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线粒体自噬与心血管疾病

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[摘要] 线粒体自噬是一种细胞内针对功能异常线粒体的选择性降解机制, 在细胞的线粒体质量控制中发挥重要作用。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/再灌注损伤和心力衰竭等。因此, 本文就线粒体自噬的定义、线粒体自噬的两大类活化启动机制(包括泛素依赖型和受体依赖型两大途径及其分子通路)、线粒体自噬水平密切相关的线粒体动力学(包括线粒体分裂和融合过程)以及线粒体自噬在心血管疾病发生、发展中的作用等方面的研究进展作一综述。

[关键词] 线粒体自噬; 心血管疾病; 高血压; 动脉粥样硬化; 心力衰竭

Mitophagy and cardiovascular diseases

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Abstract Mitophagy is an intracellular selective elimination of dysfunctional mitochondria, which plays an important role in mitochondrial quality control in cells. Increasing recent studies indicate that mitophagy participates in the development of cardiovascular diseases, such as hypertension, atherosclerosis, myocardial ischemia /reperfusion injury, heart failure and so on. Therefore, this review summarizes the current knowledge on mitophagy definition, two main kinds of activation and initiation mechanisms of mitophagy, including ubiquitin-dependent and receptor-dependent pathways as well as their molecular mechanisms, mitochondrial dynamics which is strongly associated with the degree of mitophagy, including the process of mitochondrial division and fusion, and the role of mitophagy in the development of cardiovascular diseases.

Keywords mitophagy; cardiovascular diseases; hypertension; atherosclerosis; heart failure

蛋白质和细胞器在细胞生命周期中不断地合成与降解, 因而及时清除衰老、受损、功能异常和过剩的蛋白质和细胞器是维持细胞稳态的关键。自噬是一种进化上保守的细胞内降解机制,

能将胞内物质(如蛋白质和细胞器等)运送到溶酶体进行降解, 从而在蛋白质和细胞器的质量控制中发挥关键作用^[1-3]。自噬根据作用分子途径的不同可以分为大自噬、小自噬和伴侣介导的自

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噬^[1-5], 并参与细胞生理和病理活动的过程, 例如线粒体的更替、脂质代谢的调节、细胞内细菌和病毒的降解以及抗原的呈递等^[3,6]。线粒体作为心肌细胞中含量最丰富的细胞器, 约占心肌细胞体积的30%~40%, 在心肌细胞增殖、凋亡、信号转导及钙稳态维持等过程中发挥了重要作用^[7-10]。且实线粒体的功能障碍与心血管疾病的发生发展密切相关^[8,11]。因此, 线粒体的质量控制成为维持心肌细胞正常功能的重要前提^[8-9]。线粒体自噬是一种选择性线粒体降解方式, 即细胞受到有害因子刺激后通过特有的分子机制清除受损或功能失调的线粒体的过程, 对线粒体的质量控制至关重要^[12]。研究^[8-9,11]表明: 线粒体自噬能够通过不同的途径调节心血管活动, 进而参与了高血压、动脉粥样硬化、心肌缺血/再灌注损伤和心力衰竭等心血管疾病的病理生理过程。

1 线粒体自噬的定义与分子机制

“线粒体自噬”这一术语首先由Lemaster于2005年提出, 其定义为通过特定机制吞噬受损线粒体的过程, 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^[13]。在哺乳动物细胞中, 有多条信号通路参与介导了线粒体自噬的过程^[14-16]。因而, 线粒体自噬根据吞噬囊泡与受损线粒体识别机制的不同可大致分为泛素依赖型及受体依赖型两大类^[15]。

1.1 泛素依赖型

假定激酶蛋白1(PTEN induced putative kinase 1, PINK1)/Parkin为最具代表性的泛素依赖型通路^[15]之一。PINK1是一种具有氨基末端线粒体靶向信号的丝氨酸/苏氨酸激酶, 在正常的线粒体中, PINK1利用其氨基末端的线粒体靶向序列, 通过外膜转位酶和内膜转位酶复合体进入线粒体内, 并被线粒体内膜上的相关蛋白酶降解^[14]。然而, 当线粒体受损时, 其膜电位发生去极化, 抑制PINK1转位至线粒体内膜, PINK1的降解也随之受到抑制, 进而堆积在线粒体外膜上^[17]。PINK1于线粒体外膜上的累积是其激活Parkin(一种细胞质的E3泛素连接酶)的重要步骤, PINK1可以磷酸化Parkin使其激活, 并将其从胞质募集至受损线粒体的外膜上^[18]。同时, PINK1还可以磷酸化线粒体融合蛋白2(mitofusin2, Mfn2), 使其作为心肌细胞线粒体中Parkin的受体发挥作用, 而这一过程又可以

进一步诱导Parkin聚集至线粒体外膜上^[19-20]。激活后的Parkin不仅能够识别受损的线粒体^[18], 还能将泛素连接到位于线粒体的底物上, 使线粒体外膜蛋白泛素化^[21]。微管相关蛋白1轻链3(microtubule-associated protein 1A/1B-light chain 3, LC3)是吞噬囊泡上的一种表面分子, 这些泛素化蛋白作为LC3接头识别位点, 自噬系统接头蛋白如视神经病变诱导反应蛋白(optineurin, OPTN)、核点蛋白52(nuclear dot protein 52, NDP52)、p62和Beclin-1等可以与之结合, 并与LC3相互作用, 从而锚定到吞噬囊泡的隔离膜上, 使其与受损线粒体融合形成自噬体, 从而启动线粒体自噬^[22-23]。

1.2 受体依赖型

受体依赖型线粒体自噬是另一大类别启动机制, 依靠受损线粒体外膜上的FUNDC1(FUN14 domain containing 1)、BNIP3(BCL2 interacting protein 3)以及NIX(Nip3-like protein X)等具有LIR(LC3-interacting region)的蛋白直接与LC3相互作用从而被吞噬囊泡识别。

1.2.1 FUNDC1 通路

FUNDC1是一种氨基末端具有LIR结构的受磷酸化调控活性的线粒体外膜蛋白, 在生理条件下, FUNDC1的LIR模体在Ser13处被CK2激酶(casein kinase 2)磷酸化, 在Tyr18处被Src激酶(Src kinase)磷酸化, 从而抑制了其于LC3的相互作用^[24]。而在缺氧条件下, Src激酶和CK2激酶被抑制, 同时线粒体磷酸酶PGAM5(phosphoglycerate mutase family member 5)在Ser13处与FUNDC1结合使其去磷酸化, 去磷酸后的FUNDC1能够通过LIR与LC3结合从而介导线粒体自噬^[24-25]。而且, 在缺氧条件下FUNDC1也能被ULK1(unc-51-like autophagy activating kinase 1)在Ser17处磷酸化以促进其与LC3结合^[26]。

FUNDC1还可以与视神经萎缩相关蛋白1(optic atrophy protein1, OPA1)及动力相关蛋白1(dynamin-related protein1, Drp1)相互作用, 以调节线粒体动力学及线粒体自噬水平^[27]。在正常条件下, FUNDC1通过与内质网钙联蛋白结合, 定位于内质网-线粒体接触位点上, 并与OPA1相互作用以促进线粒体融合^[27-28]。在应激条件下, FUNDC1与OPA1相互作用减弱, 但与Drp1相互作用增强, 促使FUNDC1从OPA1解离并与Drp1结合^[27]。而且在缺氧条件下, FUNDC1和内质网钙联蛋白的结合被抑制, 而与Drp1的结合被增强^[28], 上述2种机制均导致Drp1向线粒体募集并促进线粒体分裂, 从而进

一步促进线粒体自噬的发生^[27-28]。

1.2.2 BNIP3/Nix 通路

BNIP3和Nix是一种具有相同LIR模体的线粒体外膜蛋白,其羧基末端的跨膜结构域可以与线粒体外膜结合,从而定位于线粒体外膜上;其氨基末端则延伸至胞质中,通过LIR与LC3相关分子结合,招募吞噬囊泡以隔离受损的线粒体^[29]。和NIX不同的是,BNIP3的同源二聚化是其与LC3相互作用的必要条件^[30]。NIX通过调节线粒体自噬在哺乳动物红细胞的分化及成熟过程中发挥着不可或缺的作用^[31-32]。Zhang等^[33]研究表明:在低氧条件下,低氧诱导因子-1 α (hypoxia-inducible factor 1 α , HIF-1 α)可以通过上调BNIP3和NIX的表达来提高细胞内线粒体自噬的水平。与FUNDC1类似,BNIP3/Nix与LC3的相互作用也受磷酸化调控。位于BNIP3 LIR模体的Ser17处和Ser24处的磷酸化促进了其与LC3的结合^[34]。同样,位于Nix LIR模体的Ser34处和Ser35处的磷酸化也增强了它与LC3的相互作用^[35]。

BNIP3/Nix通路与PINK1/Parkin通路之间彼此联系。BNIP3可以诱导Drp1向线粒体移位,促进线粒体分裂、Parkin募集以及线粒体自噬。BNIP3能抑制PINK1被相关蛋白酶降解,并稳定线粒体外膜上的PINK1,以促进Parkin向线粒体募集,从而促进泛素依赖型线粒体自噬的启动^[36]。而Nix也可以被Parkin泛素化,泛素化后的Nix能够招募一种LC3依赖和泛素依赖的自噬受体:NBR1(neighbor of Brca1 gene 1)到线粒体,从而促进受体依赖型线粒体自噬的发生^[37]。因此,线粒体自噬两大类启动机制并不是孤立的,而是相互联系和协同的,复杂而精确地控制线粒体自噬的有效进行。这些仍然需要进一步深入研究,以期解开线粒体自噬的分子机制。

2 线粒体动力学与线粒体自噬

线粒体动力学包括线粒体的融合及分裂过程,其与线粒体自噬水平密切相关,且二者相互影响,在线粒体的质量控制中发挥重要作用^[38]。线粒体分裂是线粒体自噬启动的必要前提^[39]。线粒体分裂蛋白1(fission 1, Fis1)与Drp1相互作用介导线粒体的分裂,以切割受损的线粒体部分;而OPA1和Mfn1/2则负责调控线粒体的融合^[38,40]。受损线粒体由于其膜电位发生去极化,导致OPA1以及被Parkin泛素化后的Mfn1/2被蛋白酶水解,使其无法与线粒体网络融合,进而通过线粒体自噬被清除。如前所述,FUNDC1和BNIP3/Nix通路可以

通过与OPA1、Drp1相互作用,以调节线粒体的融合分裂以及线粒体自噬的水平^[27-28]。抑制OPA1介导的线粒体融合可增强线粒体自噬的作用,而抑制Drp1所介导的线粒体分裂则抑制了线粒体自噬的发生^[39]。因此,以线粒体动力学为靶点的干预可能是调控线粒体自噬进而防治心血管疾病的新方向和策略。

3 线粒体自噬与心血管疾病

3.1 高血压

线粒体自噬在高血压动物模型和由高血压刺激因素(如血管紧张素II)诱导的细胞模型中均能被检测到^[41-42]。PINK1/Parkin是介导线粒体自噬的关键通路之一,而编码Parkin的PARK2基因的遗传变异则会导致血压水平的升高。而且,增强线粒体自噬能够发挥降压和保护心血管的作用。Eisenberg等^[43]研究证实:在高盐饮食喂养的Dahl盐敏感大鼠(一种由高血压导致的充血性心力衰竭的动物模型)中,喂养亚精胺可降低大鼠血压,增加肌动蛋白磷酸化,防止心肌肥厚和舒张功能下降,从而延缓了心力衰竭的进展;且根据食物问卷调查,在人群中高水平的亚精胺饮食与血压水平的下降以及较低的心血管疾病发病率相关。Chen等^[44]采用自发性高血压大鼠(spontaneously hypertensive rats, SHR)和血管紧张素II诱导的血管平滑肌细胞(vascular smooth muscle cells, VSMC)模型,研究发现:虾青素可以通过增加PINK、Parkin、线粒体转录因子A以及线粒体DNA(mtDNA)等表达来促进线粒体自噬和线粒体的生物合成,从而减轻了高血压所致的血管重塑。然而,Zhang等^[42]研究表明:线粒体自噬的增加与肾血管性高血压所致的心功能不全相关,而血管紧张素II受体拮抗剂缬沙坦可以通过降低心肌细胞中线粒体自噬的水平来发挥心脏保护作用。线粒体自噬在高血压发病过程中表现出功能差异,可能与疾病的不同模型,不同阶段和不同物种的差异有关,因而有必要进一步的探索。

3.2 动脉粥样硬化

线粒体自噬水平与氧化修饰低密度脂蛋白(oxidized low density lipoprotein, ox-LDL)高度相关,而ox-LDL则是促进动脉粥样硬化发生发展的关键因素。体外研究^[45-46]发现活化线粒体自噬抑制了ox-LDL所诱导的人VSMC的凋亡。增强PINK1的表达能够提高线粒体自噬的水平,从而增加了

其对VSMC的保护作用, 而沉默PINK1基因则逆转了这一作用^[45-46]。脂质激活的真核细胞起始因子2 α (eukaryotic initiation factor 2 alpha, eIF2 α)也可以通过抑制Parkin介导的线粒体自噬, 促进高脂血症诱导的动脉粥样硬化相关炎症反应^[47]。此外, 磷酸酶和张力蛋白同源物(phosphatase and tensin homolog, PTEN)能够通过抑制线粒体自噬促进内皮细胞凋亡^[48]。与之相反, 核受体亚家族4组A成员1(nuclear receptor subfamily 4 group A member 1, NR4A1)能够通过CaMKII-Parkin-线粒体自噬途径促进ox-LDL介导的内皮细胞凋亡和动脉粥样硬化形成^[49]。线粒体靶向治疗是动脉粥样硬化的一种前瞻性治疗方案, 有关线粒体分裂的特异性抑制剂如: 线粒体分裂抑制剂1(mitochondrial division inhibitor 1, Mdivi-1)和P110(一种抑制Drp1和Fis1相互作用的肽)等, 目前正在研究中^[50]。

3.3 心肌缺血 / 再灌注损伤

过度激活线粒体自噬所导致的线粒体大量丢失, 以及线粒体自噬不足所致的功能障碍的线粒体堆积都对心肌有害。适当增加线粒体自噬却能够减轻心肌缺血/再灌注(ischemia/reperfusion, I/R)损伤。治疗性低温能够通过增加心肌线粒体自噬来减轻心肌I/R损伤后的炎症反应和纤维化, 从而改善心功能^[51]。富氢的生理盐水和阿魏酸则能够通过增加PINK1/Parkin介导的线粒体自噬来减轻心肌I/R损伤中的炎症反应和细胞凋亡^[52-53]。且三碘甲状腺原氨酸处理后和解偶联蛋白2(uncoupling protein 2, UCP2)也可以通过增强PINK1依赖的线粒体自噬途径, 对I/R损伤的心肌起到保护作用^[54-55]。然而, 研究也发现线粒体自噬可能会促进心肌I/R损伤。Lee等^[56]采用H9C2细胞缺氧/复氧模型研究发现: 维生素D分别通过抑制Drp1/Mff、BNIP3/LC3B减少缺氧/复氧诱导的线粒体分裂及线粒体自噬, 维持线粒体结构和功能完整性, 从而减轻I/R所致的心肌损伤。G蛋白偶联雌激素受体1(G protein-coupled oestrogen receptor 1, GPER1)和Notch1通过抑制PINK1/Parkin介导的线粒体自噬来维持线粒体结构的完整性, 从而在I/R损伤过程中发挥其对心肌的保护作用^[57-58]。鞣花酸则通过抑制BNIP3介导的线粒体自噬来改善I/R损伤后心肌细胞的凋亡及线粒体损伤^[59]。线粒体的这种双面性仍然有待于进一步研究。

3.4 心力衰竭

研究^[60]表明: 线粒体自噬的标志物在心力衰

竭患者中表达增加, 例如PINK1、Parkin和BNIP3等。AMP依赖的蛋白激酶 α 2(AMP-activated protein kinase alpha 2, AMPK α 2)和酮可以提高线粒体自噬的水平, 从而阻止心力衰竭的发生^[61-62]。转铁蛋白受体(transferrin receptor 1, Tfr1)通过增加线粒体自噬活性, 在心力衰竭过程中对心脏发挥保护作用^[63]。而线粒体钙单向转运体(mitochondrial calcium uniporter, MCU)和线粒体外膜18 kD的线粒体转位蛋白(mitochondrial translocator protein, TSPO)能够抑制线粒体自噬, 从而诱导压力超负荷性心力衰竭的发生^[64-65]。以上研究表明线粒体自噬在心力衰竭的发生发展中对心脏有保护性作用。然而, 线粒体自噬活性的过度增加所导致的线粒体过度清除则会促进心力衰竭的进展。胰岛素样生长因子II(insulin-like growth factor II, IGF-II)及其受体(IGF-IIR)在心力衰竭的发生发展中起着至关重要的作用。Drp1引起的线粒体过度分裂增强了Rab9依赖的线粒体自噬, 从而促进了心力衰竭过程中IGF-IIR诱导的线粒体功能障碍, 并最终降低了心肌细胞的存活率^[66-67]。近年来, 使用靶向作用于线粒体的小分子物质已经逐渐成为心力衰竭的替代治疗策略之一, 如Mfn1- β IIPKC的选择性拮抗剂(peptide that selectively antagonizes Mfn1- β IIPKC association, SAM β A)通过选择性地抑制心力衰竭时Mfn1- β IIPKC的过度激活, 减少线粒体分裂以及功能失调的线粒体的累积, 从而能够减缓射血分数降低乃至射血分数保留的心力衰竭的进展^[68]。

越来越多的研究认为, 通过调节线粒体自噬及线粒体动力学以实现线粒体的质量控制, 可能是治疗心血管疾病的新策略。除上述物质外, 一些天然药物, 如梓醇、红景天苷等, 能够通过增强线粒体自噬的活性, 发挥心肌保护作用^[69]。

4 结语

线粒体自噬是机体的一种选择性降解机制, 主要通过泛素依赖型和受体依赖型途径活化启动, 而且不同途径间存在相互联系和影响。虽在体外已有技术能够检测心肌的线粒体自噬水平, 但在体内仍需研发一种准确而有效的检测方法, 且以非侵入性的方式评估人类心肌的线粒体自噬水平面临着更大的挑战。线粒体自噬在诸如高血压、动脉粥样硬化、心肌缺血/再灌注性损伤和心力衰竭等心血管疾病的发病过程中具有“双刃剑”效应。线粒体的双层膜结构是阻碍某些药物

(如天然药物等)作用的关键屏障。因此,一方面需要阐明线粒体自噬在心血管疾病中调控机制,进而精准而适度调控线粒体自噬过程使其有利于心血管疾病的防治。另一方面则需要筛选更多靶向作用于线粒体的药物或通过纳米技术增加药物对于线粒体内外膜的渗透性;确定线粒体自噬相关蛋白的作用靶点和特定心血管疾病之间更为直接的联系,并促进其从基础研究成果转化为临床实践,以开发更有效的心血管疾病治疗药物或物理疗法以期最终造福心血管疾病患者。

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