行政院國家科學委員會專題研究計畫 期中進度報告

Exploring the role of inflammation and immune reaction in mediating Helicobacter pylori-independent--探討發炎與免疫相關基因多形性與幽門桿菌治療後胃黏膜相關淋巴組織淋巴瘤各種不同腫瘤緩解反應的關係(子計畫二)(1/3)

期中進度報告(精簡版)

計畫類別：整合型
計畫編號：NSC 95-2321-B-002-024-
執行期間：95年08月01日至96年07月31日
執行單位：國立臺灣大學醫學院一般醫學科

計畫主持人：吳明賢
共同主持人：王秀伯

處理方式：期中報告不提供公開查詢

中華民國 96年05月31日

行政院國家科學委員會團隊研究計畫成果報告

主計畫：探討發炎與免疫相關基因多形性與幽門桿菌治療後胃黏膜相關淋巴組織淋巴瘤各種不同腫瘤緩解反應的關係 (1/3)

Main Project: Exploring the role of inflammation and immune reaction in mediating Helicobacter pylori-independent transformation of gastric mucosa-associated lymphoid tissue lymphoma (1/3)

子計畫二：探討發炎與免疫相關基因多形性與幽門桿菌治療後胃黏膜相關淋巴組織淋巴瘤各種不同腫瘤緩解反應的關係

Sub-Project 2: Determination of the relationship between polymorphisms in inflammation and immune regulation genes and various tumor response of gastric mucosa-associated lymphoid tissue lymphoma to H. pylori eradication therapy

計畫類別：□個別型計畫　■整合型計畫

計畫編號： NSC95-2321-B-002-024

執行期間：　96年 8月 1日至 99年 7月 31日

整合型計畫：
計畫主持人：鄭安理醫師
子計畫二主持人：吳明賢醫師

處理方式：　□可立即對外提供參考
■一年後可對外提供參考
□兩年後可對外提供參考
(必要時，本會得展延發表時限)

執行單位：台大醫學院一般醫學科

中華民國 96 年 5 月 28 日

中文摘要

目前認為幽門桿菌感染和宿主免疫反應間的失調是幽門桿菌感染後有不同預後及致病機轉的基本原因，故誘發和調控發炎反應的因子可能決定感染的預後。胃黏膜異常發炎反應與發生和抗發炎細胞素的表現有關，不同個人間細胞素的表現與分泌差異頗大，而且可能由基因上的單核苷酸多型性(簡稱SNP)調控，這些SNP可以影響細胞素整體表現與分泌，此種個人遺傳體質在發炎基因上的不同表現可以部分解釋感染疾病為何有不同的預後。雖然如此，過去在此方面的研究大部分聚焦於個人易感性而幽門桿菌依存性和治療預後，並且比對幽門桿菌依存性有關的SNP與其它基因變化的研究仍對付之闕如。

第一年的計畫中，吾人首先收集62位胃MALToma患者及250位健康對照者做CTLA4 (49 A/G, -318 C/T, and CT60 A/G), CD 28(IVS3+ 17T/C)，和ICOS (c.602 A/G and c. 1624 C/T)的基因型分析。結果顯示胃MALToma患者的幽門桿菌感染率(90.3%)明顯較對照者(66.4%)為高($p<0.001$, 表 1。CTLA4-318 C/T基因型者得到胃MALToma危險性較低(OR=0.3, p=0.022)，而CTLA4 -49G/G基因型則危險性較高(OR=4.1, p=0.044)。在幽門桿菌感染陽性者，CTLA4 -49G/G基因型的危險性更高(OR=6.4, p=0.047 表2及3)。帶有-318C-49G haplotype者得到胃MALToma機會約提高4倍(OR=4.2, p=0.04)。去除幽門桿菌後胃MALToma是否得到完全緩解則與腫瘤期別有關但與基因型無關。

由於chemokine在發炎扮有關鍵角色，因此為了進一步了解chemokine及其receptor基因多型性的角色，我們收集67位胃MALToma及290位健康對照，針對5個相關基因進行44個SNPs分析，初步結果發現CXCR5及CX3CL1可能與MALToma有關(表 4,表 5)，這些SNP都是首次証實與胃MALToma之致病機轉相關。

在往後的計畫執行期間，吾人將收集更多具完整治療追蹤的胃MALToma病患，並進行有關chemokine和其receptor基因多型性的功能性分析，另外我們也會將這些基因型的結果將進一步與臨床參數比對。

關鍵詞：單一核苷酸多形性、臨床預後、胃黏膜相關淋巴組織淋巴瘤

Abstract

The observed genetically determined differences in inflammatory response might account for some of the heterogeneity of infectious diseases. However, most studies in this context focus on susceptibility rather than HP dependence and studies centering on correlation of genetic polymorphisms with HP-dependent status and other genetic changes remain lacking.

In the first-year grant period, we have enrolled 62 patients with gastric MALToma and 250 unrelated healthy controls. Genotyping for CTLA4 (49 A/G, -318 C/T, and CT60 A/G), CD28 (IVS3+17 T/C), and ICOS (C.602 A/G and c.1624 C/T) was performed. The results revealed that H. pylori infection was significantly higher in patients with gastric MALT lymphoma (90.3%) compared with controls (66.4%; $p<0.001$)(Table 1). The CTLA4-318 C/T genotype was associated with a lower risk of developing gastric MALT lymphoma (odds ratio [OR]=0.3; p=0.022), whereas CTLA4 49 G/G genotype was linked to a higher risk (OR=4.1; p=0.044). In patients with H. pylori infection, CTLA4 49 G/G genotype was associated with an even higher risk (OR=6.4; p=0.047)(Table 2 & 3). Carriage of the tightly linked -318C -49G haplotype conferred a four-fold higher susceptibility to MALToma (OR=4.2; p=0.042). Complete remission after H. pylori eradication was related to tumor stage but not to genotypes or haplotypes. These results indicate a genetic link of CTLA4 gene polymorphisms to development of gastric MALT lymphoma and indirectly support the crucial role of host activated T cells in the MALT lymphomagenesis.

Given the crucial role of chemokine in inflammation, we further analyzed 44 SNPs in 5 candidate chemokine & its receptor genes in 67 cases of gastric MALToma and 290 controls. The preliminary results revealed CXCR5 & CX3CL1 gene polymorphisms may be associated with gastric MALToma (Table 4& 5). These novel polymorphisms were first reported to be relevant in gastric MALTomagenesis.

In the following grant period, we will enrolled more cases of gastric MALToma with various treatment outcomes. Furthermore, functional studies of chemokine and its receptor polymorphisms will he performed and correlated with clinical parameters.

Keywords: single nucleotide polymorphisms, clinical outcome, mucosa-associated lymphoid tissue lymphoma

Table 1. Demographic Characteristics of Patients With Gastric MALT Lymphoma and Healthy Controls

Characteristic	Patients with MALT Lymphoma (n=62) No.	%	Controls (n=250) No.	%	*P*
Age, years					0.837
Mean	56.2		55.8		
Standard deviation	13.4		12.7		
Sex					
Male	32	51.6	127	50.8	0.909
Female	30	48.4	123	49.2	
Helicobacter pylori infection					
Negative	6	9.7	84	33.6	<0.001
Positive	56	90.3	166	66.4	
Tumor grade					
Low	36	58.1	—	—	
High	26	41.9	—	—	
Tumor stage					
Ⅰ$_E$	38	61.3	—	—	
Ⅱ$_E$	14	22.6	—	—	
Ⅲ$_E$	1	1.6	—	—	
Ⅳ$_E$	9	14.5	—	—	

Abbreviation: MALT, mucosa-associated lymphoid tissue

Table 2. Distribution of Genotype Frequencies in Patients With Gastric MALT Lymphoma and Healthy Controls

	MALT Lymphoma Patients (n=62)		Controls (n=250)		Odds Ratio		
Genotype	No.	%	No.	%	Ratio	95% CI	*P*
CTLA4-318 C/T							
C/C	59	95.2	209	83.6	1.0		—
C/T	3	4.8	40	16.0	0.3	0.1 to 0.9	0.022
T/T	0	0	1	0.4	—	—	—
CTLA4 49 A/G							
A/A	2	3.2	29	11.6	1.0		—
A/G	26	41.9	102	40.8	3.7	0.8 to 16.5	0.069
G/G	34	54.8	119	47.6	4.1	0.9 to 18.2	0.044
CTLA4 CT60 A/G							
A/A	3	4.8	17	6.8	1.0		—
A/G	20	32.2	79	31.6	1.4	0.4 to 5.4	0.591
G/G	39	62.9	154	61.6	1.5	0.4 to 5.1	0.577
CD28 IVS3+ 17 T/C							
C/C	1	1.6	1	0.4	1.0		—
C/T	9	14.5	57	22.8	0.2	0.0 to 2.8	0.153
T/T	52	83.9	192	76.8	0.3	0.0 to 4.4	0.326
ICOS c.602 A/C							
A/A	43	69.3	167	66.8	1.0		—
A/C	19	30.6	77	30.8	1.0	0.5 to 1.8	0.890
C/C	0	0	6	2.4	—	—	—
ICOS c.1624 C/T							
C/C	55	88.7	223	89.2	1.0		—
C/T	7	11.3	27	10.8	1.1	0.4 to 2.5	0.912
T/T	0	0	0	0	—	—	—

Abbreaivatoin: MALT, mucosa-associated lymphoid tissue

Table 3. Distribution of CTLA4 49 Genotype Frequencies in Patients With and Without Helicobacter pylori infection

Genotype	MALT Lymphoma Patients (No.)	Controls (No.)	Odds Ratio		*P*
			Ratio	95% CI	
H. pylori positive					
A/A	1	15	1.0		—
A/G	21	71	4.4	0.6 to 35.6	0.129
G/G	34	80	6.4	1.0 to 50.2	0.047
H. pylori negative					
A/A	1	14	1.0		—
A/G	5	31	2.3	0.2 to 21.2	0.466
G/G	0	39	—	—	—

Abbreviation: MALT, mucosa-assocaited lymphoid tissue

Table 4. Genotype distribution and Hardy-Weinberg Equilibrium test

			Control				Case				HWE test for control	Heterozygosity for control
			percent	count			percent	count				
Gene	**SNP_ID**	**Assay_ID**	**AA:AB:BB**	**AA**	**AB**	**BB**	**AA:AB:BB**	**AA**	**AB**	**BB**		
CCL_20	**rs7581084**	**-51053**	100:0:0	130	0	0	100:0:0	32	0	0	-	0
	rs1049617	**51065**	100:0:0	289	0	0	100:0:0	67	0	0	-	0
	rs7607579	**51090**	100:0:0	288	0	0	100:0:0	67	0	0	-	0
CCR_6	**rs3093006**	**51048**	99.6:0.4:0	288	1	0	100:0:0	67	0	0	0.9765	0.0035
	rs3093021	**51052**	82:17.6:0.4	233	50	1	78.8:18.2:3	52	12	2	0.3247	0.1761
	rs9459886	**51055**	100:0:0	289	0	0	100:0:0	67	0	0	-	0
	rs3093009	**51057**	76.2:23.1:0.7	215	65	2	82.1:16.4:1.5	55	11	1	0.2181	0.2305
	rs3093023	**51061**	18.5:49.1:32.4	53	141	93	16.9:41.5:41.5	11	27	27	0.9724	0.4913
	rs17860846	**51062**	100:0:0	288	0	0	100:0:0	66	0	0	-	0
	rs6931699	**51066**	0.4:12.2:87.5	1	35	252	0:13.6:86.4	0	9	57	0.8535	0.1215
	rs1855025	**+*51071**	17.7:59.9:22.4	41	139	52	30:60.9:8.7	14	28	4	0.0022	0.5991
	rs17860852	**51077**	100:0:0	289	0	0	100:0:0	66	0	0	-	0
	rs3093005	**51078**	0.35:12.6:87.1	1	36	249	0:13.6:86.3	0	9	57	0.8026	0.1259
	rs9459884	**51080**	100:0:0	274	0	0	100:0:0	63	0	0	-	0
	rs17860854	**51081**	100:0:0	288	0	0	100:0:0	63	0	0	-	0
	rs13215685	**+51082**	100:0:0	288	0	0	100:0:0	66	0	0	-	0
CX3CL_1	**rs2239351**	***51068**	95.4:4.3:0.4	247	11	1	98.3:1.7:0	57	1	0	0.0336	0.0425
	rs4151117	**51070**	12.1:44.6:43.3	35	129	125	9.1:40.9:50	6	27	33	0.8465	0.4464
	rs223815	**+51075**	0:3.8:96.2	0	11	278	1.5:12.1:86.4	1	8	57	0.7415	0.0381
	rs12928117	**51085**	100:0:0	290	0	0	100:0:0	67	0	0	-	0
CX3CR_1	**rs3732380**	**51056**	89.3:10.7:0	258	31	0	94:6:0	63	4	0	0.3353	0.1073

	rs3732379	**51059**	97.2:2.8:0	280	8	0	95.5:4.5:0	64	3	0	0.8111	0.0278
	rs2853708	**51060**	94.1:0.35:0.6	270	1	16	90.9:0:9.1	60	0	6	<.0001	0.0035
	rs17038674	**+51069**	0.4:5.0:94.6	1	14	264	0:11.7:88.3	0	7	53	0.0976	0.0502
	rs3732378	**51073**	96.9:3.1:0	280	9	0	95.5:4.5:0	63	3	0	0.788	0.0311
	rs11710546	**51088**	96.9:3.1:0	281	9	0	95.5:4.5:0	64	3	0	0.7884	0.031
	rs1050592	**51089**	0:3.1:96.9	0	9	281	0:4.48:95.5	0	3	64	0.7884	0.031
	rs2853709	***51091**	0:1.1:98.9	0	3	266	0:1.8:98.2	0	1	55	0.9267	0.0112
CXCL_13	**rs3192975**	**51064**	100:0:0	285	0	0	100:0:0	67	0	0	-	0
	rs1802209	**51067**	0.4:9.9:89.8	1	28	255	0:4.5:95.5	0	3	63	0.8054	0.0986
	rs11868	**51072**	90:9.6:0.4	260	28	1	93.9:6.1:0	62	4	0	0.7912	0.0969
	rs1052563	**51084**	100:0:0	290	0	0	100:0:0	67	0	0	-	0
CXCR_5	**rs630923**	**51049**	0.4:14.5:85.1	1	42	246	0:10.5:89.6	0	7	60	0.5725	0.1453
	rs3922	**51050**	13.6:45.6:40.8	39	131	117	7.5:34.3:58.2	5	23	39	0.8086	0.4564
	rs3741330	**51051**	100:0:0	289	0	0	100:0:0	67	0	0	-	0
	rs3741331	**51054**	76.1:21.8:2.1	217	62	6	83.6:16.4:0	56	11	0	0.5304	0.2175
	rs11574669	**51058**	100:0:0	282	0	0	100:0:0	67	0	0	-	0
	rs665648	**-51063**	100:0:0	220	0	0	100:0:0	57	0	0	-	0
	rs3136698	**51074**	100:0:0	288	0	0	100:0:0	66	0	0	-	0
	rs1063929	**51076**	100:0:0	289	0	0	100:0:0	66	0	0	-	0
	rs676925	**51079**	72.6:26.4:1	209	76	3	86.4:13.6:0	57	9	0	0.171	0.2639
	rs1053881	**51086**	100:0:0	290	0	0	100:0:0	67	0	0	-	0

- + NGC-SNP 組建議可能有 genotyping 不穩定情形，不適合進行分析 (疑似有 primer dimmer 的現象，但不確定是否會干擾到實驗結果)。
- * NGC-SNP 組建議沒有 call 出 data 的爲特定 allele，建議以其平台再次確認這些 assay 的實驗結果。。
- - genotyping 成功率低。

Table 5. Test for Genotype, Allele, Trend, dominant and recessive models

			p value of Single point association test				Test for dominant model				Test for recessive model			
Gene	**SNP_ID**	**assay**	**Genotype**	**Allele**	**Trend**	**Fisher**	**control**	**case**	**P_PCHI**	**Fisher**	**control**	**case**	**P_PCHI**	**Fisher**
CCL_20	**rs7581084**	**-51053**	-	-	-	-	130:0	32:0	-	-	130:0	32:0	-	-
	rs1049617	**51065**	-	-	-	-	289:0	67:0	-	-	289:0	67:0	-	-
	rs7607579	**51090**	-	-	-	-	288:0	67:0	-	-	288:0	67:0	-	-
CCR_6	**rs3093006**	**51048**	0.62969	0.62993	0.62969	1	289:0	67:0	-	-	288:1	67:0	0.62968	1
	rs3093021	**51052**	0.10222	0.29992	0.29753	0.13246	283:1	64:2	0.0335	0.09244	233:51	52:14	0.54026	0.59808
	rs9459886	**51055**	-	-	-	-	289:0	67:0	-	-	289:0	67:0	-	-
	rs3093009	**51057**	0.42334	0.41311	0.40103	0.31606	280:2	66:1	0.53241	0.47352	215:67	55:12	0.30381	0.33456
	rs3093023	**51061**	0.36672	0.26548	0.27038	0.37234	194:93	38:27	0.16066	0.19201	53:234	11:54	0.77075	0.85992
	rs17860846	**51062**	-	-	-	-	288:0	66:0	-	-	288:0	66:0	-	-
	rs6931699	**51066**	0.84696	0.86824	0.86671	0.86668	36:252	9:57	0.8026	0.83786	1:287	0:66	0.63166	1
	rs1855025	**+*51071**	0.03417	0.02032	0.00942	0.03278	180:52	42:4	0.03407	0.04257	41:191	14:32	0.04715	0.06633
	rs17860852	**51077**	-	-	-	-	289:0	66:0	-	-	289:0	66:0	-	-
	rs3093005	**51078**	0.86938	0.94218	0.94141	0.86891	37:249	09:57	0.87924	0.84131	1:285	0:66	0.63047	1
	rs9459884	**51080**	-	-	-	-	274:0	63:0	-	-	274:0	63:0	-	-
	rs17860854	**51081**	-	-	-	-	288:0	63:0	-	-	288:0	63:0	-	-
	rs13215685	**+51082**	-	-	-	-	288:0	66:0	-	-	288:0	66:0	-	-
CX3CL_1	**rs2239351**	***51068**	0.58784	0.27505	0.30312	0.75668	258:1	58:0	0.63552	1	247:12	57:1	0.31259	0.47532
	rs4151117	**51070**	0.56446	0.28354	0.28689	0.62539	164:125	33:33	0.31964	0.33891	35:254	6:60	0.48858	0.66933
	rs223815	**+51075**	0.00265	0.00052	0.00078	0.00269	11:278	9:57	0.00178	0.00475	0:289	1:65	0.03613	0.18592

	rs12928117	**51085**	-	-	-	-	290:0	67:0	-	-	290:0	67:0	-	-
CX3CR_1	**rs3732380**	**51056**	0.23872	0.25125	0.23872	0.3608	289:0	67:0	-	-	258:31	63:4	0.23872	0.3608
	rs3732379	**51059**	0.46954	0.47305	0.46954	0.44123	288:0	67:0	-	-	280:8	64:3	0.46954	0.44123
	rs2853708	**51060**	0.50866	0.15644	0.31342	0.40659	271:16	60:6	0.28668	0.26883	270:17	60:6	0.34713	0.4039
	rs17038674	**+51069**	0.13891	0.10349	0.11291	0.15712	15:264	7:53	0.07276	0.08423	1:278	0:60	0.64234	1
	rs3732378	**51073**	0.56156	0.56495	0.56156	0.47275	289:0	66:0	0.63225	1	280:9	63:3	0.56156	0.47275
	rs11710546	**51088**	0.57379	0.57708	0.57379	0.47706	290:0	67:0	-	-	281:9	64:3	0.57379	0.47706
	rs1050592	**51089**	0.57379	0.57708	0.57379	0.47706	9:281	3:64	0.57379	0.47706	0:290	0:67	-	-
	rs2853709	***51091**	0.67887	0.67981	0.67887	0.53249	3:266	1:55	0.67887	0.53249	0:269	0:56	-	-
CXCL_13	**rs3192975**	**51064**	-	-	-	-	285:0	67:0	-	-	285:0	67:0	-	-
	rs1802209	**51067**	0.34493	0.14175	0.14456	0.3755	29:255	3:63	0.15027	0.23319	1:283	0:66	0.62926	1
	rs11868	**51072**	0.57509	0.29435	0.29711	0.57411	288:1	66:0	0.63225	1	260:29	62:4	0.31578	0.47974
	rs1052563	**51084**	-	-	-	-	290:0	67:0	-	-	290:0	67:0	-	-
CXCR_5	**rs630923**	**51049**	0.60184	0.33401	0.32541	0.54321	43:246	7:60	0.34694	0.43677	288:1	67:0	0.62969	1
	rs3922	**51050**	0.03036	0.00961	0.01084	0.03553	170:117	28:39	0.00962	0.01351	39:248	5:62	0.17114	0.21837
	rs3741330	**51051**	-	-	-	-	289:0	67:0	-	-	289:0	67:0	-	-
	rs3741331	**51054**	0.28044	0.12701	0.13141	0.34324	279:6	67:0	0.23095	0.59961	217:68	56:11	0.18893	0.25404
	rs11574669	**51058**	-	-	-	-	282:0	67:0	-	-	282:0	67:0	-	-
	rs665648	**-51063**	-	-	-	-	220:0	57:0	-	-	220:0	57:0	-	-
	rs3136698	**51074**	-	-	-	-	288:0	66:0	-	-	288:0	66:0	-	-
	rs1063929	**51076**	-	-	-	-	289:0	66:0	-	-	289:0	66:0	-	-
	rs676925	**51079**	0.05831	0.02163	0.01712	0.05021	285:3	66:0	0.40502	1	209:79	57:9	0.01935	0.01825
	rs1053881	**51086**	-	-	-	-	290:0	67:0	-	-	290:0	67:0	-	-

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