Original Article

Significant Association between Serum Monokine Induced by Gamma Interferon and Carotid Intima Media Thickness

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***Aim*: The immune system may play an important role in the pathogenesis of cardiovascular disease. T cell-driven inflammation in human hypertension and atherosclerosis has recently been revealed. In the present study, we evaluated the association between serum levels of the C-X-C chemokine receptor type 3 chemokines and the carotid intima media thickness (IMT) in humans.**

***Methods*: One hundred sixty-four consecutive patients undergoing baseline and 2-year follow-up carotid IMT (110 men, 62.4 ± 10.0 years) were enrolled. The maximum carotid IMT (max-IMT) and the mean carotid IMT (mean-IMT) were measured at baseline and after 24 months. Clinical and laboratory variables, including serum levels of the monokine induced by gamma interferon (MIG) and interferon gamma-induced protein 10 (IP-10), were analyzed at the time of initial enrollment.**

***Results*: The baseline max- and mean-IMT were 0.992 ± 0.235 and 0.793 ± 0.191 mm, respectively. The serum levels of MIG and IP-10 significantly correlated with the carotid IMT. However, there was no significant correlation between the serum levels of MIG or IP-10 and IMT changes. A multivariate regression analysis revealed the serum MIG to be independently associated with the carotid IMT (max-IMT: $\beta = 0.194$, $p = 0.010$; mean-IMT: $\beta = 0.184$, $p = 0.016$) when controlled for age, sex, diabetes mellitus history, smoking history, body mass index, blood pressure, total cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and aspirin and statin medication.**

***Conclusions*: Circulating MIG levels are independently associated with the carotid IMT, after adjusting for confounding factors and medications. These findings indicate the potential clinical implication of MIG with respect to early atherosclerosis in humans.**

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Key words: Chemokine, MIG, Atherosclerosis, Carotid IMT

Introduction

Atherosclerosis is a chronic inflammatory process. Various factors contribute to the progression of vascular lesions, thus leading to inflammatory responses within the vessel wall[1)]. Recent studies have suggested that pathologic T cell driven inflammatory responses play a key role in the progression of atherosclerosis[2, 3)]. These T cell-related inflammatory responses involve interactions between cytokines, adhesion molecules, and chemokines[4, 5)]. Mach *et al.* have demonstrated that T cell-activating C-X-C chemokines are highly expressed in human atheroma-associated cells throughout all stages of plaque development[6)]. Other studies have revealed that deletion of T cell specific chemokines or their receptors within atherosclerotic lesions inhibits the development of atherosclerosis[7, 8)].

T-helper (Th) 1-associated chemokines, such as the monokine induced by gamma interferon (MIG/CXCL9), interferon gamma-induced protein 10 (IP-10/CXCL10), and interferon-inducible T-cell alpha chemoattractant (I-TAC/CXCL11), are induced by interferon gamma (IFN-γ) and elicit their chemotac-

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tic functions by interacting with the C-X-C chemokine receptor type 3 (CXCR3). An increased expression of IFN-γ and these IFN-γ-inducible CXCR3 chemokines has been detected in patients with coronary artery disease[9]. An antagonist of CXCR3 was also shown to attenuate atherosclerotic plaque formation in low-density lipoprotein receptor-deficient mice by blocking the migration of $CXCR3^+$ effector T cells from the peripheral circulation into atherosclerotic lesions[10]. Recent human studies also reported that circulating CXCR3 chemokines are elevated in patients with essential hypertension or aortic aneurysms[11, 12]. These data indicate that CXCR3 chemokines may therefore play a role in the development of atherosclerosis.

The thickening of the intima-media of the carotid artery is commonly associated with age-related vascular pathology and atherosclerosis[13]. In the present study, we evaluated the association between the serum levels of CXCR3 chemokines and either the carotid intima media thickness (IMT) or the presence of carotid plaque in humans.

Methods

Study Participants

We enrolled 164 consecutive individuals who consented to the baseline and 2-year follow-up carotid IMT measurements and additional blood sampling for serum CXCR3 chemokine measurement at the Severance Cardiovascular Hospital as part of the Yonsei Cardiovascular Genome Center cohort between January 2010 and July 2013. Hypertension was defined as either a documented systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg over three different visits prior to receiving anti-hypertensive medication. Diabetes mellitus (DM) was defined as a fasting plasma glucose level greater than 126 mg/dL, HbA1c more than 6.5% or a history of therapy for DM. At the time of initial enrollment, patients underwent a complete physical examination and laboratory assessment. Patients with the following conditions were excluded from this study: prior myocardial infarction, valvular heart disease, congestive heart failure, peripheral vascular disease, malignant debilitating disease, severe respiratory disease, history of inflammatory disease and/or use of anti-inflammatory medications, history of atrial fibrillation or other serious arrhythmia, malignant hypertension (>200/140 mm Hg), and secondary hypertension. This study received prior approval from the Institutional Review Board of the Yonsei University College of Medicine, and all procedures complied with institutional guidelines. All participants provided informed consent prior to enrollment.

Carotid Ultrasound Evaluation

Both common carotid arteries were examined with a high-resolution real-time 8-MHz linear scanner (Acuson X300, Siemens, Munich, Germany). The IMT of the far wall was measured 10 mm proximal to bifurcation using an automated edge detection algorithm and dedicated software (Syngo Arterial Health Package, Siemens, Munich, Germany). The mean IMT (mean-IMT) was determined as the average value of the measured IMT, and the largest IMT value was recorded as the maximum IMT (max-IMT). The individual representative value was the average of the left and right values. Interobserver and intraobserver variability was evaluated through correlation tests on 10 randomly sampled data. The correlation coefficient for interobserver reliability of the max- and mean-IMT was 0.828 ($p=0.007$) and 0.838 ($p=0.006$), respectively. The intraobserver test-retest reliability testing revealed that the correlation coefficient was 0.999 for the max-IMT ($p<0.001$) and 0.996 for the mean-IMT ($p<0.001$), respectively. The presence of carotid plaque was defined as a thickness of >1.5 mm at any site or a focal structure encroaching into the arterial lumen of more than 50% of the surrounding IMT value.

Cytometric Bead Array

The concentration of each circulating CXCR3 chemokine (MIG and IP-10) was determined by flow cytometry using the BD cytometric bead array technique according to the manufacturer's instructions (BD Biosciences, San Jose, CA, USA). Briefly, 50 μL of mixed capture beads and 50 μL of each serum sample were incubated for 1 h at room temperature. Next, 50 μL of mixed phycoerythrin detection reagents were added to the sample-bead mixture and incubated for 2 h at room temperature. The samples were then washed and acquired on a BD LSR II instrument (BD Biosciences, San Jose, CA, USA), and the data were analyzed using the FlowJo software program version 9.2 for Mac (TreeStar, San Carlos, CA, USA).

Statistical Analysis

Continuous variables were summarized as the mean ± standard deviation, and categorical variables were summarized as the percentage of the group total. The continuous variables were compared using independent *t* tests. Pearson's correlation analysis was used to determine the simple correlation between the continuous variables. To examine the association between

serum CXCR3 chemokines and the carotid IMT, a multiple linear regression analysis controlling for age, sex, DM history, smoking history, body mass index (BMI), blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (hsCRP), and aspirin and statin medication was performed. The triglyceride, hsCRP, MIG and IP-10 values were log transformed for the analysis. A p-value < 0.05 was considered to be significant. The adjusted R square of the regression model for max-IMT, which was adjusted for 11 independent variables excluding serum MIG, was 0.326. After the addition of serum MIG, the adjusted R square value increased to 0.351. A sample size of more than 136 patients was able to achieve 95% power to detect the change of the adjusted R square using an F-test with a significance level (alpha) of 0.05. All statistical analyses were performed with the SPSS 13.0 software program (SPSS Inc., Chicago, IL, USA).

Results

Clinical Characteristics and Laboratory Findings

The baseline characteristics of study participants are summarized in **Table 1**. The mean age was 62.4 ± 10.0 years, and the mean systolic blood pressure (SBP) was 132.6 ± 19.3 mmHg. The study population was relatively overweight (mean BMI: 25.2 ± 3.0 kg/m^2). The serum MIG levels ranged from 13.13-1394.52 pg/mL, and the serum IP-10 levels ranged from 24.49-1805.51 pg/mL. We did not find any gender-specific differences between the serum levels of CXCR3 chemokines and the carotid IMT values.

Table 1. Baseline characteristics of the study participants

Clinical variables	
Age (years)	62.4 ± 10.0
Men	110 (67.1%)
Hypertension	104 (63.4%)
DM	44 (26.8%)
Current Smoker	22 (13.4%)
Aspirin medication	129 (78.7%)
Clopidogrel medication	33 (20.1%)
Statin medication	123 (75.0%)
BMI (kg/m^2)	25.2 ± 3.0
SBP (mmHg)	132.6 ± 19.3
Laboratory variables	
Total cholesterol (mg/dL)	158.4 ± 41.0
HDL-cholesterol (mg/dL)	44.7 ± 12.4
LDL-cholesterol (mg/dL)	86.9 ± 35.9
Triglyceride (mg/dL)	136.2 ± 83.5
hsCRP (mg/L)	1.7 ± 3.0
MIG (pg/mL)	97.6 ± 134.2
IP-10 (pg/mL)	191.7 ± 187.5
Carotid measurements	
Max-IMT (mm)	0.992 ± 0.235
Mean-IMT (mm)	0.793 ± 0.191
Plaque	106 (64.6%)
Δmax-IMT (mm)	0.015 ± 0.150
Δmean-IMT (mm)	0.007 ± 0.108

DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; MIG, monokine induced by gamma interferon; IP-10, interferon gamma-induced protein 10; IMT, intima media thickness. Data are presented as the mean ± SD or n (%).

Association of Serum CXCR3 Chemokine Levels and the Carotid IMT

There were no significant correlations between the carotid IMT changes during the follow-up period and the serum levels of MIG ($r = -0.145$, $p = 0.070$ for Δmax-IMT; $r = -0.131$, $p = 0.102$ for Δmean-IMT) or IP-10 ($r = -0.124$, $p = 0.121$ for Δmax-IMT; $r = -0.092$, $p = 0.253$ for Δmean-IMT). Additionally, we performed a cross-sectional analysis of the relationship between baseline carotid IMT and these CXCR3 chemokine levels. Among the total study participants, 106 patients (65%) had carotid plaque. The serum level of MIG was significantly higher in patients with carotid plaque than those without (117.7 ± 160.4 vs 61.0 ± 44.5 pg/mL, $p = 0.001$; **Fig. 1**). However, the serum level of IP-10 was comparable between the two patient-groups (208.4 ± 221.7 vs 161.2 ± 92.3 pg/mL, $p = 0.124$).

Next, the correlation between the carotid IMT and the clinical variables, including CXCR3 chemokines, was analyzed (**Table 2**). Both the max-IMT and mean-IMT were significantly and positively correlated with age, DM history, BMI, and SBP and both were negatively correlated with HDL-cholesterol. There was a significant positive relationship between the carotid IMT and the serum levels of MIG ($r = 0.305$, $p < 0.001$ for max-IMT; $r = 0.294$, $p < 0.001$ for mean-IMT) and IP-10 ($r = 0.203$, $p = 0.009$ for max-IMT; $r = 0.182$, $p = 0.020$ for mean-IMT).

A multiple linear regression analysis was performed to examine the predictive power of serum CXCR3 chemokines on the carotid IMT (**Table 3**). After controlling for age, sex, DM history, smoking history, BMI, SBP, total cholesterol, HDL-cholesterol, hsCRP, and aspirin and statin medication, the regression model revealed that the serum level of MIG was independently associated with the carotid IMT ($\beta = 0.194$, $p = 0.010$ for max-IMT; $\beta = 0.184$, $p = 0.016$ for

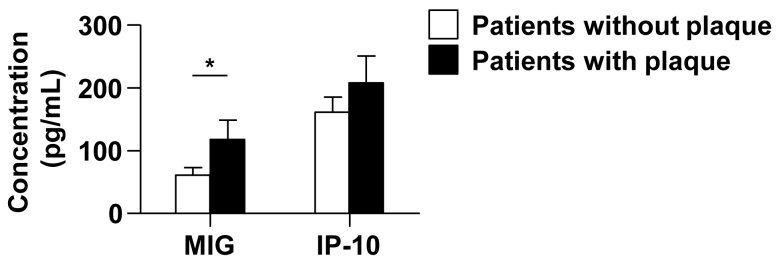

Fig. 1. Serum levels of MIG and IP-10 in patients with and without carotid plaques.

MIG, monokine induced by gamma interferon; IP-10, interferon gamma-induced protein 10. *$p<0.05$.

Table 2. Correlation between the carotid IMT and clinical variables, including CXCR3 chemokines

	Max-IMT		Mean-IMT	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Age	0.483	<0.001	0.473	<0.001
Men	0.100	0.202	0.088	0.265
DM history	0.228	0.003	0.224	0.004
Current Smoker	0.032	0.687	0.033	0.679
Aspirin medication	0.185	0.018	0.210	0.007
Clopidogrel medication	−0.001	0.993	0.018	0.815
Statin medication	0.128	0.103	0.136	0.083
BMI	0.170	0.029	0.172	0.027
SBP	0.288	<0.001	0.271	<0.001
Total cholesterol	−0.043	0.581	−0.039	0.622
HDL-cholesterol	−0.170	0.030	−0.155	0.047
LDL-cholesterol	0.013	0.869	0.025	0.749
Triglyceride*	0.031	0.689	0.001	0.992
hsCRP*	0.052	0.512	0.054	0.492
MIG*	0.305	<0.001	0.294	<0.001
IP-10*	0.203	0.009	0.182	0.020

IMT, intima media thickness; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; MIG, monokine induced by gamma interferon; IP-10, interferon gamma-induced protein 10. *These values were log transformed.

mean-IMT). However, the multiple linear regression analysis controlling for the same variables indicated that the serum level of IP-10 was not independently associated with either the max-IMT ($\beta=0.094$, $p=0.183$) or the mean-IMT ($\beta=0.072$, $p=0.316$).

Discussion

In the present study, we found a significant association between MIG, one of the CXCR3 binding T cell chemoattractants, and the thickening of the intima-media of the carotid artery. Previously, we demonstrated that T cell-driven inflammation may be important in the pathogenesis of hypertension and that MIG and IP-10 were significantly elevated in hypertensive subjects[11]. As a result, we sought to extend this finding to demonstrate the association of T cell chemokines with atherosclerosis. To the best of our knowledge, this is the first human study to demonstrate a correlation between the serum levels of MIG and the carotid IMT. These findings suggest that T cell driven inflammation may play a substantial role in the progression of atherosclerosis in humans.

The role of inflammation in the progression of

Table 3. Multiple linear regression analysis of the association between the carotid IMT and circulating levels of MIG

	Max-IMT (R^2=0.351)		Mean-IMT (R^2=0.330)	
	Regression coefficient	*p*-value	Regression coefficient	*p*-value
Age	0.346	<0.001	0.339	<0.001
Men	0.035	0.619	0.025	0.719
DM history	0.191	0.005	0.186	0.007
Current Smoker	0.045	0.490	0.051	0.450
Aspirin medication	0.058	0.448	0.093	0.233
Statin medication	0.064	0.429	0.058	0.481
BMI	0.112	0.099	0.115	0.093
SBP	0.213	0.002	0.194	0.005
Total cholesterol	0.159	0.048	0.161	0.050
HDL-cholesterol	−0.208	0.005	−0.188	0.013
hsCRP*	−0.065	0.362	−0.057	0.427
MIG*	0.194	0.010	0.184	0.016

IMT, intima media thickness; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; MIG, monokine induced by gamma interferon. *These values were log transformed.

atherosclerosis has been well established[14]. In particular, the Th1 immune response has been reported as an important determinant of human atherosclerosis pathogenesis in several independent studies[15, 16]; however, the downstream effectors of the Th1 response involved in the pathogenesis of atherosclerosis remain poorly understood. One of the main functions of Th1 cells is to secrete IFN-γ, which promotes the expression of adhesion molecules and the production of cytokines and chemokines by endothelial cells and macrophages[17]. IFN-γ induces the secretion of MIG and IP-10, which signal through CXCR3, expressed by activated Th1 cells[18]. Previous studies have reported that IFN-γ-inducible CXCR3 chemokines co-localize in human atherosclerotic plaques[6]. Consistent with this finding, patients with coronary artery disease show a higher expression of MIG, IP-10 and IFN-γ mRNA and a higher percentage of constitutive $CXCR3^+$ cells[19]. In this study, we relate these findings by demonstrating that individuals with increased carotid IMT have significantly elevated serum levels of circulating MIG and IP-10.

Chemokines are small cytokines or signaling proteins that are involved in a variety of processes during physiological and pathological conditions. Previous studies suggest a functional role for the T cell chemokines MIG and IP-10 as well as their receptor CXCR3 in chronic inflammatory diseases, including atherosclerosis[20, 21]. The antibody-mediated blockade of CXCR3 resulted in diminished recruitment of Th1 cells into the sites of inflammation in mice[20]. Okamoto *et al.* reported that adiponectin inhibits the production of CXCR3 chemokines in macrophages and thus reduces T cell recruitment in atherogenesis[21].

According to our data, the serum levels of MIG were found to be independently associated with both the max- and mean-IMT after adjusting for factors known to influence carotid IMT, such as age, blood pressure, smoking history, plasma cholesterol, and hsCRP[22, 23]. The serum levels of IP-10 did not significantly correlate with the carotid IMT. This differential impact on the carotid IMT may be related to the differential bioavailability of MIG and IP-10. One possible explanation is that the sites which mediate IFN-γ responsiveness in the promoter region for the gene encoding MIG differ from those of IP-10[24, 25]. The preferential contribution of a single CXCR3 chemokine to disease pathology has been reported in other inflammatory models, such as IP-10 in mouse models of hepatitis virus or dengue virus infection[26, 27]. MIG has been shown to independently contribute to the pathological response to herpes simplex virus type 1 or cytomegalovirus infection and also in human immune-mediated kidney diseases[28-30]. Further studies regarding the precise biological role of MIG in the pathogenesis of atherosclerosis are therefore needed.

In the present study, no significant association was found between the serum levels of CXCR3 chemokines with the progression of carotid IMT during the 2-year follow-up period. A recent study on treated hypertensive patients failed to prove a significant predictive role of carotid IMT changes for cardiovascular

outcome[31]. This may be due in part to the small magnitude of IMT changes in a relatively short period of time. Additionally, the impact of IMT changes may be masked by the large inter-subject variability of baseline carotid IMT.

Although we demonstrated an independent relationship between the serum levels of MIG and the carotid IMT, this study is still associated with some limitations. First, the relatively small study population limits the power of the study. Second, our findings can only demonstrate an association, and not causality, between the serum level of MIG and the carotid IMT. However, the results of this study suggest a potential effect of the serum MIG on the progression of atherosclerosis. Third, the study population was relatively old and overweight, and carotid plaque was present in approximately 65% of the patients, which may have confounded both the measurement of the carotid IMT and the plasma level of MIG. Therefore, these findings should not be extended to the general population. Despite these limitations, we believe that our findings are substantial enough to generate new hypotheses for future clinical and translational research.

In conclusion, the circulating MIG levels are independently associated with the carotid IMT, after adjusting for confounding factors and medications. The results from this study increase our understanding of T cell driven inflammation in atherosclerosis and suggest that MIG may be a useful biomarker of early atherosclerosis in humans. The roles of CXCR3 chemokines and T cell driven inflammation in the progression of atherosclerosis require further investigation in prospective studies with larger populations.

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Conflict of Interest

The authors declare no conflicts of interest.

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