肌浆网钙漏流与心力衰竭

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摘要 钙离子在心脏兴奋-收缩偶联中发挥关键作用, 全细胞钙浓度升高通过激活相关信号通路参与基因表达的调控已受到广泛的关注. 肌浆网是心肌细胞重要的钙库, 在维持细胞内钙稳态起非常重要的作用, 是心肌兴奋-收缩偶联的关键因素. 舒张期心肌细胞肌浆网RyR2通道活性增强, 异常开放增加或关闭不全, 钙离子异常释放, 引起肌浆网钙漏流. 心力衰竭时肌浆网功能障碍, 越来越多的研究表明, 心力衰竭尤其是在终末期, 肌浆网钙漏流所介导的心肌细胞局部钙信号增强, 从而引起心脏发生结构、功能的重构. 本文就肌浆网钙漏流的发生机制及其在心力衰竭发生发展中的作用和研究进展进行简要综述, 并提出展望, 以期对临床心力衰竭的预防和治疗及有效药物的开发应用提供理论依据.

关键词 肌浆网, 钙漏流, 心力衰竭, RyR2

心血管疾病是世界上发生率和死亡率最高的疾病之一, 随着病程的进展, 心脏发生代偿性肥大, 进而失代偿, 并进一步恶化为心力衰竭(简称心衰). 虽然心血管疾病的诊断与治疗已经取得了很大的进展, 但心衰在全世界的发病率与死亡率仍居高不下, 且呈逐年升高趋势. 心力衰竭是由多因素引起的疾病, 其内在的分子机制还不是很清楚, 因此, 其发病机制和防治一直是近年来本领域的研究热点.

钙离子, 作为细胞内第二信使, 在心肌细胞动作电位形成和兴奋-收缩偶联(excitation-contraction coupling, ECC)中, 起着不可或缺的作用^[1]. 心肌细胞对钙离子复杂而又精细的调控, 使得细胞内钙离子保持动态平衡, 从而保证细胞正常的舒缩功能. 不仅如此, 钙信号对于心肌细胞基因表达和正常结构的维持等多种功能都具有重要调节作用, 异常钙信号激活与多种心血

管疾病的发生发展密切相关.

近年来, 钙信号异常在心肌梗死和压力负荷性心肌肥大所造成心力衰竭(heart failure, HF)中的作用也受到高度重视. 压力负荷型(高血压为最常见原因)心肌肥大为例, 在心脏后负荷增加早期, 心肌细胞收缩期钙瞬变(Ca^{2+} transient)显著增高, 通过激活calcineurin-NFAT、钙调蛋白激酶 II (CaM kinase II, CaMK II)等信号通路引起心肌肥大发生. 细胞内 Ca^{2+} 升高还可激活NF- κ B转录活性, 引起心肌肥大^[2]. 心力衰竭时, 心肌细胞钙超载, 即静息期胞浆钙离子浓度升高, 是导致心脏舒缩功能障碍的重要原因^[3,4]. 近些年来, 系列研究工作发现心衰的心肌细胞同样出现舒张期RyR (ryanodine receptor)异常开放, 它通过造成肌浆网(sarcoplasmic reticulum, SR)钙漏流增加^[5], 使SR钙库容量(SR Ca^{2+} content)部分耗竭, 导致收缩期钙瞬变(Ca^{2+} transient)减小, 心肌收

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缩力减弱. SR钙漏流通过启动一系列损伤机制, 造成心律失常、心肌细胞损伤和重构等多方面心脏结构与功能的损害^[6-10].

1 肌浆网钙漏流

SR是心肌ECC的关键因素, 决定了心肌细胞内 Ca^{2+} 释放的时空同步性. 心肌细胞动作电位传来时, 心肌细胞去极化, 细胞膜上的L-型钙通道(L-type Ca^{2+} channel, LCC)开放, 细胞外钙离子内流, 内流的钙离子激发肌浆网上的Ryanodine受体(RyR receptor), 而SR钙经RyR钙释放通道释放到胞浆. 收缩期SR上RyR通道激活, SR钙库内储存的钙离子大量释放入胞浆, 引起心肌细胞收缩; 舒张期RyR通道关闭, 阻止胞浆钙的升高同时保持正常的SR钙库容量. 因此, Ryanodine受体对保持胞内钙的平衡起着非常重要的作用^[11,12].

收缩期RyR的功能对心脏收缩至关重要已广为人知, 而随着激光共聚焦显微成像技术的快速发展和钙荧光染料, 人们得以在真实细胞环境下实时动态呈现活细胞RyR的活动及功能, 舒张期RyR活动对心脏功能的影响才逐渐被认识^[8-10]. 心肌细胞RyR的活动是以4~6个相邻的成簇状分布的RyR为一个单元同步开放, 形成细胞内钙信号的最小单位——钙火花(calcium spark)^[13]. 钙火花发放频率和时空动力学特性反映了舒张期心肌细胞RyR通道的功能状态. 正常心肌细胞舒张期RyR通道主要处于关闭状态, 钙火花频率较低^[8-10,13]. 在病理刺激下, 如心力衰竭, 舒张期心肌细胞肌浆网RyR2活性增强, 通道异常开放增加或关闭不全, 钙离子异常释放, 钙火花频率显著升高, 引起SR钙漏流, 钙库耗竭, 导致收缩期细胞内钙释放不足, 钙瞬变(Ca^{2+} transient)降低, 继而心肌收缩力降低. 本研究组系列的工作也发现高频钙火花介导的SR钙漏流是引起烧伤心脏收缩功能障碍的一个重要机制^[14,15]. 而细胞内 Ca^{2+} 升高后激活相关信号通路, 引起基因转录和蛋白质翻译后修饰, 进而造成心律失常、心室重构等多方面损害^[16-21].

2 心力衰竭钙漏流的发生机制

2.1 RyR2受体的结构及其调节

RyR是一种钙释放通道, 位于心肌细胞肌浆网与细

胞膜和T管L型钙通道相对应的交接处, 与L型钙通道构成心肌细胞兴奋-收缩偶联的基本功能单位. RyR有3种亚型: RyR1, RyR2和RyR3, 心肌以RyR2为主. RyR2是肌浆网上的高分子量同源四聚体, 许多调节蛋白可以结合RyR2参与其功能调节, 这些调节蛋白主要有LCC、钠钙交换体($\text{Na}^+/\text{Ca}^{2+}$ exchanger, NCX)和肌浆网钙泵(sarco/endoplasmic reticulum Ca^{2+} -ATPase, SERCA). 除此之外, 每个RyR2亚单位结合1个FK506-结合蛋白(FK binding protein, FKBP, 心脏以FKBP12.6^[22,23]为主)、钙-钙调素依赖的蛋白激酶II (calmodulin-dependent protein kinase II, CaMK II)、1个cAMP依赖的蛋白激酶(protein kinase A, PKA)、1个蛋白磷酸酶1 (PP1)和1个蛋白磷酸酶2A (PP2A), 后二者分别催化RyR2的磷酸化和去磷酸化, RyR2磷酸化后与FKBP12.6解离, 通道开放, 去磷酸化后与FKBP12.6重新结合并关闭通道. 因此, RyR2作用的正常发挥与其结合蛋白密不可分^[24].

研究表明, 心衰时肌浆网RyR2受体密度下调而亲和力增加, 并且下调的程度与心力衰竭的程度呈正相关^[25]. 这是由于RyR2受体下调介导肌浆网钙漏流, 影响心肌细胞内钙稳态, 激活钙离子依赖性的钙调神经磷酸酶/活化T细胞核因子(calcineurin/nuclear factor of activated T cells, CaN/NFAT)信号通路, 通过调节肥厚相关基因的转录, 从而引起心脏发生结构、功能的重构, 心脏功能下降^[25].

2.2 RyR2受体的调节障碍

(1) FK506结合蛋白(FKBPs)表达下调. 在上述偶联蛋白中以FKBPs的作用最为重要, 且研究较为透彻. FKBPs与RyR2按4:1的关系紧密结合, 即组成RyR2同聚体的每个亚基结合1分子FKBPs^[25]. 近年来研究显示, 心脏存在FKBP12和FKBP12.6, 二者均可与RyR2结合, 只是分子量不同^[26]. 尽管FKBP12的水平远高于FKBP12.6, 但是FKBP12.6与RyR2的亲和力远大于FKBP12, 故RyR2优先与FKBP12.6结合^[27]. FKBP12.6分子量为12.6 kD, 含有2416~2430 aa, 与RyR2结合, 使其稳定处于关闭状态, 并调节RyR2与邻近的多个RyR2通道间的门控偶联, 使相邻的RyR2通道得以同步开放和关闭, 从而阻止舒张期钙渗漏. 而FKBP12.6与RyR2的解离导致通道间解偶联^[28], 心肌细胞对胞浆内 Ca^{2+} 活化的敏感性增强, 引起肌浆网钙漏流, 从而影响心肌的收缩功能.

作为肌质网RyR2的重要调节蛋白,FKBP12.6对于RyR2的功能以及心脏的正常收缩和舒张有重要意义。因此,FKBP12.6成为钙稳态失调相关的心血管疾病的重要靶点。大量研究表明,心衰时FKBP12.6的表达水平显著降低,其从RyR2解离^[23,29],对RyR2的稳定性作用也随之降低,增加了RyR2通道在心肌细胞舒张期异常开放的概率,导致肌浆网钙漏流,钙库耗竭,收缩期钙瞬变降低,继而心肌收缩力降低,而且FKBP12.6与RyR2解离使得RyR2通道收缩时开放和舒张时关闭协调性发生紊乱,进一步加重心肌舒缩障碍,最终出现心力衰竭。在体外实验和利用腺病毒载体在成年兔心肌细胞过表达FKBP12.6,都可以降低肌浆网钙漏流,减少钙火花的发放频率、幅度和时程,增加心肌细胞对Ca²⁺的摄取率,从而增加钙瞬变和肌浆网钙库容量^[27,30,31]。因此FKBP12.6对RyR2的功能起着分子调节开关的作用,有可能作为治疗心肌功能异常的靶点。

(2) CaMK II 和蛋白激酶A (PKA)信号通路激活。大量证据表明,钙调蛋白依赖的蛋白激酶 II (CaMK II) 和蛋白激酶A (PKA)信号通路在心肌肥厚过程中发挥重要作用。高血压、心肌肥大等心血管疾病状态下,血浆及组织局部的儿茶酚胺类物质均显著增加,直接兴奋心肌细胞 β -肾上腺素受体,激活依赖cAMP的PKA以及CaMK II 信号通路,CaMK II 使RyR2磷酸化^[23]。正常心肌每个RyR2通道仅有一个PKA位点被磷酸化,而心力衰竭时则有3~4个PKA位点被磷酸化。RyR2磷酸化后与FKBP12.6解离,RyR2构象改变,RyR2的Ca²⁺敏感度和活性增加,引起肌浆网钙漏流,胞浆内Ca²⁺超载,心脏舒缩功能紊乱。*Rnd3/RhoE*基因缺失可通过激活PKA信号通路导致RyR2磷酸化,引起心肌细胞舒张期肌浆网钙漏流^[32]。而给予CaMK II 抑制剂KN-93和RyR2阻滞剂雷尼丁均能显著抑制心肌肥厚的发生^[33]。

在心力衰竭时,PKA和CaMK II 对RyR2调节作用现存在很大争议。在心衰时RyR2受体存在3个高度磷酸化位点,分别是RyR2-Ser2808, S2814和S2031,CaMK II 上调并激活,介导RyR2-Ser2814高度磷酸化,显著引起舒张期肌浆网钙漏流,引起心力衰竭和心源性猝死^[34]。而PKA介导的心肌细胞RyR2-Ser2808高度磷酸化不会改变FKBP12.6与RyR2的结合能力,也不会显著增加肌浆网钙漏流。因此,van Oort等人^[7]提出,在从心肌肥大到心力衰竭的转变过程中,CaMK II 介导的RyR2磷酸化引起的心肌细胞舒张期肌浆网钙漏流发挥着重

要的作用,而不依赖PKA的磷酸化。

(3) 活性氧自由基增加。RyR2分子含有大量巯基,每分子RyR2含~84个游离巯基,对活性氧自由基(reactive oxygen species, ROS)非常敏感。RyR2一旦被氧化修饰即发生构象变化,引起FKBP12.6与之解离,降低RyR2稳定性,从而增加SR钙漏流^[35,36]。以往的研究发现,现体内生成的一种活性氧自由H₂O₂提高重构到脂质双层膜上RyR通道的开放概率,增加骨骼肌细胞钙火花的发放频率^[37,38]。细胞内大量生成的ROS引起的RyR氧化应激是迄今发现的最重要的机制之一。而Yano等人^[39]最近的研究证实氧化应激降低RyR稳定性,使之易于激活。迄今报道的心脏病理刺激(如心衰)所引起的SR钙漏流都与氧化应激引起的RyR2构象改变,FKBP12.6与RyR2解离使之稳定性降低有关^[6,23,35,36]。

3 心力衰竭钙漏流的治疗

在临床上,心力衰竭患者常规应用 β 受体阻滞剂,这主要是由于 β 受体阻滞剂可能降低RyR2磷酸化水平,减少肌浆网钙漏流,增强心功能,明显降低心力衰竭死亡率^[40]。令人振奋的是,特异性作用于舒张期肌浆网钙漏流的药物已经被研发出来了,在用于治疗心律失常的同时,也可用于心力衰竭的治疗。如正处于II期临床试验阶段的新型特效口服药S44121 (ISRCTN14227980),它可以稳定RyR2与其调控蛋白间的相互作用,抑制舒张期肌浆网钙漏流。但这种试剂对心力衰竭患者的临床作用尚不明确,亟待深入研究^[41]。

FKBP12.6在RyR2功能稳定性的维持中起着分子开关的作用,FKBP12.6与RyR2结合则保持RyR2功能稳定性,否则,RyR2变得异常活跃,引起肌浆网钙漏流增加^[42]。多种病理刺激引起的SR钙漏流都引起FKBP12.6与RyR2解离^[43],因此,稳定FKBP12.6与RyR2的结合是对抗SR钙漏流的最佳治疗措施。近来的研究报道,1,4-benzothiazepine的衍生物JTV 519 (又名K201),具有增加FKBP12.6与RyR2的亲合力,提高RyR2稳定性,减少SR异常钙漏流的作用^[44]。2007年,澳大利亚心脏病专家David Kaye和Monash大学临床药理学系主任Henry Krum在*Nat Rev Drug Discov*联合撰文介绍新发现的具有潜在应用前景的抗心力衰竭药物的靶标,其中列举了JTV 519^[45]。该药物通过抑制SR钙漏流从而发挥治疗心衰和心律失常的作用在动物实验已得到

广泛认识^[46]. 该药物已证实对心衰及心衰诱发的心律失常具有良好的治疗作用^[47], 并且该药治疗房颤的作用已在美国进入 II 期临床试验.

肌浆网钙漏流有助于深入而具体地了解心肌细胞肥大、损伤的发生、发展病理过程, 对预防和治疗心肌肥厚、心力衰竭及有效药物的开发应用具有十分重要的理论意义和应用价值.

4 展望

随着激光共聚焦高速显微成像技术和新一代钙荧光染料的问世, 完整细胞内更微观的局部钙信号逐渐被发现, 随着对其功能的研究人们惊奇地发现, 局部钙信号与细胞生理和病理功能密切相关, 局部钙信号与全细胞钙信号在细胞功能调节上相辅相成, 甚至可能起着与全细胞钙信号完全相反的作用. 例如, 在

平滑肌细胞膜下局部钙信号活动增强非但不同于全细胞钙升高引起平滑肌收缩, 反而通过 Ca^{2+} 激活的大电导钾通道引起平滑肌舒张^[48]. 还有研究发现, SR 钙漏流与骨骼肌的高强度运动适应以及神经元的学习和记忆等相关, 进一步表明局部钙信号在生理和病理结构功能重塑中起重要作用^[49,50]. 最近, 在 *Proc Natl Acad Sci USA* 上报道了一项激动人心的发现, 缺血/再灌注损伤的心肌细胞虽然全细胞 Ca^{2+} transient 减低, 但局部钙信号——RyR 异常活跃, SR 钙漏流激活心肌细胞 Calcineurin-NFAT 信号通路, 触发一系列病理改变和转录机制, 引起缺血/再灌注损伤心脏发生结构、功能的重构^[51], 同时 SR 钙漏流引起线粒体钙积聚, 从而进一步加重缺血/再灌注心肌损伤^[52]. 这一突破性发现率先将心肌细胞局部钙信号活动与心肌重构联系起来. 局部钙信号的发现为正常生命活动调节和疾病发生机制的研究开辟了一条新的途径, 使研究更为深入和精准.

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Sarcoplasmic reticulum calcium leak and heart failure

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Calcium ions play a key role in maintaining the equilibrium of excitation-contraction coupling process in the heart. The increased calcium concentration is primarily responsible for the whole cell activation, relevant signaling pathways involved in regulation of sarcomeric gene expression, and have broader effects on cardiac functioning. Sarcoplasmic reticulum, playing an important role in maintaining the intracellular calcium homeostasis, is the critical factor involved in excitation-contraction coupling in cardiomyocytes. The increased activity of ryanodine receptor 2 (RyR2) channel in diastolic phase leads to its abnormal opening and/or incomplete closing, inducing significant calcium leak from sarcoplasmic reticulum. More and more evidences indicate that, abrupt increase in local calcium concentration, especially in end-stage heart failure, leads to sarcoplasmic reticulum abnormalities as well as reorganization of cardiac structure and its function. Here, we primarily emphasized on the mechanism responsible for calcium leak and explored its therapeutic option, if any, to prevent the development and progression of heart failure by regulating the increased calcium concentration locally.

sarcoplasmic reticulum, calcium leak, heart failure, RyR2

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