌细胞的舒张电位、动作电位持续时间和膜电导有关[40-41]。

目前研究表明，线粒体还可转运其他离子，尤其是金属离子，如镁离子（Mg^{2+}）[42]、锌离子（Zn^{2+}）[43]、铝离子（Al^{3+}）[44]、锰离子（Mn^{3+}）[45]、铁离子（Fe^{3+}/Fe^{2+}）[46]和铜离子（Cu^{2+}）[47]等，目前在心肌细胞线粒体中仅有Mg^{2+}和Zn^{2+}转运通道的研究较为深入。线粒体Mg^{2+}对调节线粒体氧化呼吸链功能[48]、心肌细胞能量代谢[49]、细胞质和基质之间的ADP/ATP的交换[50]和MCU的活性[51]等方面至关重要。线粒体Mg^{2+}内流主要由线粒体内膜上的线粒体RNA剪接蛋白2（mitochondrial RNA splicing 2，MRS2）和Lpe10介导[52-53]，外流由SLC41A3和线粒体载体蛋白Mme1介导[54-55]。特别的是，膜电位较低时MRS2可介导Mg^{2+}外流[56]。而线粒体Zn^{2+}稳态与心肌细胞氧化应激状态的关系更为紧密，Zn^{2+}流入和流出线粒体主要由锌转运蛋白（Zrt/Irt-like protein，ZIP）和锌转运体（Zinc transporters，ZnT）这两类蛋白介导[43]，但是在急性缺血期Zn^{2+}可通过MCU进入线粒体[57]。

2　线粒体离子通道与心血管疾病

2.1　心力衰竭

心力衰竭是指由心脏收缩和/或舒张功能障碍所致的心脏射血功能下降[58]，常常伴随严重线粒体功能障碍[59]。目前研究表明线粒体离子通道功能异常是改变心衰患者线粒体功能的重要原因，特异性调节这些通道的活性具有明显的心脏保护作用[60]。

目前认为Ca^{2+}和Na^+转运与心功能的关系最为紧密，线粒体钙超载被认为是心力衰竭的关键病理生理机制[61-62]，其中VDCA、MCUC、mPTP和mNCLX对心功能的影响最大。VDAC1在心肌梗塞和心功能障碍患者的心肌组织中显著过表达，而抑制VDAC1表达将减少心房肌的过度纤维化[63]，这有助于改善心功能。VDAC2与心肌细胞内和线粒体钙信号传导有关，心肌细胞VDAC2表达缺失将导致兴奋-收缩耦合严重受损，与心肌病和心力衰竭的发生发展都密切相关[6]。MCU基因敲除小鼠的线粒体钙摄取功能明显受损，将显著降低应激状态下的心功能（如心率适应性加速受损）[64-67]。当心力衰竭发生后，患者的心脏负荷将不同程度地增加，肌浆网迅速释放Ca^{2+}，$[Ca^{2+}]_i$上升促进钙离子向线粒体中转移[68]，但线粒体钙超载将直接诱导mPTP开放[69]，这将进一步加重线粒体功能障碍，最终导致心肌细胞死亡[70]。

当心力衰竭发生后，心肌细胞$[Na^+]_i$升高，这增加mNCLX活性并促进Na^+向线粒体内流，导致线粒体内膜质子梯度和$[Ca^{2+}]_m$下降，进而导致ATP水平下降[71]。mNCLX对心功能具有保护作用，使用他莫昔芬诱导成年小鼠心肌细胞mNCLX的编码基因Slc8b1表达下降将促进心肌重塑、心力衰竭和猝死的发生，而mNCLX过表达可有效减少心肌缺血引起的心肌细胞坏死和心力衰竭[7,28]，这可能归因于心力衰竭和心肌细胞缺氧后，线粒体钙摄取主要由mNCLX而不是MCU介导，而提升衰竭心脏的心肌细胞线粒体钙摄取的能力有助于恢复能量供需平衡[30,72]。此外，使用mNCLX抑制剂CGP-37157将改善心力衰竭患者的心肌细胞的代谢失衡（包括Krebs循环、碳水化合物、脂肪酸和氨基酸代谢），并减少$[Ca^{2+}]_m$和ATP水平下降这些不良现象[72-73]。不仅如此，CGP-37157还可延缓豚鼠模型中心力衰竭的进程和心力衰竭相关心脏性猝死的发生[74]。因而，抑制心肌细胞钠超载或抑制mNCLX可能是改善心力衰竭代谢失调的新方法。

此外，Tuncay等[75]的研究表明，高血糖诱导心肌细胞线粒体中ZIP7表达降低和ZnT7表达升高，其通过影响高血糖心肌细胞的肌质网-线粒体偶联，而在心功能不全的进展中发挥重要作用。这可能与线粒体Zn^{2+}转运具有调节心肌细胞Zn^{2+}水平、氧化应激状态、线粒体膜电位、钙信号转导、线粒体形态以及基因表达等作用密切相关[43]。

2.2　糖尿病性心肌病

糖尿病性心肌病是一种由糖代谢紊乱引起的，

除外冠心病、先天性心脏瓣膜疾病和高血压等原发性心血管疾病引起的心肌病[76],表现为心肌肥厚、舒张功能不全和不同程度的收缩功能降低,最终进展为心力衰竭[77]。尽管糖尿病性心肌病的发病机制尚未完全阐明,但胰岛素缺乏早期心肌细胞即可出现线粒体功能障碍,线粒体离子通道表达和功能异常与糖尿病性心肌病的发生发展密切相关[78-80]。

目前研究表明,线粒体钙处理异常促进糖尿病心肌病患者心功能下降和心力衰竭[81]。糖尿病心肌病的发生常常与心肌细胞代谢变化有关,糖尿病大鼠心肌细胞线粒体MCU表达下降及钙摄取减少所致的能量代谢紊乱可能是促进糖尿病心肌病进展的重要机制。主要表现为葡萄糖利用率明显降低,脂肪酸氧化供能的比例上升,而Diaz等[82]研究发现恢复MCU水平,提高$[Ca^{2+}]_m$水平可有效逆转糖尿病性心肌病相关的代谢改变,这可能成为糖尿病心肌病治疗的新靶点。类似的,Suarez等[83]发现在糖尿病小鼠心肌细胞中不仅MCU表达下降,其他MCUC亚单位(如MCUb和EMRE)的表达也发生改变,引起$[Ca^{2+}]_m$浓度、丙酮酸脱氢酶复合体活性和线粒体产能降低,进而导致心功能下降,而使用腺病毒恢复MCU水平后,糖尿病小鼠心肌细胞线粒体钙处理异常和由其产生的不良后果也得到改善。此外,糖尿病可下调心肌细胞中MICU1的表达,与糖尿病个体的心肌肥大、纤维化和心肌细胞凋亡相关[84]。值得注意的是,糖尿病患者的心肌线粒体对Ca^{2+}诱导的mPTP开放的敏感性增加[85],这可能会加重糖尿病患者心肌细胞凋亡,进一步增加糖尿病性心肌病的发病风险。

除外线粒体钙摄取异常,线粒体K^+通道异常可能也与糖尿病性心肌病的发生有关,如Fancher等[86]发现糖尿病小鼠心肌细胞心肌线粒体中mitoK$_{ATP}$的表达水平和功能下降,Lu等[87]发现2型糖尿病大鼠冠状动脉平滑肌细胞中BK_{Ca}通道开放率和开放时间下降,可能与BK_{Ca}通道β1亚基的表达降低有关,这为探索糖尿病性心肌病的发病机制提供了新方向。

2.3 缺血再灌注损伤

心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury,MIRI)是指心肌血液供应中断一段时间后再恢复血流灌注,导致心肌梗死面积增加和心脏收缩功能障碍,有时会发生严重的恶性心律失常,MIRI伴随着明显的线粒体结构和功能异常[88]。

线粒体钙超载诱导的mPTP开放导致的线粒体断裂和心肌细胞死亡是MIRI的最重要机制之一[89],mPTP抑制剂Cyclosporin A(CsA)是最早研究的线粒体药物之一,可有效减轻动物实验心肌缺血再灌注损伤。在Ⅱ期试验中,急性心肌梗死期间给予CsA可减少核磁共振评估的梗死面积[90],但随后的Ⅲ期试验显示CsA治疗无效[91]。此外,抑制线粒体钙摄取的离子通道(如MCU)也可一定程度减轻mPTP开放,从而减轻急性缺血再灌注损伤的程度,表现为心肌梗死面积和心功能下降程度较小[65],而心肌细胞MCUB基因特异性缺失小鼠的心肌梗死面积更大,并伴有更严重的病理性心脏重构,然而在过表达MCUB的小鼠模型中,Mcub在MIRI发生后的2~3 d内被特异性诱导上调,减少mPTP开放,随后心肌缺血介导的不良病理生理反应得到改善[92-93]。此外,VDAC1在心肌梗死患者的心肌组织中显著过表达[63],表明VDAC可能是缺血/再灌注损伤的重要调节位点。

线粒体K^+通道主要通过缺血预处理和缺血后处理作用抑制再灌注时的mPTP开放而发挥心脏保护作用[94-95]。选择性激活心脏mitoK$_{ATP}$通道将促进线粒体肿胀、线粒体膜轻度去极化和线粒体钙释放来减轻缺血再灌注损伤的程度,并有效提高研究对象的存活率,而抑制该通道将削弱这些保护作用[96-98]。MitoK$_{Ca}$通道的心脏保护作用与mitoK$_{ATP}$通道类似[99-100],其中SK_{Ca}通道往往在心肌缺血时被激活,而BK_{Ca}通道主要在再灌注期间打开[101]。MitoK$_{Ca}$通道在MIRI发生后主要通过缺血预处理[102]、减少Ca^{2+}内流和钙超载[99]、改变线粒体动力学和线粒体体积[103-104]、减少ROS大量生成[22,105-106],来发挥心脏保护功能[107]。在心肌缺血前给予SK_{Ca}通道激动剂后,心肌细胞内O^{2-}和$[Ca^{2+}]_m$水平较对照组下降,NADH和FADH下降程度减轻,以及梗死面积明显减小[108],而抑制该通道后心肌细胞死亡增加[109]。在心脏缺血再灌注后给予MitoK$_{Ca}$通道的激动剂和抑制剂,分别发现了心脏保护作用和不良反应[110]。心肌细胞线粒体$K_{V7.4}$通道也发挥重要的心脏保护作用,是另一个治疗缺血再灌注损伤的潜在靶点[111]。

此外,一种细胞内Cl^-通道阻滞剂IAA-94通过降低心脏线粒体的钙潴留能力而加重心肌梗死,并可去除由缺血预处理和CsA的有利作用,因而认为IAA-94敏感的Cl^-通道在在缺血再灌注损伤中发挥的心脏保护作用[34]。

2.4 心律失常

心律失常是指心脏节律或节率异常,主要机制包括起搏细胞自律性增强或抑制、触发和折返,严

重的心律失常将导致心源性猝死[112]。线粒体功能障碍被认为是心律失常的重要原因[113]，其中线粒体离子稳态对调节心脏电生理至关重要[114]。

线粒体中过量的ROS主要通过IMAC外流，并触发线粒体内膜电位和心肌细胞动作电位震荡[115]，而Aon等[116]研究发现这种震荡可能导致缺血再灌注损伤期间的恶性心律失常。Akar等[117]发现阻断IMAC通道可减轻动作电位缩短和改善心肌细胞兴奋性，从而防止再灌注性心律失常的发生，特别是在缺血再灌注发生前阻断该通道将有效减少室颤的发生。Brown等[118]的研究也得到了类似的结论。

心房颤动是最常见的快速性心律失常之一，Wiersma等[119]发现心房颤动实验模型系统中快速起搏的HL-1心房肌细胞$[Ca^{2+}]_m$的调节受损以及线粒体功能下降。MCU对快反应细胞的心率适应性增加至关重要，MCU基因敲除小鼠在应激状态下心率增加受损，但不影响其静息心率[120]，侧面反映抑制MCU可以减少病理性心动过速。在应用MCU特异性抑制剂Ru360后，心肌缺血后心律失常的发生率下降，与减少mPTP的开放有关[121]。不仅如此，抑制MCU的表达可显著减轻继发于房颤的心房重构[119]，这可能改善房颤患者的不良预后。此外，mNCLX通道也可调节HL-1心房肌细胞的自律性，下调心肌细胞mNCLX的表达将显著延长动作电位和Ca^{2+}浓度瞬变的速度[122]。

现有研究表明K_{Ca}通道的表达和功能影响心脏节律和心率，其中SK_{Ca}通道对心房肌细胞动作电位复极有重要作用，敲除SK_{Ca}基因易于诱发房性心律失常，激活该基因将降低心房颤动和室性心律失常的发生率[123]，而慢性房颤患者心房肌细胞的SK_{Ca}通道表达水平明显降低[124-125]，但尚不能确定是心肌细胞膜还是线粒体内膜中SK_{Ca}通道起决定性作用。Imlach等[126]在小鼠中的研究发现，心脏中的BK_{Ca}通道直接参与心率调节，而抑制BK_{Ca}通道后心率显著降低。Patel等[127]得出了类似的结论。此外，遗传学研究推测BK_{Ca}通道极可能与家族性房颤相关，该疾病的遗传位点位于10q22-q24，而编码BK_{Ca}通道的KCNMA1基因位于10q23[128]。

2.5　肺动脉高压

肺动脉高压是一种严重的肺部疾病，表现为肺血管阻力持续增加、严重的肺动脉重构和右心功能障碍[129-130]，主要的病理特征是肺动脉平滑肌细胞、成纤维细胞和内皮细胞过度增殖和凋亡[129]，目前临床上多应用血管扩张剂治疗该疾病，但仅对4.6%的患者有效[131]，因而亟需探索治疗该疾病的新思路。

已知$mitoK_{ATP}$与肺动脉高压的发生密切相关，PKCβ-PICK1-$mitoK_{ATP}$通道-mitoROS信号轴可增强缺氧条件下的肺血管收缩[132]，激活$mitoK_{ATP}$通道将导致人肺平滑肌细胞增殖增加，同时减少凋亡[133]，二者均促进肺动脉高压的发生。重要的是，越来越多的研究支持肺动脉内皮细胞凋亡是肺动脉高压的初始步骤，这将刺激肺血管平滑肌细胞的增殖[134]，而尼可地尔通过激活$mitoK_{ATP}$通道和增加内皮型一氧化氮合酶（endothelial nitric oxide synthase，eNOS）表达抑制缺氧诱导的人肺动脉内皮细胞凋亡，从而有效抑制肺动脉高压发生的初始步骤[135]。此外，尼可地尔还可以通过激活$mitoK_{ATP}$通道抑制糖尿病大鼠血管平滑肌细胞增殖和迁移[136]，这为糖尿病合并肺动脉高压患者提供了新的治疗方向。值得注意的是，$mitoK_{ATP}$通道的抑制剂5-HD通过阻断线粒体膜去极化，增加K_V通道的表达，降低转化生长因子-β1或单核细胞趋化因子-1信号通路介导的肺动脉高压，有效阻止肺动脉高压的发展[137]。因而，$mitoK_{ATP}$通道的活性过高或过低都不利于肺动脉压力的控制。

近年来，Hong等[138]提出由MCU下调和MICU1上调所致的MCUC功能障碍可能是肺动脉高压的发病机制，$[Ca^{2+}]_m$降低抑制丙酮酸脱氢酶活性和葡萄糖氧化，同时$[Ca^{2+}]_i$增加促进肺动脉平滑肌细胞增殖、迁移和裂变，更为直接的证据是抑制正常肺动脉平滑肌细胞的MCU表达将诱导肺动脉高压的发生，而恢复MCU表达将逆转上述不良后果。值得注意的是，特发性肺动脉高压患者的肺血管内皮细胞线粒体中的ANO1表达增加，可能通过增加线粒体ROS、降低线粒体膜电位，增加p38磷酸化，并诱导细胞凋亡诱导因子的释放诱导肺动脉高压的发生[36]。

3　总结与展望

表1总结了特异性相对较高的线粒体离子通道的激活剂和抑制剂。尽管很多基础研究在探索线粒体靶向治疗，但目前尚无可用于临床的调节线粒体功能的药物，尤其是针对线粒体离子通道的药物。目前认为限制线粒体离子通道靶向制剂发展的障碍主要有以下几点：细胞膜和线粒体膜离子通道结构的相似性影响了药物的特异性；线粒体的膜电位较高（约-180 mV），且线粒体基质是带负电的碱性环境，更有利于亲脂性、带正电和弱酸性药物的积累，这限制了肽抑制剂的应用；目前对离子通

道的认知仍非常有限,许多线粒体离子通道的确切分子组成仍不确定,并且这些通道激活或抑制所触发的线粒体保护机制尚未明确;线粒体离子通道相关药物的合适给药剂量、安全性和药物代谢动力学仍需进一步研究。

线粒体离子通道的结构和功能对心血管疾病的影响至今未完全阐明,虽然目前对线粒体离子通道特异性较高的药物在基础实验中获得了较好结论,但均未能正式在临床上应用,最有可能的原因是线粒体离子通道的表达和功能具有组织器官特异性,并且各通道间可能存在相互作用网络。总之,靶向于心肌细胞的线粒体离子通道来防治心血管疾病是一个极具前

表1 各线粒体离子通道相关的心血管疾病及其激活剂和抑制剂

Table 1 Cardiovascular diseases related to mitochondrial ion channels and their activators and inhibitors

线粒体离子通道	疾病	激活剂	抑制剂
VDAC1	心力衰竭		VBIT-4[63]
	缺血再灌注损伤		
VDAC2	心力衰竭	Efsevin[6]	
MCUC	心力衰竭		Ru360[121, 139]
	心力衰竭		Ru265[140]
	缺血再灌注损伤		DS16570511[141]
	心律失常		Mitoxantrone[142]
	肺动脉高压		
MICU1	心力衰竭	MCU-i4、MCU-i11[143]	
Ryanodine receptor		Imperatoxin A[144]	Ruthenium red、Ryanodine
mPTP	心力衰竭		Cyclosporin A[90, 91, 145-148]
	缺血再灌注损伤		PKF220-384、NIM811
	心律失常		Debio 025[94, 149]
mNCLX	心力衰竭		CGP-37157(CGP)[72-74]
	心律失常		
mitoK$_{ATP}$	心力衰竭	Diazoxide[94, 96, 133, 150-151]	5-hydroxydecanoate[96, 133, 150-154]
	缺血再灌注损伤	Spiro-cyclic derivative A[96]	
	肺动脉高压	Glyburide[151, 155]	
		Indoline-2-carboxylic ethyl esters[153]	
		Nicorandil、minoxidil[135, 154, 156]	Tertiapin Q[157]
		BMS-180448[152]	
		BMS191095[152, 158-159]	
mitoBK$_{Ca}$	心力衰竭	NS1619、NS11021[99, 160-161]	Iberiotoxin、Charybdotoxin[126, 127, 162]
	缺血再灌注损伤	CGS7181、CGS7184[163]	Paxilline[99, 126, 164]
	心律失常	17β-estradiol [165]	Lolitrem B
mitoSK$_{Ca}$	缺血再灌注损伤	DCEBIO[108]	Apamin[166]
	心律失常	TRAM34、NS309[108]	UCL1684
		NS8593[108]	
		CyPPA[167]	
mitoK$_{V7.4}$	缺血再灌注损伤	Retigabine、Flupirtine[111]	XE991[111]
IMAC	心律失常		4'-Cl-DZP[117-118]
CLIC	缺血再灌注损伤		IAA-94[34]
ANO1	肺动脉高压		
ZIP7、ZnT7	心力衰竭		

景的领域,深入探索如何将相关激活剂和抑制剂应用于临床是未来的努力方向。

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