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(1/3)

Susceptibility factors and environmental risks in the development and progression of gastric cancer(1/3)

計畫類別：□個別型計畫　■整合型計畫

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子計畫主持人：

註：整合型計畫總報告與子計畫成果報告請分開編印各成一冊，彙整一起繳送國科會

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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多因子、多步驟過程，環境因子及遺傳因子皆占有一席之地。胃癌本身並非單一均質的疾病，而且不同個體暴露於外來的致癌因子會有相當大的反應差異。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。本計劃將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(包括微量營養元素，鹽類及幽門螺旋桿菌等)獨立的致癌作用及彼此交互影響而導致胃癌的發生。(2)探討宿主處理致癌物之代謝酵素(細胞色素 p450)之多形性在胃癌致癌過程中的角色。(3)瞭解宿主之人類白血球抗原基因(HLA)在胃癌致癌過程中的角色。

在第一年的計劃中，吾人前瞻性地收集 106 例胃癌和 208 例健康對照，收案當時，每名對象除以結構成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，以 polymerase chain reaction with sequence specific primers (PCR-SSP) 方式進行 HLA class II 基因的 DNA typing，結果顯示胃癌與對照著在 DRB1 的 allele frequencies 並無統計上差別(Table 1)，但在 DQB1 的 allele frequencies 分佈上(Table 2)，胃癌患者有較高比率的 DQB1＊0602(9.4% vs 3.6%，p<0.05)，和較低比率的 DQB1＊0301 (14.6% vs 23.8%，P<0.05)。進一步分析 HLA-DQB1*0301 及＊0602 與臨床病理特徵的關係，發現具 HLA-DQB1＊0602 之胃癌有較高比率為男性(16/3 vs 50/37，p<0.05)且腫瘤位置靠胃近端(12/7 vs 28/59, p<0.05)；而 HLA-DQB1＊0301 之胃癌則有較多為瀰漫型胃癌(20/10 vs 30/46，p<0.05)和較低的幽門螺旋桿菌血清陽性率(14/16 vs 58/18，p<0.05)。吾人初步結果顯示 HLA-DQB1＊0602 可增加男性及近端胃癌的易感性，HLA-DQB1＊0301 反而有較低的幽門螺旋桿菌感染率及胃癌危險性。

在第二年的計劃中，吾人除了繼續收集更多的病案外(預計收滿 200 例胃癌)外，將利用吾人已建立的 DNA typing 分析病案與對照的 CYP-2E1，GST-T1，GST-M1，IL-1 和 TNF-α等的基因型，以進一步了解胃癌的宿主易感性。另外吾人也將對環境因子中的定性資料建檔，並開始建立定量血中微量元素的方法。

關鍵詞：胃癌、人類白血球抗原、幽門螺旋桿菌、分子流行病學

Table 1. Frequencies of the DRB1 alleles in Taiwanese gastric cancer patients and controls

DRB1 Alleles	Controls (n=208)	Gastric Cancer (n=106)
01	2(0.5%)	2(0.9%)
04	50(12.0%)	31(14.6%)
07	12(2.9%)	6(2.8%)
08	50(12.0%)	24(11.3%)
09	62(14.9%)	36(17.0%)
10	8(1.9%)	3(1.4%)
11	38(9.1%)	12(5.7%)
12	64(15.4%)	22(10.4%)
13	15(3.6%)	8(3.8%)
14	20(4.8%)	15(7.1%)
15	41(9.9%)	27(12.7%)
16	22(5.3%)	8(3.8%)
17	32(7.7%)	18(8.5%)

Table 2. Frequenies of the DQB1 alleles in Taiwanese gastric cancer patients and controls

DQB1 Alleles	Controls (n=208)	Gastric Cancer (n=106)
02	44(10.6%)	23(10.8%)
0301	99(23.8%)	31(14.6%)*
0302	31(7.5%)	22(10.4%)
0303	62(14.9%)	37(17.5%)
0401	20(4.8%)	11(5.2%)
0402	4(1.0%)	3(1.4%)
0501	13(3.1%)	8(3.8%)
0502	41(9.9%)	20(9.4%)
0503	11(2.6%)	6(2.8%)
0601	61(14.7%)	24(11.3%)
0602	15(3.6%)	20(9.4%)*
0603	3(0.7%)	0(0%)
0605	12(2.9%)	7(3.3%)

*P=0.0018 by Chi-square test, Pc=0.023 after Bonferroni correction

Table 3. Clinicopathologic characteristics and HLA-DQB1*0301 and *0602 status of 106 Taiwanese patients with gastric cancer

Characteristics	HLA-DQB*0301		HLA-DQB1*0602	
	Positive (n=30)	Negative (n=76)	Positive (n=19)	Negative (n=87)
Mean age (years)	61.1±14.4	62.3±13.5	63.5±12.0	61.6±14.1
Gender (M/F)	15/15	51/25	16/3[a]	50/37
Tumor location				
cardia/body	10	20	12[b]	28
angle/antrum	20	56	7	59
Tumor stage				
early	6	13	4	15
advanced	24	63	15	72
Lymph node matastasis				
positive	21	58	14	65
negative	9	18	5	22
Histologic subtype				
diffuse	20[c]	30	12	38
intestinal	10	46	7	49
H. pylori secopositivity				
positive	14[d]	58	13	59
negative	16	18	6	28

a: p=0.037 b: p=0.012 c: p=0.012 d: p=0.003

Abstract

Gastric cancer (GC) remains a common disease 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. Therefore, we believe that an effective way to study gastrocarcinogenesis should be through a multidisciplinary approach with special emphasis on individual suscecptibility to carcinogenic exposure and on the interaction between genetic alterations and environmental influence. The specific aims include (1) to elucidate the independent or interactive effects of multiple environmental risk factors of GC including Helicobacter pylori (H. pylori) infection, dietary patterns, salt and micronutrient. (2) to investigate the genetic polymorphisms of cytochrome p450 isoenzymes which may influence detoxification of environmental carcinogen to explain individual variability in gastrocarcinogenesis. (4) to redefine the possible pathogenic association between human leukocyte antigen (HLA) class II alleles and gastrocarcinogenesis.

In the first year grant period, we have prospectively enrolled 106 patients with gastric cancer and 208 healthy controls. Structured questionnaires and blood were obtained when enrolled. Genomic DNAs were extracted from buffy coat and subjected to polymerase chain reaction with sequence specific primers for DNA typing of HLA class II gene. Comparison of allele frequencies between gastric cancer and healthy controls showed no difference at HLA-DRB1 locus (Table 1). Patients with gastric cancer had a higher frequency of DQB1*0602 (9.4% vs. 3.6%, $p<0.05$) and a lower frequency of DQB1*0301 (14.6% vs. 23.8%, $p<0.05$) than healthy controls (Table 2). Correlation of HLA-DQB1 status with clinicopathologic features revealed 19 gastric cancer with HLA-DQB1*0602 were associated with predominance of male gender (16/3 vs 50/37, $p<0.05$) and proximal location (12/7 vs 28/59, $p<0.05$). in contrast, 30 patients with HLA-DQB1*0301 tended to have a higher ratio of diffuse subtype (20/10 vs. 30/46, $p<0.05$) and a lower seropositivity of H. pylori (14/30 vs 58/76, $p<0.005$). These results indicate HLA-DQB1*0602 confers susceptibility to gastric cancer for male gender and proximal location while HLA-DQB1*0301 may have protective effect through resistance to H. pylori infection.

In addition to collecting more cases as scheduled (200 cases), DNA typing of CYP2E1, GST-T1, GST-M1, IL-1 and TNF-α will be analyzed in the second year grant period to further elucidate host susceptibility of gastric cancer. Integration of these data with environmental factors through coding of descriptive data and quantitiative data of micronutrients will also be conducted.

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

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即將發表之論文

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