科学通报
评 述
《中国科学》杂志社
SCIENCE CHINA PRESS

cGAS-STING通路的经典和非经典功能

许银丰[1*], 刘依洋[1], 吴心仪[1], 万伟[2*]

1. 湖南第一师范学院基础生物学实验室, 长沙 410205
2. 浙江大学医学院生物化学系, 杭州 310058
* 联系人, E-mail: yinfengxu@hnfnu.edu.cn; wanwei@zju.edu.cn

2025-01-18 收稿, 2025-03-18 修回, 2025-04-21 接受, 2025-04-21 网络版发表
国家自然科学基金(92354303, 32370795)、湖南省科技创新计划(2022RC1171)、长沙市杰出创新青年培养计划(kq2406019)和湖南省自然科学基金(2022JJ30186)资助

摘要 cGAS-STING通路是哺乳动物细胞内主要的DNA感应通路. 在外源病原体感染或者自身细胞损伤条件下, 来源于病原体或者自身细胞的DNA片段通常会部分泄漏至细胞质中, 继而结合并激活cGAS蛋白并促使后者合成第二信使cGAMP分子, cGAMP随后结合并激活内质网定位的STING蛋白, 导致STING从内质网脱离并开始在细胞内转运. 在STING转运过程中, 蛋白激酶TBK1和IKK被STING招募并激活, 活化的TBK1和IKK随后促进转录因子IRF3和NF-κB由细胞质进入细胞核, 刺激I型干扰素和炎性细胞因子的表达并启动先天免疫反应. 近年来的多项研究发现, 除了上述经典功能, cGAS-STING通路还参与调控细胞自噬、溶酶体生物发生和离子稳态等多种不同的生物学过程. 在生物进化过程中, cGAS-STING通路的部分非经典功能出现的时间早于其经典功能, 表明诱导I型干扰素和炎性细胞因子的合成是cGAS-STING通路在生物进化的晚期获得的一个新功能. 最近的研究揭示, STING蛋白激活以后可充当氢离子通道介导氢离子的转运, 并且封闭其离子通道活性不影响I型干扰素和炎性细胞因子的合成, 仅抑制细胞自噬和溶酶体生物发生等cGAS-STING通路的非经典功能. 本文将围绕cGAS-STING通路的经典和非经典功能综述近年来的研究进展.

关键词 cGAS, STING, 先天免疫, 细胞自噬, 溶酶体

先天免疫(innate immunity)是机体对抗病原体感染的第一道防线. 先天免疫系统利用分布于细胞内外的多种不同的模式识别受体(pattern recognition receptor, PRR)感应细胞内外的病原体的不同组分, 继而激活细胞的先天免疫反应. 例如, 分布于细胞膜外表面的受体TLR4(Toll-like receptor 4)可识别并结合细胞外来源于革兰氏阴性菌的脂多糖(lipopolysaccharide, LPS), 分布于细胞内的受体RIG-I(retinoic acid-inducible gene I)可识别并结合来源于病毒的双链RNA[1~3]. DNA作为细胞内承载遗传信息的载体, 在被鉴定为遗传物质之前, 就曾被发现可以强烈激活机体的免疫反应[4]. 除了入侵的病原体, 机体细胞的细胞核和线粒体内同样含有大量的DNA, 机体细胞的免疫反应在何种条件下特异性地被DNA激活以及潜在的分子基础, 曾是先天免疫领域长期悬而未决的重大科学问题. 2008年起, 多个实验室先后独立发现内质网(endoplasmic reticulum, ER)定位的跨膜蛋白STING(stimulator of interferon genes)对于DNA介导的免疫反应必不可少[5~8]. 然而, STING蛋白本身无法结合DNA, 表明STING不是细胞内直接识别DNA的感受器. 2013年, 华人科学家陈志坚发现cGAMP(cyclic GMP-AMP)合成酶cGAS(cGAMP synthase)是细胞内主要的DNA感受器[9,10]. 正常条件

引用格式: 许银丰, 刘依洋, 吴心仪, 等. cGAS-STING通路的经典和非经典功能. 科学通报
Xu Y, Liu Y, Wu X, et al. The canonical and non-canonical functions of the cGAS-STING pathway (in Chinese). Chin Sci Bull, doi: 10.1360/TB-2025-0055

下，核基因组和线粒体基因组分别被核膜和线粒体膜包裹，与细胞质隔离开来. 而在核膜或者线粒体膜受损条件下，来源于核基因组或者线粒体基因组的DNA片段通常会部分泄漏至细胞质中. 此外，在病原体感染条件下，来源于病原体的DNA也会部分泄漏至宿主细胞的细胞质中. 上述自体或者异体来源的细胞质DNA继而结合并激活cGAS蛋白. cGAS激活以后合成第二信使cGAMP分子，后者直接结合并激活内质网定位的STING蛋白，进而启动STING蛋白的细胞内转运过程，最终促进I型干扰素和炎性细胞因子的合成等经典功能，以及促进细胞自噬和溶酶体生物发生等非经典功能.

1 cGAS-STING通路的经典功能

在不结合DNA的情况下，cGAS蛋白处于未激活状态，无法有效合成cGAMP分子，从而规避cGAS-STING通路的异常激活. 而在病原体入侵或者自身细胞受损的条件下，来源于病原体或者自身细胞的DNA片段通常会出现在细胞质中，继而被cGAS蛋白识别. cGAS与DNA片段以2:2的比例结合形成复合物，触发cGAS蛋白变构并活化[11,12]. cGAS-DNA复合物形成以后还可通过相分离在细胞质中进一步形成液滴状的超分子复合物，从而极大地提高cGAS蛋白的活性[13]. 活化的cGAS蛋白利用ATP和GTP合成cGAMP分子，cGAMP继而直接结合内质网定位的STING蛋白并引起后者显著的构型改变，导致STING蛋白从内质网脱离并形成单层膜的囊泡. 而后，STING囊泡相继在内质网高尔基中间体(ER-Golgi intermediate compartment，ERGIC)、高尔基体(Golgi)、内吞体(endosome)和溶酶体(lysosome)等膜性细胞器之间进行转运. 在STING囊泡转运过程中，STING蛋白利用其羧基端的CTT(C-terminal tail)结构域招募并激活蛋白激酶TBK1(TANK-binding kinase 1)和IKK(IκB kinase)，后者继而促进转录因子IRF3(interferon regulatory factor 3)和NF-κB(nuclear factor kappa B)由细胞质进入细胞核. 在细胞核内，IRF3和NF-κB在其他转录相关组分的协助下启动I型干扰素和炎性细胞因子的转录(图1)[11,12,14].

I型干扰素和炎性细胞因子合成以后分泌到细胞外，可通过结合自身或者其他临近细胞表面的相应受体，启动相应的信号转导通路，调控细胞的代谢、生长和增殖等，以及诱导一系列ISG(interferon-stimulated gene)基因的表达. 这些ISG分子合成以后既可继续作

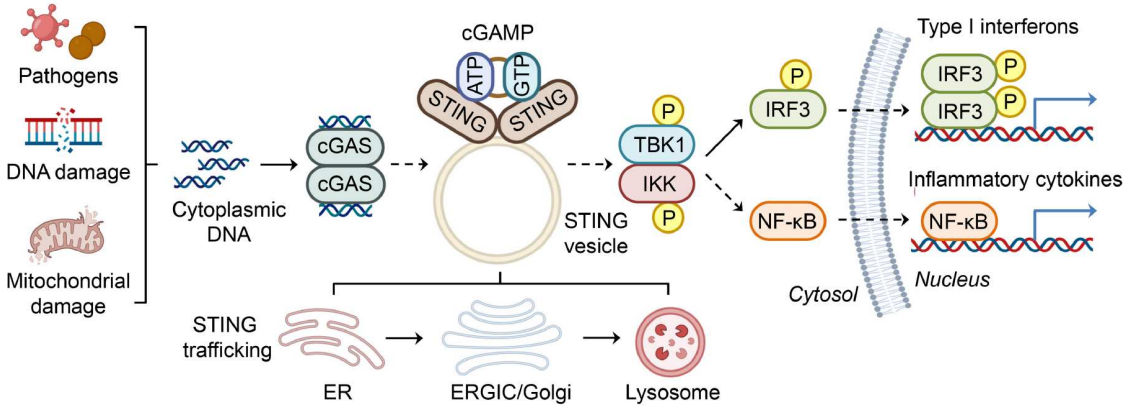

图 1 (网络版彩色)cGAS-STING通路的经典功能. 在病原体感染、核DNA损伤或者线粒体损伤等条件下，来源于病原体基因组、核基因组或者线粒体基因组的DNA片段可部分泄漏至细胞质中. 细胞质中的DNA片段随后被cGAS蛋白识别并激活cGAS蛋白. 活化的cGAS蛋白继而利用细胞质中的ATP和GTP合成第二信使cGAMP分子，后者直接结合内质网定位的STING蛋白，导致STING蛋白从内质网脱离并形成STING囊泡. STING囊泡随后在细胞内膜性细胞器之间开始转运. 在STING蛋白的转运过程中，STING蛋白招募并激活蛋白激酶TBK1和IKK，继而促使转录因子IRF3和NF-κB由细胞质进入细胞核内. 在细胞核内，IRF3和NF-κB刺激I型干扰素和炎性细胞因子的表达，进而启动细胞的先天免疫反应. 图片使用BioRender制作

Figure 1 (Color online) The canonical function of the cGAS-STING pathway. Upon pathogen infection or cell damage, cytoplasmic DNA, released from pathogen, nuclear or mitochondrial genome, is recognized by the enzyme cGAS. DNA bound cGAS then uses ATP and GTP to synthesize cGAMP. Following that, cGAMP directly binds to ER-localized STING and leads to STING export from the ER. During STING trafficking across intracellular membrane compartments including ER, ERGIC/Golgi and lysosome, the protein kinases TBK1 and IKK are recruited to STING vesicles for activation. TBK1 and IKK then activate transcription factors IRF3 and NF-κB by triggering their nuclear translocation from the cytosol. In the nucleus, IRF3 and NF-κB stimulate the expression of a wide array of genes including type I interferons and inflammatory cytokines, thereby inducing the innate immune responses. Figure is created using BioRender

用于自身细胞进一步促进免疫相关效应蛋白的表达放大免疫反应，也可以通过促进T细胞和NK细胞等免疫细胞的招募引起适应性免疫(adaptive immunity)的激活[11,12,14].

以上cGAS-STING通路的经典功能可激活机体的抗病原体和抗肿瘤免疫反应，分别抑制病原体的感染和肿瘤的发生发展[15,16]. 然而, 该通路的异常激活也会引发过度且持续的炎症反应，造成自身细胞的死亡和自身组织的损伤，导致自身免疫病和神经退行性疾病等相关疾病的发生[17].

2 cGAS-STING通路的非经典功能

2.1 诱导细胞自噬

细胞自噬(autophagy)是真核生物特有且高度保守的依赖溶酶体(lysosome)的降解途径，可分为巨自噬(macroautophagy)、微自噬(microautophagy)和分子伴侣介导的自噬(chaperone-mediated autophagy). 一般而言的细胞自噬主要指巨自噬，其显著特征是待降解底物由双层膜结构的自噬小体(autophagosome)包裹. 在营养缺乏、缺氧或者病原体感染等应激条件下，自噬前体(phagophore)靶向蛋白聚集体、受损细胞器和入侵病原体等待降解底物，继而延伸、长大形成闭合的自噬小体，后者随后与溶酶体融合将底物运送至溶酶体内进行降解[18,19]. 细胞自噬对于维持细胞内环境稳定至关重要, 其功能紊乱与衰老(aging)、癌症(cancer)、代谢性疾病(metabolic disorder)和神经退行性疾病(neurodegenerative disease)等密切相关[20~22].

哺乳动物细胞中的LC3(microtubule-associated protein 1 light chain 3)和GABARAP(GABA type A receptor-associated protein)蛋白家族是酵母中Atg8(autophagy-related 8)的同源蛋白, 其成员在细胞自噬的多个阶段均发挥重要调控作用. LC3(为了叙述简明, 如无特别说明, LC3指代LC3和GABARAP蛋白家族)的脂质化修饰(lipidation)是其行使功能的前提条件. 经过脂质化修饰, 水溶性的LC3转化为膜结合形式, 通过蛋白相互作用将下游的效应蛋白募集到自噬前体膜处发挥功能. 在细胞自噬过程中, 膜结合的LC3在自噬膜的延伸、自噬底物的招募和自噬小体与溶酶体融合等多个阶段均发挥关键调控作用[23].

LC3的脂质化经由一个类泛素化的修饰反应完成. 首先，全长的LC3在半胱氨酸蛋白酶ATG4的特异切割作用下暴露出羧基端的甘氨酸残基; 然后，在E1样酶ATG7、E2样酶ATG3和E3样酶ATG12-ATG5-ATG16L1复合物的顺序作用下, LC3的甘氨酸残基共价连接上脂质分子磷脂酰乙醇胺(phosphatidyl ethanolamine, PE). 水溶性的LC3由此转化为膜结合形式的LC3-PE[23]. 在营养缺乏等诱导的经典自噬中，蛋白激酶ULK1(unc-51-like kinase 1)复合物被招募至自噬前体处并被激活, 其随后继续激活脂激酶VPS34/PIK3C3(phosphatidylinositol 3-kinase catalytic subunit type 3)复合物, 促使后者在自噬前体处合成脂质分子3-磷酸磷脂酰肌醇(phosphatidylinositol-3-phosphate, PI3P), 从而启动细胞自噬. 自噬前体处的PI3P通过直接结合作用招募WIPI2(WD repeat domain phosphoinositide-interacting protein 2)等下游效应蛋白，WIPI2随后通过与ATG16L1蛋白直接相互作用招募ATG12-ATG5-ATG16L1复合物，促进水溶性的LC3在自噬前体处转化为膜结合形式的LC3-PE[24~28].

近年的多项研究先后发现, cGAS-STING通路可通过诱导细胞自噬促进病原体清除[29~32]. 在海葵等低等生物中, STING蛋白缺乏羧基端的CTT结构域, 没有激活下游蛋白激酶TBK1和IKK的能力, 因此无法诱导I型干扰素和炎性细胞因子的合成. 然而, 海葵中的STING蛋白仍然能够诱导LC3的脂质化和细胞自噬的起始. 此外, 在哺乳动物细胞内表达缺乏CTT结构域的STING蛋白，STING在激活以后仍可以通过诱导细胞自噬促进细胞质DNA以及DNA病毒的清除. 以上实验数据表明细胞自噬是cGAS-STING通路的一个更为原始的功能. 调控经典自噬起始的关键上游因子ULK1复合物和VPS34复合物似乎不为cGAS-STING通路诱导的细胞自噬所需要, 而脂质PI3P的结合蛋白WIPI2蛋白仍然在此种类型的细胞自噬中不可或缺[29]. 后续的进一步研究揭示，在cGAS-STING通路诱导的细胞自噬中, WIPI2蛋白似乎可以通过不依赖脂质PI3P的方式完成招募. 机制研究表明, STING囊泡处的STING蛋白可直接结合WIPI2蛋白，后者继而招募ATG12-ATG5-ATG16L1复合物，促进LC3的脂质化和自噬小体的形成(图2)[33,34]. 目前关于STING诱导的细胞自噬的分子机理仍然知之甚少，调控此种自噬类型的蛋白机器和潜在的信号通路亟待后续深入的系统性研究予以鉴定和阐明.

cGAS-STING通路诱导的细胞自噬不仅能介导入侵病原体的清除，还会促进细胞质DNA、cGAS、

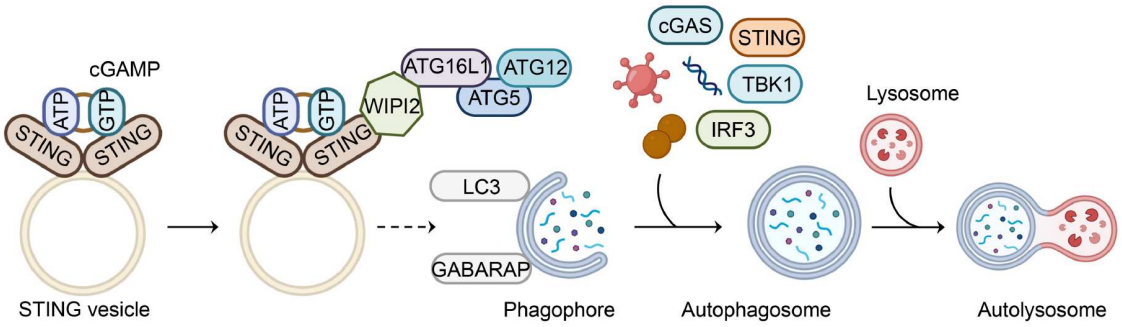

图 2 (网络版彩色)cGAS-STING通路诱导细胞自噬的基本过程. STING囊泡处的STING蛋白直接结合WIPI2蛋白, 后者继而通过结合ATG16L1蛋白招募ATG12-ATG5-ATG16L1复合物, 促进LC3的脂质化和自噬小体的形成. 自噬小体包裹细胞质DNA、入侵病原体以及cGAS-STING通路的多个组分, 通过与溶酶体融合促进自噬底物的降解. 图片使用BioRender制作

Figure 2 (Color online) The general process of the cGAS-STING pathway-induced autophagy. Following activation, STING recruits WIPI2 to STING vesicles by direct interaction. WIPI2 further interacts with ATG16L1 and recruits ATG12-ATG5-ATG16L1 complex, thereby promoting LC3 lipidation and autophagosome formation. Finally, autophagosomes fuse with lysosomes to degrade autophagy cargoes, including cytoplasmic DNA, invading pathogens, and several components of the cGAS-STING pathway. Figure is created using BioRender

STING、TBK1和IRF3等信号分子的降解(图2)[29,31,34~38]. 换言之, cGAS-STING通路诱导的细胞自噬在清除病原体的同时也会限制cGAS-STING通路的激活强度, 进而避免持续过高的炎症反应, 防止对自身细胞造成损害. 此外, STING蛋白激活以后还可以通过包括微自噬在内的不同途径运送至溶酶体进行降解, 以快速终止cGAS-STING信号[39~43].

2.2 调控LC3在单层膜囊泡上的脂质化

除了定位于双层膜的自噬小体, 脂质化的LC3还可以定位于细胞内的单层膜囊泡, 如内吞体和溶酶体等, 从而调控内吞和溶酶体微自噬等生物学过程[44~48]. cGAS-STING通路诱导的LC3脂质化修饰也可以发生于单层膜STING囊泡处. 与细胞自噬不同, WIPI2蛋白不为这一过程所需要. 研究表明, 定位于单层膜STING囊泡上的质子泵(V-ATPase)负责ATG12-ATG5-ATG16L1复合物的招募, 继而促进LC3-PE的原位形成. 单层膜STING囊泡处的LC3-PE对于cGAS-STING通路的激活以及后续I型干扰素的合成没有显著作用, 表明其不参与调控cGAS-STING通路的经典功能[44]. 近年来的多项研究陆续揭示, 单层膜STING囊泡处LC3的脂质化主要调控cGAS-STING通路的一些非经典功能.

2.2.1 调控NF-κB通路的激活

单层膜STING囊泡处的LC3-PE可促进E3泛素连接酶LUBAC(linear ubiquitin chain assembly complex)的招募[49]. LUBAC是哺乳动物细胞内目前已鉴定的唯一的介导蛋白线性泛素化(linear ubiquitination)的E3泛素连接酶. 在不同的生理病理刺激下, LUBAC通过介导不同底物的线性泛素化修饰, 参与调控NF-κB通路、细胞死亡和细胞自噬等不同的生物学过程[50,51]. 研究表明, STING囊泡处的LC3-PE招募LUBAC后, 可在原位促进线性泛素化修饰过程, 进而在NF-κB通路的激活过程中发挥一定的作用(图3)[49]. 然而, LC3-PE促进LUBAC招募的机制仍然不明. 考虑到LUBAC介导的线性泛素化修饰还参与调控细胞内多种不同的生物学过程, cGAS-STING通路很有可能通过调控LUBAC介导的蛋白线性泛素化修饰在其中也发挥一定的作用.

2.2.2 促进溶酶体生物发生

溶酶体是真核细胞内重要的降解中心. 无论是细胞外还是细胞内的物质, 均可经由内吞和细胞自噬等多种不同的途径被运送至溶酶体内进行降解[52~54]. 溶酶体的降解活性受到营养状态等细胞内外刺激的严密调控. 转录因子TFEB(transcription factor EB)、TFE3(transcription factor E3)和MITF(microphthalmia-associated transcription factor)是哺乳动物细胞内调控溶酶体生物发生的主导因子. 它们通过激活一系列溶酶体相关基因的转录促进溶酶体的生物发生, 进而提高细胞内溶酶体的降解活性[55,56]. 蛋白激酶mTORC1(mechanistic target of rapamycin complex 1)作为细胞内主要的营养感受器之一, 通过控制TFEB的亚细胞分布影响其转录活性, 将细胞的营养状态与溶酶体的活性关联起来. 在营养丰富条件下, mTORC1激活, 直接磷酸化TFEB的多个位点, 主要包括S122、S142和S211位点. 以上位点的磷酸化均参与调控TFEB的亚细胞分布, 其

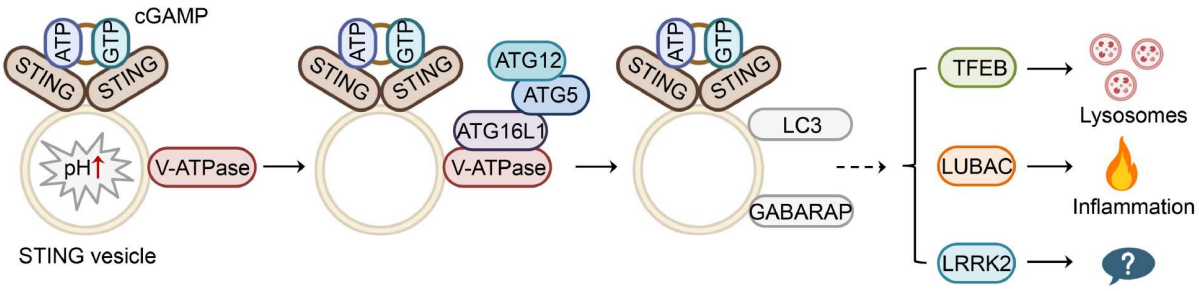

图 3 (网络版彩色)cGAS-STING通路诱导单层膜上LC3脂质化修饰的生物学功能. STING蛋白激活以后, 可充当氢离子通道促进STING囊泡内的氢离子外流, 进而升高STING囊泡内的pH, 促进STING囊泡处的V-ATPase招募ATG12-ATG5-ATG16L1复合物, 继而促进LC3和GABARAP在STING囊泡处完成脂质化修饰. 脂质化的LC3和GABARAP随后激活转录因子TFEB促进溶酶体生物发生, 以及激活E3泛素连接酶LUBAC部分促进NF-κB通路的活化. 此外, 脂质化的GABARAP也可招募并激活蛋白激酶LRRK2, 然而潜在的生物学功能尚不明确. 图片使用BioRender制作

Figure 3 (Color online) The biological functions of the cGAS-STING pathway-induced LC3 lipidation on single-membranes. Following activation, STING protein functions as a proton channel and promotes proton leakage, which raises pH value within STING vesicles and activates the V-ATPase-ATG16L1 axis, resulting in LC3 and GABARAP lipidation onto STING vesicles. Lipidated LC3 and GABARAP then activate transcription factor TFEB to induce lysosome biogenesis, and activate E3 ubiquitin ligase LUBAC to partially enhance NF-κB activity. In addition, lipidated GABARAP can recruit and activate protein kinase LRRK2. However, the physiological significance of STING-induced LRRK2 activation remains unclear. Figure is created using BioRender

中S211位点的磷酸化通过促进TFEB与14-3-3蛋白相互作用促进TFEB的细胞质定位. 在营养缺乏条件下, mTORC1的活性降低, TFEB的磷酸化水平随之下降, 其与14-3-3蛋白的相互作用受到抑制, TFEB进而由细胞质进入细胞核内, 并启动溶酶体相关基因的转录[57~60]. 目前, S122和S142位点的磷酸化如何控制TFEB的亚细胞分布仍然不甚明确, 潜在的分子机理亟待后续研究予以阐明.

最近, 多项独立的研究共同发现, cGAS-STING通路可通过激活TFEB及其同家族蛋白TFE3和MITF促进溶酶体生物发生. 单层膜STING囊泡处GABARAP的脂质化修饰而非下游蛋白激酶TBK1和IKK的激活介导TFEB的活化, 表明诱导溶酶体生物发生也是cGAS-STING通路的一项进化上更为原始的功能. 进一步的机制研究揭示, STING囊泡处脂质化的GABARAP通过蛋白相互作用结合FLCN/FNIP蛋白复合物, 导致其作为GAP(GTPase-activating protein)无法作用于下游的小GTP酶(small GTPase)RagC/D, 进而导致后者无法招募TFEB, 从而特异性抑制mTORC1对TFEB的磷酸化, 并促使TFEB由细胞质进入细胞核内, 最终启动溶酶体相关基因的转录(图3). 功能研究表明, cGAS-STING通路介导的溶酶体生物发生对于溶酶体稳态的维持、入侵病原体的清除以及衰老细胞的存活均至关重要[61~66].

STING囊泡处脂质化的GABARAP蛋白还可促进蛋白激酶LRRK2(leucine-rich repeat kinase 2)的招募和激活(图3)[67]. 然而, cGAS-STING通路介导的LRRK2的激活发挥何种生物学功能尚不明确. 考虑到LRRK2的异常激活与炎症性肠病和帕金森病等的发生发展密切相关[68,69], cGAS-STING通路是否通过调控LRRK2的活性影响炎症性肠病和帕金森病等的病理进程也是一个值得研究的问题.

2.3 调控细胞内的离子稳态

最近的两项独立研究共同证明, STING蛋白激活以后可充当氢离子通道介导STING囊泡内氢离子的外流. 化合物C53(compound 53)是一种独特的STING激活剂, 可在激活STING蛋白的同时封闭其离子通道活性[70,71]. 利用C53的这一特性, 研究者发现, 封闭STING蛋白的离子通道活性可显著抑制STING囊泡处LC3的脂质化修饰. 然而, C53并不影响I型干扰素和炎性细胞因子的合成[72], 表明STING蛋白的离子通道活性似乎不参与调控cGAS-STING通路的经典功能. 后续的研究揭示, STING蛋白激活后作为氢离子通道介导STING囊泡内氢离子外流进入细胞质中, 导致STING囊泡内的pH升高, 进而激活V-ATPase-ATG16L1信号轴, 促进LC3在单层膜STING囊泡处完成脂质化修饰(图3)[70,71]. 以上研究也表明, STING蛋白介导的氢离子外流是触发LC3在单层膜STING囊泡处进行脂质化修饰的上游事件.

细胞内离子稳态的改变也是触发NLRP3(NOD-, LRR- and pyrin domain-containing protein 3)炎症小体(inflammasome)激活的重要因素之一[73,74]. cGAS-

STING通路激活以后可显著促进NLRP3炎症小体的激活以及炎性细胞因子的分泌. 封闭STING蛋白的离子通道活性能够显著抑制cGAS-STING通路激活引起的NLRP3炎症小体的活化[70]. 考虑到细胞内多种离子, 特别是钾离子, 参与调控NLRP3炎症小体的激活[73,74], STING蛋白是否真的是通过影响氢离子的稳态调控NLRP3炎症小体的激活仍然需要后续深入的研究予以澄清.

除了介导氢离子的转运, STING蛋白还可能作为钙离子通道介导STING囊泡内的钙离子流入细胞质中. 在某些特定条件下激活cGAS-STING通路, 然后利用钙离子螯合剂处理细胞, 可部分抑制蛋白激酶TBK1的活化, 表明STING蛋白调控的钙离子转运可能部分参与cGAS-STING通路的信号转导过程[75]. 然而, 钙离子通过何种机制发挥调控作用仍然未知. 此外, STING蛋白激活以后是否真的可以充当钙离子通道也需要更为直接的实验证据予以明确.

3 展望

cGAS-STING通路诱导的LC3脂质化修饰既可以发生在双层膜的自噬小体上, 也可以发生在单层膜的STING囊泡上, 二者似乎分别由WIPI2蛋白和质子泵V-ATPase招募ATG12-ATG5-ATG16L1复合物介导完成. 然而, 细胞内的何种信号调控ATG12-ATG5-ATG16L1复合物的选择性招募, 进而决定LC3在自噬小体还是单层膜STING囊泡上完成脂质化修饰尚不明确, 亟待未来的研究予以揭示.

STING蛋白激活以后可以充当离子通道介导氢离子由STING囊泡内流入细胞质中, 进而调控LC3的脂质化、溶酶体的生物发生、NLRP3炎症小体的活化和蛋白激酶LRRK2的激活等过程. 然而, 除了氢离子, STING蛋白是否可以介导STING囊泡内其他离子的转运并不明确. 显然, 系统性研究该问题有可能揭示cGAS-STING通路新的生物学功能. 此外, cGAS-STING通路的经典功能与众多的非经典功能之间是否存在一定的相互调控关系仍然未知, 值得未来的研究予以阐明.

近年来的多项研究相继发现了cGAS-STING通路的多个全新功能, 而且主要是cGAS-STING通路更为原始的功能. cGAS-STING通路是否还有其他新功能仍然值得深入研究. 作为先天免疫反应的重要组成部分, cGAS-STING通路在病原体的清除过程中发挥重要作用. 近年来的研究表明, cGAS-STING通路的异常激活还参与衰老、自身免疫病、癌症和神经退行性疾病等生理病理过程的发生与进展[76,77]. cGAS-STING通路既可以在部分癌症类型中促进抗肿瘤免疫的激活, 也可以在另一部分癌症类型中促进癌细胞的生存和转移[78~80]. 考虑到cGAS-STING通路众多不同的下游功能, cGAS-STING通路可能在不同的细胞中激活不同的下游功能, 进而在不同的生理病理过程中发挥不同的调控作用. 显然, 系统性阐明cGAS-STING通路在不同组织和器官中的共有和特有功能, 不仅具有重大的理论研究意义, 还将会为基于cGAS-STING通路的药物研发提供更为精准的干预靶点.

参考文献

1 Kumagai Y, Akira S. Identification and functions of pattern-recognition receptors. J Allergy Clin Immunol, 2010, 125: 985–992
2 Li D, Wu M. Pattern recognition receptors in health and diseases. Sig Transduct Target Ther, 2021, 6: 291
3 Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell, 2010, 140: 805–820
4 Flavell R A, Sefik E. Sensing DNA as danger: the discovery of cGAS. Immunity, 2024, 57: 2251–2254
5 Ishikawa H, Barber G N. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature, 2008, 455: 674–678
6 Jin L, Waterman P M, Jonscher K R, et al. MPYS, a novel membrane tetraspanner, is associated with major histocompatibility complex class II and mediates transduction of apoptotic signals. Mol Cell Biol, 2008, 28: 5014–5026
7 Sun W, Li Y, Chen L, et al. ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. Proc Natl Acad Sci USA, 2009, 106: 8653–8658
8 Zhong B, Yang Y, Li S, et al. The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation. Immunity, 2008, 29: 538–550
9 Sun L, Wu J, Du F, et al. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science, 2013, 339: 786–791
10 Wu J, Sun L, Chen X, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science, 2013, 339: 826–830

11 Chen Q, Sun L, Chen Z J. Regulation and function of the cGAS–STING pathway of cytosolic DNA sensing. Nat Immunol, 2016, 17: 1142–1149
12 Ritchie C, Carozza J A, Li L. Biochemistry, cell biology, and pathophysiology of the innate immune cGAS–cGAMP–STING pathway. Annu Rev Biochem, 2022, 91: 599–628
13 Du M, Chen Z J. DNA-induced liquid phase condensation of cGAS activates innate immune signaling. Science, 2018, 361: 704–709
14 Xu Y, Wan W. Lysosomal control of the cGAS-STING signaling. Trends Cell Biol, 2024, 34: 622–625
15 Cheng Z, Dai T, He X, et al. The interactions between cGAS-STING pathway and pathogens. Sig Transduct Target Ther, 2020, 5: 91
16 Tian Z, Zeng Y, Peng Y, et al. Cancer immunotherapy strategies that target the cGAS-STING pathway. Front Immunol, 2022, 13: 996663
17 Decout A, Katz J D, Venkatraman S, et al. The cGAS–STING pathway as a therapeutic target in inflammatory diseases. Nat Rev Immunol, 2021, 21: 548–569
18 Xu Y, Wan W. Acetylation in the regulation of autophagy. Autophagy, 2023, 19: 379–387
19 Yim W W Y, Mizushima N. Lysosome biology in autophagy. Cell Discov, 2020, 6: 6
20 Aman Y, Schmauck-Medina T, Hansen M, et al. Autophagy in healthy aging and disease. Nat Aging, 2021, 1: 634–650
21 Klionsky D J, Petroni G, Amaravadi R K, et al. Autophagy in major human diseases. EMBO J, 2021, 40: e108863
22 Xu Y, Wan W. Emerging roles of p300/CBP in autophagy and autophagy-related human disorders. J Cell Sci, 2023, 136: jcs261028
23 Mizushima N. The ATG conjugation systems in autophagy. Curr Opin Cell Biol, 2020, 63: 1–10
24 Dooley H C, Razi M, Polson H E J, et al. WIPI2 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12–5-16L1. Mol Cell, 2014, 55: 238–252
25 Polson H E J, de Lartigue J, Rigden D J, et al. Mammalian Atg18 (WIPI2) localizes to omegasome-anchored phagophores and positively regulates LC3 lipidation. Autophagy, 2010, 6: 506–522
26 Wan W, Liu W. MTORC1 regulates autophagic membrane growth by targeting WIPI2. Autophagy, 2019, 15: 742–743
27 Wan W, You Z, Xu Y, et al. mTORC1 phosphorylates acetyltransferase p300 to regulate autophagy and lipogenesis. Mol Cell, 2017, 68: 323–335. e6
28 Wan W, You Z, Zhou L, et al. mTORC1-regulated and HUWE1-mediated WIPI2 degradation controls autophagy flux. Mol Cell, 2018, 72: 303–315.e6
29 Gui X, Yang H, Li T, et al. Autophagy induction via STING trafficking is a primordial function of the cGAS pathway. Nature, 2019, 567: 262–266
30 Liu D, Wu H, Wang C, et al. STING directly activates autophagy to tune the innate immune response. Cell Death Differ, 2019, 26: 1735–1749
31 Prabakaran T, Bodda C, Krapp C, et al. Attenuation of cGAS-STING signaling is mediated by a p62/SQSTM1-dependent autophagy pathway activated by TBK1. EMBO J, 2018, 37: e97858
32 Watson R O, Manzanillo P S, Cox J S. Extracellular M. tuberculosis DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. Cell, 2012, 150: 803–815
33 Wan W, Liu W. STING recruits WIPI2 for autophagosome formation. Autophagy, 2024, 20: 928–929
34 Wan W, Qian C, Wang Q, et al. STING directly recruits WIPI2 for autophagosome formation during STING-induced autophagy. EMBO J, 2023, 42: e112387
35 Cai Y, Zhu Y, Zheng J, et al. NBR1 mediates autophagic degradation of IRF3 to negatively regulate type I interferon production. Biochem Biophys Res Commun, 2022, 623: 140–147
36 Chen M, Meng Q, Qin Y, et al. TRIM14 inhibits cGAS degradation mediated by selective autophagy receptor p62 to promote innate immune responses. Mol Cell, 2016, 64: 105–119
37 Xu Y, Qian C, Wang Q, et al. Deacetylation of ATG7 drives the induction of macroautophagy and LC3-associated microautophagy. Autophagy, 2024, 20: 1134–1146
38 Zhao X, Di Q, Yu J, et al. USP19 (ubiquitin specific peptidase 19) promotes TBK1 (TANK-binding kinase 1) degradation via chaperone-mediated autophagy. Autophagy, 2022, 18: 891–908
39 Balka K R, Venkatraman R, Saunders T L, et al. Termination of STING responses is mediated via ESCRT-dependent degradation. EMBO J, 2023, 42: e112712
40 Gentili M, Liu B, Papanastasiou M, et al. ESCRT-dependent STING degradation inhibits steady-state and cGAMP-induced signalling. Nat Commun, 2023, 14: 611
41 Kuchitsu Y, Mukai K, Uematsu R, et al. STING signalling is terminated through ESCRT-dependent microautophagy of vesicles originating from recycling endosomes. Nat Cell Biol, 2023, 25: 453–466
42 Liu Y, Xu P, Rivara S, et al. Clathrin-associated AP-1 controls termination of STING signalling. Nature, 2022, 610: 761–767
43 Zhao Y, Zhou C, Tian W, et al. A specific module of ESCRT regulates STING activity termination by controlling STING degradation. Sci Bull, 2024, 69: 1000–1005
44 Fischer T D, Wang C, Padman B S, et al. STING induces LC3B lipidation onto single-membrane vesicles via the V-ATPase and ATG16L1-WD40 domain. J Cell Biol, 2020, 219: e202009128

45 Fletcher K, Ulferts R, Jacquin E, et al. The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. EMBO J, 2018, 37: e97840
46 Goodwin J M, Walkup Iv W G, Hooper K, et al. GABARAP sequesters the FLCN-FNIP tumor suppressor complex to couple autophagy with lysosomal biogenesis. Sci Adv, 2021, 7: eabj2485
47 Hooper K M, Jacquin E, Li T, et al. V-ATPase is a universal regulator of LC3-associated phagocytosis and non-canonical autophagy. J Cell Biol, 2022, 221: e202105112
48 Lee C, Lamech L, Johns E, et al. Selective lysosome membrane turnover is induced by nutrient starvation. Dev Cell, 2020, 55: 289–297.e4
49 Fischer T D, Bunker E N, Zhu P P, et al. STING induces HOIP-mediated synthesis of M1 ubiquitin chains to stimulate NF-κB signaling. EMBO J, 2025, 44: 141–165
50 Emmerich C H, Schmukle A C, Walczak H. The emerging role of linear ubiquitination in cell signaling. Sci Signal, 2011, 4: re5
51 Spit M, Rieser E, Walczak H. Linear ubiquitination at a glance. J Cell Sci, 2019, 132: jcs208512
52 Lawrence R E, Zoncu R. The lysosome as a cellular centre for signalling, metabolism and quality control. Nat Cell Biol, 2019, 21: 133–142
53 Xu H, Ren D. Lysosomal physiology. Annu Rev Physiol, 2015, 77: 57–80
54 Yang C, Wang X. Lysosome biogenesis: regulation and functions. J Cell Biol, 2021, 220: e202102001
55 Sardiello M, Palmieri M, di Ronza A, et al. A gene network regulating lysosomal biogenesis and function. Science, 2009, 325: 473–477
56 Settembre C, Di Malta C, Polito V A, et al. TFEB links autophagy to lysosomal biogenesis. Science, 2011, 332: 1429–1433
57 Martina J A, Puertollano R. Rag GTPases mediate amino acid–dependent recruitment of TFEB and MITF to lysosomes. J Cell Biol, 2013, 200: 475–491
58 Roczniak-Ferguson A, Petit C S, Froehlich F, et al. The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis. Sci Signal, 2012, 5: ra42
59 Settembre C, Zoncu R, Medina D L, et al. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. EMBO J, 2012, 31: 1095–1108
60 Vega-Rubin-de-Celis S, Peña-Llopis S, Konda M, et al. Multistep regulation of TFEB by MTORC1. Autophagy, 2017, 13: 464–472
61 Huang T, Sun C, Du F, et al. STING-induced noncanonical autophagy regulates endolysosomal homeostasis. Proc Natl Acad Sci USA, 2025, 122: e2415422122
62 Lv B, Dion W A, Yang H, et al. A TBK1-independent primordial function of STING in lysosomal biogenesis. Mol Cell, 2024, 84: 3979–3996.e9
63 Tang Z, Xing C, Araszkiewicz A, et al. STING mediates lysosomal quality control and recovery through its proton channel function and TFEB activation in lysosomal storage disorders. Mol Cell, 2025, 85: 1624–1639.e5
64 Tapia P J, Martina J A, Contreras P S, et al. TFEB and TFE3 regulate STING1-dependent immune responses by controlling type I interferon signaling. Autophagy, 2025, doi: 10.1080/15548627.2025.2487036
65 Xu Y, Wang Q, Wang J, et al. The cGAS-STING pathway activates transcription factor TFEB to stimulate lysosome biogenesis and pathogen clearance. Immunity, 2025, 58: 309–325.e6
66 Xu Y, Wan W. Induction of lysosome biogenesis is a novel function of the CGAS-STING1 pathway. Autophagy, 2025, 21: 1163–1164
67 Bentley-DeSousa A, Roczniak-Ferguson A, Ferguson S M. A STING–CASM–GABARAP pathway activates LRRK2 at lysosomes. J Cell Biol, 2025, 224: e202310150
68 Liu Z, Lenardo M J. The role of LRRK2 in inflammatory bowel disease. Cell Res, 2012, 22: 1092–1094
69 Usmani A, Shavarebi F, Hiniker A. The cell biology of LRRK2 in Parkinson's disease. Mol Cell Biol, 2021, 41: e00660-20
70 Liu B, Carlson R J, Pires I S, et al. Human STING is a proton channel. Science, 2023, 381: 508–514
71 Xun J, Zhang Z, Lv B, et al. A conserved ion channel function of STING mediates noncanonical autophagy and cell death. EMBO Rep, 2024, 25: 544–569
72 Pryde D C, Middya S, Banerjee M, et al. The discovery of potent small molecule activators of human STING. Eur J Med Chem, 2021, 209: 112869
73 Kelley N, Jeltema D, Duan Y, et al. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. Int J Mol Sci, 2019, 20: 3328
74 Swanson K V, Deng M, Ting J P Y. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol, 2019, 19: 477–489
75 Kim S, Koch P, Li L, et al. Evidence for a role of calcium in STING signaling. bioRxiv, 2017. Doi: 10.1101/145854v1
76 Motwani M, Pesiridis S, Fitzgerald K A. DNA sensing by the cGAS–STING pathway in health and disease. Nat Rev Genet, 2019, 20: 657–674
77 Paul B D, Snyder S H, Bohr V A. Signaling by cGAS–STING in neurodegeneration, neuroinflammation, and aging. Trends Neurosci, 2021, 44: 83–96
78 Du J, Qian M, Yuan T, et al. cGAS and cancer therapy: a double-edged sword. Acta Pharmacol Sin, 2022, 43: 2202–2211
79 Lanng K R B, Lauridsen E L, Jakobsen M R. The balance of STING signaling orchestrates immunity in cancer. Nat Immunol, 2024, 25: 1144–1157
80 Samson N, Ablasser A. The cGAS–STING pathway and cancer. Nat Cancer, 2022, 3: 1452–1463

Summary for “cGAS-STING通路的经典和非经典功能”

The canonical and non-canonical functions of the cGAS-STING pathway

Yinfeng Xu[1*], Yiyang Liu[1], Xinyi Wu[1] & Wei Wan[2*]

[1] *Laboratory of Basic Biology, Hunan First Normal University, Changsha 410205, China*
[2] *Department of Biochemistry, Zhejiang University School of Medicine, Hangzhou 310058, China*
* Corresponding authors, E-mail: yinfengxu@hnfnu.edu.cn; wanwei@zju.edu.cn

The cyclic GMP-AMP (cGAMP) synthase (cGAS)-stimulator of interferon genes (STING) pathway serves as the central DNA-sensing mechanism in mammalian cells. Upon pathogen infection or cellular stress, DNA fragments, derived from the pathogen, the nucleus, or the damaged mitochondria, can be partially leaked into the cytoplasm of the cell. The enzyme cGAS is then bound and activated by cytoplasmic DNA and utilizes ATP and GTP to produce a second messenger molecule called cGAMP. Following that, cGAMP directly binds to endoplasmic reticulum (ER)-localized adaptor protein STING and induces a dramatic conformational change of STING, triggering the exit of STING from the ER. During the trafficking of STING across the intracellular membrane compartments including ER, ERGIC, Golgi, and lysosome, the protein kinases TANK-binding kinase 1 (TBK1) and IκB kinase (IKK) are recruited and activated by STING. These protein kinases then induce the nuclear translocation of transcription factors interferon (IFN) regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB) from the cytoplasm. In the nucleus, IRF3 and NF-κB drive the expression of type I IFNs and inflammatory cytokines, thereby stimulating the initiation of innate immune responses.

In addition to the canonical function, a number of non-canonical functions of the cGAS-STING pathway have emerged. Of note, several non-canonical functions, such as induction of autophagy and activation of lysosome biogenesis, predate the emergence of the canonical function, suggesting them as the primordial functions of the cGAS-STING pathway. During STING-induced autophagy, STING directly recruits WD-repeat domain phosphoinositide-interacting protein 2 (WIPI2) to stimulate the lipidation of microtubule-associated protein 1 light chain 3 (LC3) and GABA type A receptor-associated protein (GABARAP) and the formation of autophagosomes. Interestingly, STING-induced lipidation of LC3 and GABARAP can also occur on single-membrane vesicles, which is regulated by the V-ATPase-ATG16L1 axis. Several independent studies have revealed that STING-induced GABARAP lipidation on single-membrane vesicles activates transcription factor EB (TFEB) and its prologs to stimulate the expression of lysosome-related genes, thereby enhancing lysosome biogenesis. STING-induced GABARAP lipidation also activates the protein kinase leucine-rich repeat kinase 2 (LRRK2). However, the physiological significance of STING-induced LRRK2 activation remains elusive. Recently, STING protein has been identified as a proton channel. Moreover, the proton channel activity of STING is required for several non-canonical functions rather than the canonical function of the cGAS-STING pathway. Upon activation, STING mediates the leakage of protons within STING vesicles, which raises the pH value and activates the V-ATPase-ATG16L1 axis, resulting in LC3 and GABARAP lipidation onto single-membrane STING vesicles. This suggests that the proton channel activity of STING is required for the cGAS-STING pathway-induced lysosome biogenesis. The non-canonical functions of the cGAS-STING pathway, including autophagy induction and lysosome biogenesis, seem to represent a cell-autonomous strategy of the cell in fighting against pathogen infection.

In this paper, we aim to summarize the current knowledge on the canonical and non-canonical functions of the cGAS-STING pathway and discuss the remaining issues needed to be addressed in the future.

cGAS, STING, innate immunity, autophagy, lysosome

doi: 10.1360/TB-2025-0055