

cGAS-STING信号通路在心血管疾病中的作用

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摘要 环鸟苷酸腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS)作为一种DNA感受器通过识别胞质DNA产生环鸟苷酸-腺苷酸(cyclic GMP-AMP, cGAMP)并激活干扰素基因刺激因子(stimulator of interferon gene, STING)及一系列下游通路从而介导免疫及炎症反应。近年来研究发现, cGAS-STING所介导的信号通路在心肌梗死、心力衰竭、心肌炎等多种心血管疾病中被显著激活, 提示其在心血管系统疾病的发病进程中扮演重要角色。为了更深入地了解cGAS-STING信号通路在心血管疾病中的作用, 该文就cGAS的生化特点、cGAS-STING介导的信号通路及其在心血管疾病中的作用等方面的研究进展进行综述。

关键词 cGAS; STING; 炎症反应; 心血管疾病

The Impact of cGAS-STING Signal Pathway in Cardiovascular Diseases

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Abstract cGAS (cyclic GMP-AMP synthase) is a DNA sensor that generates cGAMP (cyclic GMP-AMP) by recognizing cytoplasmic DNA, which subsequently activates the STING (stimulator of interferon gene) and a series of downstream pathways to mediate immune and inflammatory responses. In recent years, emerging evidences show that cGAS-STING signal pathways are significantly activated in a variety of cardiovascular diseases such as myocardial infarction, heart failure and myocarditis, suggesting that it may play an important role in the pathogenesis of cardiovascular diseases. To further understand the functions of cGAS-STING signal pathways in cardiovascular diseases, this article summarizes the biochemical characteristics of cGAS and the role of cGAS-mediated signal pathways in cardiovascular diseases.

Keywords cGAS; STING; inflammatory response; cardiovascular disease

现今, 随着血管紧张素转换酶抑制剂^[1]、血管紧张素II受体阻滞剂^[2]、醛固酮受体阻断剂^[3]、 β -肾上腺素受体阻断剂^[4]及兼有血管紧张素II受体阻滞剂和增加利钠肽水平双重作用的血管紧张素受体脑啡肽酶抑制剂^[5]等心血管类药物的临床合理应用明

显降低了心血管疾病如心肌梗死、心力衰竭的死亡率及再住院率。但即便如此, 2017年死于心血管疾病(cardiovascular disease, CVD)的人数约占全世界死亡人数的32%^[6]。因此, 如何降低心血管疾病的发生、延缓心血管疾病的恶化并改善心血管疾病患者

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的预后, 仍是需要攻克的一大全球公共卫生问题。

环鸟苷酸腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS), 又名MB21D1, 是一种DNA传感器, 与双链DNA(double-stranded DNA, dsDNA)结合后被活化并产生环鸟苷酸-腺苷酸(cyclic GMP-AMP, cGAMP), cGAMP可作为第二信使活化干扰素基因刺激因子(stimulator of interferon gene, STING), 进而促进炎症反应, 并在宿主抗病原体、肿瘤免疫、自身免疫性疾病和衰老相关炎症中发挥独特和关键的作用^[7-9]。炎症因子及炎症介质早已被证明在心血管疾病如心力衰竭^[10]、心肌梗死^[11]等疾病的发生及发展过程中发挥重要的作用, 且近来研究发现cGAS-STING信号通路在心肌梗死、心力衰竭中被显著激活, 提示cGAS-STING信号通路在心血管疾病的发病进程中扮演重要的角色。因此, 进一步明确cGAS-STING信号通路在心血管系统中的作用, 将可能为寻找干预心血管疾病的新靶点提供方向^[7-8]。本篇综述将主要从cGAS的生化学特点、cGAS-STING介导的信号通路及在心血管系统中的作用进行概述。

1 cGAS的结构与生物化学特点

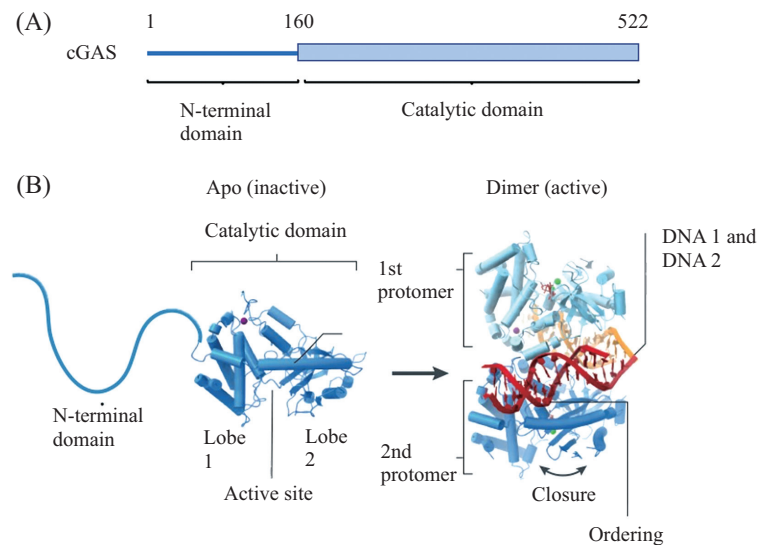
1.1 cGAS结构

人类cGAS基因定位于人染色体6q13, 其编码

的cGAS由522个氨基酸组成, 包含一个可介导cGAS与细胞膜结合的长度为160个氨基酸的N末端及一个长度为362个氨基酸的核苷酸转移酶结构域, 该结构域呈双叶结构, 其催化结构域位于两叶间裂缝处^[12-13](图1)。每个cGAS表面存在两个可与DNA结合的位点, 即A位点及B位点, A位点主要在cGAS与DNA结合后的构象变化中发挥作用, B位点主要参与cGAS二聚体与DNA的协同结合^[14]。dsDNA与cGAS结合后将诱导cGAS构象变化, 形成由cGAS及dsDNA构成的2:2的二聚体结构, 每个dsDNA分别与二聚体中一个cGAS的A位点及另一个cGAS的B位点结合^[14-15]。近年来, 研究发现cGAS表面存在第三个结合位点, 即C位点, 且C位点与cGAS二聚体的形成及cGAS活化密切相关^[16]。

1.2 cGAS细胞定位

研究报道, cGAS广泛存在于细胞内, 它可位于细胞质、细胞核, 甚至还可定位于细胞膜的胞质侧。早在2006年, STETSON和MEDZHITOV^[17]发现胞质DNA可通过不依赖于Toll样受体的机制促进I型干扰素的产生, 进而首次提出“胞质DNA传感器”这一概念, 即核膜将某种DNA的天然免疫识别受体分隔在胞质中, 在保证其与胞质DNA结合的同时避免其与自身基因组DNA相互作用。直至2013年,



A: 人cGAS全长示意图, 其包括由160个氨基酸构成的N末端及由322个氨基酸构成的活性结构域; B: cGAS结构示意图(左图), DNA与cGAS结合并形成二聚体结构后通过促进cGAS构象改变、暴露cGAS活性位点从而激活cGAS(右图)。

A: schematic drawing of human full-length cGAS domain, containing a 160-amino-acid N-terminal domain along with a 362-amino-acid catalytic domain; B: schematic drawing of cGAS structure (Left). DNA binding and dimer formation activate cGAS by ordering of an active site activation loop and closure of the active site channel (Right).

图1 cGAS的结构及其活性构象(根据参考文献[7]修改)

Fig.1 cGAS structure and its active conformation (modified from reference [7])

CHEN等^[9]通过分离纯化及定量质谱分析首次发现了属于核苷酸转移酶超家族的cGAS, 并证明cGAS与胞质DNA结合后可通过促进I型干扰素的产生发挥“胞质DNA传感器”的作用。但是, “胞质DNA感受器”这一假说目前尚存在诸多争议。首先, 不同学者发现在人胚胎肾细胞、人宫颈癌细胞、巨噬细胞及人髓系白血病单核细胞(human myeloid leukemia mononuclear cell, THP-1)等多种细胞类型的细胞核中均存在丰富的cGAS^[18]。其次, 除了痘病毒之外, 大部分DNA病毒都是在细胞核内进行DNA复制, cGAS活化生成I型干扰素介导的抗病毒反应同样是抑制病毒在细胞核内复制的重要机制, 这一机制在cGAS基因敲除小鼠中亦得以验证^[19-20]。因此, 正常情况下, 定位于细胞核内的cGAS如何做到不与自身DNA相结合或处于失活状态呢? 最新研究发现, 细胞核内的核小体核心颗粒(nucleosome core particle, NCP)是重要的cGAS抑制因子。它可以通过多种机制竞争性抑制cGAS的活化, 包括NCP对A位点或B位点的空间占位或串联B位点及C位点形成cGAS-NCP链阻止cGAS与DNA结合, 同时还可抑制cGAS的二聚化过程^[21]。

cGAS除了定位于细胞质、细胞核外, 最新报道显示其在THP-1、永生化的骨髓来源巨噬细胞等细胞中, 还可通过N末端与磷脂酰肌醇4,5二磷酸相互作用定位于细胞膜内侧, 且N末端缺失的cGAS对自身DNA的反应性升高, 对于痘病毒DNA的反应性降低^[22]。学者们认为, cGAS定位于细胞膜不仅使其与内源性DNA分隔, 还可以促进cGAS更快、更高效地与病毒DNA反应^[22]。

1.3 cGAS翻译后修饰

蛋白水解、乙酰化、谷氨酰化、泛素化、甲基化、SUMO化及磷酸化等是精准调控cGAS活性的重要机制^[7]。SONG等^[23]通过对GFP-cGAS进行质谱分析发现, GFP-cGAS中存在6个磷酸化位点及8个乙酰化位点, 且磷酸化S305位点及乙酰化K384、K414位点可抑制cGAS依赖的凋亡, 但是乙酰化K198位点反而促进细胞因子的产生。DAI等^[24]发现, 阿司匹林可通过乙酰化cGAS抑制cGAS激活, 从而有效抑制TREX1^{-/-}小鼠的I型干扰素反应并延长小鼠生存期, 更重要的是, 予以低剂量阿司匹林即可明显抑制Aicardi-Goutieres综合征患者的I型干扰素反应。DNA病毒感染后, 细胞中含半胱氨酸的天冬氨酸

蛋白水解酶-1可通过切割cGAS中D140、D157位点以减少cGAMP产生、抑制I型干扰素反应^[25]。最新研究表明, 蛋白精氨酸甲基转移酶5(protein arginine methyltransferase 5, PRMT5)可通过甲基化cGAS的R124位点, 抑制cGAS与DNA的结合并减少I型干扰素的产生, 将cGAS的R124位点的精氨酸替换为赖氨酸或者予以PRMT5抑制剂均可减少cGAS甲基化并促进下调的I型干扰素反应显著恢复^[26]。理解cGAS的翻译后修饰机制及其作用将有助于进一步阐明cGAS-STING通路介导的相关疾病的机制。

2 cGAS-STING下游的信号通路及其生物学功能

2.1 cGAS-STING-TBK1-IRF3经典通路介导I型干扰素反应

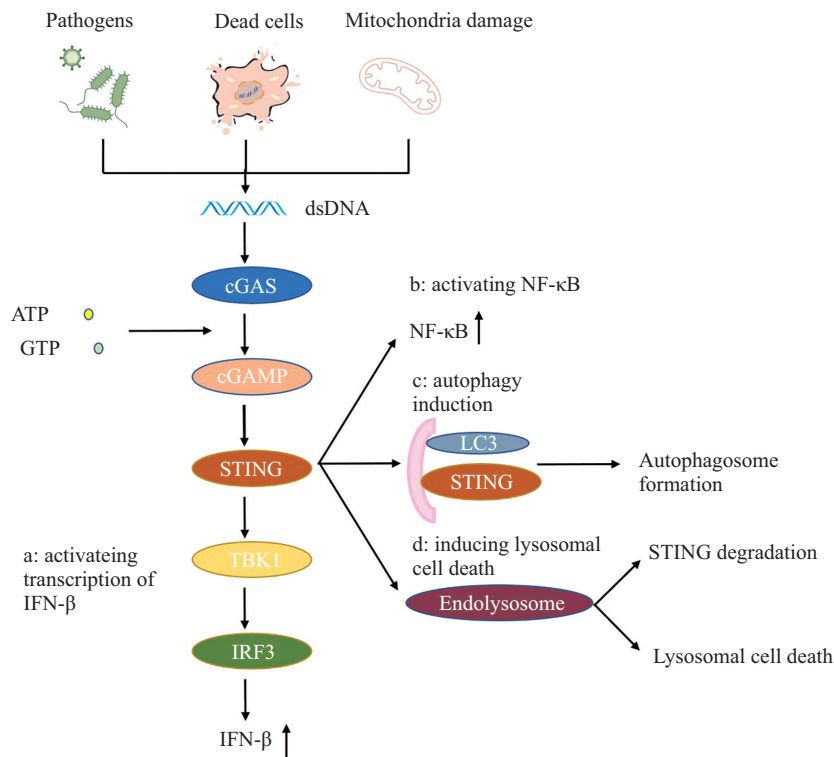
目前研究发现, cGAS与dsDNA结合后形成一个2:2的二聚体并被激活, 且>16 bp的dsDNA即可同时与cGAS表面的A位点及B位点结合并激活cGAS^[14]。LUECKE等^[27]研究发现, 在较高浓度(1.67 μg/mL) DNA的环境下, 88~4 003 bp的dsDNA刺激THP1细胞后I型干扰素的表达无明显差异, 但是在较低浓度(0.167 μg/mL)及低浓度(0.016 7 μg/mL) DNA的情况下, dsDNA促进I型干扰素表达的能力与dsDNA长度成正比, 这一特点使得胞质内微生物DNA在低浓度的情况下同样能激活保护性免疫反应^[15]。与dsDNA结合后cGAS活性结构域构象发生改变, 以ATP、GTP为底物经两步反应生成2',3'-cGAMP^[13]。随后cGAMP将作为第二信使结合并活化定位于内质网上的STING^[28]。STING活化后出现构象改变并形成多聚体复合物, 且从内质网转移至高尔基体^[29-31]。转移至高尔基体的STING蛋白上两个半胱氨酸残基(Cys88/91)被棕榈酰化。尽管棕榈酰化的具体机制尚不清楚, 但这一过程为STING及下游分子的激活所必需的^[32]。与此同时, STING将通过其C末端的TANK结合激酶1(TANK-binding kinase 1, TBK1)结合序列招募并磷酸化TBK1, 活化的TBK1进一步磷酸化位于其相邻的STING蛋白C末端的保守共有序列(phosphorylation of a conserved consensus motif, pLxIS), 随后干扰素调节因子3(interferon regulatory factor 3, IRF3)将与磷酸化的pLxIS序列结合并靠近TBK1, 进而促进IRF3的磷酸化, 最终促使IRF3二聚体化后进入细胞核, 从而促进I型干扰素的表达(图

2a)^[33-35]。cGAS-STING通路是抗病原体免疫反应的重要机制之一。大量证据证明, cGAS-STING通路在1型单纯疱疹病毒及卡波西肉瘤相关疱疹病毒等DNA病毒感染中通过诱导I型干扰素反应发挥重要的抗病毒免疫作用^[36-37]。

2.2 cGAS-STING-NF-κB途径介导炎症反应

除了经典的cGAS-STING-TBK1-IRF3通路外, 目前研究发现cGAS-STING信号通路还可以通过不依赖IRF3的其他途径发挥更多功能^[8]。尽管过去的研究发现, cGAS-STING信号通路介导炎症反应与核因子-κB(nuclear factor-kappa B, NF-κB)、丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)的激活相关, 但是cGAS-STING信号通路活化NF-κB、MAPK机制尚不明确。YU等^[38]研究发现, 核蛋白TAR DNA/RNA结合蛋白43可通过打开

线粒体通透性转换孔, 导致线粒体DNA(mitochondrial DNA, mtDNA)释放入胞质, 激活cGAS-STING通路, 上调NF-κB。在肌萎缩侧索硬化症(amyotrophic lateral sclerosis, ALS)患者的诱导性多能干细胞起源的运动神经元及ALS模型小鼠中予以STING抑制剂后, 小鼠大脑皮质和脊髓中的NF-κB表达显著降低且神经变性疾病得到明显改善。此外, ABE等^[39]及FANG等^[40]研究发现, TBK1的活化能进一步上调NF-κB的表达。然而, DE OLIVEIRA MANN等^[41]的研究显示, 人及小鼠细胞中STING的C末端缺失突变后, NF-κB表达未见明显下降。亦有研究表明, 在果蝇中STING可通过不依赖于TBK1的免疫缺陷途径促进NF-κB的表达(图2b)^[42]。尽管TBK1在STING介导的NF-κB激活中所扮演的角色仍有待进一步探究, 但学者们认为NF-κB的活化是完全诱导I型干扰素反应的重要条件之一,



a: cGAS与DNA结合后经过一系列构象改变从而转变为活性状态, 并以ATP及GTP为原料合成2',3'-cGAMP, 随后, 2',3'-cGAMP将结合并活化STING。TBK1活化后将促进TBK1依赖性的IRF3磷酸化, 并促进IFN-β的表达。b: NF-κB的活性既可能被TBK1活化后的下游所调控, 亦可被源自STING中尚未确定的机制调控。c: STING促进LC3的脂化及自噬小体的形成。d: 活化的STING将被分选至溶酶体从而被降解, 然而溶酶体内STING的累积可导致溶酶体通透性增加并诱导细胞死亡, 这一现象被称为溶酶体细胞死亡。

a: upon binding to DNA, cGAS undergoes a conformational change to an active state and produces 2',3'-cGAMP from ATP and GTP, which is subsequently binding to and activates STING. Followed by TBK1 activation, then leading to TBK1-dependent phosphorylation of IRF3 and transcriptionally promote IFN-β expression. b: activation of NF-κB is either governed downstream of TBK1 activation or emanates from a yet to be identified mechanism in STING. c: STING promotes LC3 lipidation and autophagosome formation. d: activated STING is trafficked to endolysosomes for degradation. STING accumulation in lysosomes leads to lysosomal membrane permeabilization and following cell death known as lysosome-dependent cell death.

图2 cGAS-STING信号通路及其生物学功能

Fig.2 cGAS-STING signal pathways and its biological functions

在NF- κ B未活化或抑制NF- κ B表达的细胞中转染dsDNA或感染病毒后仅能产生少量I型干扰素^[43-44]。

2.3 cGAS-STING-LC3途径介导自噬小体形成

cGAS-STING信号通路除了通过激活IRF3、NF- κ B发挥抗病原体感染的作用外,还能通过诱导自噬在一些病原体感染如结核分枝杆菌、单纯疱疹病毒及某些革兰阳性细菌感染中发挥抗病原体感染的作用^[45-47]。当STING与cGAMP结合并被活化后,STING从内质网转移至内质网-高尔基体中间体(endoplasmic reticulum-golgi intermediate compartment, ERGIC),含有STING的ERGIC将作为LC3脂化的来源,这是自噬小体形成的关键步骤,同时,cGAMP也可能通过依赖于WIPI2和ATG5途径促进LC3脂化(图2c)^[7,47]。GUI等^[47]研究发现,海葵中的STING虽然缺少C末端,但依然能诱导自噬,提示诱导自噬可能是STING古老且原始的功能。因此,cGAS-STING信号通路中依赖于TBK1及IRF3表达I型干扰素的途径与其诱导自噬的途径是互不关联的,但是两者在抗病毒感染及炎症反应等生物学作用中可以互补。

2.4 cGAS-STING介导溶酶体性细胞死亡

感染、无菌性炎症以及癌症导致各种DNA损伤后,释放至胞质的DNA可以导致多种类型的细胞死亡。其中,cGAS-STING信号通路诱发的溶酶体性细胞死亡途径可能是胞质DNA诱导细胞程序性死亡的重要机制之一(图2d)^[48]。STING结合并活化TBK1后将从高尔基体被分选至Ras相关蛋白7阳性的溶酶体,最后在溶酶体中被降解^[47,49]。近来,研究发现在人髓系细胞中,胞质DNA诱导cGAS-STING信号通路活化后,STING将转移至溶酶体,通过增加溶酶体通透性诱导溶酶体破裂,随后导致溶酶体细胞死亡,同时溶酶体性细胞死亡将促进胞质K⁺外流,激活NOD样受体家族3炎症小体,进一步促进细胞死亡及促炎症因子的释放^[50]。但是,STING从高尔基体转移至溶酶体后,最终是被溶酶体降解还是诱导溶酶体性细胞死亡的机制尚不明确。

3 cGAS-STING通路对心血管系统的致病作用

3.1 心肌梗死

急性心肌梗死是一种由于冠脉堵塞或冠脉供需氧失衡导致心肌缺血坏死的疾病,心肌细胞损伤及死亡后损伤相关分子模式(damage-associated

molecular patterns, DAMPs)的释放将激活固有免疫反应。有研究发现,心肌梗死后外周血单核细胞的增多是心肌梗死患者左室重构的独立预测因子,提示单核细胞在心肌梗死的发生及发展中发挥重要作用^[51]。KING等^[52]通过对小鼠心肌梗死区域的细胞群进行单细胞RNA测序分析,分离出一群单核细胞来源的干扰素诱导细胞(interferon-inducible cells, IFNICs),且IFNICs可通过吞噬外源DNA激活cGAS-STING信号通路以促进I型干扰素的产生并参与心肌梗死后心室重构,而cGAS、IRF3、IFNAR基因敲除或予以I型干扰素受体中和抗体则能有效改善小鼠的心室重构。巨噬细胞可分为M1及M2表型,不同表型的细胞分别发挥不同的作用,M1型巨噬细胞主要发挥促炎症作用及抗微生物作用,M2表型主要发挥抗炎及促进修复作用,CAO等^[53]研究发现,急性心肌梗死后抑制cGAS的表达将促进巨噬细胞向M2表型转化,从而减轻心梗后心肌损伤,促进心肌修复。因此,抑制cGAS-STING信号通路的激活可能对心肌梗死具有治疗价值。

心肌梗死后心肌细胞损伤的形式包括细胞坏死、细胞凋亡及自噬。细胞凋亡过程中活化的Bax(Bcl-2-associated X protein)/BAK(Bcl-2 homologous antagonist/killer)在线粒体外膜成孔,使mtDNA流入胞质^[54-55]。这提示在心肌梗死中除了细胞外DNA外,胞质mtDNA亦可能激活cGAS-STING信号通路。但是在结扎小鼠左冠状动脉第4天后,梗死区红色标记的非干扰素反应细胞呈现典型的具有肌节的心肌细胞形态,绿色荧光标记的干扰素反应细胞为非心肌细胞^[52]。因此,心肌细胞损伤后mtDNA释放入细胞是否可激活cGAS-STING信号通路及其在心肌细胞损伤过程中所发挥的作用仍需进一步实验验证。

3.2 心力衰竭

心力衰竭是一种由心脏结构或功能异常引起的,以呼吸困难、下肢浮肿和乏力等症状以及颈静脉压增高、肺水肿及外周水肿等体征为特征的综合征,是全球范围内死亡率不断增加的主要原因之一^[56]。越来越多的证据表明,心力衰竭是一种慢性炎症性疾病,炎症通路的激活将会进一步导致左室重构及左室功能障碍,但炎症在心力衰竭的发展中的作用机制目前尚不明确,且在RENEWAL^[57]、EXACT-HF^[58]、OPT-CHF^[59]等临床试验中对于心

力衰竭患者的抗炎治疗未见明显疗效,因此探明其他炎症通路在心力衰竭中的作用机制,有助于寻找新的防治心力衰竭的潜在靶点^[10-11,60-61]。研究表明,在继发于缺血性心脏病的心力衰竭患者中,植入左心室辅助装置可有效抑制cGAS及其下游CXCL10的表达,提示cGAS-STING信号途径在心力衰竭中被有效激活^[53]。HU等^[62]研究发现,在压力超负荷诱导小鼠心力衰竭模型中,抑制cGAS-STING信号通路可以减少炎症因子及炎症细胞浸润、抑制心肌细胞凋亡,从而改善心肌重构,保护心脏功能。有关心力衰竭与cGAS-STING信号通路的研究尚处于起步阶段,cGAS-STING信号通路在心力衰竭的疾病进程中所发挥的具体作用及其靶向cGAS-STING通路对心力衰竭的干预价值仍有待进一步研究和探讨。

3.3 心肌炎

病毒、细菌、真菌、寄生虫感染及其他非感染因素(如自身免疫性心肌炎及药物作用)是心肌炎的常见病因^[63]。病毒感染诱发炎症反应,进而导致心肌细胞坏死或凋亡是心肌炎发生发展的重要的病理生理机制之一^[64-65]。近来有研究表明,cGAS-STING信号通路在病毒性心肌炎中发挥“双刃剑”的作用,一方面,病毒感染后胞质中的病毒DNA能激活cGAS-STING信号通路,促进I型干扰素的产生从而发挥抗病毒作用,另一方面,cGAS-STING信号通路的激活也将诱导炎症反应并进一步加重心肌损伤^[66-67]。除病毒性心肌炎外,cGAS同样在其他微生物感染及非感染性心肌炎中发挥重要作用。在脂多糖诱导的脓毒症心肌损伤小鼠模型中,STING及p-IRF3表达水平明显增加,敲除STING基因能明显抑制脂多糖诱导的心肌细胞炎症、凋亡及焦亡,并改善小鼠心功能,延长小鼠生存期^[68]。研究发现,克氏锥虫感染可有效激活多聚ADP核糖聚合酶1-cGAS-NF- κ B通路并通过促进炎症巨噬细胞的转化最终促进心肌炎的发生,抑制cGAS的激活可有效抑制这一炎症反应^[69]。此外,cGAS在自身免疫性心肌炎的发生发展中同样扮演着重要的角色。在TREX1基因敲除诱导的自身免疫型心肌炎小鼠模型中,予以靶向抑制cGAS的药物可显著降低模型小鼠心脏组织中IFN- β 、干扰素刺激基因及cGAMP的表达,并抑制心内膜纤维化及炎症反应^[70]。由此可见,

cGAS-STING信号通路在心肌炎的发生、发展及预后等方面发挥重要作用,在保证cGAS-STING信号通路发挥抗病原体作用的基础上,如何避免其诱导过度炎症反应进一步损伤心肌,这一问题仍有待更深入的研究。

3.4 心血管疾病相关危险因素介导cGAS-STING信号通路

衰老、吸烟及肥胖等心血管疾病危险因素也通过介导cGAS-STING信号通路促进心血管疾病的发生发展。细胞衰老是一种由于各种因素引起的细胞周期停滞状态,衰老细胞可分泌多种炎症因子,被统称为衰老相关分泌表型(senescence-associated secretory phenotype, SASP),SASP细胞产生一系列自分泌和旁分泌因子导致内皮功能障碍、内膜增厚、动脉粥样硬化、心血管重构、心律失常及心力衰竭等心血管病变^[71]。氧化应激、辐射、癌基因激活及药物可通过cGAS-STING信号通路调控SASP因子的生成,促进细胞衰老并调控SASP因子生成^[72-73]。棕榈酸作为游离脂肪酸中的主要类型之一,可通过损伤线粒体、释放mtDNA,进而激活mtDNA-cGAS-STING-IRF3通路最终引起内皮细胞炎症及胰岛素抵抗,而STING^{st/st}小鼠中这一反应明显减弱^[74]。有学者通过对PolSenior项目(旨在评估 ≥ 65 岁的波兰人的健康和社会经济状况的多中心、跨学科项目)的参与者进行基因分型,发现STING 293Q等位基因突变的肥胖或吸烟的患者患心血管疾病的概率更低,并证明STING与衰老相关疾病特别是心血管疾病息息相关^[75-76]。除此之外,HUANG等^[77]研究同样证明,细菌内毒素脂多糖诱导mtDNA释放入胞质后能激活cGAS-STING信号通路,并通过磷酸化Yes相关蛋白1使其失活以抑制血管内皮细胞的增殖,而cGAS基因敲除小鼠的血管内皮再生能力明显改善。大量临床研究表明,阿尔茨海默病的患者合并心血管事件的概率明显升高,而褪黑素可通过ALDH2调节cGAS-STING-TBK1通路所介导的线粒体自噬以改善小鼠APP^{swe}/PS1^{dE9}突变引起的线粒体损伤及心功能^[78]。这些研究结果均表明,cGAS在心血管疾病中发挥重要的作用,其可能通过多种不同的机制来影响心血管疾病的发生发展。

4 小结与展望

综上所述,cGAS-STING信号通路可以通过介

导炎症、调节免疫、促进自噬、促进衰老多种不同的机制影响心血管疾病如心肌梗死、心力衰竭、心肌炎等的发生发展。动物实验研究已证实,抑制cGAS-STING信号通路可明显改善多种心血管疾病如心肌梗死、心力衰竭、心肌炎等状态下的心功能,并延长实验动物生存期,提示cGAS-STING信号通路可能成为心血管疾病干预的潜在靶点。然而,心血管系统疾病的种类繁多且机制复杂,目前有关cGAS-STING信号通路在具体的、不同的心血管疾病中的机制探讨仍不全面,且证据尚有限或仍存有争议,如心肌梗死后抑制cGAS表达将促进血管生成,而在主动脉缩窄处理的小鼠中抑制cGAS-STING通路不影响血管生成^[53,62]。出现这两种截然相反的结果可能与选用小鼠模型不同及所选择的观察时间点有所差异有关。由此可见,目前cGAS-STING信号通路在心血管疾病中的病理生理机制还有待进一步深入研究。随着对cGAS-STING信号通路在心血管疾病中的研究不断深入,相信其可为探索心血管疾病的病理生理机制提供更多的实验证据,并为寻找新的心血管疾病干预靶点提供潜在可能性。

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