行政院國家科學委員會專題研究計畫　成果報告

台灣地區登革病毒感染的分子流行病學與化學激素的角色

(2/2)

計畫類別： 個別型計畫
計畫編號： NSC91-2320-B-002-081-
執行期間： 91 年 08 月 01 日至 92 年 07 月 31 日
執行單位： 國立臺灣大學公共衛生學院流行病學研究所

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報告類型： 完整報告
報告附件： 國外研究心得報告
處理方式： 本計畫可公開查詢

中　華　民　國 93 年 3 月 29 日

中文摘要

嚴重臨床症狀的登革出血熱與較為輕微症狀的登革熱之免疫致病機制差異至今尚未被釐清。本研究目的是探討登革出血熱與登革熱病人致病過程中的 3 種人類化學激素(RANTES, Mig, MIP-1α chemokines)分泌變化是否有差異性存在，且此差異是否與登革病患臨床狀的嚴重度有所關連。

研究群是以 2002 年月至 2003 年 3 月高屏地區通報登革熱病例為研究對象，並經由台灣疾病管制局確認登革出血熱病例共 23 名與登革熱病例共 77 名，另取 46 名健康對照組作為比較,進行抽血，以流式細胞儀分析細胞表面人類化學激素受體及酵素免疫試劑測人類化學激素分泌量，並請醫護人員進行問卷訪談並追蹤症狀。

結果發現：(1) 登革熱病患體內 CD4/CD3+T 細胞比值顯著低於健康對照組（33.19±2.21 vs 40.13±15.94, p=0.03）；(2) 登革出血熱與登革熱確定病例的人類化學激素如 RANTES（各為 13.69±3.46 ng/ml 與 19.56±2.74 ng/ml, p=0.14)、Mig（各為 653.45± 85.89 pg/ml 與 664.63± 59.60 pg/ml, p=0.23）均比健康人有顯著較高的分泌量，但此兩種登革病人的 MIP-1a 分泌量(各為 26.99± 11.56pg/ml 與 38.59± 9.86pg/ml)卻較健康人為低(92.47±13.55 pg/ml, p<0.01)；(3) 不同的化學激素在病程之動態分泌量有所不同,人類化學激素如 Mig 的分泌量在登革出血熱/登革熱病例急性期高於恢復期，相對地 RANTES 分泌量在登革出血熱/登革熱病例急性期卻低於恢復期。

本研究初步結果推論登革熱出血熱/登革熱病患其人類化學激素分泌變化有差異性存在，登革出血熱病患體內人類化學激素 Mig 在發燒後頭三天(感染急性期)有較高的分泌，可能加速吸引帶有 CXCR3 之 T 細胞至受感染部位，且因 RANTES 有持續性的分泌,由此三者的協同作用,會增進 $CD8^{+}$T 細胞中 CCR5 的表現量，進而引起相關的細胞受到傷害，結果造成病人的嚴重出血。未來實有必要再更急性早期採集登革病人血液檢體,以整合病毒量.免疫活化標誌與血液動態指標,以徹底明瞭登革出血熱病人的免疫致病機轉.

關鍵字：登革熱、人類化學激素、人類化學激素受體、登革病毒免疫、免疫流行病學

Abstract

Mechanism of immunopathogenesis in leading to dengue hemorrhagic fever (DHF) versus mild form of dengue fever (DF) during the same epidemic has not been fully understood. The specific aims of this study were to determine whether there are differences in the levels of chemokines (RANTES, Mig and MIP-1a) associated with hemorrhage between DHF and DF patients or clinical complications.

A prospective cohort study recruited 23 DHF and 77 DF patients caused by dengue virus serotype 2 plus 46 healthy donors from Aug. 2 to Mar. 31, 2003 in Kaohsiung and Pingtung. Levels of RANTES, Mig, MIP-1a were measured in serum samples collected at both the first visit and subsequent repeated visits. Mann-Whitney U and Spearman correlation test were used to compare the relationship between above each chemokine and clinical status of DF vs DHF or hemodynamic/ biochemical laboratory results, and their kinetic changes at different time points after the onset of fever, respectively.

Ratios of CD4/CD3+T cells in DF patients was lower significantly compared to healthy controls (DF patients: 33.19$\pm$ 2.21 vs healthy controls: 40.13 $\pm$ 15.94, P=0.03). There were higher serum levels of RANTES (DHF: 13.69$\pm$3.46 vs DF: 19.56$\pm$2.74, P=0.14), Mig (DHF: 653.45$\pm$ 85.89 vs DF: 664.63$\pm$ 59.60, P=0.23) and lower levels of MIP-1a (DHF: 26.99$\pm$ 11.56 vs DF: 38.59$\pm$ 9.86, P=0.56). However, serum levels of RANTES, Mig were significantly higher than healthy controls ($P<0.05$), whereas levels of MIP-1a in dengue patients were significantly lower than compared to healthy controls ($P<0.05$). The serum levels of chemokine were also compared after fever onset. Levels of Mig in DHF and DF patients after fever onset$\leqq$7 days were higher than that after fever onset >7 days. In contrast, levels of RANTES in DHF and DF patients were lower after fever onset $\leqq$7 days than that after fever onset >7 days..

In conclusion, the serum chemokine kinetic patterns of DHF were different from DF patients. These effects may lead to infected cells damages and then cause hemorrhage. A closer examination of the production of these chemokines and the activation of dengue virus infected target cells in the early phase of dengue virus infection is warranted to attain a better understanding of immunopathgenesis of DHF.

Keywords: Dengue hemorrhagic fever, Innate Immunity, Immunological Responses, Chemokine, Taiwan.

Introduction and Literature Review

Understanding on the pathogenesis of DHF/DSS provides more insights to prevent severe dengue cases and decreasing case fatality rate. Exaggerated cellular immune responses to dengue virus infection which are driven by cross-reactive memory T lymphocytes may result in increasing disease severity and DHF【Rothman et al., 1999】. Dysregulation of certain innate and bystander immune activation might play an important role in exacerbating disease progression during dengue virus infection.

Chemokines are involved in the recruitment of leukocytes to sites of infection via a cascade of coordinated events. Chemokines are synthesized and secreted by macrophages/monocytes, endothelial cells, fibroblasts, epithelial cells, and neutrophils during inflammation including RANTES, MIP-1α, IP-10, and Mig and function to induce leukocytes adherence to vascular endothelium and extravasation into tissues. Furthermore, chemokines might play an important role in the pathogenesis of dengue virus infection, because levels of certain chemokines , such as IL-8 and RANTES, were elevated during dengue virus infection *in vitro* or *in vivo* 【Lin et al., 2000; King et al., 2002】.

However, other chemokines in the immunopathogenesis of dengue virus infection have not been explored. In our present study, we attempted to obtain an integrated view of the chemokine-cehmokine receptors after dengue virus infection by obtaining repeated measurements of blood samples from patients of dengue hemorrhagic fever and dengue fever during the largest epidemic of DHF in Taiwan in 2002' and comparing the similarities and differences in quantitative kinetic changes between these two groups of dengue patients with different clinical severity.

MATERIALS and METHODS

A. Study Areas

Study areas include past and present epidemic areas of dengue. Past epidemic areas were (1) Kaohsiung County and City, and (2) Pingtung County and City. Physicians/nurses working at the sentinel hospitals/clinics in these study areas collected blood samples for this study.

B. Study Populations

The study subjects include confirmed DF, confirmed DHF/DSS cases, and the healthy controls. The diagnosis of dengue infection was confirmed by the Center of Disease Control (CDC), Taiwan. Both dengue-consensus and type-specific primers for reverse-transcriptase polymerase chain reaction (RT-PCR). (>10 PFU is detectable) and serologic tests (dengue-specific IgM seropositive or 4-fold serotiter rise but Japanese-specific IgM seronegative) are used for confirming dengue virus will be conducted mainly in our lab at National Taiwan University (NTU) to minimize false results. Healthy donors chose people who lived in the area of Taipei City without indigenous dengue cases reported.Patients with serotype one, three, and four confirmed from laboratory tests (PCR and antibody tests) are analysis separately.

C. Clinical Diagnosis of Dengue Fever and Dengue Hemorrhagic Fever/Dengue Shock Syndrome

Clinical diagnosis of dengue fever and dengue hemorrhagic fever/dengue shock syndrome was defined according to the criteria of the World Health Organization. All patient with dengue hemorrhagic fever had thrombocytopenia ($\leq$100,000/mm^3) and hemocencentration (hematocrit $\geq$ 20% of recovery value) or > 1mm of pleural effusion detected on the right lateral chest radiograph.

D. Interview and Questionnaire

A personal interview based on standardized questionnaire will be conducted by nosocomial infection control nurses who are well-trained on interview techniques and questionnaire details in their hospitals. Questions are briefly listed as following:

1. **Demographic Data:** Gender, age, birth date and living areas
2. **Medical History:** Underlying diseases such as allergy, hypertension,

hepatitis, diabetes are included. In addition, History of dengue for case and his/her family members, relatives, neighbors, coworkers and classmates are recorded.

3. **Date of Onset:** Including the first date of fever, and other symptoms and signs of dengue.
4. **Clinical complication:** To record patients who develop clinical complications such as ascites, pleural effusion, or petechiae during their hospital stay.
5. **Clinical hematologic data**: WBCs, lymphocyte, hematocrit, platelet, ALT, AST
6. **Risk Factors**: Travel history to those dengue hyper-endemic or epidemic areas during the incubation time.

E. Collection of Blood Samples

Two blood samples will be collected from confirmed dengue cases using vacuum syringes with anti-coagulant (EDTA) for flow cytometry and without anti-coagulant for chemokine tests. Serum collected through day 7 after fever onset are referred to as acute-phase samples. Convalescent serum refer to specimens collected 8 days or more after fever onset. The samples will be immediately placed on ice and transported to our laboratory in the ice-filled bottle/box by express service.

F. Laboratory Methods

1. Flow Cytometry

Using whole blood samples and stained with florescence conjugated with cell surface CD molecule antibody right after those samples' arrival to quantitate subpopulations of T cells, including CD45RO, CD62L. CCR5 and CXCR3 stained to detect chemokine receptor expression.

2. CD Masker Staining

Collect blood especially by venipuncture into a sterile K3 EDTA VACUTAINER blood collection tube. Follow the collection tube manufacturer's guidelines for the minimun volume of blood to be collected. Store anticoagulated blood at room temp (20^{o} to 25^{o} C) until ready for staining and lysing. Refer to the appropriate package insert for storage restrictions prior to staining.

Analyze on the FACS brand flow cytometer. Mix samples thoroughly before acquisition. Refer to the appropriate package insert for storage restrictions prior to analysis.

3. Quantitation of Chmeokines

Serum levels of RANTES (cat.no.DRN00), IP-10 (cat.no.DIP100), Mig (cat.no. DCX900), MIP-1α (cat.no. DMA00) were measured by use of commercial ELISA kits (Quantikine, R&D System). As described by the manufacturer, lower detection limits for the assays are 8 pg/ml for RANTES, 1.67 pg/ml for IP-10, 3.84 pg/ml for Mig, 10 pg/ml for MIP-1α.

G. Statistical Data Analysis

All information was compiled with *EXCELL* software (Office 2000, Microsoft) and analyzed by *The Statistic Analysis Software 8.2* (SAS, Institute, Inc). Serum chemokine levels were compared by use of the Kruskall-Wallis test, a nonparametric analysis of variance. When the test revealed significant differences between the study groups, 2-group comparisons were done with the Mann-Whitney U test. The Wilcoxon signed rank test was used for comparison of paired samples from each individual. Correlations between variables were evaluated with Spearman correlation test. $P < 0.05$ was considered a statistically significance difference between groups.

Results

Serum samples from 138 individuals were selected for analysis and were categorized into the following groups: 34 DHF patients , 90 DF patients , and 14 healthy controls (table 2). Between onset of fever and days of collecting serum samples varied between the groups, but the differences were not statistically significant (table 2). We can find that DHF patients were older(50.59±13.78), had more underlying disease of diabetes(29.41%) and collected more earlier whole blood samples at less than 7 days after onset of fever(58.82%) .

After fever onset ≦7 days represented the acute or early phase of illness, a time when ongoing inflammatory responses were likely to be at a maximum. After fever onset ＞7 days represented likely a late or convalescent phase of illness, a time when inflammation would be expected to be resolving or be in a preterminal stage in those who succumbed to disease.

A. Fundamental immunological markers in patients of DF versus DHF

There were differences in the ratios of CD4+T/CD3+T cells (DHF:36.34± 5.18; DF:33.19 ± 2.21) and CD8+T/CD3+T cells (DHF: 27.34 ± 3.60; DF: 30.20± 1.89) in DHF and DF patients compared with Healthy controls (CD4+T/CD3+T cells: 40.13 ± 2.35; CD8+T/CD3+T cells: 31.88 ± 1.62; Table 3).

The significant differences only existed in the ratio of CD4+T/CD3+T cells in DF patients compared with healthy controls (P=0.03). There were differences in the CD3+ T cells absolute numbers in DHF (3140.6±907.8)and DF(3143.6±400.93) patients compared to healthy controls(4567.4±482.85). The CD3+ T cells absolute numbers were significant differences were present in DF and healthy controls (p=0.02). There were differences in the CD4+ T cells and CD8+ T cells absolute numbers in DHF (CD4+ T cells: 1959.9±431.09; CD8+T cells: 1933.2±457.2)and DF(CD4+ T cells: 1869.8±157.16; CD8+T cells: 1899.3±226.93) patients compared to healthy controls(CD4+ T cells: 2582.9±208.7; CD8+T cells: 2085.8±202.61). Similar significant differences were observed in CD4+ T cells absolute numbers in DF patients compared to healthy controls (p=0.01).

B. Kinetic changes of CD4/CD8 ratio in DHF vs DF patients

The ratio of CD4/CD8 T cells in Dengue Hemorrhagic Fever patients declined at

late phase. Only one Dengue Hemorrhagic Fever patients elevated slightly in first and second time points (Figure 1). The decrease of CD4/CD8 ratio was not only found in the Dengue Hemorrhagic Fever patients, but also in the Dengue Fever patients. The eight of thirteen Dengue Fever patients declined the ratio of CD4/CD8 T cells between early and late phase, whereas five Dengue Fever patients rised up gradually at late phase.

C. The levels of chemokines (RANTES, MIP-1a, Mig) in DHF vs DF patients and healthy donors

All the serum levels of three chemokines RANTES(DHF:13.69±3.46 ng/ml; DF:19.56±2.74 ng/ml), and Mig(DHF:653.45±85.89 pg/ml; DF:664.63±59.60 pg/ml) in dengue patients were significantly higher than healthy controls ($p<0.01$）（Table 6; Figure 2, 3） whereas the serum level of MIP-1α in dengue patients were significantly （DHF:26.99±11.56 pg/ml; DF:38.59±9.86 pg/ml）lower than healthy controls($p<0.01$) （Table 6, Fig3）

D. Variation of the serum levels of chemokines at different days after onset of fever in DHF vs DF patients.

The mean serum levels of Mig(DHF:763.83±118.43 pg/ml; DF:713.28±67.08 pg/ml) after fever onset ≤ 7 days were higher than those after fever onset＞7 days in both DHF(IP10: 2.74±0.98 ng/ml; Mig:487.88±102.3 pg/ml) and DF(Mig:580.96± 113.86 pg/ml) patients.. However, the serum levels of RANTES after fever onset ≤ 7 days(DHF:9.78±3.25 ng/ml; DF:11.82±2.10 ng/ml) was lower than that after fever onset＞7 days(DHF:19.57±6.94 ng/ml; DF:33.19±5.72 ng/ml). In addition, the levels of RANTES, IP-10 and Mig at two different time periods after fever onset were significantly higher than healthy controls（$p<0.01$） whereas the levels of MIP-1α at two different time periods after fever onset were significantly lower than healthy controls（$p<0.01$）.

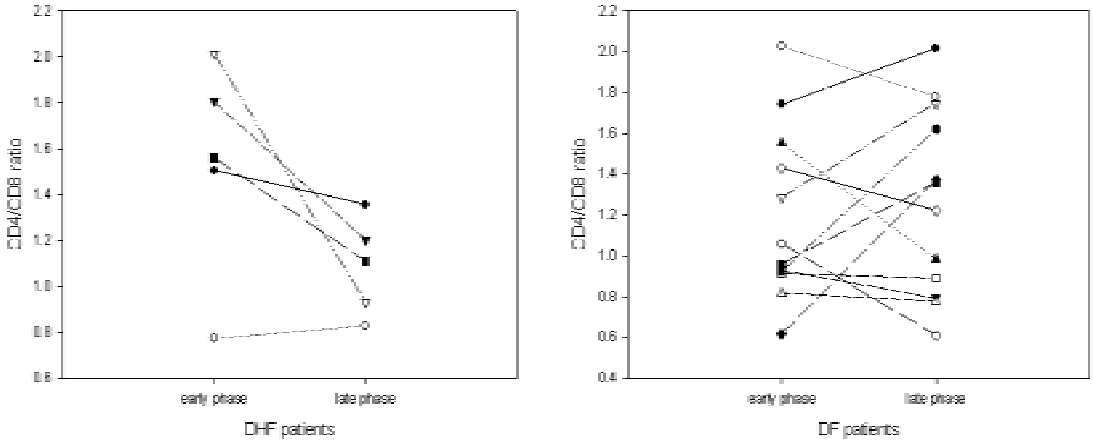

Figure 1. Kinetic changes of Ratios of CD4/CD8 in DHF and DF patients.

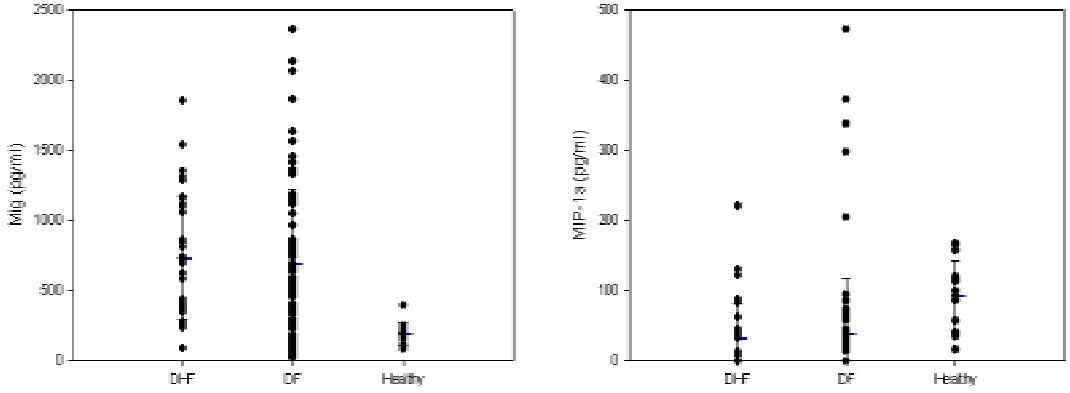

Figure 3. The serum levels of MIP-1 alpha and Mig chemokines in patients of dengue hemorrhagic fever versus dengue fever compared with healthy controls.

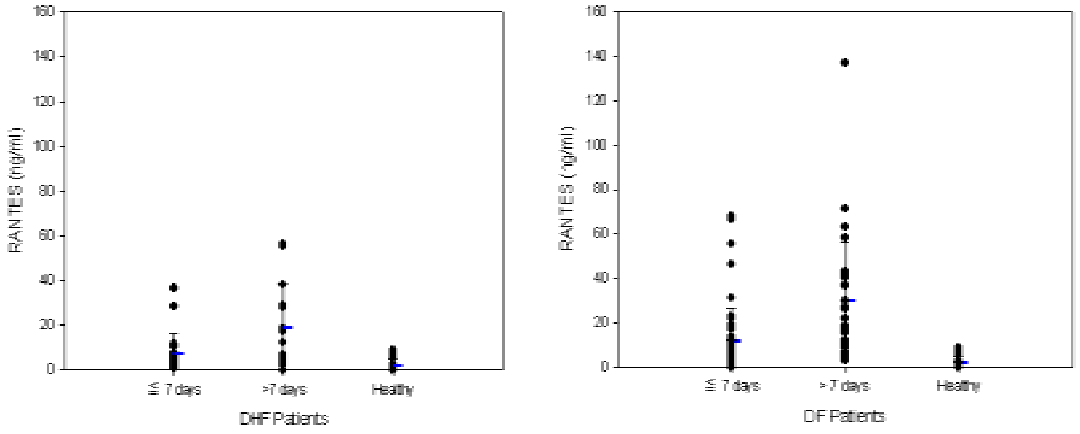

Figure 4. **The serum levels of RANTES chemokines at two time intervals (<7 days vs >7 days after the onset of fever) in patients of dengue hemorrhagic fever and dengue fever**

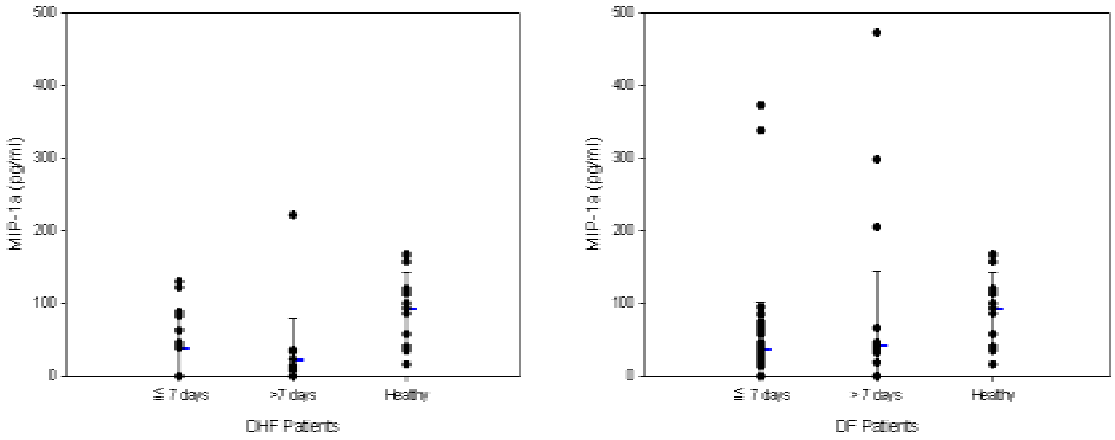

Figure 7. **The Serum levels of MIP-1a chemokines at two time intervals (<7 days vs >7 days after the onset of fever) in patients of dengue hemorrhagic fever and dengue fever**

Table 2. The demographic characteristics and medical history of study subjects in chemokine studies in Taiwan, 2003

Characteristics	DHF (n=34)		DF (n=90)		Healthy Controls (n=14)	
Age, years(Mean±SD)	50.59±13.78		44.34±14.83		28.78±7.08	
<30	2	(5.88%)	17	(18.89%)	12	(85.71%)
30~44	7	(20.59%)	18	(20%)	1	(7.14%)
45~59	17	(50%)	46	(51.11%)	1	(7.14%)
60~74	8	(23.53%)	9	(10%)	0	
Gender						
Males	18	(51.52%)	49	(54.44%)	9	(64.29%)
Females	16	(48.48%)	41	(45.56%)	5	(35.71%)
Clinical History						
DM	10	(29.41%)	13	(14.44%)		
Asthma	2	(5.88%)	0			
Gout	0		2	(2.22%)		
HBsAg(+)	0		3	(3.33%)		
DM+Gout	2	(5.88%)	0			
DM+HbsAg(+)	0		3	(3.33%)		
Samples Collected at Days after the Onset of Fever						
≦7 days	20	(58.82%)	59	(65.56%)		

Table 3. Comparison of T cell subsets among DHF versus DF patients adjusted the medical history and healthy controls in Taiwan, 2003

* P values are Wilcoxon rank sum comparisons of data from the columns of Healthy controls.

CD Markers and Chemokine Receptors	DHF(n=10)		DF(n=63)		Healthy Control (n=46)
	Mean±SE	P value*	Mean±SE	P value*	Mean±SE
CD4 (% of CD3)	36.34±5.18	NS	33.19±2.21	0.03	40.13±2.35
CD62L+CD45RO- (%of CD4)	7.96±5.32	NS#	9.44±2.10	NS	18.24±3.56
CD62L+CD45RO+ (%of CD4)	8.17±5.31	NS	10.11±2.02	NS	11.19±2.20
CD62L-CD45RO+ (%of CD4)	9.88±6.03	NS	12.61±2.53	NS	9.28±2.02
CCR5 (%of CD4)	5.12±1.71	NS	7.02±1.16	NS	4.20±0.82
CXCR3 (%of CD4)	19.76±5.99	NS	21.81±2.69	NS	21.53±2.85
CD8 (% of CD3)	27.34±3.60	NS	30.20±1.89	NS	31.88±1.62
CD62L+CD45RO- (%of CD8)	7.09±4.49	NS	7.07±1.79	NS	19.44±4.07
CD62L+CD45RO+(%of CD8)	4.66±2.59	NS	6.15±1.62	NS	3.09±0.71
CD62L-CD45RO+ (%of CD8)	9.91±5.18	NS	12.86±2.65	NS	12.02±2.39
CCR5 (%of CD8)	12.48±3.52	NS	13.93±2.02	NS	10.62±1.64
CXCR3 (%of CD8)	26.78±8.37	NS	23.75±2.87	0.001	43.39±4.40
CCR5+/CD62L+CD45RO-CD3+	0.72±0.46	NS	0.48±0.17	NS	0.24±0.16
CCR5+/CD62L+CD45RO+ CD3+	0.23±0.16	NS	0.57±0.32	NS	0.69±0.42
CCR5+/CD62L-CD45RO+ CD3+	2.66±2.01	NS	1.99±0.87	NS	1.79±0.98
CXCR3+/ CD62L+CD45RO-CD3+	6.59±3.40	NS	7.37±2.10	NS	7.03±2.07
CXCR3+/ CD62L+CD45RO+CD3+	10.45±6.97	NS	4.80±1.83	NS	6.14±2.42
CXCR3+/ CD62L-CD45RO+CD3+	9.58±6.39	NS	5.84±2.08	NS	7.25±2.84

#NS = not significant (p >0.05)

Table 6. Levels of Chemokine in the serum samples of DHF versus DF patients adjusted medical history

Chemokines	DHF			DF			Healthy controls	
	n	Mean±SE	P value[#]	n	Mean±SE	P value[#]	n	Mean±SE
RANTES (ng/ml)	20	13.69±3.46	<0.01	69	19.56±2.74	<0.001	14	2.21±0.78
IP-10 (ng/ml)	20	4.74±0.69[a]	<0.001	56	3.39±0.63	<0.001	9	0.15±0.03
Mig (pg/ml)	20	653.45±85.89	<0.001	69	664.63±59.60	<0.001	13	190.85±22.53
MIP-1α (pg/ml)	20	26.99±11.56	<0.001	69	38.59±9.86	<0.001	14	92.47±13.55

[#] P value compared to Healthy controls

[a].P <0.05, vs. DF patients

DISCUSSION

This research focuses on the study of possible roles of chemokines and chemokine receptors from innate immunity to adaptive immunity in dengue patients manifested different clinical severity. Several major findings have not been documented in literature.

A. Differences in Dengue Patients versus Healthy Controls: Kinetic Changes of CD4/CD8 ratio in DHF and DF Patients

Dengue patients are usually leukopenic for several days during the acute infection. Our observation that Dengue patients, regardless DHF or DF had lower expression of CD4+ T and CD8+ T cells than healthy donors.

The ratio of CD4/CD8 T cells in DHF patients declined at late phase（After fever onset ＞7days）.The 8 of 13 Dengue Fever patients declined the ratio of CD4/CD8 T cells between early and late phase, too. The appearance of atypical lymphocytes may be the T-cytotoxic/suppressor cells（$CD3^+/CD8^+$ T cells）that contribute to the imbalance between CD4 and CD8 T cells during dengue infection. The CD4/CD8

ratio changes was observed within two time points（≤ 7 days and ＞7 days after fever onset）. Frequent analysis of the immune parameters after dengue infection will help to understand the interaction between dengue virus and the host.

B. Chemokines

After dengue virus infection, various chemokines were released with different quantities, durations and kinetics. The levels of RANTES, and Mig were higher than healthy controls. By contrast, the levels of MIP-1α was lower compared to healthy controls, whereas the levels of MIP-1α had different magnitude and kinetics of secretion in Dengue Hemorrhagic Fever and Dengue Fever patients. Secretion of MIP-1α may have roles in the immunopathology and may contribute to fever and bone marrow suppression observed in Dengue Fever and Dengue Hemorrhagic Fever patients【Spain- Santana et al., 2001】. Paradoxically, the fact that MIP-1α recruit monocytes to the site of infection might provide dengue virus infection. Dendritic calls are potent antigen-presenting cells that can initiate immune responses by presenting antigens to secondary lymphoid and prime naïve T cells there. It is found that the ability of dengue virus to infect both human dendritic cells and skin Langerhans cell【Libraty et al., 2001】.Maturing DC are also an abundant and strategic source of chemokines. It's temping to speculate that these lower levels of MIP-1α may affect dengue virus infected DC undergo maturation and transport dengue virus antigen to lymphoids organs to initiate immunity. Other factors, such initial burst chemokines of DC response to acute viremia may also play a role and there warrant further study at this issue.

In addition, secretion of RANTES persisted at high levels long after fever onset in Dengue Hemorrhagic Fever and Dengue Fever patients. This might result from

stability of this mediators or constant production.

C. Immunopathological Significanc

In our present study, we attempted to obtain an integrated view of the chemokine-chemokine receptors of human dengue virus infection by using Dengue Hemorrhagic Fever and Dengue Fever patients' repeat serum samples and comparing the production kinetics and dose responses.

The clinical symptoms of Dengue Fever and Dengue Hemorrhagic Fever present the signs of local inflammation, which may result from extravasation of lymphocytes to sites of infection. The onset and peak of chemokine and chemokine receptor production by different dengue virus infected target cells indicated that these molecules may play a role in early recruitment of different subsets of leukocytes and participate in the early response to viral infection as well as tissue injury【Okayama et al., 2000】. These may suggest that a possible cooperative interaction between these target cells and lymphocyte trafficking by different production of chemokines

We found the serum levels of RANTES, IP-10 and Mig were higher in Dengue Hemorrhagic Fever and Dengue Fever patients. RANTES, IP-10, and Mig were shown to recruit and activate T lymphocytes with memory phenocyte【Raghupathy et al., 1998 】and then might b important for rapid T cell effector functions during secondary dengue virus infection.

It's known that MIP-1a, RANTES, and IP-10 can induce NK cells activation, chemotaxis, adhesion and transendothelial migration. Therefore, regulation of NK cells activity by these mediators may affect dengue virus infection and tissue injury.

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