TRPC6与心血管疾病关系的研究进展

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摘要 瞬时受体电位通道6(transient receptor potential cation channel 6, TRPC6)是瞬时受体电位离子通道家族的成员之一, 属于非选择性阳离子通道。TRPC6广泛分布于大脑、神经、心脏、血管、肺、肾、胃肠道等器官组织中, 可被渗透压变化、机械刺激、二酰基甘油激活, 进而参与体内多种疾病的病理生理过程。研究发现, TRPC6的失调与心血管系统疾病的发病机制关系密切, 且TRPC6与心血管疾病关系的研究成为近来热点。该文主要介绍TRPC6的结构特点及其与心血管系统相关疾病关系的最新研究进展。

关键词 TRPC6; 心血管疾病; 心肌缺血再灌注损伤; 心肌肥厚; 心肌纤维化; 高血压

Research Progress on the Relationship between TRPC6 and Cardiovascular Diseases

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Abstract TRPC6 (transient receptor potential cation channel 6) is one of the members of transient receptor potential ion channels, which is a non-selective cation channel. TRPC6 is widely distributed in organs and tissues such as the brain, nerves, heart, blood vessels, lung, kidney, gastrointestinal tract, etc. It can be activated by osmotic pressure change, mechanical stimulation and diacylglycerol, and then participates in the pathophysiological processes of many diseases in the body. Studies have found that the disorder of TRPC6 is closely related to the pathogenesis of cardiovascular diseases, and the relationships between TRPC6 and cardiovascular diseases have become research hotspots. This article mainly introduces the structural characteristics of TRPC6 and the latest research progress in its relationship with cardiovascular system-related diseases.

Keywords TRPC6; cardiovascular diseases; myocardial ischemia-reperfusion injury; myocardial hypertrophy; myocardial fibrosis; hypertension

瞬时受体电位(transient receptor potential, TRP)通道是一类非电压依赖性阳离子通道, 首次在果蝇的视觉传导研究中被发现[1]。在哺乳动物中, TRP通道主要分为7个亚家族: TRPC、TRPV、TRPM、TRPML、TRPN、TRPA和TRPP。TRPC亚家族包括TRPC1、TRPC2、TRPC3、TRPC4、TRPC5、TRPC6、TRPC7 7个成员, TRPV亚家族包括TRPV1、TRPV2、TRPV3、TRPV4、TRPV5、TRPV6 6个成员, TRPM亚家族包括TRPM1、TRPM2、TRPM3、TRPM4、TRPM5、TRPM6、TRPM7、TRPM8 8个成员, TRPML亚家族包括TRPML1、TRPML2、TRPML3 3个成员, 而TRPN

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亚家族的具体分型尚不明确，TRPA亚家族中目前仅发现TRPA1这1个成员，TRPP亚家族包括TRPP1、TRPP2、TRPP3、TRPP4、TRPP5 5个成员[2-3]。其中TRPC6在体内分布广泛，并参与了多种疾病的病理生理过程，在疾病的发生发展中起着重要作用。本文将对TRPC6在心血管系统疾病中的研究进展进行综述。

1 TRPC6的结构与生理功能

1.1 TRPC6的结构

TRPC6由931个氨基酸构成，表达于细胞膜上并具有6个跨膜结构域(TM1~6)，第五和第六跨膜区之间有1个功能孔域，由此区域构成了非选择性阳离子通道[4-5]。TRPC6结构的N-端与C-端均位于细胞内，C-端尾部包含1个钙调蛋白三磷酸肌醇受体磷酸肌醇结合位点(calmodulin IP3 receptor phosphoinositide-binding site, CIRPIB)，CIRPIB是蛋白质相互作用的位点，可能参与TRPC6的激活[6]。TRPC6是非选择性阳离子通道，磷脂酶C(phospholipase C, PLC)、二酰基甘油(DAG)、1-油酰基-2-乙酰基-sn-甘油、酪氨酸蛋白激酶、20-羟基二十碳四烯酸、酪氨酸激酶、钙调蛋白激酶II均可直接激活TRPC6，此外，机械刺激、渗透压和pH的变化亦可间接激活TRPC6，进而使其参与多种疾病的病理生理过程。

1.2 TRPC6的生理功能

TRPC6的主要生理功能是调节Na^+、K^+、Ca^{2+}等阳离子信号转导，其功能异常导致的Ca^{2+}失调是心血管系统生理功能异常的重要因素。研究发现，TRPC6受到细胞内外Ca^{2+}、钙调蛋白和磷脂酰肌苷以及蛋白丝氨酸和酪氨酸磷酸化的复杂调控[7]。TRPC6在血管平滑肌中有表达[8]，激活血管平滑肌中的TRPC6，可通过G蛋白偶联受体和酪氨酸激酶受体调节血管张力[9-10]。研究表明，缺氧性肺血管收缩过程中也有TRPC6的参与[11]，TRPC6还与吞噬体活性的恢复[12]、细胞自噬的发生[13]、血小板的活化[14-15]以及肿瘤细胞稳态的改变[16]等密切相关。除了上述生理功能外，TRPC6还参与了多种疾病的病理生理过程。

2 TRPC6与心血管系统疾病

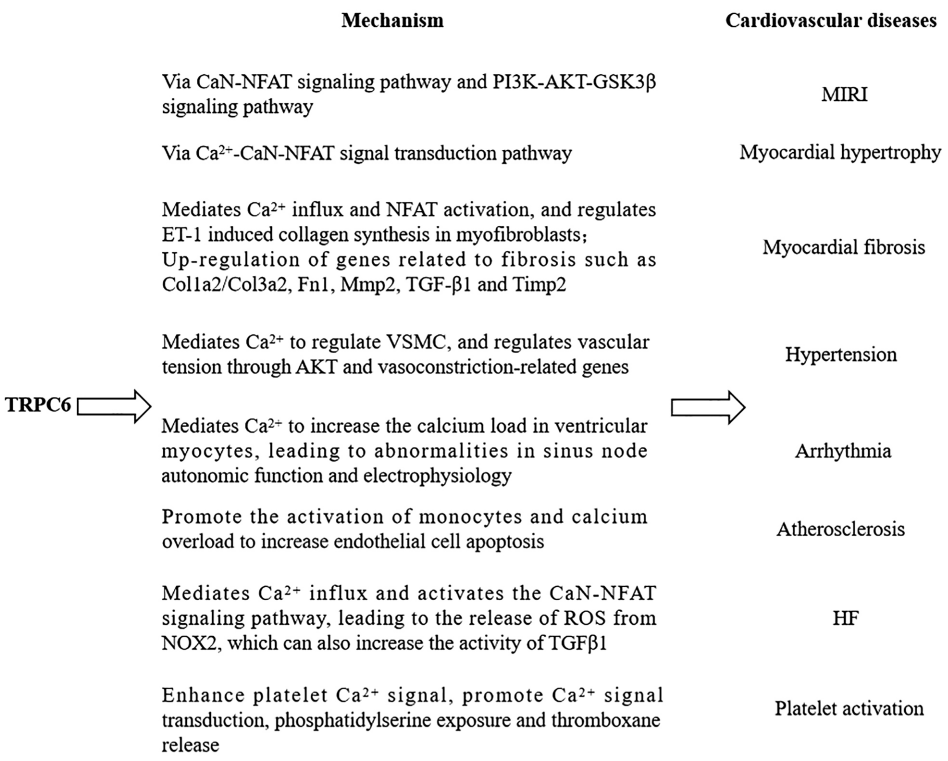
TRPC6广泛存在于心血管系统，主要表达于心肌细胞、成纤维细胞、血管内皮细胞以及血管平滑肌细胞(vascular smooth muscle cell, VSMC)等中，参与这些细胞的代谢和稳态的维持，在心血管系统疾病的病理生理过程中发挥重要作用(图1)。

2.1 TRPC6与MIRI

心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury, MIRI)是缺血心肌在恢复血流后常出现的并发症[17]，且TRPC6可参与MIRI的发生。MARAL等[18]在Wistar雄性大鼠MIRI的研究中发现，短期的高强度训练(high-intensity interval training, HIIT)通过提高血浆Klotho(一种与衰老相关的蛋白，能够促进血管损伤的修复)的水平和降低缺血再灌注期间TRPC6通道蛋白的表达减小心肌梗死面积，进而增强对缺血再灌注心脏的保护作用。此研究认为，TRPC6的表达降低可增加NO及其代谢物水平，从而抑制心肌细胞的凋亡，减轻MIRI[19-20]。还有研究表明，TRPC6参与丹参素对缺血再灌注心肌的保护过程[21]。丹参素预处理后的H9c2细胞在缺氧复氧诱导再灌注损伤过程中，磷酸化氨基末端激酶(phosphorylated-c-Jun N-terminal kinase, p-JNK)表达下调，其下游的核转录因子-κB(nuclear factor kappa-B, NF-κB)和TRPC6表达水平均显著降低，从而抑制Ca^{2+}内流，进而减轻钙超载和MIRI，因此丹参素可通过减少p-JNK-NF-κB-TRPC6途径诱发的钙超载减轻MIRI并抑制H9c2细胞凋亡[21-22]。此外，在*TRPC3/6/7*基因敲除小鼠心肌缺血再灌注过程中，钙调神经磷酸酶(calcineurin, CaN)-活化T细胞核因子(nuclear factor of activated T cell, NFAT)信号通路下调和磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)-蛋白激酶B(protein kinase B, AKT)-糖原合成酶激酶3β(glycogen synthase kinase 3β, GSK3β)信号通路上调，导致心肌细胞凋亡减少[23]，其机制可能是抑制TRPC6的表达，促进了PI3K/AKT(磷脂酰肌醇3-激酶/蛋白激酶B)的激活，增加了该信号通路下游的GSK3β表达，进而上调了抗凋亡蛋白Bcl2的表达，从而减轻了心肌在缺血再灌注过程中的损伤。因此，TRPC6主要通过CaN-NFAT信号通路和PI3K-AKT-GSK3β信号通路参与MIRI。

2.2 TRPC6与心肌肥厚

心肌肥厚是心肌细胞的代偿反应，表现为心肌细胞体积增加、心肌细胞凋亡增多及间质纤维化加重，当心肌细胞失代偿则发展为心力衰竭(heart



CaN-NFAT: 钙调神经磷酸酶–活化T细胞核因子; PI3K-AKT-GSK3β: 磷脂酰肌醇3-激酶–蛋白激酶B-糖原合成酶激酶3β; MIRI: 心肌缺血再灌注损伤; ET-1: 内皮素-1; TGF-β1: 转化生长因子-β1; NOX2: NADPH氧化酶2; HF: 心力衰竭。

CaN-NFAT: calcineurin-nuclear factor of activated T cell; PI3K-AKT-GSK3β: phosphatidylinositol 3-kinase-protein kinase B-glycogen synthase kinase 3β; MIRI: myocardial ischemia-reperfusion injury; ET-1: endothelin-1; TGF-β1: transforming growth factor-β1; NOX2: NADPH oxidase 2; HF: heart failure.

图1 TRPC6介导心血管系统疾病

Fig.1 TRPC6 mediates cardiovascular diseases

failure, HF)。受Ca^{2+}调节的CaN-NFAT通路异常是导致心脏肥大的关键因素, 而心肌细胞Ca^{2+}储存操作钙通道(store-operated Ca^{2+} entry, SOCE)的激活与TRPC6的表达水平有关[24-25]。在Ang II引起的心肌肥大中, Ang II诱导的PLC激活产生的DAG直接激活TRPC6, 介导阳离子(Na^+、Ca^{2+})流入细胞, 使其膜电位升高, 激活电压依赖性L型Ca^{2+}通道, 使Ca^{2+}内流激活大鼠新生心肌细胞中的CaN/NFAT通路, 进而介导肥大反应[26]。TRPC6表达增加也可导致心肌细胞中肌浆网(sarcoplasmic reticulum, SR) Ca^{2+}负荷增加, 从而激活CaN-NFAT信号通路, 进而导致心肌肥厚[27-28]。还有研究表明, DAG可通过Ca^{2+}/Na^+泵增加心肌细胞内Ca^{2+}水平, 进而激活CaN-NFAT信号通路, 介导心肌肥大反应; 另外, DAG可通过激活TRPC6上调细胞外调节蛋白激酶(ERK)表达, 从而介导心肌肥大反应[29-30]。在压力超负荷心脏中, TRPC6选择性拮抗剂BI 749327可下调TRPC6表达, 并降低其下游的NFAT活化水平, 减轻心肌肥厚[31]。以上的研究表明, TRPC6与心肌肥厚关系密切, 可通过Ca^{2+}-CaN-NFAT信号转导途径导致心肌肥厚。

2.3 TRPC6与心肌纤维化

成纤维细胞是心肌纤维化过程的主要作用细胞, 它们向成肌纤维细胞的转化在细胞外基质蛋白的产生中起着重要作用, 而这些细胞外基质蛋白与心脏纤维化联系密切[32-33]。研究表明, Galpha 12/13介导的TRPC6通道的上调参与持续的Ca^{2+}内流和NFAT激活, 并负调节内皮素-1(endothelin-1, ET-1)诱导的成肌纤维细胞胶原蛋白的合成, 从而抑制心肌纤维化[34]。胶原蛋白受体盘状结构域受体2(discoidin domain receptor 2, DDR2)和整联蛋白β1(integrin-β1)可共同介导组织纤维化, 在DDR2-integrin-β1通路下游, 上调α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)和TRPC6可促进Yes相关蛋白(Yes-associated protein, YAP)活化, 从而增强胶原蛋白的表达, 进而调节心肌纤维化[35]。

敲除小鼠*TRPC6*基因可减轻小鼠压力超负荷引

起的心肌纤维化，但不能减轻压力负荷增高引起的心功能障碍，也不能减少压力超负荷引起的心肌活性氧(reactive oxygen species, ROS)的产生[36]。另外，α-Klotho(一种I型单次跨膜糖蛋白)作为成纤维细胞生长因子-23(fibroblast growth factor-23, FGF-23)的受体辅助因子[37]，可通过降低TRPC6表达抑制心肌纤维化，从而表现出心脏保护作用[38]。在小鼠体内实验研究中发现，TRPC6特异性抑制剂BI 749327可抑制TRPC6的表达，进而抑制Col1a2/Col3a2、Fn1、Mmp2、TGF-β1和Timp2等纤维化相关基因的表达，从而导致心肌组织间质纤维化减少[39]。因此，TRPC6表达下调既可减轻心肌细胞肥大，又可抑制心脏成纤维细胞的形成。

2.4 TRPC6与高血压

TRPC6在原发性高血压机制中的作用与调控VSMC胞内Ca^{2+}浓度有关，而Ca^{2+}活动异常是高血压发生的重要因素之一。TRPC6表达上调可导致VSMC向病理表型转化，而使用TRPC6抑制剂则会逆转这一变化，并改善高血压模型动物的高血压[40]。研究表明，TRPC6通过与第10号染色体同源缺失性磷酸酶–张力蛋白(phosphatase and tension homolog deleted on chromosome ten, PTEN)耦联调节VSMC的表型转化，TRPC6的表达下调可减弱TRPC6与PTEN的相互作用，并抑制AKT活性，从而抑制血管平滑肌收缩，进而舒张血管、降低血压[41]。在对肺动脉平滑肌细胞的研究中，*TRPC6*被证实是miR-26a-5p的靶基因，且长链非编码RNA(lncRNA) AC068039.4通过下调miR-26a-5p使TRPC6的表达水平降低，从而抑制肺部血管重塑，改善肺动脉高压[42]。而Notch信号(Notch信号可影响细胞正常形态发生变化的多个过程)可直接或间接地激活TRPC6，导致肺动脉平滑肌细胞通过TRPC6通道流入的Ca^{2+}增加，引起肺动脉平滑肌收缩，加重肺动脉高压，应用TRPC6通道阻滞剂和缺失*TRPC6*基因则可抑制肺动脉高压的发展[43]。以上研究表明，TRPC6介导的Ca^{2+}可调节VSMC收缩，TRPC6还可通过AKT以及与血管收缩相关的基因调节血管张力，进而参与血管性高血压的病理生理过程。

2.5 TRPC6与心律失常

TRPC6参与了非瓣膜性房颤的发生[44]，其机制可能是TRPC6和SOCE通过促进心肌细胞自发性Ca^{2+}内流，导致心脏心电重构，继而触发心律失常[45]。心房机械牵张反应可激活心内膜TRPC6，引起房性心律不齐[46]，其机制可能是激活TRPC6，增加心室肌细胞中的钙负荷，进而触发心律失常[47]。GK(Goto-Kakizaki) 2型糖尿病大鼠的体内实验研究表明，其窦房结TRPC6表达与自发性心率降低有关，可能是其窦房结TRPC6下调导致TRPC6介导的Ca^{2+}内流减少，从而导致窦房结自律性功能异常[48]。心房和心室中TRPC6与L型钙通道通过Ca^{2+}调节心脏起搏、传导，应用TRPC6通道阻滞剂可减少TRPC6介导的Ca^{2+}内流，从而阻碍心率失常的发生[49]。因此，TRPC6主要通过其介导的Ca^{2+}调节心脏节律和电生理，进而参与心率失常。

2.6 TRPC6与动脉粥样硬化

研究表明，患代谢综合征猪的冠状动脉表现出明显的动脉粥样硬化，其冠状动脉平滑肌细胞膜TRPC6上调，而长期使用盐皮质激素受体抑制剂螺内酯，会使其冠状动脉平滑肌细胞膜TRPC6表达明显下调，且抑制冠状动脉过度收缩和动脉粥样硬化[50]。另外，单核细胞活化后与动脉血管内皮黏附，并向内皮迁移，这对于动脉粥样硬化的早期发病机制至关重要，而上调TRPC6则可促进单核细胞的活化，进而促进动脉粥样硬化的发展[51]。血管内皮细胞凋亡是动脉粥样硬化发展的关键过程[52]，而miR-26a可靶向*TRPC6*，使TRPC6表达下调，抑制TRPC6引起的钙超载，从而抑制内皮细胞凋亡，减缓动脉粥样硬化发展[53]。以上研究表明，TRPC6主要通过单核细胞的活化和钙超载参与动脉粥样硬化的调节。

2.7 TRPC6与HF

TRPC6在心脏中过表达会增加HF的风险[54]，在高血糖诱导的HF小鼠研究中发现，TRPC6可以与NADPH氧化酶2(NADPH oxidase 2, NOX2)相互作用，且NOX2负调控TRPC6的表达，当高血糖诱导的TRPC3-NOX2蛋白复合物水平增加时，游离的NOX2含量减少，作用于TRPC6的NOX2也相应减少，从而上调TRPC6加剧糖尿病性HF[55-56]。TRPC6上调引起的Ca^{2+}内流增加可激活CaN-NFAT信号通路，诱导NOX2释放ROS，进而诱发HF[57]。在HF模型小鼠的研究中发现，HF组TRPC6表达明显高于假手术组，其机制可能是心室内皮糖蛋白促进TRPC6表达和增强TGF-β1活性，导致HF的发生[58]，而使用TRPC6抑制剂则可减轻压力超负荷引起的HF[59]。因此，TRPC6通过NOX2、ROS、TGF-β1参与调节HF，上

调TRPC6蛋白表达可加剧HF, 而抑制TRPC6蛋白表达则可减轻HF。

2.8 TRPC6与血小板活化

研究表明, 抑制TRPC6可降低血小板的钙通量并抑制血小板活化, 维持血小板的正常功能和稳态[60-61]。激活磷脂酶产生的DAG可直接激活血小板表面的TRPC6, 放大血小板Ca^{2+}信号, 促进Ca^{2+}信号转导、磷脂酰丝氨酸暴露以及血栓烷释放, 从而加剧血小板活化和血栓形成[62-63]。研究发现, TRPC6通道对小鼠血小板外pH敏感, 将*TRPC6*基因敲除小鼠的血小板暴露于酸性pH环境中可以消除凝血酶诱发的血小板聚集[64]。预先用TRPC6特异性抑制剂孵育血小板可抑制凝血酶诱发的血小板颗粒分泌, 从而抑制血小板活化[65-66]。*TRPC6*基因敲除小鼠的血小板胞内钙浓度生理性升高受阻, 血小板聚集, 颗粒分泌等功能出现缺陷, 提示*TRPC6*可能成为治疗血栓性疾病的一个新靶标[67]。以上研究表明, TRPC6介导的Ca^{2+}浓度升高在血小板活化过程中至关重要, 因此, 在一些由血小板活化引起的血栓性疾病中, 特异性的TRPC6抑制剂可能是新的药物干预靶点。

3 结语

综上所述, TRPC6在心肌梗死、心肌肥厚、心肌纤维化、高血压、心率失常、动脉粥样硬化、HF和血管栓塞性疾病中发挥了重要作用, 目前对于TRPC6在上述心血管系统疾病中的研究还处在基础的理论研究阶段, 其在心血管系统疾病的诊断、治疗方面的应用有待进一步研究予以揭示和阐明。

参考文献 (References)

[1] JARDIN I, LOPEZ J J, DIEZ R, et al. TRPs in pain sensation [J]. Front Physiol, 2017, 8(3): 392-9.

[2] HIMMEL N J, COX D N. Transient receptor potential channels: current perspectives on evolution, structure, function and nomenclature [J]. Proc Biol Sci, 2020, 287(1309): 1-9.

[3] LEE J, MOON S J, CHA Y, et al. Drosophila TRPN(=NOMPC) channel localizes to the distal end of mechanosensory cilia [J]. PLoS One, 2010, 5(6): e11012-23.

[4] TSAGARELI M, NOZADZE I. An overview on transient receptor potential channels superfamily [J]. Behav Pharmacol, 2020, 31(5): 413-34.

[5] TANG Q L, GUO W J, ZHENG L, et al. Structure of the receptor-activated human TRPC6 and TRPC3 ion channels [J]. Cell Res, 2018, 28(7): 746-55.

[6] TSAGARELI M, NOZADZE I. An overview on transient receptor potential channels superfamily [J]. Behav Pharmacol, 2020, 31(5): 413-34.

[7] DIETRICH A, GUDERMANN T. TRPC6: physiological function and pathophysiological relevance [J]. Handb Exp Pharmacol, 2014, 222(1): 157-88.

[8] INOUE R, OKADA T, ONOUE H, et al. The transient receptor potential protein homologue TRP6 is the essential component of vascular alpha(1)-adrenoceptor-activated Ca^{2+}-permeable cation channel [J]. Circ Res, 2001, 88(3): 325-32.

[9] ZOLTAN N, EMILY H, MICHAEL J R, et al. Pressure-induced constriction of the middle cerebral artery is abolished in TrpC6 knockout mice [J]. Am J Physiol Heart Circ Physiol, 2020, 319(1): H42-50.

[10] SPASSOVA M A, HEWAVITHARANA T, XU W, et al. A common mechanism underlies stretch activation and receptor activation of TRPC6 channels [J]. Proc Natl Acad Sci USA, 2006, 103(44): 16586-91.

[11] MALCZYK M, ERB A, VEITH C, et al. The role of transient receptor potential channel 6 channels in the pulmonary vasculature [J]. Front Immunol, 2017, 8(1): 707-16.

[12] RIAZANSKI V, GABDOULKHAKOVA A G, BOYNTON L S, et al. TRPC6 channel translocation into phagosomal membrane augments phagosomal function [J]. Proc Natl Acad Sci USA, 2015, 112(47): E6486-95.

[13] LIU Z W, DU Z Q, LI K, et al. TRPC6-mediated Ca^{2+} entry essential for the regulation of nano-ZnO induced autophagy in sh-sy5y cells [J]. Neurochem Res, 2020, 45(7): 1602-13.

[14] ORTIZ-MUNOZ G, YU M A, LEFRANCAIS E, et al. Cystic fibrosis transmembrane conductance regulator dysfunction in platelets drives lung hyperinflammation [J]. J Clin Invest, 2020, 130(4): 2041-53.

[15] ZIMMERMAN G A. Platelets: inflammatory effector cells in the conflagration of cystic fibrosis lung disease [J]. J Clin Invest, 2020, 130(4): 1632-4.

[16] SANCHEZ C J, LOPEZ J J, GONZALEZ G L, et al. Functional role of TRPC6 and STIM2 in cytosolic and endoplasmic reticulum Ca^{2+} content in resting estrogen receptor-positive breast cancer cells [J]. Biochem J, 2020, 477(17): 3183-97.

[17] CACCIOPPO A, FRANCHIN L, GROSSO A, et al. Ischemia reperfusion injury: mechanisms of damage/protection and novel strategies for cardiac recovery/regeneration [J]. Int J Mol Sci, 2019, 20(20): 5024-31.

[18] RAMEZ M, RAJABI H, RAMEZANI F, et al. The greater effect of high-intensity interval training versus moderate-intensity continuous training on cardioprotection against ischemia-reperfusion injury through Klotho levels and attenuate of myocardial TRPC6 expression [J]. BMC Cardiovasc Disord, 2019, 19(1): 118-25.

[19] RAMEZ M, RAMEZANI F, NASIRINEZHAD F, et al. High-intensity interval training increases myocardial levels of klotho and protects the heart against ischaemia-reperfusion injury [J]. Exp Physiol, 2020, 105(4): 652-65.

[20] FALLAHI A, GAEINI A, SHEKARFROUSH S, et al. Cardioprotective effect of high intensity interval training and nitric oxide metabolites [J]. Iran J Public Health, 2015, 44(9): 1270-6.

[21] MENG Y, LI W Z, SHI Y W, et al. Danshensu protects against ischemia/reperfusion injury and inhibits the apoptosis of h9c2 cells by reducing the calcium overload through the p-JNK-NF-

κB-TRPC6 pathway [J]. Int J Mol Med, 2016, 37(1): 258-66.

[22] ZHANG W, ZHU T B, CHEN L L, et al. MCP-1 mediates ischemia- reperfusion-induced cardiomyocyte apoptosis via MCPIP1 and CaSR [J]. Am J Physiol Heart Circ Physiol, 2020, 318(1): H59-71.

[23] HE X J, LI S T, LIU B J, et al. Major contribution of the 3/6/7 class of TRPC channels to myocardial ischemia/reperfusion and cellular hypoxia/reoxygenation injuries [J]. Proc Natl Acad Sci USA, 2017, 114(23): E4582-91.

[24] AVILA-MEDINA J, MAYORAL-GONZALEZ I, GALEANO-OTERO I, et al. Pathophysiological significance of store-operated calcium entry in cardiovascular and skeletal muscle disorders and angiogenesis [J]. Adv Exp Med Biol, 2020, 1131(1): 489-504.

[25] EDER P. Cardiac remodeling and disease: SOCE and TRPC signaling in cardiac pathology [J]. Adv Exp Med Biol, 2017, 993(12): 505-21.

[26] ONOHARA N, NISHIDA M, INOUE R, et al. TRPC3 and TRPC6 are essential for angiotensin II-induced cardiac hypertrophy [J]. EMBO J, 2006, 25(22): 5305-16.

[27] YAMAGUCHI Y, IRIBE G,NISHIDA M, et al. Role of TRPC3 and TRPC6 channels in the myocardial response to stretch: linking physiology and pathophysiology [J]. Prog Biophys Mol Biol, 2017, 130(11): 264-72.

[28] AHMAD A A, STREIFF M E, HUNTER C, et al. Modulation of calcium transients in cardiomyocytes by transient receptor potential canonical 6 channels [J]. Front Physiol, 2020, 11(1): 44-53.

[29] DEISL C, FINE M, MOE O W, et al. Hypertrophy of human embryonic stem cell-derived cardiomyocytes supported by positive feedback between Ca^{2+} and diacylglycerol signals [J]. Pflugers Arch, 2019, 471(8): 1143-57.

[30] SANNA B, BUENO O F, DAI Y S, et al. Direct and indirect interactions between calcineurin-NFAT and MEK1-extracellular signal-regulated kinase 1/2 signaling pathways regulate cardiac gene expression and cellular growth [J]. Mol Cell Biol, 2005, 25(3): 865-78.

[31] LIN B L, MATERA D, DOERNER J F, et al. In vivo selective inhibition of TRPC6 by antagonist BI 749327 ameliorates fibrosis and dysfunction in cardiac and renal disease [J]. Proc Natl Acad Sci USA, 2019, 116(20): 10156-61.

[32] INOUE R, KURAHARA L H, HIRAISHI K, et al. TRP channels in cardiac and intestinal fibrosis [J]. Semin Cell Dev Biol, 2019, 94(8): 40-9.

[33] EVDOKIA B, OLGA B, OLGA G, et al. Myocardial hypertrophy and fibrosis are associated with cardiomyocyte beta-catenin and TRPC6/calcineurin/NFAT signaling in spontaneously hypertensive rats with 5/6 nephrectomy [J]. Int J Mol Sci, 2021, 22(9): 1-13.

[34] NISHIDA M, ONOHARA N, SATO Y, et al. Galpha12/13-mediated up- regulation of TRPC6 negatively regulates endothelin-1-induced cardiac myofibroblast formation and collagen synthesis through nuclear factor of activated T cells activation [J]. J Biol Chem, 2007, 282(32): 23117-28.

[35] HARIKRISHNAN V, TITUS A S, COWING R T, et al. Collagen receptor cross-talk determines α-smooth muscle actin-dependent collagen gene expression in angiotensin II-stimulated cardiac fibroblasts [J]. J Biol Chem, 2019, 294(51): 19723-39.

[36] ODA S, NUMAGA-TOMITA T, KITAJIMA N, et al. TRPC6 counteracts TRPC3-nox2 protein complex leading to attenuation of hyperglycemia-induced heart failure in mice [J]. Sci Rep, 2017, 7(1): 7511-24.

[37] MEMMOS E, PAPAGIANNI A. New insights into the role of FGF-23 and klotho in cardiovascular disease in chronic kidney disease patients [J]. Curr Vasc Pharmacol, 2021, 19(1): 55-62.

[38] SUASSUNA P G A, CHEREM P M, DE CASTRO B B, et al. αKlotho attenuates cardiac hypertrophy and increases myocardial fibroblast growth factor 21 expression in uremic rats [J]. Exp Biol Med, 2020, 245(1): 66-78.

[39] LIN B L, MATERA D, DOERNER J F, et al. *In vivo* selective inhibition of TRPC6 by antagonist BI 749327 ameliorates fibrosis and dysfunction in cardiac and renal disease [J]. Proc Natl Acad Sci USA, 2019, 116(20): 10156-61.

[40] NISHIDA M, TANAKA T, MANGMOOL S, et al. Canonical transient receptor potential channels and vascular smooth muscle cell plasticity [J]. J Lipid Atheroscler, 2020, 9(1): 124-39.

[41] NUMAGA-TOMITA T, SHIMAUCHI T, ODA S, et al. TRPC6 regulates phenotypic switching of vascular smooth muscle cells through plasma membrane potential-dependent coupling with PTEN [J]. FASEB J, 2019, 33(9): 9785-96.

[42] QIN Y H, ZHU B Q, LI L Q, et al. Overexpressed lncRNA AC068039.4 contributes to proliferation and cell cycle progression of pulmonary artery smooth muscle cells via sponging miR-26a-5p/TRPC6 in hypoxic pulmonary arterial hypertension [J]. Shock, 2021, 55(2): 244-55.

[43] YAMAMURA H, SUZUKI Y, YAMAMURA A. Pathophysiological roles of TRPC6 channels in pulmonary arterial hypertension [J]. Nihon Yakurigaku Zasshi, 2020, 155(4): 230-5.

[44] DUZEN I V, YAVUZ F, VURUSKAN E, et al. Leukocyte TRP channel gene expressions in patients with non-valvular atrial fibrillation [J]. Sci Rep, 2017, 7(1): 9272-88.

[45] WEN H R, ZHAO Z H, FEFELOVA N, et al. Potential arrhythmogenic role of TRPC channels and store-operated calcium entry mechanism in mouse ventricular myocytes [J]. Front Physiol, 2018, 9(1): 1785-97.

[46] NIKOLOVA-KRSTEVSKI V, WAGNER S, YU Z Y, et al. Endocardial TRPC6 channels act as atrial mechanosensors and load-dependent modulators of endocardial/myocardial cross-talk [J]. JACC Basic Transl Sci, 2017, 2(5): 575-90.

[47] WEN H, ZHAO Z H, FEFELOVA N, et al. Potential arrhythmogenic role of TRPC channels and store-operated calcium entry mechanism in mouse ventricular myocytes [J]. Front Physiol, 2018, 9(1): 1785-94.

[48] HOWARTH F C, QURESHI M A, JAYAPAPRAKASH P, et al. The pattern of mRNA expression is changed in sinoatrial node from Goto-Kakizaki type 2 diabetic rat heart [J]. J Diabetes Res, 2018, 1(1): 8454078-93.

[49] XIAO X, LIU H X, SHEN K, et al. Canonical transient receptor potential channels and their link with cardio/cerebro-vascular diseases [J]. Biomol Ther, 2017, 25(5): 471-81.

[50] LI W N, CHEN X J, RILEY A M, et al. Long-term spironolactone treatment reduces coronary TRPC expression, vasoconstriction, and atherosclerosis in metabolic syndrome pigs [J]. Basic Res Cardiol, 2017, 112(5): 54-67.

[51] TANO J Y K, LEE R H, VAZQUEZ G, et al. Macrophage function in atherosclerosis: potential roles of TRP channels [J]. Chan-

nels, 2012, 6(3): 141-8.
[52] PENG N, MENG N, WANG S Q, et al. An activator of mTOR inhibits oxLDL-induced autophagy and apoptosis in vascular endothelial cells and restricts atherosclerosis in apolipoprotein E-/- mice [J]. Sci Rep, 2014, 4(1): 5519-27.
[53] ZHANG Y, QIN W, ZHANG L Y, et al. MicroRNA-26a prevents endothelial cell apoptosis by directly targeting TRPC6 in the setting of atherosclerosis [J]. Sci Rep, 2015, 5(1): 9401-16.
[54] NORTON N, CROOK J E, WANG L, et al. TRPC6 association of genetic variants at with chemotherapy-related heart failure [J]. Front Cardiovasc Med, 2020, 7(1): 142-54.
[55] ODA S, NUMAGA-TOMITA T, KITAJIMA N, et al. TRPC6 counteracts TRPC3-nox2 protein complex leading to attenuation of hyperglycemia-induced heart failure in mice [J]. Sci Rep, 2017, 7(1): 7511-9.
[56] NISHIYAMA K, TANAKA T, NISHIMURA A, et al. TRPC3-based protein signaling complex as a therapeutic target of myocardial atrophy [J]. Curr Mol Pharmacol, 2021, 14(2): 123-31.
[57] YAMAGUCHI Y, IRIBE G, NISHIDA M, et al. Role of TRPC3 and TRPC6 channels in the myocardial response to stretch: linking physiology and pathophysiology [J]. Prog Biophys Mol Biol, 2017, 130(1): 264-72.
[58] MORINE K J, PARUCHURI V, QIAO X Y, et al. Endoglin selectively modulates transient receptor potential channel expression in left and right heart failure [J]. Cardiovasc Pathol, 2016, 25(6): 478-82.
[59] NISHIDA M. Roles of heterotrimeric GTP-binding proteins in the progression of heart failure [J]. J Pharmacol Sci, 2011, 117(1): 1-5.
[60] ORTIZ-MUNOZ G, YU M A, LEFRANCAIS E, et al. Cystic fibrosis transmembrane conductance regulator dysfunction in platelets drives lung hyperinflammation [J]. J Clin Invest, 2020, 130(4): 2041-53.
[61] VEMANA H P, KARIM Z A, CONLON C, et al. A critical role for the transient receptor potential channel type 6 in human platelet activation [J]. PLoS One, 2015, 10(4): e0125764-75.
[62] CHEN W, THIELMANN I, GUPTA S, et al. Orai1-induced store-operated Ca^{2+} entry enhances phospholipase activity and modulates canonical transient receptor potential channel 6 function in murine platelets [J]. J Thromb Haemost, 2014, 12(4): 528-39.
[63] HARPER M T, LONDONO J E C, QUICK K, et al. Transient receptor potential channels function as a coincidence signal detector mediating phosphatidylserine exposure [J]. Sci Signal, 2013, 6(281): ra50.
[64] BERNA E A, ALBARRAN L, DIONISIO N, et al. The canonical transient receptor potential 6 channel is sensitive to extracellular pH in mouse platelets [J]. Blood Cells Mol Dis, 2014, 52(1): 108-15.
[65] LOPEZ E, BERNA N, BERNA-ERRO A, et al. Relationship between calcium mobilization and platelet α- and δ-granule secretion, a role for TRPC6 in thrombin-evoked δ-granule exocytosis [J]. Arch Biochem Biophys, 2015, 585(1): 75-81.
[66] LOPEZ E, BERNA E A, SALIDO G M, et al. FKBP25 and FKBP38 regulate non-capacitative calcium entry through TRPC6 [J]. Biochim Biophys Acta, 2015, 1853(1): 2684-96.
[67] PAEZ E E V, LIN O A, KARIM Z A, et al. Mouse transient receptor potential channel type 6 selectively regulates agonist-induced platelet function [J]. Biochem Biophys Rep, 2019, 20(1): 100685-98.

勘误声明

2021年43卷第4期, 题为《模块式教学在医学细胞生物学教学中的有机结合》, 作者为王玉、陈萍、董静、吕艳欣、张春艳、伦志强、李鹏辉、张嵩一文由于作者疏忽, 文章勘误: 805页脚注中“批准号: GJB130400”更正为“批准号: GJB1320400”, “Grant No.GJB130400”更正为“Grant No.GJB1320400”。

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