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述评

- 665 重视HBsAg定量检测在慢性乙型肝炎全程管理中的价值
封波, 郑佳睿
- 661 葛根芩连汤治疗肠道疾病的研究进展
舒雁, 惠华英, 谭周进

文献综述

- 668 紧密连接蛋白Claudin-3在肝胆疾病中的研究进展
许祖知, 费书珂
- 674 STING信号通路在肝脏疾病中的作用及研究进展
魏霞, 张定棋, 张霖璋, 刘伟, 刘平, 徐莹

临床实践

- 680 牙线牵引辅助内镜黏膜下挖除术在治疗胃黏膜下肿瘤中的应用
许捷鸿, 陈志新
- 686 酪酸梭菌活菌片对胆囊结石腹腔镜术后腹泻患者营养状况、Th1/Th2细胞及预后的影响
王凌, 林霞, 戚国勇

消 息

- 660 《腹痛的诊断、鉴别诊断与治疗》书讯
679 《世界华人消化杂志》修回稿须知
692 《世界华人消化杂志》性质、刊登内容及目标

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EDITORIAL

- 655 Importance of quantitative HBsAg detection in whole course management of patients with chronic hepatitis B
Feng B, Zheng JR
- 661 Progress in treatment of intestinal diseases with Gegen Qinlian decoction
Shu Y, Hui Y, Tan ZJ

REVIEW

- 668 Progress in research of tight junction protein claudin-3 in hepatobiliary systemic diseases
Xu ZZ, Fei SK
- 674 Role of STING signaling pathway in liver diseases
Wei X, Zhang DQ, Zhang LZ, Liu W, Liu P, Xu Y

CLINICAL PRACTICE

- 680 Application of dental floss traction assisted endoscopic submucosal excision in treatment of gastric submucosal tumors
Xu JH, Cheng ZX
- 686 Effect of live *Clostridium typhimurium* tablets on nutritional status, Th1/Th2 cells, and prognosis of patients with diarrhea after laparoscopic surgery for gallbladder stones
Wang L, Lin X, Qi Y

Contents

World Chinese Journal of Digestology
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COVER

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STING信号通路在肝脏疾病中的作用及研究进展

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Role of STING signaling pathway in liver diseases

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Abstract

The cGAS-STING signaling pathway is an important part of the innate immune system, which could trigger the expression of a series of inflammatory factors represented by interferon type 1 (IFN-1). This pathway plays an important role in many diseases such as infectious diseases, autoimmune diseases, and tumors. In recent years, it has been found that the cGAS-STING signaling pathway is important in the physiological and pathological processes of the liver, and is closely related to the progression of liver diseases. This paper reviews the role of the cGAS-STING signaling pathway in common liver diseases such as chronic hepatitis B, alcoholic liver disease, nonalcoholic fatty liver disease, and liver cancer, as well as its application in the treatment of liver diseases.

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Key Words: cGAS-STING; Signaling pathway; Liver diseases; Innate immune system; Inflammatory reaction

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摘要

cGAS-STING信号通路是固有免疫系统的重要组成部分, 可以触发以 I 型干扰素(interferon type 1, IFN-1)为代表的一系列炎症因子的表达, 其在感染性疾病、自身免疫性疾病及肿瘤等多种疾病中发挥着重要作用。近年来, 研究发现cGAS-STING信号通路在肝脏疾病的进展密切相关。本文就cGAS-STING信号通路在慢性乙型肝炎、酒精性肝病、非酒精性脂肪性肝病、肝癌等常见肝脏疾病中的作用及其在肝脏疾病治疗中的应用现状作一综述。

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关键词: cGAS-STING; 信号通路; 肝脏疾病; 固有免疫系统; 炎症反应

核心提要: cGAS-STING信号通路是天然免疫领域的重要发现, 近年来, 研究发现cGAS-STING信号通路在肝脏疾病的进展密切相关, 本文总结了cGAS-STING信号通路在多种肝脏疾病中的作用及其潜在治疗意义, 深入了解cGAS-STING信号通路可能为治疗肝脏疾病提供新的思路。

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0 引言

常见的肝脏疾病包括病毒性肝炎、酒精性肝病(alcoholic liver disease, ALD)、非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)以及相关的肝纤维化、肝硬化和肝细胞癌(hepatocellular carcinoma, HCC)等。由于肝脏疾病的病理机制复杂, 其发生与发展是多因素、多步骤的复杂过程, 药物及手术治疗存在一定的局限性, 肝移植是终末期肝病唯一有效的治疗方法, 但肝源的缺乏和终身用药的副作用限制了其应用。因此, 积极探索肝脏疾病的病理机制及药物治疗方法具有重要意义。已有证据表明cGAS-STING信号通路参与多种肝脏疾病的病理过程, 它触发了与自噬、免疫逃逸和有丝分裂相关的炎症风暴, 同时在宿主抵抗病毒和细菌入侵过程也起到至关重要的作用, 是目前肝脏疾病机制及治疗研究的一个重要潜在方向。

1 cGAS-STING信号通路概述

STING(stimulator of interferon genes, STING), 也称干扰素激活基因, 首次在2008年被揭示是先天性免疫信号的调节剂。cGAS-STING信号通路是天然免疫领域的重大发现。当存在病毒或其他致病因素所导致的细胞DNA损伤时, 损伤的DNA会诱导环状GMP-AMP合成酶(cyclic GMP-AMP synthase, cGAS)构象变化, 并催化环鸟嘌呤腺嘌呤(cyclic GMP-AMP, cGAMP)的产生。cGAMP作为第二信使, 招募位于内质网上的效应器蛋白STING, 促进STING从内质网通过高尔基体到核周围的运输, STING作为通路的关键效应蛋白, 会促使TANK结合激酶1(TANK-binding kinase 1, TBK1)磷酸化激活, 随后一方面促进干扰素调节因子3(interferon regulatory factor 3, IRF3)核转位, 产生 I 型干扰素(interferons, IFNs); 另一方面, STING会活化IκB激酶(inhibitor of nuclear factor kappa-B kinase, IKK), IKK将细胞内NF-κB-IκB复合物的IκB亚基调节位点的丝氨酸磷酸化, 进而被蛋白酶降解, 从而释放NF-κB二聚体进入细胞核, 与有NF-κB结合位点的基因结合, 启动转录进程, 促进炎症因子分泌, 发挥促进炎症的作用^[1]。由于STING在多种细胞类型中广泛表达, 并能调控不同的程序性细胞死亡途径, 所以对cGAS-STING信号通路的认识在过去十年中迅速增长, 许多研究表明cGAS-STING信号通路参与多种疾病, 包括炎症、感染、自身免疫性疾病、代谢紊乱和肿瘤等^[2-3]。最近的研究表明^[4-7], cGAS-STING信号通路也参与了病毒性肝炎、ALD、NAFLD、肝损伤和HCC等多种疾病的病理过程, 我们总结了cGAS-STING信号通路在多种肝脏疾病中的作用及其潜在治疗意义, 深入了解cGAS-STING信号通路可能为治疗肝脏疾病提供新的思路。

2 cGAS-STING信号通路在肝脏疾病

2.1 cGAS-STING信号通路与慢性肝炎 病毒性肝炎是一个重大的公共卫生问题, 从流行趋势来看, 乙型肝炎病毒(hepatitis B virus, HBV)与丙型肝炎病毒(hepatitis C virus, HCV)仍是慢性肝炎、肝硬化和HCC最重要的致病因素^[8]。因此, 探讨HBV感染的细胞内分子机制至关重要。有研究报道显示cGAS-STING信号通路有着优越的抗病毒能力, 可检测细胞质中的病毒DNA, 如单纯疱疹病毒-1、人类免疫缺陷病毒、腺病毒、人类巨细胞病毒等^[9, 10]。当然, 除了识别DNA病毒, 它也可以识别并抵抗RNA病毒, 特别是阳性的单链RNA(single stranded RNA, ssRNA)病毒^[11]。在对HBV的研究过程中, 有研究者发现cGAS-STING信号通路通过激活下游Toll样受体3(toll-like receptor 3, TLR3)产生干扰素β(interferon

β , IFN- β)抑制HBV的复制^[12-14]。另一方面, HBV可逃避cGAS效应通路及免疫系统的识别和攻击, 导致肝细胞慢性感染, 例如HBV聚合酶可破坏STING的K63泛素化, 并通过与STING相互作用最终抑制IFN- β 的产生^[4]。Hu等^[14]将HBV病毒质粒(pHBV1.3)与表达cGAS和STING质粒共转染至HepG2细胞, 发现当HepG2细胞被共转染后, 乙肝病毒RNA水平显著降低, 而HBV DNA水平和e抗原分泌减少5倍, 乙肝病毒RNA在细胞中比例明显减少, 并且在人肝细胞系L02和pHBV1.3转染的小鼠模型中也获得了类似的结果。相比于肝细胞, Kupffer细胞(kupffer cells, KCs), 即肝巨噬细胞有更高的STING蛋白表达量, 它可以吞噬病毒感染细胞, 减轻机体病毒携带量, 但同时, HBV病毒核心也可以通过cGAS-STING信号通路激活Kupffer细胞上的Toll样受体2(toll-like receptor 2, TLR2), 并通过产生白介素10(interleukin 10, IL-10)抑制HBV特异性T细胞应答^[15-17]。肝细胞中cGAS-STING表达水平的降低以及针对cGAS-STING信号转导的HBV逃逸机制在一定程度上促进了肝细胞慢性HBV感染。在HCV与STING相关的研究中, 有报道称HCV编码的非结构蛋白4B(non-structural protein 4B, NS4B)能够直接与STING结合削弱了STING和TBK1之间的相互作用, 阻断干扰素信号的转导^[18-20]。另有研究显示在机体受到外来刺激时, 内质网局部的STING可以移位到细胞质并与TBK1结合, 这时NS4B蛋白可能在内质网保留STING, 从而抑制STING与TBK1的相互作用^[21]。NS4B还可能通过竞争性地与STING结合干扰线粒体抗病毒信号蛋白(mitochondrial antiviral signaling protein, MAVS), 阻断STING和MAVS之间的相互作用, 强烈抑制MAVS介导的IRF-3的磷酸化。综上所述, cGAS-STING信号通路与HBV及HCV之间有着密切关联, 靶向cGAS-STING信号通路可能是增强宿主对HBV及HCV免疫应答的一种治疗选择。

2.2 cGAS-STING信号通路与酒精性肝病 ALD造成肝硬化的死亡率占肝硬化相关疾病的50%, ALD的病因和发病机制复杂, 目前先天免疫功能障碍和过度炎症反应已被证实是ALD发生的重要原因之一^[22]。对ALD患者肝细胞的基因分析结果显示, cGAS-STING通路的激活水平与ALD的严重程度相关。cGAS可通过连接蛋白(主要是Cx32)组成的细胞间通道驱动肝细胞和非实质细胞中IRF3的激活^[23-25]。IRF3的激活可引起酒精诱导的肝细胞细胞凋亡, 继而促进炎症反应, 导致ALD的发生。因此, cGAS和Cx32是ALD发病机制的关键, 可作为潜在的ALD治疗靶点。

2.3 cGAS-STING信号通路与非酒精性脂肪性肝病 NAFLD已成为全球最主要的慢性肝病之一^[26], 是当下

研究的热点, 但同时, 其预防和治疗也存在诸多难点, 目前尚无批准上市的特异性药物^[5]。NAFLD常发生于肥胖人群和代谢综合征患者, 主要以肝细胞内脂肪过度沉积为主要特征, 病程包括单纯性脂肪肝、非酒精性脂肪性肝炎和NASH相关肝硬化^[27]。有研究表明, 在高脂肪饮食(high fatty diet, HFD)的小鼠模型中, STING参与了糖脂代谢过程, 喂养高果糖而不表达STING的小鼠表现出肝脏脂肪、炎症及纤维化的减少, 这表明STING的激活可能促进了肝脏脂肪及炎症的生成^[28]。此外, STING-IRF3轴参与了NAFLD和早期ALD中凋亡通路的激活, STING-IRF3轴可通过与线粒体上相关蛋白Bcl-2、Bax相互作用, 激活线粒体凋亡通路, 造成肝细胞凋亡, 上调炎症通路^[29,30]。另有研究发现单核细胞源性巨噬细胞和肝脏KCs中STING的激活促进了TBK1、c-Jun氨基末端激酶(c-Jun-N-terminal kinase, JNK)和NF- κ B的磷酸化^[31], 导致转化生长因子 α (transforming growth factor- α , TGF- α)和白介素1 β (interleukin-1 β , IL-1 β)生成, 这些细胞因子的产生触发肝细胞炎症通路, 并产生转化生长因子 β 1(transforming growth factor β 1, TGF- β 1), 诱导肝星状细胞(hepatic stellate cells, HSCs)的激活, 造成脂肪沉积和纤维化, 最终驱动NAFLD发生^[32], 甚至进一步发生肝硬化和HCC。

2.4 cGAS-STING信号通路与肝癌 病毒性肝炎, 如HBV、HCV是HCC发生的重要原因, 此外还有过度饮酒、脂肪肝等。目前, 现代医学治疗肝癌方式主要包括手术切除、射频消融术、肝动脉栓塞化疗术及放疗等, 但临床疗效有限, 预后较差, 严重影响了患者的生存质量^[33]。近年来, 发现cGAS-STING在抗肿瘤免疫反应中起着积极的作用, 其与HCC的发生发展也密切相关。有报道显示, 在一定的条件下, 癌细胞的细胞核和线粒体DNA会以多种形式泄漏到胞质中, cGAS-STING信号通路被激活, 促进IFN- β 的释放, IFN- β 的产生增强了宿主抵抗肿瘤细胞的能力。同时, IFN- β 对树突状细胞(dendritic cells, DCs)的成熟至关重要^[34]。DCs中cGAS-STING信号可以通过吞噬死亡或受损的癌细胞、外泌体转移和cGAMP连接被激活, 然后, DCs在IFN- β 的诱导下迁移到肿瘤组织, 激活肿瘤特异性CD8⁺T细胞, 从而诱导全身抗肿瘤免疫来控制局部和远处的肿瘤生长^[35]。此外, 癌细胞中cGAS-STING信号通路的激活也会招募免疫细胞清除癌细胞, 例如增强癌细胞对自然杀伤细胞(natural killer cells, NKs)和细胞毒性T淋巴细胞(cytotoxic T lymphocyte, CTL)的免疫攻击的敏感性^[36]。同时, 基于对多个数据库的分析, 确定了cGAS-STING通路的关键基因与人类样本的HCC表型之间的联系, 发现丝氨酸-苏氨酸激酶PI3家族成员ATR和ATM是HCC中潜在的激酶

靶点, ATR抑制剂增强了肝癌放疗的抗肿瘤活性, 并且可激活胞质中cGAS-STING通路^[37].

2.5 cGAS-STING信号通路其他肝脏疾病 综上所述, cGAS-STING也可能参与其他肝脏疾病发生发展过程, 如肝纤维化、自身免疫性肝病和肝损伤^[38,39]. 有报道显示, 在NAFLD患者中, STING表达水平与肝纤维化程度呈正相关, 巨噬细胞中STING激活诱导TGF- β 1释放, 从而刺激肝星状细胞活化而导致纤维化. 关于cGAS-STING信号转导和其他原因引起的肝纤维化的研究报道尚未出现. 因此, cGAS-STING信号通路参与肝纤维化发生和逆转的机制也需要进一步的研究. 基于cGAS-STING信号通路在固有免疫和适应性免疫调节过程中的重要性, cGAS-STING信号通路可能与自身免疫性肝病密切相关. 近年来, cGAS和STING被发现参与肝脏酒精、辐射和缺血/再灌注(ischemia/reperfusion injury, IRI)等肝损伤相关进程^[40]. 有研究证明^[41,42], 酒精喂养的小鼠体内表现出cGAS-STING信号水平的升高, 这是因为酒精刺激使得内质网(endoplasmic reticulum, ER)应激引发cGAS-STING通路激活和IRF3磷酸化, 进而导致肝细胞凋亡并伴有早期肝纤维化, 而cGAS驱动的IRF3激活是通过肝细胞间的缝隙连接传递实现的, 这个过程可加重肝损伤的程度. 另一项研究报告称^[43], cGAS敲除小鼠在IRI反应中表现出更严重的肝损伤, 而被STING siRNA转染的小鼠表现出更低水平的肝损伤^[44]. 还有报道将IRI的改善归因于cGAS对肝细胞自噬的诱导^[43]. 总的来说, cGAS-STING信号通路激活加剧炎症和组织损伤的证据目前是充分的, 但仍然需要进一步研究cGAS是通过经典细胞因子的产生加重组织损伤, 还是通过自噬减轻组织损伤, 以及哪种作用占主导地位.

3 cGAS-STING信号通路临床应用进展

如前所述, 激活cGAS-STING信号通路对肝病毒感染和肿瘤具有显著的抑制作用, 因此成为近年来肝病免疫学和肿瘤学领域的热门靶点. 目前, 研究的重点主要集中在蛋白水平的临床应用靶向药物, 包括STING激动剂和抑制剂. 在基因水平上的治疗研究进展主要集中在肝炎病毒, 特别是HBV感染. 有临床研究报道称cGAS-STING信号通路在肝癌放疗免疫应答的过程中发挥关键作用, 放疗诱导的外源DNA损伤可作为胞质DNA激活cGAS-STING信号通路, 诱导产生IFN- α , 促进放疗效果^[45]. 此外, cGAS-STING信号通路激动剂还可以与免疫检查点阻断剂治疗、CAR-T治疗、溶瘤病毒治疗等联合使用^[46]. 当然, 最常见的临床应用研究是STING激动剂作为癌症疫苗佐剂^[47], 适当的使用可在克服免疫耐受和增强肿瘤特异性免疫中起着重要作用.

4 结论和展望

综上所述, 越来越多的证据表明cGAS-STING信号通路在多种肝脏疾病的发病机制中发挥重要作用. 在乙型病毒性肝炎和HCC中, cGAS-STING信号通路抑制疾病进展, 激活该通路可显著提高治疗效果. 而在ALD和NAFLD中该通路起促进疾病进展的作用. 作为新发现的通路, cGAS-STING具有广阔的临床应用前景, 是治疗研究的一个重要潜在方向, 如何用好这把“双刃剑”是我们思考的问题.

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