行政院國家科學委員會專題研究計畫成果報告

胃癌之形成與進展之宿主感受因子與環境因子之研究(3/3)

Susceptibility factors and environmental risks in the development and progression of gastric cancer(3/3)

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中 文 摘 要

胃癌是全世界好發的癌症，也是台灣重要的癌症死因之一。胃癌的發生及進展為許多因子交互作用、透過許多步驟來完成。環境因子及遺傳因子皆占有一席之地，而且不同的每個個體暴露於外來的致癌因子時，反應會有相當大的差異。過去國內在胃癌的研究則多屬片斷性及描述性，因此存在不少複雜的干擾因子而造成相互予盾的結果。在國科會的支持下，我們負責的子計劃是由環境因子與宿主遺傳因子兩方面來討胃癌之致癌過程，目標在於：(1)釐清各種環境危險因子(包括抽煙及幽門螺旋桿菌等)單獨的致癌作用及彼此的交互作用如何導致胃癌的發生。(2)探討每個人處理胃癌致癌物之代謝酵素(例如細胞色素p450)有何差異。(3)瞭解每個人的人類白血球抗原基因(HLA)及細胞素(cytokine)基因在胃癌致癌過程中所扮演的角色。

在三年的計劃中，吾人前瞻性地收集胃癌和健康對照，每名對象除以結構式問卷進行標準化診視外，亦採取個案的血液檢體。經過分離後，吾人抽取白血球中的 DNA，並收集不同患者的血清。利用這些檢體分析幽門螺旋桿菌感染和各種基因多形性與發生胃癌的危險性。在環境因子方面，幽門螺旋桿菌感染與抽煙可增加胃癌發生機會，其危險比分別為 1.7 和 1.87；另外吾人也注意到某些特殊組織病理型態的胃癌與 Epstein-Barr virus 感染有關。在宿主因子方面，HLA 的分析發現，胃癌患者有較高比率的 DQB1＊0602(9.4% vs 3.6%，危險比：2.79，p<0.05)，和較低比率的 DQB1＊0301 (14.6% vs 23.8%，危險比：0.55，p<0.05)。而有關致癌物代謝酵素基因方面，以 Pst I / Rsa I 測到的 CYP-2E1 C2/C2 基因型在胃癌的比例(33/356, 9.3%)明顯地高於對照組(9/278, 3.2%, 危險比：2.9，p=0.0015)，至於 GSTT1 及 GSTM1 的基因型則沒有統計上差別。在胃癌之抑癌基因研究方面，以 201 例胃癌及 196 例健康對照組發現 E-cadherin 在-160C→A polymorphism 對胃癌的影響，以 C/C 基因型 (4/201, 2%)較對照組有明顯減低(16/196, 9.7%，危險比：0.2，p<0.005)；而 p53 的

codon 72 基因多型性則和胃癌危險性無明顯相關；在細胞素的基因多型性方面，吾人探討 IL-1, IL-4, IL-10 和 TNF-α 等基因型與胃癌之危險性，結果發現 IL-1 與 IL-4 在胃癌與對照病人的分佈沒有差別，但 IL-10 在-1082 A→G 則有較高的胃癌危險性(危險比 2.29)，而 TNF-α 的-308 G→A 則與 Epstein-Barr 病毒相關胃癌的危險性有關，其危險比為 3.0。

上述各種環境因子和宿主基因型與胃癌危險性的關係以表一總結，吾人的研究進一步証實胃癌的發生為多重因子疾病，而且不同的胃癌型態在致病機轉和危險因子也明顯有所不同。

關鍵詞：胃癌、人類白血球抗原、幽門螺旋桿菌、分子流行病學

表一、各種環境因子與宿主之基因型與胃癌發生的關係

因子	相關	危險比
幽門螺旋桿菌	正	1.70
抽煙	正	1.87
EB 病毒	正	- (註 1)
HLA-DQB1*0301	正	2.79
HLA-DQB1*0602	負	0.55
CTP2E1 – C2/C2	正	2.90
E-cadherin (-160C→A)	負	0.2
p53 (codon 72)	無	-
GST-T1	無	-
GST-M1	無	-
IL-1	無	-
IL-4	無	-
IL-10 (-1082)	正	2.29
TNF-α (-308)	正	3.0 (註 1)

註 1：主要與類淋巴上皮細胞胃癌(lymphoepitheloid-like gastric cancer)有關

Abstract

Gastric cancer (GC) remains a common diseases with a dismal prognosis in the world as well as in Taiwan. The development and progression of GC is a multifactorial and multistep process in which genetic and environmental factors interact. Marked heterogeneity of tumor behaviors and host responses to exogenous risk factors exist in GC. Most studies of gastrocarcinogenesis in Taiwan have been fragmented and descriptive. Under the support of National Science Council, our project focused on the role of environmental and host factors in tumorigenesis of GC. The specific aims include (1) to elucidate the independent or interactive effects of multiple enviromental risk factors including Helicobacter pylori (H. pylori) and smoking (2) to investigate genetic polymorphisms of xenobiotic-metabolizing enzymes which may influence detoxification of environmental carcinogen to explain individual variability in gastrocarcinogenesis (3) to redefine the possibe pathogenic association between human leukocyte antigen (HLA) class II alleles, cytokine genes, and GC.

In the three year grant period, we have propectively enrolled patients with GC and healthy controls. Structured questionnaires and blood were obtained when enrolled. Genomic DNAs were extracted from buffy coat. Blood and DNA sere subjected to analyze H. pylori infection and genetic polymorphisms on the risk of GC. With respect to environmental factors, our results revealed both H. pylori infection and smoking could increase the risk of GC with the adds ratio (OR) 1.7 and 1.87 respectively. In addition, we have observed some subtypes of GC with special histologic features are closely related to Epstein-Barr virus infection. As regards to host factors, comparison of allele frequencies between GC and health controls in HLA class II gene has shown patients with GC had a higher frequency of DQB1*0602 (9.4% vs. 3.6%, OR:2.79, $p<0.05$) and a lower frequency of DQB1*0301 (14.6% vs. 23.8%, $p<0.05$) than healthy controls. The distribution of c2/c2 genotype of

CYP2E1, detected by Pst I or Rsa I digestion, was significantly different between patients with GC (33/356, 9.3%) and controls (9/278, 3.2%, OR:2.9, p=0.0015). In contrast, the prevalence of GSTT1 and GSTM1 null genotype was similar in controls and GC. The –160C→A polymorphism in the promoter region of E-cadherin gene has been analyzed in 201 GC cases and 196 unaffected controls. The frequency of variant A/A genotype in GC case (4/201, 2%) was significantly lower than that of controls (19/196, 9.7%, OR:0.2, p<0.005). The codon 72 polymorphism of p53 was, however, not associated with the risk of GC. In polymorphisms of cytokine genes, we have investigated IL-1, IL-4, IL-10, TNF-α and the risk of GC. Our results have demonstrated that no difference in the distribution of IL-1 and IL-4 polymorphisms between GC and controls. In contrast, -1082A→G promoter polymorphism of IL-4 has carried a higher risk of developing GC (OR:2.29) while –308 G→A promoter polymorphism of TNF-α is linked to the risk of Epstein-Barr virus-associated GC (OR:3.0).

Taken together, the various environmental- and host-related risks of GC are summarized in Table1. Our investigations have confirmed gastric carcinogenesis is a multifactorial process and further underlined risk factors and pathogenesis vary for different subtypes of GC.

Key words:Gastric cancer, Human leukocyte antigen (HLA), Helicobacter pylori, Molecular epidemiology

Table 1. Summary of relationships between different environmental or host factors and gastric cancer

Factor	Association	Odds ratio
H. pylori infection	Postitive	1.70
Smoking	Postitive	1.87
EB virus	Postitive	- (Note1)
HLA-DQB1*0301	Postitive	2.79
HLA-DQB1*0602	Negative	0.55
CTP2E1 – C2/C2	Postitive	2.90
E-cadherin (-160C→A)	Negative	0.2
p53 (codon 72)	nil	-
GST-T1	nil	-
GST-M1	nil	-
IL-1	nil	-
IL-4	nil	-
IL-10 (-1082)	Postitive	2.29
TNF-α (-308)	Postitive	3.0 (Note 1)

Note1: mainly restricted to Epstein-Barr-virus-associated gastric cancer

參 考 文 獻

1. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process. Cancer Res 1992;52:6735-6740.
2. Tahara E. Molecular mechanism of stomach carcinogenesis. J Cancer Res Clin Oncol 1993;119:265-272.
3. Forman D. Gastric carcinogenesis: an overview. Eur J Gastroenterol Hepatol 1994;6:1073-1075.
4. Fuchs CS, Mayer RJ. Gastric carcinoma. N Engl J Med 1995;333:32-41.
5. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 1993;85:1483-1492.
6. Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. Semin Oncol 1996;23:281-291.
7. Goldstone AR, Quirke P, Dixon MF. Helicobacter pylori infection and gastric cancer. J Pathol 1996;179:129-137.
8. Lin JT, Wang JT, Wang TH, et al. Helicobacter pylori infection in a randomly selected population healthy volunteers, and patients with gastric ulcer and gastric adenocarcinoma: a seroprevalence study in Taiwan. Scand J Gastroenterol 1993;28:1067-1072.
9. Lin JT, Wang LY, Wang JT, et al. A nested case-control study on the association between Helicobacter pylori infection and gastric cancer risk in a cohort of 9775 men in Taiwan. Anticancer Res 1995;15:603-606.
10. Lin JT, Wang LY, Wang JT, et al. Ecological study of the association between Helicobacter pylori infection and gastric cancer in Taiwan. Dig Dis Sci 1995;40:385-388.
11. Chen SY, Liu TY, Chen MJ, et al. Seroprevalences of hepatitis B and C viruses and Helicobacter pylori infection in a small isolate population at

high risk of gastric and liver cancer. Int J cancer 1997;71:776-779.

12. Crespi M, Citarda F. Helicobacter pylori and gastric cancer: an overrated risk. Scand J Gastroenterol 1996;31:1041-1046.
13. Perera FP. Molecular epidemiology: insights into cancer susceptibility, risk assessment and prevention. J Natl Cancer Inst 1996;88:496-509.
14. Yu MW, Gladek-Yarborough A, Chiamprasert S, et al. Cytochrome p450 2E1 and glutathione S-transferase M1 polymorphism and susceptibility to hepatocellular carcinoma. Gastroenterology 1995;109:1266-1273.
15. Lin JT, Wu MS, Hsiao JT, et al. Genetic polymorphisms of xenobiotic metabolizing enzymes and cancer susceptibility. J Intern Med ROC 1996;7:286-294.
16. Tomlinson IPM, Bodmer WF. The HLA system and the analysis of multifactorial genetic disease. Trends Genet 1995;11:493-498.
17. Lee JE, Lowy AM, Thompson WA, et al. Association of gastric adenocarcinoma with the HLA class II gene DQB1*0301. Gastroenterology 1996;111:426-432.
18. Yu MW, Zhang YJ, Li Y, et al. Influence of vitamin A, C, E, andβ -carotene on alfatoxin B, binding to DNA in woodchuck hepatocytes. Cancer 1994;73:596-604.
19. Chen CJ, Yu MW, Liaw YF, et al. Chronic hepatitis B carriers with null genotypes of glutathione S-transferase M1 and T1 polymorphisms who are exposed to alfatoxin are at increased risk of hepatocellular carcinoma. Am J Hum Genet 1996;59:128-134.
20. Shen SW, Hu CY, Lin CY, et al. Human leukocyte antigen polymorphisms in the Taiwan population. J Formos Med Assoc 1999; 98: 11-18.

已發表論文

1. Wu MS, Shun CT, Wu CC, Hsu TY, Lin MT, Chang MC, Wang HP, **Lin JT** (2000) Epstein-Barr virus – associated gastric carcinomas: relation to H. pylori infection and genetic alterations. Gastroenterology 118;1031-1038. [SCI]
2. Wu MS, Huang SP, Chang YT, Shun CT, Chang MC, Lin MT, Wang HP, **Lin JT** (2002). Tumor necrosis factor-α and interleukin –10 promoter polymorphisms in Epstein-Barr virus associated gastric carcinoma. J Infect Dis 185:106-109 [SCI]
3. Wu MS, Huang SP, Chang YT, Lin MT, Shun CT, Chang MC, Wang HP, Chen CJ, **Lin JT** (2002). Association of the –160C→A promoter polymorphism of E-cadherin gene with gastric cancer risk. Cancer 94: 1443-1448 [SCI]
4. Wu MS, Hsieh RP, Huang SP, Chang YT, Lin MT, Chang MC, Shun CT, Sheu JC, **Lin JT** (2002) Association of HLA-DQB1*0301 and HLA-DQB1*0602 with different subtypes of gastric cancer in Taiwan. Jpn J Cancer Res. 93:404-410. [SCI]
5. Wu MS, Chen CJ, Lin MT, Wang HP, Shun CT, Sheu JC, **Lin JT** (2002). Genetic polymorphisms of cytochrome p450 2E1, glutathione S-transferase M1 and T1, and susceptibility to gastric carcinoma in Taiwan. Int J Colorectal Dis 17:338-343 [SCI]