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NF-κB 在幽门螺杆菌感染介导的胃癌发生发展中的作用 *

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摘要 目的：探讨核因子 -κB(nuclear factor-κB，NF-κB)在幽门螺杆菌感染介导的胃癌发生发展中的作用。**方法：**选择 2016 年 3 月至 2019 年 3 月在本院诊治的胃部疾病患者 110 例，采用 qPCR 检测 NF-κB 相对表达情况，采用免疫印记法检测幽门螺杆菌(*Helicobacter pylori*，*Hp*)感染情况并进行相关性分析。**结果：**在 110 例患者中，病理诊断为胃癌 9 例(胃癌组)和良性胃部疾病 101 例(良性组，其中浅表性胃炎 52 例、萎缩性胃炎 26 例、不典型增生 23 例)。胃癌组的幽门螺杆菌感染率为 88.9 %，显著高于良性组的 10.9 % (P<0.05)。胃癌组的 NF-κB 表达阳性率为 77.8 %，显著高于良性组的 14.9 % (P<0.05)。在 110 例患者中，直线相关性分析显示幽门螺杆菌感染、NF-κB 表达阳性与胃癌有显著正相关性(P<0.05)。受试者工作特征曲线 (receiver operating characteristic curve，ROC)显示幽门螺杆菌感染、NF-κB 表达阳性鉴别诊断胃癌的曲线下面积分别为 0.669 和 0.713。**结论：**NF-κB 在胃癌中呈现高表达状况，也多伴随有幽门螺杆菌感染，两者存在显著相关性，共同介导胃癌的发生发展。

关键词：核因子 -κB；幽门螺杆菌；胃癌；相关性；胃炎

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Role of NF-κB in the Development of Gastric Cancer Mediated by *Helicobacter Pylori* Infection*

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ABSTRACT Objective: To investigate the role of nuclear factor-κB (NF-κB) in the development of gastric cancer mediated by *Helicobacter pylori* infection. **Methods:** From March 2016 to March 2019, a total of 110 patients with gastric diseases diagnosed and treated were enrolled. qPCR were used to detect the relative expression of NF-κB, and *Helicobacter pylori* (*Hp*) infection were detected by immunoblotting. And carry out correlation analysis. **Results:** In the 110 patients, there were 9 patients of gastric cancer (gastric cancer group) and 101 patients of benign gastric disease (benign group that included 52 patients of superficial gastritis, 26 patients of atrophic gastritis, and 23 patients of dysplasia). The *Helicobacter pylori* infection rates were 88.9 % in the gastric cancer group, which were significantly higher than that in the benign group (10.9 %) (P<0.05). The positive rates of NF-κB expression in gastric cancer group were 77.8 %, which were significantly higher than that in benign group (14.9 %)(P<0.05). In the 110 patients, linear correlation analysis showed that *Helicobacter pylori* infection and NF-κB expression were positively correlated with gastric cancer (P<0.05). The receiver operating characteristic curve (ROC) showed that the area under the curve of *Helicobacter pylori* infection and NF-κB positive differential diagnosis of gastric cancer were 0.669 and 0.713, respectively. **Conclusion:** NF-κB are highly expressed in gastric cancer, and it are accompanied by *Helicobacter pylori* infection. There are significant correlation between them which together mediate the development of gastric cancer.

Key words: Nuclear factor-κB; *Helicobacter pylori*; Gastric cancer; Correlation; Gastritis

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前言

胃癌在人群中具有很高的发病率。该病在发病早期无特异性症状或明显不适体征，使得很多患者在就诊时已处于晚期，导致死亡率增加[1]。该病的具体发病机制还不明确。目前幽门螺杆菌(*Helicobacter pylori*，*Hp*)感染被公认的胃癌第一致癌因子[2,3]。幽门螺杆菌感染可以引起胃粘膜慢性炎症，继而出现粘膜非典型增生、萎缩等，最终形成胃癌[4]。癌基因的异常表达、抑癌基因的失活均可以引起胃粘膜上皮细胞增殖与凋亡失衡，诱发胃癌[5,6]。核因子 -κB(nuclear factor-κB，NF-κB)是一种细胞核

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内信号转导因子,其信号通路是一种能够调控细胞增殖和凋亡的信号级联放大反应通路，具有调控肿瘤相关基因转录的作用[7,8]。研究表明,NF-κB 的过表达与多种癌症密切相关[9,10],特别是 NF-κB 活化后进入细胞核内,启动相关癌基因的转录,从而诱发肿瘤的发生与发展[11]。近年来,研究发现幽门螺杆菌感染后 NF-κB 呈持续激活状态，能上调 NF-κB 信号通路关键因子的表达,可导致慢性炎症、肿瘤的发生,主要是通过调控基因转录参与肿瘤细胞的增值和转移[12]。因此活化的 NF-κB 在肿瘤的发生发展中发挥了重要的作用,但是在幽门螺杆菌感染介导的胃癌的发病中的作用报道尚少。并且尽管胃癌早期的诊断和辅助治疗改善了预后,但是患者 5 年的生存率仍不理想,因此,本文具体探讨了 NF-κB 在幽门螺杆菌感染介导的胃癌发生发展中的作用,希望有助于提高胃癌的早期检出率,为今后胃癌的治疗提供新思路和靶点。

1 资料与方法

1.1 研究对象

选择 2016 年 3 月至 2019 年 3 月在本院诊治的胃部疾病患者 110 例,纳入标准:临床资料完整;首诊患者;检测前未行任何治疗。排除标准:患有其他系统肿瘤或严重疾病者;孕妇、哺乳期及过敏体质者;严重心肺肝肾功能不全者;临床资料缺乏者;3 个月内参加过其他临床试验者。

1.2 NF-κB 表达检测

取所有患者的空腹静脉血 2-3 mL,取全血组织,按照 RNA 提取试剂盒的步骤提取全血总 RNA,逆转录成 cDNA 后扩增,采用 qPCR 检测 NF-κB 相对表达情况,引物由上海生工公司设计和合成,检测试剂盒购自上海西唐生物科技有限公司,选取了 U2 作为内参,NF-κB 上游引物:5-'CTGGGCA-CAAGTCGTTTATGA'-3，下游引物:5-'CTGGAGCCG-GTAGGGAAG'-3,每个样本做三个复孔,结果取其均值,以 Ct 值相对值≤ 25 代表为阳性。

1.3 幽门螺杆菌感染及分型检测

选择 1.2 中的血液样本,低温离心(1000 rpm 离心 10 min)分离上层血清,用免疫印记法于体外定性检测人血清中多种幽门螺杆菌 IgG 抗体情况，确认幽门螺杆菌感染情况并进行分型,操作均严格按照说明书进行。记录所有患者的舒张压、收缩压、性别、年龄、体重指数等指标,同时记录患者的病理检查结果。

1.4 统计学分析

应用 SPSS 22.00,计量数据以均数± 标准差表示,对比为 t 检验;计数数据以率表示,对比为 x^2 检验,相关性分析采用直线相关性分析,P<0.05 有统计学意义。

2 结果

2.1 病理结果

在 110 例患者中,病理诊断为胃癌 9 例(胃癌组)和良性胃部疾病 101 例(良性组,其中浅表性胃炎 52 例、萎缩性胃炎 26 例、不典型增生 23 例)。两组一般资料对比差异无统计学意义(P>0.05)。见表 1。

表 1 两组一般资料对比

Table 1 Comparison of general data between the two groups

Groups	n	SBP (mmHg)	BMI (kg/m^2)	DBP (mmHg)	Gender (male / female)	Age (years)
Gastric cancer group	9	127.22± 14.20	22.48± 2.19	81.30± 10.77	5/4	50.23± 5.38
Benign group	101	125.55± 13.98	22.10± 1.98	80.92± 8.92	51/50	51.44± 4.27

2.2 幽门螺杆菌感染情况对比

胃癌组的幽门螺杆菌感染率为 88.9 %,显著高于良性组的 10.9 %(P<0.05)。见表 2。

表 2 两组幽门螺杆菌感染情况对比(例,%)

Table 2 Comparison of *Helicobacter pylori* infection in two groups (n, %)

Groups	n	Type Ⅰ	Type Ⅱ	Total
Gastric cancer group	9	6	2	8(88.9)*
Benign group	101	8	3	11(10.9)

Note: Compared with the benign group, *P<0.05.

2.3 NF-κB 表达阳性率对比

胃癌组的 NF-κB 表达阳性率为 77.8 %，显著高于良性组的 14.9 %(P<0.05)。见表 3。

表 3 两组 NF-κB 表达阳性率对比(例,%)

Table 3 Comparison of positive rate of NF-κB expression between the two groups (n, %)

Groups	n	NF-κB expression positive	NF-κB positive rate of expression
Gastric cancer group	9	7	77.8*
Benign group	101	15	14.9

2.4 相关性分析

在 110 例患者中，直线相关性分析显示幽门螺杆菌感染、NF-κB 表达阳性与胃癌有显著正相关性(P<0.05)。见表 4。ROC 显示幽门螺杆菌感染、NF-κB 表达阳性鉴别诊断胃癌的曲线下面积分别为 0.669 和 0.713。

表 4 幽门螺杆菌感染、NF-κB 表达阳性与胃癌的相关性(n=110)

Table 4 Correlation between *Helicobacter pylori* infection, NF-κB expression and gastric cancer (n=110)

Index	Helicobacter pylori infection	NF-κB positive expression
r	0.452	0.673
P	0.012	0.000

3 讨论

胃癌是临床上常见的消化道恶性肿瘤，也是与幽门螺杆菌感染相关的恶性肿瘤[13]。幽门螺杆菌感染可对泌酸腺胃粘膜造成损伤，可产生内因子抗体，导致胃粘膜上皮细胞增殖与凋亡失衡，从而诱发胃癌的发生[14]。绝大部分胃癌患者的生存期在 5 年以上，但是对于晚期胃癌患者，仅 30 %左右患者的生存期在 5 年以上[15]。并且从胃良性病变发展到胃癌的时间比较长，因此对胃癌患者进行早期诊断，是治疗及预后的关键[16]。本研究显示胃癌组的幽门螺杆菌感染率为 88.9 %，显著高于良性组的 10.9 %。当前也有研究显示 20 %左右的慢性胃炎患者存在幽门螺杆菌感染，及时根除幽门螺杆菌能预防胃炎向胃癌的发展[17,18]。

胃癌是世界范围内普遍发生的恶性肿瘤之一，但是胃癌的发生、发展的机制还不明确。现代研究显示胃炎在抗原物质刺激下，可大量刺激粘附分子、前炎症性细胞因子、转录因子等的生成，导致恶性疾病的发生[19,20]。NF-κB 是一个多向性核转录因子，具有多向调节功能，在正常状态下，NF-κB 以三聚体的形式存在于细胞质中，没有转录活性[21]。NF-κB 的过表达可使得细胞分泌的促炎因子表达减少，而抑炎因子表达增多，从而参与肿瘤的发生与发展。已有研究显示 NF-κB 可以提高凋亡抑制蛋白的表达而抑制瘤细胞的凋亡，加速恶性肿瘤的发展[22,23]。本研究显示胃癌组的 NF-κB 表达阳性率为 77.8 %，显著高于良性组的 14.9 %。当前也有研究显示，在细胞受到炎症因子等刺激时，NF-κB 从多聚体上释放而活化，从而与靶 DNA 基因结合，诱导许多基因的转录，进而改变细胞的相关信号传导，促进细胞癌变[24]。还有研究显示 NF-κB 表达与胃癌的临床分期、淋巴结转移相关，其表达异常参与肿瘤发生发展的全过程[25,26]。

胃癌的早期症状不明显，多数患者在胃癌晚期阶段才开始进行治疗，导致预后比较差，因此对胃癌发病机制的分析具有重要价值。不过胃癌的发生是一个多步骤的逐渐促进过程，其发展通常以胃炎为始，最终发展为胃癌[27,28]。本研究直线相关性分析显示幽门螺杆菌感染、NF-κB 表达阳性与胃癌有显著正相关性；ROC 曲线显示幽门螺杆菌感染、NF-κB 表达阳性鉴别诊断胃癌的曲线下面积分别为 0.669 和 0.713。从机制上分析，胃黏膜上皮细胞早期的幽门螺杆菌感染通常表现为胃炎，而后者可通过调节非编码 RNA 表达诱导胃黏膜上皮细胞的增殖，从而引起细胞癌变 [29]。同时也可激活 NF-κB 激酶的表达，使得 NF-κB 释放入细胞核内与靶基因结合，从而促进靶基因转录和表达[30]。本研究也有一定的不足，总体例数比较少，纳入指标比较少，没有进行动态性随访分析，将在下一步进行深入分析，

综上所述，NF-κB 在胃癌中呈现高表达状况，也多伴随有幽门螺杆菌感染，两者存在显著相关性，共同介导胃癌的发生发展。

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