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NF- κ B相关信号通路在胃炎-癌疾病链中的作用机制

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Mechanism of action of NF- κ B related cell signaling pathways in progression of gastritis to carcinoma

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Abstract

Gastric cancer (GC) is a major global public health problem. The evolvement pattern of "superficial gastritis-chronic atrophic gastritis-intestinal metaplasia-dysplasia-gastric carcinoma" is common in related gastric diseases. As a key factor involved in systemic stress response, inflammatory response, and apoptosis, the regulation of NF- κ B related to inflammation and apoptosis is a necessary link between inflammation and cancer progression. NF- κ B is activated in most solid tumors and lymphomas. In the critical mechanism of gastric cancer induced by gastritis with various etiologies, the upstream and downstream molecules in the NF- κ B signaling pathway are changed, and the cells are exposed to the microenvironment of inflammatory response for a long time, which ultimately leads to the development of their carcinogenic potential. This article discusses the mechanism of NF- κ B in the key risk factors for the progression of gastric disease.

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Key Words: NF- κ B; Chronic gastritis; Gastric dysplasia; Gastric cancer; Signal pathway

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摘要

胃癌(gastric cancer, GC)作为全球重大的公共卫生问题, 浅表性胃炎-慢性萎缩性胃炎-肠上皮化生-异型增生-胃癌”的发病模式在胃疾病中常见. 作为参与机体应激、炎症反应及细胞凋亡等过程中的关键因子, NF- κ B相关的炎症反应和细胞凋亡调控是炎-癌进展疾病链的必要环节, 在大多数实体肿瘤和淋巴瘤中, NF- κ B均有激活. 在各种病因诱发的胃炎致胃癌的关键节点机制中, 细胞长期在炎症反应的微环境中, NF- κ B信号通路上下游分子发生改变, 最终导致其促癌潜能的发挥. 本篇论述了NF- κ B在胃炎癌转变进展中的关键机制.

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关键词: NF- κ B; 慢性胃炎; 胃不典型增生; 胃癌; 信号通路

核心提要: NF- κ B是连接免疫、炎症与癌症内在联系的关键调节因子, 参与了幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染诱导胃上皮炎症免疫反应和凋亡调节, 与非*H. pylori*感染相关的胃炎参与激活NF- κ B通路诱发胃炎癌疾病级联, 促进炎癌转变.

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0 引言

胃癌(gastric cancer, GC)是全球最常见的恶性肿瘤之一, 2018年胃癌在癌症发病率排第五位, 是全球癌症相关死亡的第三大原因^[1,2], 中国的胃肠相关癌症发病率和死亡率分别占全球38%和41%^[2]. 研究表明, 幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染是导致胃炎进展恶变为胃癌发生的主要危险因素^[3], 除此之外, 吸烟、腌制食品摄入过量、饮酒过量和水果蔬菜摄入过低等也会增加胃癌发生的风险^[4,5], 肥胖和食管反流性胃炎亦是胃贲门癌发生的危险因素^[6,7].

1 NF- κ B是连接免疫、炎症与癌症内在联系的关键调节因子

核转录因子NF- κ B家族(nuclear factor kappa B, NF- κ B)是炎症反应过程中的核心介质, 是作为连接免疫、炎症和癌症的内在联系的重要调节因子. 它由五个相互作用的主要成员组成: NF- κ B1(p50)、p52、p65(rela)、RelB和c-Rel. 其激活主要依靠三种通路: 经典通路, 非经典通路和旁路通路. NF- κ B作为异质或同源二聚体存在于细胞

中, 通过与细胞质中的抑制性蛋白I- κ B结合而保持活性. 在大多数实体肿瘤和淋巴瘤中, NF- κ B均有激活, 与细胞长期在炎症反应的微环境和IKK/NF- κ B信号通路上游组分的突变或激活中有关, 在肿瘤进程中可以抑制细胞凋亡, 刺激肿瘤细胞增殖, 促进细胞的迁移和侵袭^[8]. 大多数研究表明, 肿瘤中发现的炎症细胞和细胞因子更有可能促进肿瘤的生长、进展和免疫抑制^[9], 持续的NF- κ B本身的激活, 最有可能发挥其致癌潜能^[10].

NF- κ B在胃粘膜免疫炎症中起着重要的中介作用. 有研究证明^[11], 无论是否存在*H. pylori*感染, NF- κ B在炎-癌转化的各个过程中均有激活. 在该疾病进展过程中参与了*H. pylori*感染、细胞凋亡、炎症反应等各个环节.

2 NF- κ B的激活参与*H. pylori*感染诱导胃上皮炎症免疫反应和凋亡调节

*H. pylori*感染是引起胃粘膜炎症的主要原因, 炎症反应引发和加速一系列以胃上皮受损、细胞凋亡增加和细胞增殖不适当为特征的致癌事件, 使正常细胞易受到肿瘤发展趋向, 这可能是胃癌发生的第一步^[12]. 研究发现^[13], 存在*H. pylori*感染的患者胃粘膜组织NF- κ B的表达明显高于未感染组织, 并且其表达与胃炎严重程度、活动度、*H. pylori*负荷、萎缩性胃炎发生呈正相关. 同时, 在肠型胃癌中, p65阳性表达也明显高于弥漫性胃癌^[14], 与胃癌的分化程度、淋巴结转移、临床分期和浸润深度均有关^[15]. 因此, NF- κ B的激活在*H. pylori*感染相关胃炎和胃癌疾病中十分常见.

胃上皮中经典NF- κ B信号通路异常导致了胃癌前病变的发生, NF- κ B1和NF- κ B2介导*H. pylori*感染对胃粘膜的作用^[16]. *H. pylori*的感染也通过介导ERK1/2 MAPK通路诱导NF- κ B转录因子, 并通过NF- κ B p50同位二聚体与HK α 启动子的结合来抑制HK α 基因的表达, HK α 作为H-K-ATP酶的启动子介导壁细胞酸分泌, 这可能是*H. pylori*相关“炎-癌”发生的机制之一^[17]. NF- κ B的激活不能缺少IkB激酶(IKK)复合物的参与, IKK β 是其激活的关键因素, 除了丝氨酸残基磷酸化之外, 酪氨酸磷酸化的IKK β 在一定程度上参与了*H. pylori*感染后NF- κ B的激活^[18]. *H. pylori*刺激导致的胃发育不良细胞中NF- κ B表达增高, 出现IKK β 的缺失, 导致细胞凋亡、活性氧和细胞坏死的增加, IL-1 α 的上调和抗凋亡基因的下调, 这代表IKK β /NF- κ B通路表达异常导致的坏死和凋亡增加, 与GD发生风险相关^[19]. *H. pylori*还能通过B淋巴细胞替代途径激活NF- κ B, 通过诱导NF- κ B 2p100到p52加工过程中B淋巴细胞趋化因子、EBI-1配体趋化因子和基质细胞衍生因子-1 α mRNA的表达上调和抗凋亡的影响, 促使淋巴细胞获得恶性潜能^[20]. TIFA在*H. pylori*感染的胃

上皮细胞中同时激活经典和替代的NF- κ B信号, 肿瘤坏死因子受体相关因子(TRAF)与TIFA相互作用蛋白触发经典的NF- κ B激活, TIFA/TRAF2相互作用使细胞凋亡抑制因子1(CIAP 1)从TRAF 2中短暂移位, CIAP 1蛋白降解, 从而促进NF- κ B通路的激活^[21]. *H. pylori*诱导胃上皮细胞凋亡和胃癌发生需要P53上调凋亡调节剂-PUMA的参与, *H. pylori*感染后, p65通过与PUMA启动子远端位点结合直接激活PUMA转录, 由TLR 2介导的NF- κ B的激活和随后的炎症细胞因子的诱导而产生GEC凋亡^[22]. 在癌细胞模型和小鼠模型*H. pylori*感染能诱导内源性DARPP-32(dopamine and cAMP-regulated phosphoprotein, molecular weight 32000)表达, DARPP-32在消化道肿瘤中的高表达具有致癌特性, DARPP的过表达和NF- κ B激活都发生在肠上皮化生的早期, 并在随后的胃肿瘤发生过程中持续存在. Hp-NF- κ B- DARPP-32信号轴的激活与胃肿瘤级联进展相关, *H. pylori*感染引起的炎症NF- κ B转录上调DARPP-32的表达, 促进细胞存活, 从而促进胃肿瘤的发生^[23].

3 *H. pylori*的致病毒力因子是激活NF- κ B关键通路的重要因素

*H. pylori*有多种致病性毒力因子, 其中细胞毒素相关蛋白(CagA)和空泡细胞毒素(VacA)是主要的*H. pylori*致病效应因子. CagA是*H. pylori*利用由cag致病性岛(cagPAI)编码的IV型分泌系统(type IV secretion system, T4SS)粘附在胃上皮细胞上, 携带cagPAI基因簇的*H. pylori*菌株与cag阴性菌株相比, 具有更强的NF- κ B活性和IL-8表达的诱导作用^[24]. *H. pylori*诱导的AGS胃上皮细胞CDNA基因表达谱的检测展示了超过80%的诱导基因(476/566)的上调依赖于cagPAI. 通过NF- κ B或ERK的信号转导通路是已知cagPAI阳性的*H. pylori*激活的主要通路^[25]. *H. pylori*诱导的胃上皮细胞DNA损伤依赖于双功能RfaE酶和cagPAI, 通过 α 激酶1/叉头相关结构域(ALPK1/TIFA)信号通路对脂多糖生物合成中间体 β -ADP-heptose进行先天免疫识别, 从而激活NF- κ B信号; 同时, 幽门螺杆菌诱导的复制应激和DNA损伤依赖于在S期感染细胞中形成的共转录RNA/DNA杂交(r-loop), 这些r-loop是 β -ADP-heptose/ALPK1/TIFA/NF- κ B信号转导的结果^[26]. CagA与转化生长因子- β -活化激酶1(transforming growth factor-beta-activated kinase 1, TAK1)的相互作用对*H. pylori*诱导的NF- κ B激活必不可少, 通过肿瘤坏死因子受体相关因子6介导的Lys63连接的TAK1的泛素化来增强TAK1的活性进而诱导NF- κ B激活^[27]. *H. pylori* cagA阳性相关的肠型胃癌通过NF- κ B/p65与c-myc、cyclinD 1和bcl-XL的高表达密切相关, 这表明NF- κ B活性的抑制是肠型胃癌的

治疗靶点^[14]. 空泡细菌毒素(VacA)最重要的生物学效应是膜孔的形成和液泡的形成, 能够侵蚀和松解胃上皮细胞之间的紧密连接, 同时具有免疫抑制作用, 如影响T细胞受体/IL2信号通路, 通过NF- κ B激活介导上调IL-8、IL-2RA、CD69和ICAM^[28]. VacA阳性*H. pylori*诱导IL-8、生长相关癌基因 α 、单核细胞趋化蛋白1和RANTES(调节活化、正常、T细胞表达和分泌)的表达, 能够激活p65/p50异二聚体和磷酸化的IKK α / β 信号, 这种作用依赖于Ca²⁺内流和活性氧中间体(ROI)的线粒体生成^[29]. VacA氨基末端476残基片段(P52)过表达可诱导THP-1细胞产生肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、一氧化氮和活性氧, 也促进THP-1细胞凋亡和NF- κ B的激活, 这可能是其诱导促炎细胞因子分泌和细胞凋亡的机制之一^[30].

4 非*H. pylori*感染相关原因参与NF- κ B通路激活诱发胃炎癌疾病级联

胆汁酸反流和慢性炎症是胃肠上皮化生(intestinal metaplasia, IM)-胃癌疾病级联反应的重要危险因素, 其介导的基因表达在调节胃上皮细胞相关的炎症反应方面至关重要. miR-92a-1-5p/FOXO 1/NF- κ B/CDX 2调节轴在胃细胞产生IM表型中起关键作用, IM组织中胆汁酸诱导miR-92-15p增加, 并通过靶向FOXO 1/FOXJ 1轴和调节NF- κ B通路, 激活CDX 2和其肠道下游标记物^[31]. 胆汁酸能够增加胃细胞NF- κ B和核受体SHP的相关作用从而增加c-Jun表达和TNF α 的产生^[32]. 另外, CDX1是肠分化的重要转录因子, 在“胃炎-化生-癌”疾病序列模式下异常表达. CDX 1启动子甲基化与染色质结构封闭、NF- κ B结合减少和转录沉默有关. 同时, CDX 1启动子的超甲基化、低甲基化和高甲基化阶段与NF- κ B信号活性呈负相关, 这些功能的相关作用促进胃肠化生的发展和癌变^[33].

N亚硝基化合物的长期接触是胃炎发生导致癌变进展的又一危险因素. 在MNNG诱导的胃癌前病变大鼠模型中, NF- κ B/p53/Ki67-凋亡信号通路的激活, 使caspase(半胱氨酸依赖性天冬氨酸特异性蛋白酶)(-3、-8和-9)、Fas、bax和bid等促凋亡蛋白上调^[34], 整合素 β 1/NF- κ B/DARPP-32/STAT 3途径的激活参与胃粘膜损伤发生, 促使胃癌前病变组织恶变趋向^[35].

一些特定基因的过表达和沉默在胃炎-胃疾病级联中也扮演着之重要角色. IL-1 β 胃特异性表达转基因小鼠会导致自发性胃炎和癌症, 与早期从骨髓源性抑制细胞(MDSCs)向胃内募集相关. GD发生时胃内MDSCs明显增加, IL-1 β 通过IL-1RI/NF- κ B途径在体外和体内激活MDSCs^[36]. 此外, TFF 1基因敲除小鼠随着时间的增加胃

黏膜幽门窦发生由胃炎向增生、低度异型增生、高级别异型增生的进展, 最终导致恶性腺癌, 胃组织NF- κ B在癌变级联过程中活性逐渐增加, 而TFF1表达逐渐下降, TFF 1的表达通过肿瘤坏死因子受体1(TNFR 1)/I α B激酶(IKK)途径抑制肿瘤坏死因子受体1(TNFR 1)介导的NF- κ B激活^[37]; NF- κ B p65和人端粒酶逆转录酶(HTERT)的活性在胃癌疾病级联进展的正相关联系可能也是肿瘤发生的重要步骤之一^[15]。肠型胃癌的p65阳性表达也明显高于弥漫性胃癌^[14], 与胃癌的分化程度、淋巴结转移、临床分期和浸润深度均有关, 这种作用可能与增强端粒酶活性相关^[15]。NF- κ B1的缺失会引起小鼠胃粘膜组织出现胃炎-萎缩-胃不典型增生-侵袭性肿瘤的发展趋势, 胃体和胃窦中IL-6、IL-11、IL-22和TNF- α 水平升高, 导致组织中STAT 1的激活, 从而导致炎症性免疫反应和胃癌的发生^[38]。也有研究发现胃粘膜由IM-GD-GC时出现死亡受体Fas抗原凋亡耐药表型, Fas Ag-FasL通过ERK 1/2激活NF- κ B的表达, 将Fas Ag信号通路从肿瘤抑制角色转化为肿瘤启动子^[39]。NF- κ B的抑制能使环氧合酶COX-2和一氧化氮合酶iNOS受到抑制, 减缓胃癌的扩散^[40]。

5 结语

NF- κ B活化对胃炎-胃肿瘤疾病进展级联有着重要影响, 在整个疾病过程中, 参与了炎症免疫反应和调节细胞凋亡等环节。NF- κ B信号的异常和持续激活有助于炎症向癌症的恶性转化, 肿瘤发生时参与了肿瘤微环境中细胞间的串扰和免疫反应。一方面, NF- κ B通路参与适应性免疫反应, 增加炎症的严重程度, 另一方面, 慢性炎症可能导致组织损伤、自身免疫性疾病和肿瘤的发生, 改变受损组织部位的遗传稳定性和表观遗传状态, 致使促肿瘤微环境的产生。因此, 除了对NF- κ B信号通路进行深入的研究和对抑制物的鉴定外, 应进一步研究NF- κ B分子网络对胃炎-胃癌协同治疗的作用, 以期寻找NF- κ B在胃炎-胃癌疾病进程中作用的潜在靶点。

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