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High Ratio of Myeloid Dendritic Cells to Plasmacytoid Dendritic Cells in Blood of Patients With Acute Coronary Syndrome

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Background: Dendritic cells (DCs) stimulate T-cells to participate in the inflammatory processes that promote the destruction of vulnerable plaques. The relationship between circulating levels of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) in patients with acute coronary syndrome (ACS) was evaluated.
Methods and Results: Blood samples were obtained from 39 patients with ACS, 41 patients with stable angina pectoris (SAP) and 43 controls. The proportion of mDCs tended to be lower in the ACS group than in the SAP group and controls. Interleukin-12 levels associated with mDCs were significantly higher in the ACS group than in control group. The proportion of pDCs was significantly lower in the ACS groups than in the other two groups. Interferon-α levels secreted by pDCs, however, were not significantly different among the 3 groups. The ratio of mDCs to pDCs ≥4 is an important value for distinguishing ACS from SAP patients and control patients through receiver operating characteristic analysis (sensitivity; 85.0%, specificity; 83.4%).
Conclusions: The ratio of mDCs to pDCs may be a useful marker for detecting ACS and the existence of vulnerable plaques. (*Circ J* 2009; **73:** 1914 – 1919)

Key Words: Acute coronary syndrome; Interferon-α; Interleukin-12; Myeloid dendritic cells; Plasmacytoid dendritic cells

Immune cells dominate early atherosclerotic lesions, while their effecter molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndrome (ACS).[1–3] T-cells predominate at the shoulder of atherosclerotic plaques and participate in the inflammatory processes that promote the destruction of existing collagen in vulnerable plaques.[3,4] Elucidation of T-cell pathophysiology and the mechanisms of T-cells' expansion provides insights into the cause of ACS and T-cells' roles therein.[5,6] Liuzzo et al suggested that monocyte activation in ACS represents a downstream effect of altered T-cells responses, characterized by the preferential production of interferon-γ and implicated an important role for T-cells in ACS patients.[7] We also reported higher numbers of interferon-γ-producing T-cells in the peripheral blood of patients with unstable angina pectoris (UAP) than in that with stable angina pectoris (SAP) and controls.[8] Recent studies showed that the function of a proportion of T-cells is controlled by dendritic cells (DCs). DCs are antigen-presenting cells with the unique ability to initiate a primary immune response to certain antigens through the activation of naive T-cells.[9,10] DCs colocalize with T-cells in atherosclerotic plaques, emphasizing their potential role in modulating T-cells function in vivo.[11,12] DCs are also localized in atherosclerotic and ruptured plaques of carotid arteries and aortas.[13–15] There are two DC subtypes with different functions: (1) myeloid DCs (mDCs), which express CD1c, CD11c, CD303 and CD141, and secrete interleukin (IL)-12 after stimulation; and, (2) plasmacytoid DCs (pDCs), which express CD123 and CD303, the IL-3 receptor α-chain; these are the major source of interferon-α.[16] Little is known about the circulating levels of mDCs and pDCs in patients with ACS. We hypothesized that analysis of peripheral DCs in patients with ACS may help to delineate local and systemic mechanisms underlying the formation of vulnerable plaques and stable plaques.

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Methods

Study Population

The study subjects were 123 patients who underwent coronary artery angiography at Kumamoto University Hospital, Kumamoto, Japan. Thirty-nine patients with a diagnosis of UAP or acute myocardial infarction (AMI) were included in the ACS group (25 men and 14 women, age range from 46 to 85 years, mean 67±11 years). Patients with AMI were admitted within 4 hours of onset of symptoms. The diagno-

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Table 1. Clinical Characteristics of the Study Population

	Control subjects (n=43)	ACS group (n=39)	SAP group (n=41)	P value (comparison between ACS and SAP groups)	P value (comparison among 3 groups)
Age (year)	64±13	67±11	68±19	0.58	0.31
M/F	19/24	25/14	25/16	0.82	0.11
Coronary risk factor					
Hyperlipidemia	22 (51%)	31 (79%)	23 (56%)	0.0279	0.01
Hypertension	21 (49%)	21 (54%)	26 (63%)	0.48	0.43
Current smoker	9 (21%)	9 (23%)	8 (20%)	0.051	0.91
Diabetes mellitus	9 (21%)	25 (64%)	19 (46%)	0.12	0.0002
White blood cell (cell/μl)	5,586±1,432	6,358±1,957	5,930±1,920	0.33	0.23
Granulocyte (%)	54.9±8.1	60.3±9.3	58.4±10.6	0.40	0.0375
Lymphocytes (%)	35.7±8.7	29.4±8.3	30.8±9.3	0.51	0.0044
Monocyte (%)	5.9±1.5	6.1±2.0	6.2±2.0	0.76	0.78
hs-CRP (mg/dl)	0.12±0.17	0.69±0.88	0.24±0.34	0.0042	0.0001
IL–12 (pg/ml)	0.171±0.195	0.874±1.830	0.507±0.761	0.56	0.0013
Interferon-α (pg/ml)	3.722±4.442	1.807±2.220	2.252±1.736	0.73	0.11
Medication on admission					
Aspirin	17 (40%)	18 (46%)	29 (71%)		
Angiotensin converting enzyme inhibitors	3 (7%)	5 (13%)	4 (10%)		
Angiotensin II type 1 receptor blockers	11 (26%)	5 (13%)	4 (10%)		
Nitrate/Nitrite	4 (9%)	4 (10%)	10 (24%)		
β-blockers	5 (12%)	7 (18%)	6 (15%)		
Calcium channel blockers	22 (51%)	16 (41%)	29 (71%)		
Diuretics	0 (0%)	5 (13%)	2 (5%)		
Statins	11 (26%)	17 (44%)	19 (46%)		

Data are mean±SD or median (25–75th percentile range). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Diabetes mellitus was defined as a fasting plasma glucose 126 mg/dl or higher or treatment with either insulin or hypoglycemic agents. Hypercholesterolemia was defined as treatment with hypolipidemic agents such as statin, or serum blood cholesterol levels 220 mg/dl or higher.
ACS, acute coronary syndrome; SAP, stable angina pectoris; hs-CRP, high sensitivity C-reactive protein; IL, interleukin.

sis of AMI was based on the presence of typical chest pain persisting for ≥30 min, ST-segment elevation of >0.2 mV in ≥2 contiguous leads on a standard 12-lead electrocardiogram, and elevation of serum creatine kinase (CK)-MB isoenzyme level to greater than twice the upper limit of the normal range. The diagnosis of UAP [Braunwald's class II B or III B] was based on the presence of chest symptoms at rest associated with transient ischemic ST-segment shifts and a normal serum level of CK-MB isoenzyme.[17] Forty-one patients were diagnosed with SAP (25 men and 16 women, age range from 46 to 85 years, mean 68±9 years). SAP patients were typified by long-term, stable angina of at least three months duration, and a positive exercise test. In addition, SAP patients were defined as those without angina episodes at rest and without previous myocardial infarction, but with angiographically documented organic stenosis of >75% in at least one of the major coronary arteries. Forty-three patients with normal coronary parameters were included in the control group (19 men and 24 women, age range from 39 to 81 years, mean 64±13 years). All controls underwent diagnostic cardiac catheterization because of a history of chest pain with multiple risk factors and/or an electrocardiographic abnormality. The coronary angiograms of the controls revealed no coronary organ stenosis (<25%) or coronary spasm after intracoronary injection of acetylcholine. Exclusion criteria were non-cardiac diseases that might interfere with our analysis: acute or chronic infections, malignancies, autoimmune diseases, hyperthyroidism and medication with immunosuppressive agents. The institutional ethics committee of the Kumamoto University approved the study, and informed consent was obtained from all patients and control subjects.

Blood Sampling

ACS, SAP and control groups donated peripheral blood samples on admission, taken by sterile venipuncture using a 21-gauge needle and collected into heparinized and plain vacutainers. Two ml of blood was drawn into a heparinized vacutainer to measure the percentages of CD1c-, CD303- and CD141-positive DCs. Serum IL-12 and interferon-α levels were measured using an enzyme-linked immunosorbent assay. Serum high-sensitivity C-reactive protein (hs-CRP) levels were quantified using immunonephelometry.[18]

Identification of DCs by Fluorescence-Activated Cell Sorting (FACS)

Whole peripheral blood samples were analyzed using the Blood Dendritic Cell Enumeration Kit (Miltenyi Biotec, Utrecht, The Netherlands) based on subset-specific blood DC antigens.[10,19] Four-color flow cytometry (FACS Calibur, Becton Dickinson, Erembodegem, Belgium) was conducted using monoclonal antibodies against CD14, CD19, CD1c, CD303 and CD141 that were directly conjugated with fluorochromes (phycoerythrin-cyanine-5, fluorescein isothiocyanate and phycoerythrin), and data were analyzed with CellQuest software (Becton Dickinson). After exclusion of cell debris, granulocytes, B cells and monocytes, the mDC-subset 1 (mDC1) and pDCs were identified through their immunopositivity for CD1c and CD303 antibodies, respectively. The mDC-subset 2 (mDC2) was identified as immunopositive for CD141, but not CD303. In the present study, we treated mDC1 and mDC2 as mDCs. The absolute numbers of blood DCs were calculated as the proportion of DCs in the leukocyte gate multiplied by absolute white blood cell count.

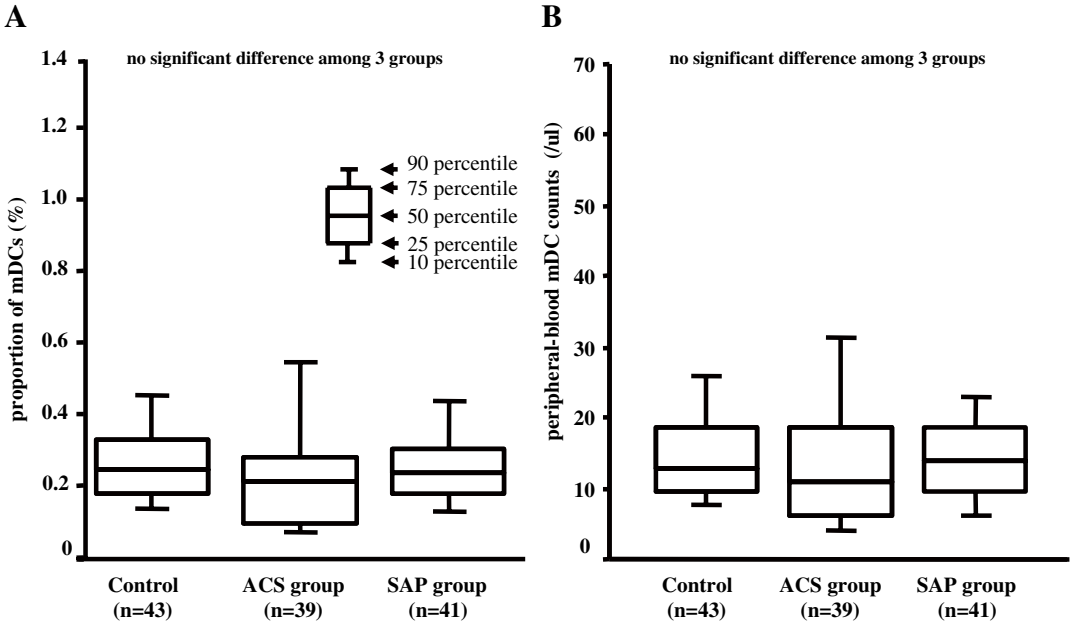

Figure 1. (**A**) Proportions of myeloid dendritic cells (mDCs) in acute coronary syndrome (ACS), stable angina pectoris (SAP) and control groups. (**B**) Absolute numbers of peripheral-blood mDCs in ACS, SAP and control groups.

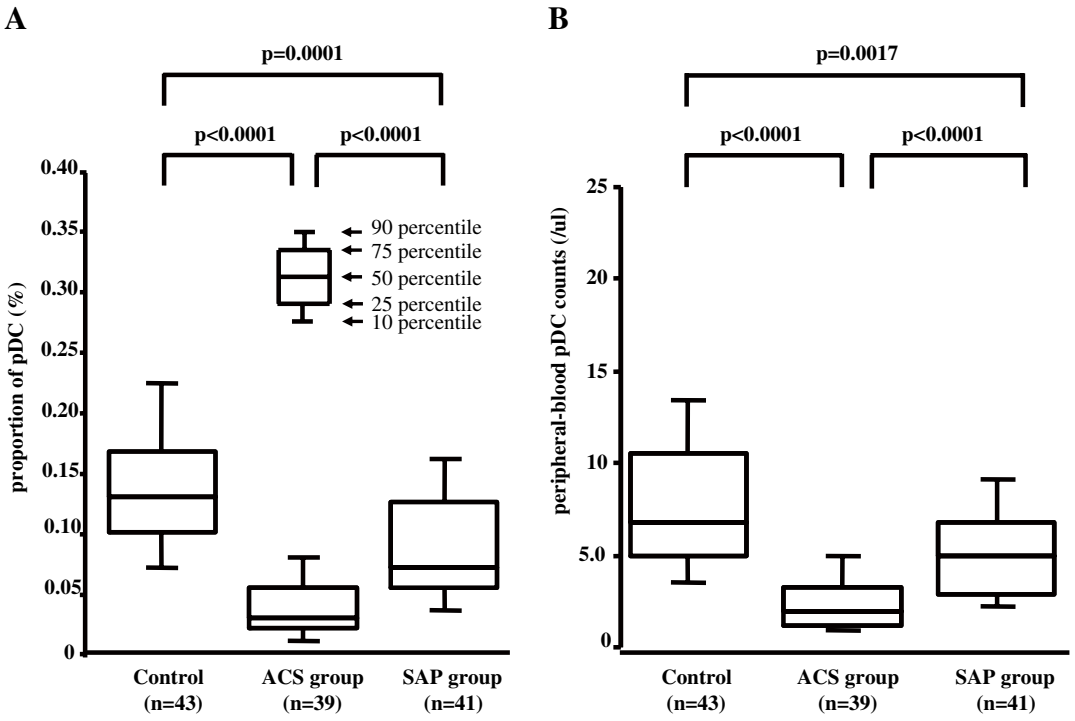

Figure 2. (**A**) Proportions of plasmacytoid dendritic cell (pDC) in acute coronary syndrome (ACS), stable angina pectoris (SAP) and control groups. (**B**) Absolute numbers of peripheral-blood pDC in ACS, SAP and control groups.

Statistical Analysis

Group data for normally distributed continuous variables were expressed as mean±SD and were compared using one-way analysis of variance or t-test. Group data for continuous variables that did not show normal distribution were expressed as median (25–75th percentile range) and compared using the Kruskal-Wallis test or Mann-Whitney's U test. Categorical data were expressed as frequencies and percentages. A P value of <0.05 was considered statistically significant. P values compared among 3 groups are shown in **Table 1** and P values compared between 2 groups are shown in **Figures 1**–**4** when there was a significant difference among 3 groups. Multiple logistic regression analysis was performed to elucidate the independent predictor of ACS. Sensitivity and specificity were calculated in order to determine the predictive value. In addition, receiver oper-

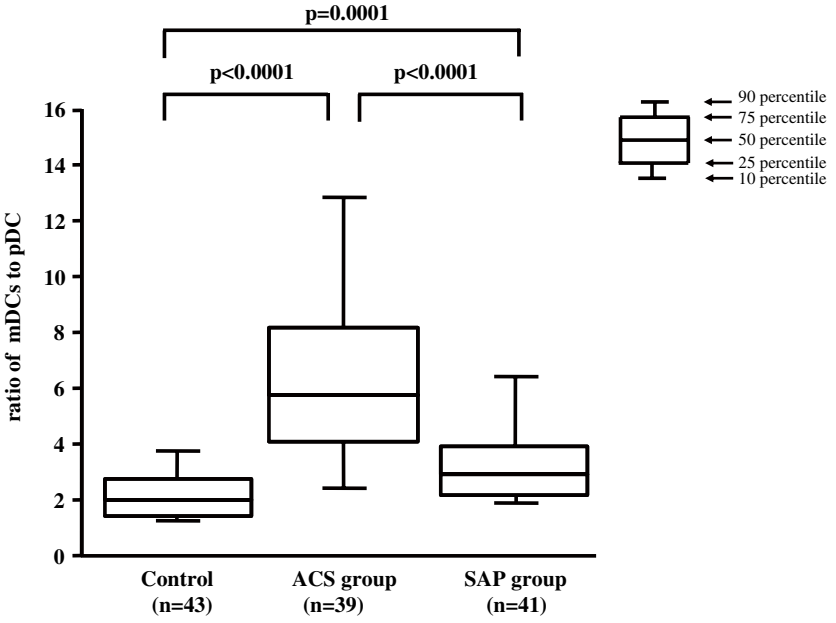

Figure 3. Comparison of myeloid dendritic cell (mDC) to plasmacytoid dendritic cell (pDC) ratios among acute coronary syndrome (ACS), stable angina pectoris (SAP) and control groups.

ating characteristic (ROC) analysis was carried out to determine the ideal cut-off for optimum specificity and sensitivity. Calculations were carried out using SPSS 15.0.1J statistical software.

Results

Patient Characteristics

The clinical characteristics of the ACS, SAP and control patients are listed in **Table 1**. All patients were matched for age, gender and frequency of coronary risk factors, except for hyperlipidemia and diabetes mellitus. We also compared patient characteristics between the ACS and SAP groups. There were no significant differences in the patient characteristics, except for hyperlipidemia, between the 2 groups.

mDCs and pDCs

There was no significant difference in absolute lymphocyte numbers among patients with ACS (n=39), those with SAP (n=41) and controls (n=43). The proportion of mDCs tended to be lower in the ACS group than in the SAP group and controls. (**Figures 1A**,**B**). On the other hand, the proportion and absolute numbers of peripheral pDCs was significantly lower in the ACS and SAP groups compared to controls (**Figures 2A**,**B**), and the proportion of peripheral pDCs was significantly lower in patients with ACS than in those with SAP (**Figures 2A**,**B**). Furthermore, the ratio of mDCs to pDCs in peripheral blood was significantly higher in the ACS and SAP groups than in controls (**Figure 3**), and it was significantly higher in the ACS group than in the SAP group (**Figure 3**).

Serum Levels of hs-CRP, IL-12, and Interferon-α

Serum hs-CRP levels were significantly higher in the ACS and SAP groups than in the control group (**Table 1**), and were significantly higher in the ACS group than in the SAP group (P=0.004). Serum IL-12 levels were significantly higher in the ACS and SAP groups than in the control group, and tended to be higher in the ACS group than in the SAP group (**Table 1**). On the other hand, there were no sig-

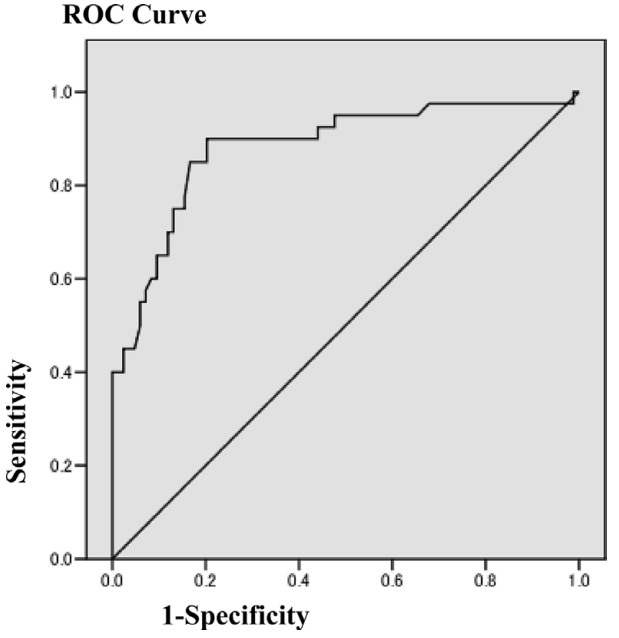

Figure 4. Plot showing receiver operating (ROC) characteristic curve for acute coronary syndrome for ratio of myeloid dendritic cells, to plasmacytoid dendritic cells.

Table 2. Multiple Logistic Regression Analysis of Hematological Findings of Independent Predictors of ACS

	OR (95%CI)	P value
hs-CRP	4.016 (0.143–111.1)	0.4140
mDC/pDC	2.632 (1.385–5.000)	0.0031
IL-12	1.594 (0.153–2.538)	0.5164
Granulocyte	1.102 (0.826–1.471)	0.5100
Max CK-MB	1.066 (0.956–1.189)	0.2500
Lymphocyte	0.987 (0.715–1.364)	0.9377

OR, odds ratio; CI, confidence interval; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; CK, creatine kinase. Other abbreviations see in Table 1.

nificant differences in the serum interferon-α levels among the 3 groups (**Table 1**).

ROC Analysis and Multiple Logistic Regressions Analysis

An attempt to determine the optimum cut-off was made by calculating the area-under-the curve for ACS. From ROC analysis, the ratio of mDCs to pDCs ≥4 had a sensitivity of 85.0% and a specificity of 83.4% for ACS (**Figure 4**). Multiple logistic regressions analysis revealed that the ratio of mDC to pDC is the only variable that was independently associated with ACS among CK-MB, Granulocyte, Lymphocytes, hs-CRP, ratio of mDC to pDC and IL-12 (**Table 2**).

Discussion

This study confirmed a lower proportion of mDCs in the blood of patients with ACS compared with controls, in support of earlier findings.[13,20] Previous studies also showed the recruitment of circulating mDC precursors into unstable atheroma and their crucial involvement in the (auto)immune mechanisms of atherosclerosis, as well as oxidized low-density lipoprotein promoting the maturation of mDCs and thus enabling T-cells activation in vitro.[21–23] Yilmaz et al suggested that the increased recruitment of mDCs into unstable plaques and increased peripheral neutrophils and lymphocytes in patients with ACS might be responsible for decreased peripheral mDCs and relative lower percentage of mDCs.[13]

We found that serum IL-12 levels associated with mDCs tended to be higher in the ACS group compared with those in the SAP group and controls. These findings suggest that mDCs in peripheral blood are activated to secrete cytokines during ACS, despite the relative decrease in blood mDCs due to atheroma sequestering.

We did find, however, that pDCs were significantly lower in the blood of patients with ACS compared with controls, again supporting previous findings.[13,20] We analyzed interferon-α secreted from pDCs as a measure of pDC activation in the present study; however, there were no significant differences in the serum interferon-α levels among the 3 groups. Niessner et al also reported the level of pDCs in unstable plaque increased and pDC amplified cytolytic T-cells functions in unstable plaque.[14,24] Furthermore, Banchereau et al suggested that this decrease in circulating pDCs reflects a drop in the production of pDCs precursors for mDC development by bone marrow.[9,25]

In the present study, the ratio of mDCs to pDCs was significantly higher in the blood of patients with ACS compared with that of SAP patients and controls, and the difference was significant among the three groups. We consider the ratio of mDCs to pDCs ≥4 is an important value for ACS in ROC analysis. In this study, 34 of 39 ACS patients (87.2%), 11 of 41 SAP patients (26.8%), and 3 of 43 controls (6.9%) showed an mDCs:pDCs ratio ≥4. The ratio of mDCs to pDCs ≥4 had a sensitivity of 85.0% and a specificity of 83.4% for ACS in this study. This ratio might therefore provide a useful marker for distinguishing vulnerable from stable plaques. Therefore, a prospective study may need to be conducted in the future to confirm it.

Serum levels of the inflammatory biomarker hs-CRP predict cardiovascular risk and some reports demonstrated the elevated levels of hs-CRP levels in patients with ACS.[26–28] The induction of CRP might require IL-12, IL-6 and tumor necrosis factor-α. Circulating levels of these inflammatory cytokines have been reported to be increased in patients with ACS. Moreover, Van Vré EA et al reported that CRP in patients with cardiovascular disease can influence DC function during atherogenesis.[29] The present study showed markedly elevated serum hs-CRP levels in ACS and SAP patients compared with controls. These data therefore indicate serum hs-CRP and IL-12 levels could be a potentially useful additional marker in patients with cardiovascular disease and DCs might play important roles in arteriosclerotic progress and rupture.

Shi et al reported that peripheral-blood mDCs increased in patients with coronary artery disease compared with the control group in men.[30] In this study, there was no significant difference in the frequency of DCs between men and women.

In conclusion, the ratio of circulating mDCs to pDCs can detect ACS and the existence of vulnerable plaques. Thus, analysis of human DCs in peripheral blood might provide a new therapeutic target in patients with coronary artery disease.

Acknowledgments

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