

胃癌患病风险基因研究进展

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Review on Genetic Susceptibility to Gastric Cancer

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Abstract:Both morbidity and mortality of gastric cancer are very high in China. The interaction of environment factors and genetic mutation plays an important role in the pathogenesis of gastric cancer. This paper is a review on genes related to gastric cancer such as metabolic enzyme genes, detoxification enzyme genes, immune related genes, DNA repair genes, oncogenes and tumor suppressor genes.

Key words:Gastric Cancer;Risk;Gene

摘 要:胃癌是我国常见的恶性肿瘤,其致病因素涉及环境及遗传等多种因素的相互作用。本文对胃癌患病风险有关的代谢酶相关基因、解毒酶基因、免疫相关基因、DNA修复基因、原癌基因及抑癌基因的研究进展作一综述。

关键词:胃癌;患病风险;基因

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0 引言

胃癌是世界范围内常见的恶性肿瘤,我国尤其高发,发病率是西方国家的6~8倍,因胃癌死亡人数占有因癌症死亡人数的23.2%^[1]。胃癌的具体发病机制目前仍不清楚,是环境因素与遗传易感性相互作用的结果,其中基因易感性在胃癌的发生发展中扮演着重要的角色。

1 代谢酶相关基因

1.1 叶酸代谢酶相关基因

叶酸的正常代谢与体内DNA的合成和甲基化密切相关,低叶酸饮食可增加包括胃癌在内的多种肿瘤的风险。亚甲基四氢叶酸还原酶基因(MTHFR)、胸腺合酶基因(TS)以及亚甲基四氢叶酸-同型半胱氨酸甲基转移酶还原酶(MTRR)与叶酸代谢密切相关。MTHFR 677 C→T, 1298 A→C两个位点的基因突变会降低其活性,影响叶酸的代谢^[2]。其 677TT相比于677CC等位基因会增加胃癌风险(OR: 1.173),尤其在亚洲人群中(OR: 1.611),但不会增加高加索人的风险,而A1298C CC基因型与677TT基因型在增

加胃癌的风险上有协同作用,但单独并不会增加胃癌风险^[3]。TS在dUMP转化成dTMP中扮演着重要的角色,TS 5'非转录加强区域(5'-untranslated enhanced region TSER)和TS 1494del6是近年来研究较多的区域,韩国一项病例对照研究中TSER的可变数目串联重复序列(variable number of tandem repeats, VNTR; 2R或者3R),TSER 2R/2R合并VNTR-3'-UTR 6个碱基的插入/缺失会增加胃癌的风险,尤其是肠型胃癌的风险(OR: 10.86)^[4]。但是一项纳入了63个关于TSER以及39个关于TS 1494del6的Meta分析发现它们与胃癌没有关联,仅亚洲人群中携带TSER 2R/2R基因型的相对3R/3R基因型会增加胃癌的风险(OR: 1.24)^[5]。MTRR的rs1801394基因多态性也会增加胃癌的风险,在共显性模型中OR: 1.39,尤其是在肥胖人群(BMI ≥ 25 kg/m²),发生胃癌的风险是9.08倍(OR: 9.08)^[6]。

1.2 解毒酶基因

外源性物质经体内细胞色素P450(CYP)酶系统代谢活化形成终致癌物,经谷胱甘肽S转移酶(GST)使致癌物降解失活。其基因的多态位点可能直接影响解毒酶的代谢活性,导致胃癌的发生。但最新的一项Meta分析显示CYP2E1 Rsa I/Pst I基因多态性与胃癌的关系不大,仅仅能够增加长期吸烟人群的胃癌的风险(OR: 1.39; 95% CI: 1.00-1.92)^[7]。Luo^[8]通过PCR-RFLP检测了252个

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样本，表明汉族人群中CYP1A1和CYP2D6基因多态性与胃癌没有关系，不过GSTM和GSTT1空白基因型会增加胃癌的风险，尤其会增加吸烟人群的风险。GSTP1是GST解毒中的一个关键酶，GSTP1 Val/Val基因型会增加中国北方人群中胃癌的风险（调整OR: 3.324），并且吸烟、饮酒，特别是Hp感染会增加胃癌的患病风险^[9]。

1.3 基质金属蛋白酶基因(matrix metalloproteinase, MMP)

MMP能有效水解细胞外基质和基底膜中的IV型胶原，与多种恶性肿瘤的发生、转移相关^[10]。Lin等^[11]研究发现 MMP2-1306C/T与胃癌风险没有关联，但金属蛋白酶-2的组织抑制因子-2379C/T、303G/A基因多态性会增加胃癌的发病风险，并且与淋巴结转移、胃癌浸润相关。在一项印度东部人群的调查中，MMP3-707 G/G及 MMP3-1612 5A/6A基因多态性会使胃癌的风险提高1.79-2.19倍，若合并Hp感染则预后更差^[12]。韩国一项调查发现MMP7 rs11568818、MMP8 rs11225395、MMP9 rs17576 和rs2250889 在胃癌的发生以及淋巴结转移方面没有关联^[13]，但MMP-9 -1562 C/T或T/T基因型会增加女性胃癌的风险（OR: 2.12），尤其会增加老年女性胃癌的风险，与胃癌的浸润以及淋巴结转移不存在相关性^[14]。

2 免疫相关基因

2.1 白细胞介素基因（interleukin,IL）

作为一种前炎症因子，IL与炎症的发生、发展关系密切。IL在胃癌中表达量增加，且晚期胃癌比早期胃癌IL-4、IL-6和IL-10 mRNA的表达量增加，提示其与胃癌发生可能相关^[15]。目前关于IL-1的研究多集中在IL-1 α 、IL-1 β 和IL-1 α （白细胞介素1受体拮抗剂），其相应的编码基因为IL-A、IL-B、IL-RN。研究发现IL-1 β 可以抑制胃酸的分泌，导致萎缩性胃炎、胃癌的风险增加。El-Omar^[16]首先在Nature上报导了IL-1B启动子区域 -31T/C和-511C/T基因多态性与胃癌患病风险相关，但后续的研究报道结论并非一致。系统分析表明IL-1B-511 T携带者较CC基因型会增加胃癌的风险（OR: 1.04–1.45），IL-1RN *2携带者较L/L会增加高加索人群中胃癌的风险（OR: 1.06–1.51），尤其是增加非贲门型胃癌以及肠型胃癌的风险，但在亚洲人群及西班牙裔人群中没有相关性^[17]。Chiurillo等^[18]对委瑞瑞拉人群的调查显示，IL-1B +3954C等位基因携带者合并cagA (+)型Hp感

染会增加萎缩性胃炎的发生率，可能增加胃癌的风险，但是来自中国四川的研究并不支持这一点^[19]。针对罗马尼亚人群的研究表明IL-4R -3223C→T会增加胃癌的风险（OR: 2.51），并以非贲门型胃癌为主（OR: 3.08）^[20]。IL-6-174 G/G 基因型会增加非贲门型胃癌的风险(OR: 2.02)^[21]，但是若不区分种族及病理类型，IL-6 -174 C/G 和-572 C/G 基因多态性与胃癌没有相关性^[22]。IL-8-251A/T，IL-10-592、-819、-1082 G/C等白介素基因多态性与胃癌及其癌前病变的遗传易感性关系密切^[21]。

2.2 人类白细胞抗原(human leukocyte antigen,HLA)

HLA基因是人类最复杂的遗传系统之一，有着高度的多态性，可分为 I（HLA-A、-B、-CW）、II（DR、DQ、DP、DOA、DOB、DM）、III类基因区。血浆中HLA- I类分子或其肽类衍生物在胃癌细胞株实验中可导致胃癌细胞的凋亡^[23]。日本研究^[24]发现，单体型分析HLA DRB1*0405 和DQB1*0401等位基因能增加胃癌尤其是肠型胃癌的患病风险(OR: 1.57)，并且与IL-10-592A/C基因多态性、Hp感染有协同作用（OR: 2.43）。HLA-DQA1 2个拷贝数相较于0个拷贝数的可以增加Hp感染者的胃癌患病风险^[25]，且HLA-DQB1基因多态性在Hp感染中扮演着重要的角色，但是HLA-DQA1或者-DQB1单体型并不会增加印尼人群胃癌的风险^[26]。CD14同样是介导炎症反应的重要因子，英国一项大样本的病例-对照研究^[27]指出CD14-159C/T基因多态性并不会增加高加索人种胃癌的患病风险，随后在中国台湾人群以及中国大陆人群中同样得到验证，而来自日本的研究^[28]指出CD14-159C/T基因多态性会降低日本老年人群（大于61岁）Hp感染患者患肠型胃癌的风险。

2.3 肿瘤坏死因子（tumor necrosis factor, TNF）

TNF作为促炎细胞因子，具有抗肿瘤、抗感染等多种功能，但是TNF α 的大量分泌可能与肿瘤的发生、发展相关。在Hp感染患者中，TNF α 表达水平显著增高可抑制胃酸的分泌。TNF α -308G/A、-1031T/C位点基因多态性会影响其转录水平，导致胃癌的易感性变化^[29]。TNF α -857 (C>T)基因多态性可增加胃窦部胃癌的风险，并且同IL-1 β -31C、IL-1 β -511T基因多态性有协同作用^[30]。

3 DNA修复基因

个体DNA修复能力的不同是个体肿瘤易感性差异的一个重要原因。X射线修复交叉互补基因

(x-ray repair cross-complementing gene,XRCC)和着色性干皮病基因(xeroderma pigmentosum gene,XP)是DNA碱基错配修复基因,在DNA错配修复中扮演着重要的角色。XPA-23A/G G等位基因携带者会降低胃贲门癌的风险,尤其是非吸烟人群。XPC8-Val499Ala 基因多态性也会影响胃贲门癌的患病风险^[31]。XPD-312 G/A G等位基因多态性会增加胃癌的风险(OR: 3.41),而751基因位点多态性与胃癌患病风险无关^[32],但其10号外显子区域的多态性会增加胃癌的风险^[33]。XRCC1-77T> C(CC)可增加胃贲门癌的风险(OR: 1.65)^[34]。中国的一项研究^[35]指出XRCC1- Arg194Trp、Arg280His、Arg399Gln基因多态性与胃癌没有关联,但Arg280His (His280His)会增加吸烟人群胃贲门癌的风险(OR: 1.59),而Meta分析指出XRCC1 Arg194Trp (Trp/Trp)会增加胃癌的风险^[36]。XRCC3 T241M 基因多态性在亚洲人群中会降低胃癌的风险(OR: 0.69),是胃癌的保护基因,但在高加索人中会增加胃癌的风险(OR: 1.45)^[37]。人错配修复基因是纠正碱基错配的主要因子,以MLH1和MSH2最为重要,可能与家族遗传性胃癌关系密切。荷兰基于Lynch综合征患者的调查发现,若患者携带MLH1或者MSH2突变会增加患胃癌的风险^[38],中国对家族性胃癌的调查也发现MLH1 -T1151A位点的突变会增加胃癌的风险,尤其是50岁以上者^[39]。

4 原癌基因及抑癌基因

E-钙黏蛋白(E-cadherin, CDH1)是细胞间、细胞与细胞基质间重要的黏附分子,其基因多态性与胃癌的关系是近年来的研究热点之一。CDH1启动子区域-160 -AA会增加胃癌的风险(OR: 3.6),而+54 T> C, -616 G> C, -3159 T> C与胃癌无关^[40],也有研究表明CDH1基因突变与胃癌无关^[41-42]。p53作为重要的抑癌基因是迄今为止研究最多的基因之一,大约与50%人类肿瘤相关。日本的研究发现在胃癌中p53突变率可达到16%,主要集中在肠型胃癌中,多为CpG的位点发生突变^[43]。p53基因多态性目前研究最多的是4号外显子的72位密码子(p53CD72),包括3种基因型:Arg/Arg、Pro/Pro、Arg/Pro。Arg/Arg会增加低分化胃腺癌风险(OR: 3.1),而Arg/Pro与中分化胃腺癌相关(OR: 3.5)^[44]。在亚洲人群中,Arg/Pro会增加弥漫性胃癌的风险(OR: 1.29)^[45]。

5 展望

胃癌的致病过程往往是一个长期积累的过程,目前对胃癌易感基因的研究正处于发展时期,主要集中在单个基因方面的研究,缺乏基因间、基因与外界环境间相互作用的研究,使得胃癌易感性因素的解释存在片面性。严格设计病例-对照研究,采用高通量基因芯片、高通量测序等新技术,研究与胃癌相关的易感基因群可能是未来的研究方向。

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