线粒体 ATP 敏感钾通道与线粒体自噬对心力衰竭的作用研究

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【摘要】心力衰竭是由心脏的收缩和/或舒张功能发生障碍,导致心室泵血功能受损引起的循环障碍症候群。临床主要表现为呼吸困难、咳嗽和咳痰。心力衰竭是心脏疾病发展的终末阶段,患者预后较差,目前心力衰竭的发病机制尚不完全明确。近年来,许多研究表明线粒体功能障碍与心力衰竭的发生发展密切相关。现对线粒体 ATP 敏感钾通道以及线粒体自噬对心力衰竭的作用进展进行综述。

【关键词】心力衰竭;线粒体 ATP 敏感钾通道;线粒体自噬
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The Role of Mitochondrial ATP-Sensitive Potassium Channel and Mitophagy in Heart Failure

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【**Abstract**】Heart failure is a circulatory disorder syndrome caused by impairment of the systolic and/or diastolic function of the heart, resulting in impaired ventricular pumping function. The main clinical manifestations are dyspnea, cough and sputum. Heart failure is the end stage of the development of heart disease with poor prognosis. Until now, the pathogenesis of heart failure is not fully clarified. In recent years, many studies have shown that mitochondrial dysfunction is closely related to the occurrence and development of heart failure. In this article, we reviewed the progress of mitochondrial ATP-sensitive potassium channels and the role of mitophagy in heart failure.

【**Key words**】Heart failure; Mitochondrial ATP-sensitive potassium channel; Mitophagy

心力衰竭(heart failure, HF)是一种由于各种原因引起心脏结构和功能损害,导致心脏舒张或收缩功能障碍,以致心输出量无法满足组织代谢需要的复杂的临床综合征。这种临床综合征是各种心脏疾病的严重表现或晚期阶段,死亡率和再住院率居高不下。2022 年最新版美国心脏病学会(ACC)HF 管理指南指出,HF 仍是全球发病率和死亡率升高的主要原因[1]。发达国家的 HF 患病率为 1.5% ~2.0%,70 岁及以上人群患病率≥10%。随着中国人口老龄化加剧,心血管疾病发病呈上升趋势,最新调查显示中国 35 ~74 岁成人慢性 HF 的患病率为 1.3% ,较 15 年前的调查结果增加了 44%[2-3]。

目前认为 HF 是慢性、自发进展性疾病,心肌重构最初可对心功能产生部分代偿,但随着心肌重构的加剧,心功能逐渐由代偿向失代偿转变,出现明显的症状和体征[3]。心肌细胞高度耗能,线粒体通过氧化磷酸化过程产生心脏的主要能源物质三磷酸腺苷(adenosine triphosphate, ATP),因此被称为心肌细胞的"能量供给站"。在 HF 的发生发展过程中,线粒体 ATP 敏感钾通道(mitochondrial ATP-sensitive potassium channels, mitoKATP)作为线粒体内膜上的内向整流钾通道,通过细胞代谢和生物电活动相偶联,其作用不容忽视。

1 mitoKATP 与 HF

1.1 mitoKATP

1983 年, Noma[4] 首先在心肌细胞上发现 ATP 敏感钾通道(ATP-sensitive potassium channel, KATP)。1991 年, Inoue 等[5] 在大鼠的肝脏线粒体内膜记录到 KATP。KATP 是由四个内向整流钾通道亚基(Kir6.1 或Kir6.2)和四个磺酰脲受体调节亚基(SUR1 或 SUR2)组成的异源八聚体,受细胞内 ATP 和 ADP 浓度的调节[6]。不同的组织具有不同的构成,线粒体膜

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上 KATP 的构成情况目前认为主要由 Kir6.1 和 SUR1 组成[7-8]，是机体内为数不多的同时与电生理和能量代谢相关的内向整流钾通道。

线粒体是动态结构，线粒体占据的心肌细胞体积与能量使用率相关。线粒体基质体积占细胞体积的 35%，具有很大的潜在空间。在静息状态下，线粒体基质膨胀，线粒体内膜和外膜之间的膜间距变窄。在压力条件下，线粒体基质收缩，膜间距增加[9-10]。随着 mitoKATP 通道的打开，这种收缩可逆转并恢复到接近正常的状态，促进相关能量合酶的合成，改善能量代谢。

线粒体基质体积稳态的主要调节剂是 K^+[11-12]。mitoKATP 通道通过维持线粒体内的钾平衡，从而控制线粒体基质体积改变；线粒体在产生能量的过程中通过 K^+ 的再摄取，可部分补偿质子泵产生的电荷转移，从而维持跨膜电位和 pH 梯度的形成；在维持线粒体正常能量代谢中发挥重要的作用[13-14]。线粒体膜电位的产生，决定了线粒体的信号传导过程。因此，为了提供稳定的线粒体功能，线粒体内膜对离子的渗透性被严格控制。当机体大量消耗 ATP 或 ATP 供需失衡时，ADP 浓度会相应增高，ADP 与调节亚基 SUR1 结合，促进 Kir6.1 的开放，增加 K^+ 的内向流动，补充质子外流的电荷流失，维持一定的线粒体膜电位，促进线粒体膜内外质子梯度的形成，从而增加 ATP 的合成[11]。

1.2　mitoKATP 在 HF 中的作用

HF 在所有形式的心脏病中都很常见。衰竭心脏的机械功能障碍是由多种因素引起的，包括神经激素紊乱、细胞外基质的积累、兴奋-收缩耦联的改变和心肌能量学的适应不良[15]。mitoKATP 作为线粒体内膜上的内向整流钾通道，与改善能量代谢、维持线粒体膜电位密切相关，在抗心肌重构、抑制心肌凋亡和改善心功能上发挥着重要作用。

研究表明，通过开放 mitoKATP，能减少心肌细胞凋亡、减轻心脏功能障碍和保护疾病模型下受损心脏。Zhou 等[16]发现左西孟旦通过选择性激活 mitoKATP 可减轻离体大鼠心脏由于低温储存引起的心脏收缩功能的降低。Niwano 等[17]发现在自身免疫性心肌病大鼠模型中，尼可地尔通过保护线粒体功能，可提高模型大鼠的左室射血分数和短轴缩短率，降低左室舒张末期压力，起到保护心脏的作用。Wang 等[18]发现 SUR2B/Kir6.1 通道开放剂纳他卡林通过 miR-1-3p/ET-1 通路纠正慢性 HF 的内皮功能障碍，纳他卡林在独立的模型上能改善血流动力学指标，降低 HF 的生物标志物心房钠尿肽和脑钠肽的表达水平。

笔者课题组前期发现，mitoKATP 的开放通过 Akt-FoxO1 信号通路改善糖尿病心肌病的心脏功能并抑制心肌细胞凋亡[19]，Kir6.1 过表达明显抑制糖尿病心肌病小鼠的脑钠肽蛋白水平，通过上调 Akt 和 FoxO1 的磷酸化从而改善心脏功能[20]。以上研究可看出，选择性开放 mitoKATP 对不同诱因导致的 HF 发挥着改善心脏功能的作用，是潜在的抗 HF 靶点。

2　线粒体自噬与 HF

2.1　线粒体自噬

2005 年，Lemasters[21]首先提出“线粒体自噬”的概念，强调线粒体自噬是通过细胞自噬选择性去除体内功能异常的线粒体。其过程包括形成吞噬囊泡；吞噬囊泡识别受损的线粒体，并与其融合形成自噬体；自噬体和溶酶体融合形成自噬溶酶体[22-23]。迄今为止，线粒体自噬的分子机制得到了广泛的研究。哺乳动物细胞具有多种线粒体自噬机制，不同的刺激可通过不同细胞环境中的多个信号级联来促进线粒体自噬。线粒体自噬调节途径分为泛素依赖型和非泛素依赖型[24-25]。泛素依赖型线粒体自噬包括 PTEN 诱导激酶 1（PTEN induced putative kinase 1，PINK1）/Parkin 信号通路介导的线粒体自噬和非 Parkin 依赖型线粒体自噬；而非泛素依赖型线粒体自噬则是直接由线粒体自噬受体介导的线粒体自噬。

PINK1/Parkin 信号通路指在压力条件下，PINK1 稳定在线粒体外膜上，促进 Parkin 募集。Parkin 泛素化几种线粒体外膜成分，poly-Ub 链随后被 PINK1 磷酸化，充当自噬机制的“吃我”信号。衔接蛋白（p62、OPTN 和 NDP52）识别线粒体蛋白上的磷酸化 poly-Ub 链，并与微管相关蛋白 1 轻链 3（microtubule-associated protein 1 light chain 3，LC3）结合启动自噬体形成，降解受损的线粒体，这一过程依赖 Parkin 的存在。而非 Parkin 依赖型通路，可通过除 Parkin 以外的其他 E3 泛素连接酶，如 Gp78、SMURF1、MUL1、SIAH1 和 ARIH1 等，将线粒体外膜底物蛋白泛素化，而后与 LC3 结合进入自噬体[26-27]。另外，PINK1 也可直接磷酸泛素化线粒体外膜自噬受体并诱导线粒体自噬[28]。

非泛素依赖型线粒体自噬主要通过线粒体外膜上的自噬受体蛋白，如 NIP3 样蛋白 X（Nip3-like protein X，NIX）、BCL2 相互作用蛋白 3（BCL2 interacting protein 3，BNIP3）和 FUN14 结构域蛋白 1（FUN14 domain-containing protein 1，FUNDC1）直接与 LC3 相互作用以介导线粒体消除[29]。NIX 和 BNIP3 磷酸化增强了它们与 LC3 的结合[30-31]。CK2 激酶和 Src 激酶以及磷酸甘油酸变位酶 5 都影响 FUNDC1 磷酸化状态，在缺氧期间调节线粒体动力学[32-33]。线粒

体自噬受体通过视神经萎缩蛋白 1 的分解和释放以及线粒体动力相关蛋白 1 在线粒体表面的募集来促进受损细胞器的裂变[34]。NIX 和 BNIP3 的 Parkin 依赖性泛素化突出了受体介导的线粒体自噬与 PINK1/Parkin 通路之间复杂的串扰[25]。不同的线粒体自噬通路之间如何相互作用参与细胞调控尚未可知。因此,关于线粒体自噬仍需进一步深入研究。

2.2 线粒体自噬在 HF 中的作用

近年来,越来越多的研究发现线粒体自噬参与心血管疾病的发生发展,如高血压、动脉粥样硬化、心肌缺血再灌注损伤和 HF 等。线粒体功能障碍是导致心肌细胞丢失和 HF 发展的主要因素。正常情况下,线粒体自噬对心肌细胞具有保护作用,HF 时上调线粒体自噬可维持心肌细胞稳态和心脏的功能,而线粒体自噬不足会加重 HF 的发展[35]。

Wang 等[36]发现在主动脉弓缩窄诱导的小鼠衰竭心脏模型中 AMP 活化蛋白激酶 α2 通过 PINK1 磷酸化增强线粒体自噬来防止 HF 的发展。Xiong 等[37]发现 PINK1/Parkin 介导的线粒体自噬在血管紧张素Ⅱ诱导的细胞毒性中具有补偿性保护作用。Billia 等[38]发现 PINK1 蛋白水平在 HF 终末期中显著降低,同时 PINK1 敲除的小鼠心肌病理性肥大,心室功能发生障碍。转铁蛋白受体 1 通过增加线粒体自噬,在 HF 过程中对心脏发挥保护作用[39]。而线粒体钙单向转运体和线粒体转运蛋白能抑制线粒体自噬,从而诱导压力超负荷性 HF 的发生[40-41]。以上研究表明线粒体自噬在 HF 的发生发展中对心脏有保护性作用。

然而,线粒体自噬的过度激活所导致的线粒体过度清除会促进 HF 的进展。Liu 等[42]发现异丙肾上腺素可激活自噬而诱导大鼠心肌肥大,姜黄素则通过降低 Beclin-1 的表达抑制自噬,从而减轻由异丙肾上腺素诱导的心肌肥大。胰岛素样生长因子Ⅱ(insulin-like growth factor Ⅱ,IGF-Ⅱ)及其受体(IGF-ⅡR)在高血压大鼠 HF 的发展中起着至关重要的作用[43]。Huang 等[44]发现 IGF-Ⅱ触发 IGF-ⅡR 激活,导致线粒体功能障碍,引起线粒体自噬和心肌细胞死亡。Drp1 引起的线粒体过度分裂增强了 Rab9 依赖的线粒体自噬,从而促进了 HF 过程中 IGF-ⅡR 诱导的线粒体功能障碍,并最终降低了心肌细胞的活力[45]。

自噬发挥的综合效应取决于病程所处的阶段,自噬活动在不同阶段执行不同的生物学效应,因而需更多的研究来充分了解自噬的调控机制。心脏应激适度诱导线粒体自噬有助于清除受损和功能失调的线粒体,可防止细胞凋亡的启动而最终导致的 HF 氧化损伤[46]。自噬,特别是线粒体自噬,在心脏肥大、心肌重构和 HF 过程中的作用被描述为依赖于环境[47]。应激条件下线粒体自噬的上调是一种保护心脏免受血液动力学刺激的适应性反应。总之,心肌细胞线粒体自噬增强是把双刃剑,既可保护心肌细胞,又可加重 HF。长期或高水平的心脏应激可引起心肌细胞内线粒体的损伤和功能障碍,从而加重 HF。因此,适当诱导或抑制心肌线粒体自噬的策略对于 HF 的治疗至关重要。

3 mitoKATP 与线粒体自噬

mitoKATP 与线粒体自噬都参与调节线粒体功能,都是线粒体质量控制不可或缺的部分。二者之间是否相互关联从而对心脏起到保护作用? 2019 年,Hu 等[48]发现星形胶质细胞 Kir6.1 敲除导致小鼠的线粒体自噬缺陷,包括 LC3-Ⅱ水平降低和 p62 表达增加,PINK1 和 Parkin 水平降低,线粒体中 Tom20 表达升高,以及 LC3 和线粒体之间的共定位减少。因此,Kir6.1 敲除星形胶质细胞中受损线粒体和线粒体活性氧的积累增加。更重要的是,星形胶质细胞线粒体自噬的恢复促进了功能失调的线粒体的消除,减少了活性氧的产生,抑制了星形胶质细胞介导的炎症,并逆转了由于 Kir6.1 缺失导致的多巴胺神经元损伤加重。这些发现证实了星形胶质细胞 Kir6.1 介导的线粒体自噬对星形胶质细胞消除促炎细胞因子和减轻多巴胺神经元损伤的重要性。由此可见,mitoKATP 可介导线粒体自噬从而对细胞产生保护作用。然而,Kir6.1/KATP 通道调节线粒体自噬的详细分子机制仍需进一步研究。

4 结语

线粒体约占心肌细胞总体积的 30%,心肌细胞的代谢、兴奋传递与收缩等所需能量离不开线粒体的正常功能,若线粒体结构功能出现紊乱,很容易导致心脏疾病的发生。近几年,以线粒体为靶点的小分子有望成为治疗 HF 的新方法,如抗氧化剂辅酶 Q10[49]和 MTP-131(也称为 SS31)[50]已进入临床试验。mitoKATP 作为线粒体上重要的离子通道,对线粒体的质量调控不可或缺。同时,线粒体自噬对线粒体的质量控制和细胞的能量代谢也非常重要。mitoKATP 的开放对心脏起保护作用,线粒体自噬的适度上调也对心脏功能有所保护,二者之间如何联系以及其中的调节机制有待进一步的探讨研究,以期为 HF 的防治提供新的作用靶点和理论依据。

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