

# 癌蛋白CagA、ERK信号通路与胃癌关系的研究进展

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广东省自然科学基金资助项目, No. 10452402301005604  
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收稿日期: 2013-08-06 修回日期: 2013-09-24  
接受日期: 2013-09-30 在线出版日期: 2013-11-08

## Association between CagA/ERK signaling pathway and gastric cancer

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Received: 2013-08-06 Revised: 2013-09-24  
Accepted: 2013-09-30 Published online: 2013-11-08

## Abstract

Cytotoxin-associated gene A (CagA) of *Helicobacter pylori* is the first identified bacterial oncoprotein that plays a critical role in gastric carcinogenesis. Upon delivery into gastric epithelial cells via type IV secretion, CagA can interfere with a number of host signaling pathways. Extracellular signal-regulated kinase (ERK) signaling pathway is a hub in cellular signal transduction, through which CagA elicits a series of cellular events including cell proliferation, apoptosis, scatter and metastasis, all of which are associated with gastric carcinogenesis. Here we perform a review of the association between CagA/ERK signaling pathway and gastric cancer.

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Key Words: *Helicobacter pylori*; CagA; ERK; Gastric cancer

Xing JM, Huang ZG. Association between CagA/ERK signaling pathway and gastric cancer. *Shijie Huaren Xiaohua Zazhi* 2013; 21(31): 3363-3368 URL: <http://www.wjgnet.com/1009-3079/21/3363.asp> DOI: <http://dx.doi.org/10.11569/wcjd.v21.i31.3363>

## 摘要

细胞毒素相关基因A蛋白(cytotoxin-associated gene A, CagA)是幽门螺杆菌重要毒力因子之一, 亦被称为细菌癌蛋白, 可通过IV型分泌系统易位进入胃上皮细胞, 干扰多条信号转导通路. 细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)通路在细胞信号传导中处于枢纽地位, 癌蛋白CagA可通过激活ERK信号通路对细胞的增殖、凋亡、分散和转移等生物学行为产生影响, 与胃癌的发生、发展有关. 本文对CagA、ERK信号通路与胃癌的研究进展做一综述.

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关键词: 幽门螺杆菌; 细胞毒素相关基因A蛋白; 细胞外信号调节激酶; 胃癌

**核心提示:** 癌蛋白细胞毒素相关基因A蛋白(cytotoxin-associated gene A, CagA)通过激活细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)信号通路导致宿主细胞发生恶性转化, 在胃癌的发生、发展过程中可能发挥重要作用. 研究CagA、ERK信号通路与胃癌的关系, 将为揭示CagA蛋白的致癌机制提供新的研究证据, 并有望为幽门螺杆菌诱发胃癌的分子机制研究提供新思路和新靶点.

邢军明, 黄志刚. 癌蛋白CagA、ERK信号通路与胃癌关系的研究进展. 世界华人消化杂志 2013; 21(31): 3363-3368 URL: <http://www.wjgnet.com/1009-3079/21/3363.asp> DOI: <http://dx.doi.org/10.11569/wcjd.v21.i31.3363>

## 0 引言

胃癌是临床上常见的恶性肿瘤之一, 在全球肿

## ■背景资料

胃癌在全球肿瘤死因谱中稳居第二位, 目前虽已明确幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染是导致胃癌的重要危险因素, 但其诱发胃癌的分子机制尚不清楚. 细胞毒素相关基因A蛋白(cytotoxin-associated gene A, CagA)是 *H. pylori* 感染导致宿主产生炎症反应的重要效应蛋白, CagA在宿主细胞内可干扰多条信号途径, 而细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)通路在细胞信号传导中处于枢纽地位. CagA蛋白可通过激活ERK信号通路对细胞的增殖、凋亡、分散和转移等生物学行为产生影响. 研究CagA蛋白、ERK信号通路与胃癌的关系, 对于揭示 *H. pylori* 相关胃癌的分子机制具有重要意义.

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## ■ 研发前沿

ERK信号通路是涉及*H. pylori*癌蛋白CagA致病机制的关键信号通路之一, ERK通路的异常激活在胃癌细胞的恶化转化过程中发挥重要作用。进一步揭示CagA蛋白激活ERK信号通路后的下游分子事件以及ERK通路与其他信号通路的相互作用关系将为CagA蛋白的致癌机制研究提供新的研究证据, 并有望为*H. pylori*诱发胃癌的分子机制研究提供新思路 and 新的靶点。

瘤死因谱中稳居第2位。尽管早已明确, 幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是人类胃癌的I类(即肯定的)致癌原, 但迄今为止, *H. pylori*诱发胃癌的分子机制尚未阐明<sup>[1-3]</sup>。细胞毒素相关基因A蛋白(cytotoxin-associated gene A, CagA)是*H. pylori*感染导致宿主产生炎症反应及癌变的重要效应蛋白, 亦被称为细菌癌蛋白。CagA蛋白在宿主细胞内通过干扰多条信号途径, 对细胞的增殖、凋亡、分化等功能产生影响, 其中细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)通路是涉及CagA蛋白致病机制的关键信号通路之一<sup>[4-6]</sup>。本文对于*H. pylori*癌蛋白CagA、ERK信号通路与胃癌的研究进展做一综述。

## 1 *H. pylori*与癌蛋白CagA

*H. pylori*是一种可长期定植于人类胃黏膜的革兰氏阴性螺旋形微需氧菌, 在全世界范围内感染率超过50%。来自世界各地的流行病学研究证实, 幽门螺杆菌感染是诱发胃癌的重要危险因素<sup>[7-9]</sup>。CagA蛋白是*H. pylori*最重要的毒力因子之一, 通常根据CagA蛋白表达与否将*H. pylori*分为两型: I型为高毒力株, 含*cagA*基因, 表达CagA和VacA蛋白, 具有空泡毒素活性; II型为低毒力株, 不含*cagA*基因, 不表达CagA和VacA蛋白, 无空泡毒素活性<sup>[10]</sup>。研究显示, 感染高毒力株患者较之感染低毒力株者, 发生萎缩性胃炎和胃腺癌的危险性明显升高, 提示CagA可能与*H. pylori*相关胃癌的发生有关<sup>[11-14]</sup>。

1993年Tunmmuru等<sup>[15]</sup>首次用酶切*H. pylori*全基因组的方法克隆到了*cagA*基因, 其开放阅读框为4821 bp, 编码1181个氨基酸, 并发现所有15株产VacA菌株均含有该基因, 命名为细胞毒素相关基因A, 相应蛋白则命名为CagA。cagA基因位于cag致病岛(cag pathogenity island, cagPAI)一侧末端, cagPAI长约40 kb, 定位于谷氨酸消旋酶基因内部, 其G+C含量(35%)与基因组中的其他部分(39%)不同, 提示该基因群可能是在进化过程中由其他生物体通过水平转移而来<sup>[16,17]</sup>。cagPAI内含有编码cagA和IV型分泌系统等31个基因。IV型分泌系统充当分子注射器样作用, 可以将CagA蛋白“注入”宿主细胞, CagA是第一个通过此方式进入真核细胞发挥作用的细菌蛋白<sup>[18,19]</sup>。

CagA蛋白易位进入宿主细胞后, 定位于宿主细胞质膜的内表面, 并在此经Src家族蛋白激

酶(Src family kinases, SFKs)作用发生酪氨酸磷酸化, 磷酸化位点位于CagA分子C端谷氨酸-脯氨酸-异亮氨酸-酪氨酸-丙氨酸(EPIYA)重复序列中的酪氨酸残基<sup>[20,21]</sup>。一般根据EPIYA重复序列可将CagA分为东亚型(含EPIYA-A、EPIYA-B和EPIYA-D重复基序, 简称A-B-D型)和西方型(含EPIYA-A、EPIYA-B和1个或多个EPIYA-C重复基序, 简称A-B-C型)<sup>[22]</sup>。CagA的东亚型与西方型相比具有较强的诱导细胞发生蜂鸟样改变的能力。感染含东亚型CagA的*H. pylori*患者其胃黏膜炎症程度及胃炎、萎缩性胃炎的严重程度均高于感染含西方型CagA的*H. pylori*患者, 提示感染含东亚型CagA的*H. pylori*菌株致胃癌的危险性更高<sup>[23-25]</sup>。

## 2 CagA与ERK通路

2.1 ERK通路 ERK是80年代末期发现的一类丝氨酸/苏氨酸激酶, 是传递丝裂原信号的信号蛋白。经典的ERK通路的信号传递过程包括: 细胞外信号→细胞受体→细胞内酪氨酸激酶→Ras蛋白→Raf蛋白→细胞外信号调节激酶激酶(extracellular-signal regulated kinase kinase, MEKK)→MEK→ERK1/2→转录因子→相关基因表达→细胞增生、转化<sup>[26-28]</sup>。其中Ras蛋白是一种类似鼠肉瘤病毒的细胞癌蛋白, 具有活化态的GTP结合构象与失活态的GDP结合构象。两种构象可以相互转变, 在信号转导过程中发挥开关作用。Ras蛋白激活将Raf蛋白从胞浆转移到胞膜, 在胞膜上Raf蛋白被激活<sup>[29,30]</sup>。Raf蛋白是丝裂原活化蛋白激酶的一种激酶, Raf蛋白被激活后, 其C端催化区能与MEK结合, 并使其催化区第Ⅷ亚区中两个丝氨酸磷酸化, 从而使MEK激活。MEK丝裂原介导的细胞外激酶属于少有的双重特异性激酶, 使酪氨酸和苏氨酸两个调节位点磷酸化而激活ERK<sup>[31,32]</sup>。激活的ERK1/2转移到胞核, 通过磷酸化转录因子、细胞骨架相关蛋白、酶等多种底物来调节相关基因表达, 进而参与细胞生长、发育、分裂、迁移及凋亡等多种生理过程<sup>[33-36]</sup>。

2.2 CagA激活ERK通路 CagA可通过依赖和不依赖于酪氨酸磷酸化的方式激活ERK通路: 首先, 酪氨酸磷酸化的CagA可激活含SH-2结构域的酪氨酸磷酸酶(tyrosine phosphatase, SHP-2), SHP-2由3个部分组成: N端区域有两个串联重复的SH-2结构域(N-SH2和C-SH2); 一个单一的催化蛋白酪氨酸磷酸酶(protein tyrosine phosphatase,

PTP)结构域和碳端部分<sup>[37-39]</sup>. SH-2结构域在蛋白质组成中专一地同含有磷酸化酪氨酸的肽类相互作用. 由SHP-2的SH-2结构域识别的肽类同源序列, 能很好地与CagA的EPIYA基序的侧翼序列吻合. SHP-2是细胞多条信息传递和细胞骨架重构中的重要蛋白, 可通过一系列被激活的受体酪氨酸激酶, 调控细胞内的信号转导事件<sup>[40-42]</sup>. 磷酸化的CagA特异性结合SHP-2的SH-2结构域使SHP-2活化, 致使Ras/Raf/MEK/ERK通路依次激活, 导致细胞骨架重排和细胞拉伸即“蜂鸟样表型”, 这是CagA蛋白导致细胞表型发生改变的主要机制之一<sup>[43,44]</sup>.

其次, CagA在体内、体外均可直接与生长因子受体结合蛋白-2(growth factor receptor-bound protein 2, GRB-2)相互作用, 发挥生长因子样作用, 激活RAS/MEK/ERK信号通路, 导致细胞增殖和胞间解离, 而这一作用与CagA酪氨酸磷酸化无关<sup>[45]</sup>. 另外, CagA还可经由RAS/RAF/MEK/ERK信号通路可直接激活核因子- $\kappa$ B(nuclear factor  $\kappa$ B, NF- $\kappa$ B), 诱导慢性炎症相关因子白介素-8(interleukin-8, IL-8)的释放, 同样该作用也与CagA酪氨酸磷酸化无关<sup>[46]</sup>.

### 3 CagA、ERK通路与胃癌

胃泌素(gastrin)是一种重要的胃肠激素, 胃泌素的表达水平随着肿瘤分化程度的降低而显著升高, 与刺激肿瘤细胞生长及肿瘤的淋巴结转移有关<sup>[47-49]</sup>. Takaishi等<sup>[50]</sup>研究认为, 在*H. pylori*感染相关性胃癌的发生、发展过程中, 胃泌素是其辅助因子. 新近Zhou等<sup>[51]</sup>发现, CagA可通过MEK/ERK和JAK2通路上调胃泌素基因的表达, 该研究为CagA激活ERK通路促进胃癌的发生提供了证据.

CagA蛋白可增加正常胃黏膜细胞对致癌物二甲基胍的敏感性, 促进正常细胞发生恶性转化. ERK1/2通路特异性抑制剂PD98059可使*cagA*转染的细胞DNA合成显著受抑制, 细胞增殖活性明显下降, 并且转染*cagA*的细胞ERK1/2活性、RAS/MAPK通路的IQGAP-2蛋白(IQ domain GTPase-activating proteins, IQGAP-2)、R-Ras和B-Raf表达水平显著高于致癌物二甲基胍处理组和对照组, 提示CagA蛋白可通过激活ERK1/2通路诱导胃黏膜上皮细胞发生转化<sup>[52]</sup>.

Meyer-ter-Vehn等<sup>[53]</sup>研究报道, 胃上皮细胞在*H. pylori*(CagA<sup>+</sup>)作用下可激活转录因子激活蛋白1(activator protein-1, AP-1), 从而诱导原

癌基因*c-fos*、*c-jun*的表达, 其作用机制与ERK/MAPK级联激活, 导致转录因子Ets样蛋白1(Ets-like protein 1, Elk-1)磷酸化及促进原癌基因*c-fos*的转录有关, 而*H. pylori*(CagA<sup>+</sup>)菌株与胃上皮细胞共培养, 并不会产生此效应, 提示CagA激活ERK通路与原癌基因的表达有关. Xu等<sup>[54]</sup>研究发现, *H. pylori*菌株(CagA<sup>+</sup>)感染以及异位表达CagA蛋白均可使鸟氨酸脱羧酶(ornithine decarboxylase, ODC)表达上调, ODC是催化多胺形成的关键酶, 而多胺是促进细胞生长的关键成分. 采用信号通路抑制剂处理细胞后发现, CagA蛋白通过激活Src/MEK/ERK/c-Myc通路, 上调ODC表达, 发挥其促进细胞增殖作用.

蛋白磷酸酶2A癌性抑制因子(cancerous inhibitor of protein phosphatase 2A, CIP2A)是新近发现的人类致癌蛋白, 在胃癌组织呈高表达<sup>[55]</sup>. Zhao等<sup>[56]</sup>报道, CIP2A表达上调与CagA蛋白及CagA的磷酸化作用有关, 并且该作用是通过激活Src/Ras/MAPK/ERK通路实现的. Liu等<sup>[57]</sup>选择永生化胃黏膜上皮细胞GES-1, 研究CagA蛋白对抑癌基因*Runx3*的影响, 结果发现CagA通过Src/MEK/ERK和p38 MAPK通路对抑癌基因*Runx3*发挥抑制作用. 综上可知, CagA蛋白可通过ERK信号通路调控生长因子、激活癌基因、抑制抑癌基因表达, 导致细胞的增殖、凋亡异常, 进而在胃癌的发生、发展过程中发挥重要作用.

此外, CagA激活ERK信号导致细胞癌变还与细胞极性有关. 在非极性上皮细胞中, CagA异常活化ERK信号通路可诱导细胞周期蛋白依赖性激酶抑制因子p21<sup>WAF1/CIP1</sup>累积, 从而导致细胞衰老样增殖阻滞; 而在极性上皮细胞中, CagA激活ERK信号可通过活化鸟嘌呤核苷酸交换因子H1-RhoA-RhoA相关激酶C-Myc信号途径抑制p21<sup>WAF1/CIP1</sup>表达, 诱导细胞增殖. 以上研究提示, CagA可利用细胞极性-ERK信号通路来诱发癌变<sup>[58]</sup>. 新近CagA激活ERK诱发癌变也获得了人群遗传易感性方面的研究证据<sup>[59]</sup>: 针对CagA激活ERK信号通路下游涉及的8个基因24个SNPs进行研究发现, ERK rs5999749、Dock180 rs4635002和C3G rs7853122等3个位点的遗传变异与胃癌有关, 首次证实了CagA激活ERK通路会增加癌症的风险, 该研究进一步丰富了与CagA、ERK信号通路有关的胃癌的病因学研究内容.

### ■ 相关报道

*H. pylori*被认为是导致胃癌的I类致癌原, 但其诱发胃癌的分子机制尚未阐明. CagA蛋白作为*H. pylori*的重要毒力因子之一, 可易位进入宿主细胞, 干扰多条信号途径, 发挥其多种生物学作用. 已有研究证实, CagA蛋白可通过激活ERK信号通路对细胞的增殖、凋亡、分散和转移等生物学行为产生影响. 研究CagA蛋白、ERK信号通路与胃癌的关系, 对于揭示*H. pylori*相关胃癌的分子机制具有重要意义.



## ■创新盘点

本文在分别介绍癌蛋白CagA、ERK信号通路的基础上,首次比较完整、系统地介绍了目前癌蛋白CagA、ERK信号通路与胃癌关系的主要研究成果。

## 4 结论

ERK信号通路是涉及*H. pylori*癌蛋白CagA致癌机制的关键信号通路之一, ERK通路的异常激活在胃癌细胞的表型恶化、细胞增殖、凋亡等过程中发挥重要作用。今后要针对CagA蛋白激活ERK信号通路后的下游分子事件、对细胞恶性生物学行为的影响、对表观遗传学标志物的作用以及ERK通路与其他信号通路的相互作用关系等进一步展开研究, 以期揭示CagA蛋白的致癌机制提供新的研究证据, 并有望为*H. pylori*诱发胃癌的分子机制研究提供新的思路和新靶点。

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## ■应用要点

该文章阐述了目前癌蛋白CagA、ERK信号通路与胃癌关系的主要研究进展,提出今后要针对CagA激活ERK信号通路后的下游分子事件、对细胞恶性生物学行为的影响、对表观遗传学标志物的作用以及ERK通路与其他信号通路的相互作用关系等展开研究,以期为进一步揭示H. pylori相关胃癌的分子机制提供重要依据。

## ■同行评价

本文比较系统地  
对目前癌蛋白  
CagA、ERK信号  
通路及胃癌关系  
的主要研究成果  
进行了综述,使读  
者对癌蛋白CagA  
与*H. pylori*相关胃  
癌的关系有了进  
一步的认识,为*H.  
pylori*诱发胃癌的  
分子机制研究提  
供了新的思路和  
新靶点.

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编辑 郭鹏 电编 鲁亚静

