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Original Article

Increased serum IL-17A is associated with HMGB1 in coronary artery disease

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Abstract: Atherosclerosis is an inflammatory disease in which a variety of immune cells and inflammatory factors are involved. The high mobility group box 1 (HMGB1)/interleukin (IL)-17A axis participates in the pathogenesis of many inflammatory diseases including some cardiovascular diseases. IL-17A, as a novel pro-inflammatory cytokine, plays an important role in the progression of atherosclerosis. Meanwhile, HMGB1 has been confirmed to be a pro-atherosclerotic mediator and a novel predictor of the severity of atherosclerotic coronary artery disease (CAD). The present study was designed to investigate the relationship between serum IL-17A and HMGB1 levels as well as the specific role of IL-17A in CAD. The levels of IL-17A in the non-ST segment elevation myocardial infarction (NSTEMI) group and ST segment elevation myocardial infarction (STEMI) group were significantly higher than that in the unstable angina pectoris (USAP) group (both $P<0.05$). And the level of IL-17A in USAP group was higher than that in the stable angina pectoris (SAP) group ($P<0.05$). However, there was no significant difference between SAP group and control group ($P>0.05$). Besides, there was a significant positive correlation between IL-17A and HMGB1 levels ($n=141$, $r=0.253$, $P<0.05$). IL-17A was suggested to be an independent risk factor for CAD by logistic regression analysis (OR=1.273, 95% CI 1.056-1.602, $P=0.0211$). These findings indicated that increased serum IL-17A is involved in the pathogenesis of atherosclerotic CAD and the HMGB1/IL-17A axis plays a specific role in atherosclerosis. In addition, IL-17A is an independent risk factor for CAD and may be a potential target for pharmacological intervention of CAD.

Keywords: Interleukin-17A, high mobility group box 1, coronary artery disease

Introduction

Atherosclerosis is a chronic inflammatory disease of the vessel wall which is associated with lipid accumulation, and both innate immunity and adaptive immunity are involved in its pathogenesis [1, 2]. Vascular inflammation is the core mechanism of atherosclerosis and plays a pivotal role in many stages of atherosclerosis, from initial leukocyte recruitment to eventual rupture of the unstable atherosclerotic plaque [1, 2]. Immune cells and their mediators directly cause arterial inflammation, and these inflammation responses are the main characteristics of atherosclerosis. Innate immune components, including macrophages and dendritic cells, and adaptive immune components, including T lymphocytes, are involved in the inflammatory responses [3, 4]. To further clarify the role of inflammation in the mechanism of atherosclerosis and its complications, some systemic inflammatory markers have been confirmed as independent risk factors involved in cardiovascular events [5], indicating that increased inflammatory levels may predict the presence and evolution of atherosclerosis.

IL-17A, as a signature cytokine produced by a new lineage of CD4+ T cells, type 17 helper cells (Th17), is a member of a new subclass of cytokines that have highly pro-inflammatory properties [6]. Emerging evidence has revealed that an increase in IL-17A level is closely associated with a range of inflammatory diseases, including inflammatory bowel disease, systemic lupus erythematosus, and osteoporosis [7-9]. Research using classical animal models of atherosclerosis provided evidence for the pro-atherogenic role of IL-17A via pro-inflammatory changes at multiple levels, such as cell adhe-

Table 1. Characteristics of patients with coronary artery disease in control, SAP, USAP, NSTEMI and STEMI groups

	Control group (n=35)	SAP (n=35)	USAP (n=34)	NSTEMI (n=11)	STEMI (n=26)
Age (years)	51±6	53±4	52±5	52±3	52±4
Smokers (%)	45.5%	50.0%	55.0%	50.0%	55.5%
Drinking (%)	27.3%	25.0%	20.0%	25.0%	27.8%
Hypertension (%)	22.7%	20.0%	25.0%	25.0%	22.2%
Aspirin (%)	45.5%	55.0%	45.0%	50.0%	55.5%
ACEI/ARB (%)	27.3%	25.0%	30.0%	25.0%	33.3%
β-blocker (%)	13.6%	15.0%	20.0%	25.0%	22.2%
Calcium blocker (%)	18.2%	15.0%	15.0%	12.5%	16.7%
Nitrate (%)	18.2%	20.0%	25.0%	25.0%	27.8%
Statins (%)	27.3%	25.0%	35.0%	37.5%	38.9%
BMI (kg/m^2)	22.5±2.1	24.2±2.5	23.6±1.7	24.3±1.8	25.4±2.2
TC (mmol/)	4.28±0.81	3.75±0.87	4.28±1.36	3.53±0.49	4.03±1.26
TG (mmol/l)	2.14±1.48	1.38±1.05	1.97±1.69	1.46±0.55	1.49±0.87
HDL-C (mmol/l)	1.18±0.37	1.12±0.24	1.12±0.27	0.94±0.22	0.91±0.38
LDL-C (mmol/l)	2.50±0.78	2.14±0.67	2.51±0.87	2.35±0.86	2.24±0.91
Glucose (mmol/l)	5.31±0.79	6.07±2.95	5.41±1.61	5.47±0.75	5.37±1.24
hs-CRP (mg/l)	1.93±3.04	2.16±2.73	4.80±1.87#,▲	5.88±1.63#,▲,■	5.70±1.35#,▲,■
IL-17A (pg/ml)	37.27±4.36	38.65±3.09	39.46±2.59#,▲	43.81±5.16#,▲,■	44.0±3.82#,▲,■
HMGB1 (pg/ml)	48.42±5.97	52.26±6.79#	56.54±7.38#,▲	59.65±7.51#,▲,■	61.65±8.02#,▲,■

Data were presented as the mean±SD or median (interquartile range) for continuous variables. SAP, stable angina pectoris; USAP, unstable stable angina pectoris; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IL-17A, Interleukin-17A; HMGB1, high mobility group box 1 protein. #P<0.05, compared to control group. ▲P<0.05, compared to SAP group. ■P<0.05, compared to USAP group.

sion, extravasation, cell activation, T cell (co) stimulation/proliferation, and antigen presentation [10]. Consistent with this result, a number of experimental and clinical studies have confirmed IL-17A as a potent pro-inflammatory factor that plays an important role in atherosclerosis [11-17].

As a highly conserved nuclear protein, HMGB1 can be passively released by necrotic cells and apoptotic cells or positively secreted by activated innate immune cells (such as macrophages and monocytes) [18, 19] and participates in promoting the inflammatory reaction, angiogenesis, ischemia/reperfusion injury, rejection after transplantation, etc. [19, 20]. Previous studies have confirmed HMGB1 as a novel pro-inflammatory factor that plays an important role in cardiovascular disease [21-23]. Hu et al. [21] showed that serum HMGB1 levels were correlated with the severity of coronary artery stenosis in patients with CAD. Recently, several clinical studies have suggested that serum HMGB1 levels in patients with CAD are significantly higher than that in control group, and HMGB1 may be a novel predictor of adverse clinical outcomes after acute myocardial infarction (AMI) [24-26].

Recent studies have shown that the HMGB1/IL-17A axis is involved in the development of a variety of inflammatory diseases, including some cardiovascular diseases. In liver ischemia/reperfusion (I/R) injury animal models and clinical research of heart transplants, researchers have found that HMGB1 could promote the release of IL-17A and specific inhibitors of HMGB1 markedly reduced the production of IL-17A and ameliorated I/R injury [27, 28]. Taken together, both HMGB1 and IL-17A play a crucial role in atherosclerotic CAD, and the HMGB1/IL-17A axis has been confirmed as a vital mechanism in many inflammatory diseases, including some cardiovascular diseases. Thus, we proposed that IL-17A and HMGB1 levels might also have specific relevance in patients with CAD.

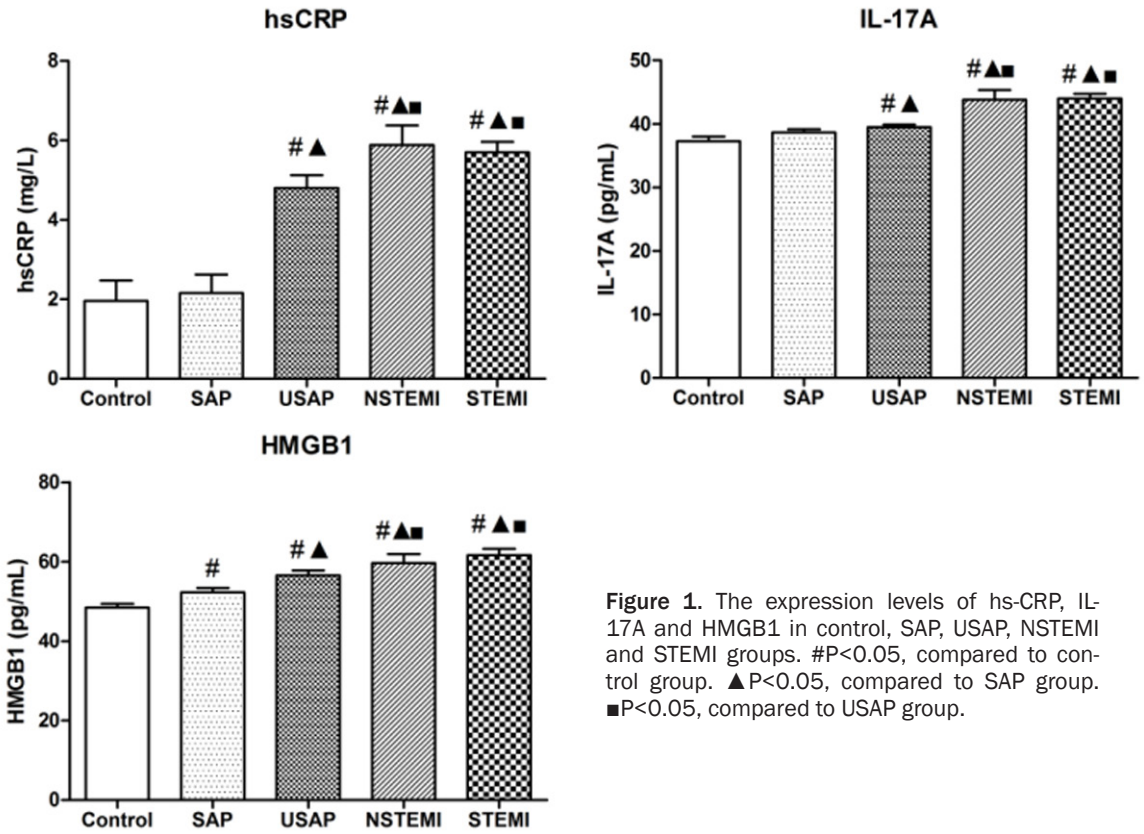

Figure 1. The expression levels of hs-CRP, IL-17A and HMGB1 in control, SAP, USAP, NSTEMI and STEMI groups. #P<0.05, compared to control group. ▲P<0.05, compared to SAP group. ■P<0.05, compared to USAP group.

We investigated the relationship between serum IL-17A and HMGB1 levels as well as the specific role of IL-17A in CAD.

Materials and methods

Study subjects

This clinical protocol was approved by the Institutional Medical Ethics Committee and was performed according to the ethical guidelines outlined in the Declaration of Helsinki.

One hundred and forty-one consecutive patients (aged 20-60 years) with suspected CAD or CAD (SAP, USAP or AMI) who agreed to participate in this study were enrolled from the Department of Cardiology, Renmin Hospital of Wuhan University, P.R. China. A coronary artery angiography was performed in all patients. Patients with a coronary artery luminal diameter narrowing of less than 50% served as control group (except USAP and AMI patients). The other patients were divided into four groups: SAP, USAP, NSTEMI and STEMI. The exclusion criteria was as follows: less than 20 years old, more than 60 years old, or those having other diseases including fever, cardiac dysfunction, arrhythmias, chronic coronary artery total occlusion, peripheral vascular disease, liver or renal dysfunction, autoimmune disease and cancer.

Sample collection and biochemical investigation

Peripheral venous blood was drawn from the antecubital vein after a 12h fasting period. Serum samples were aliquoted and stored at -80°C until further use. All samples were thawed only once.

Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose and hypersensitive C-reactive protein (hs-CRP) were measured using standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Serum IL-17A and HMGB1 levels were determined using commercially available ELISA kits (IL-17A ELISA kit II; HMGB1 ELISA kit II; Shino-Test Corporation, Tokyo, Japan) according to the manufacturer's protocol.

Table 2. Correlations between IL-17A level and cardiovascular risk factors

Variable	r	*P*
Age	-0.137	>0.05
BMI	-0.105	>0.05
TC	-0.049	>0.05
TG	0.017	>0.05
HDL-C	0.090	>0.05
LDL-C	-0.027	>0.05
hs-CRP	0.298	<0.05
Glucose	-0.039	>0.05
HMGB1	0.253	<0.05

IL-17A, Interleukin-17A; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HMGB1, high mobility group box 1 protein. Statistical significance was defined as P<0.05.

Table 3. Logistic regression analysis of the risk factors for coronary artery disease

A. Single factor analysis			
	Control (n=35)	Patients (n=106)	*p*-value
IL-17A	37.26±4.36	39.68±3.35	0.0091
TC	4.28±0.81	4.02±1.14	0.3283
TG	2.13±1.48	1.67±1.40	0.2099
HDL-C	1.19±0.37	1.10±0.26	0.2501
LDL-C	2.50±0.78	2.33±0.77	0.3721
Glucose	5.31±0.79	5.55±2.16	0.6130
Hs-CRP	1.93±3.04	2.05±2.12	0.8604
Age	56.39±10.23	62.80±10.00	0.0098
HMGB1	48.41±19.40	56.02±18.00	0.0779
B. Multiple factor analysis			
	OR	95% CI	*p*-value
IL-17A	1.273	1.056-1.602	0.02111
Age	1.084	1.030-1.150	0.00365
HMGB1	1.004	0.969-1.039	0.83420

IL-17A, Interleukin-17A; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HMGB1, high mobility group box 1 protein. Statistical significance was defined as P<0.05.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). All values were expressed as the mean ± SD or the percentage of incidence. The incidence of some clinical characteristics of CAD patients including smoking, drinking, hypertension, medication (aspirin, β-blocker, calcium blocker and nitrate, ACEI/ARB and statins) were compared with chi-square test or Fisher's exact test. Other characteristics (age, BMI, TC, TG, HDL-C, LDL-C, glucose) and serum levels of hs-CRP, IL-17A and HMGB1 among different groups were compared by One-way ANOVA. Pearson correlation coefficient was used to assess the relationship between IL-17A concentrations and other risk factors. Logistic regression analysis was used to assess the risk factors for CAD. Statistical significance was defined as P<0.05.

Results

Clinical characteristics of patients

As shown in **Table 1**, there were no significant differences in mean age, body mass index (BMI), lipid levels (TC, TG, HDL and LDL), and medication among the five groups (all P>0.05). However, significant differences in IL-17A, HMGB1 and hs-CRP were found (all P<0.05) (**Figure 1**).

The levels of IL-17A in NSTEMI group (43.81± 5.16 pg/ml) and STEMI group (44.0±3.82 pg/ml) were significantly higher compared with USAP group (39.46±2.59 pg/ml) (both P<0.05). And the level of IL-17A in USAP group was higher than that in SAP group (38.65±3.09 pg/ml) (P<0.05). However, there was no significant difference between SAP group and control group (37.27±4.36 pg/ml) (P>0.05).

The levels of HMGB1 in SAP group (52.26±6.79 pg/ml), USAP group (56.54±7.38 pg/ml), NSTEMI group (59.65±7.51 pg/ml) and STEMI group (61.65±8.02 pg/ml) were significantly higher compared with control group (48.42± 5.97 pg/ml) (all P<0.05). In detail, among the four experimental groups, the levels of HMGB1 in the latter two groups were significantly higher than the other two groups, while in SAP group the level of HMGB1 was the lowest (all P<0.05).

Association of IL-17A levels to cardiovascular risk factors

Correlations of IL-17A levels with HMGB1 and several cardiovascular risk factors are shown in **Table 2**. There was a significant positive correlation between IL-17A and HMGB1 levels (n=141, r=0.253, P<0.05). The IL-17A levels were also correlated with hs-CRP (n=141, r= 0.298, P<0.05).

Logistic regression analysis of risk factors for CAD

In **Table 3**, logistic regression analysis was performed to determine risk factors for CAD. And single-variable logistics regression found significant difference of IL-17A and age between CAD group and control group (both $P<0.05$). Then further multilple-variable logistic regression analysis revealed IL-17A to be an independent risk factor for CAD (OR=1.273, 95% CI 1.056-1.602, P=0.0211).

Discussion

IL-17A, as an inflammatory cytokine mainly secreted by Th17 cells, has been confirmed to be implicated in numerous immune and inflammatory diseases primarily as a pro-inflammatory regulator by inducing the release of various inflammatory mediators, such as cytokines (IL-6, TNF-α and IL-1β), chemokines (Cxcl1 (KC/Groα), MCP-1 (Ccl2), IL-8), adhesion molecules, and growth factors [29, 30]. Given its wide and potent pro-inflammatory activity, accumulating evidence has revealed that IL-17A plays a pivotal role in the pathogenesis of cardiovascular diseases, including atherosclerosis [31]. Recently, animal models and clinical studies have provided direct evidence about the pro-atherogenic function of IL-17A [10, 13-17, 32-34]. Hashmi et al. [35] found a significant increase in IL-17A level in the acute coronary syndrome (ACS) group compared with normal group, which was also positively correlated with hs-CRP and IL-6 levels. The authors proposed that IL-17A might be a potential predictor in ACS, which was consistent with an Iranian study [36]. Another clinical study showed that compared with SAP and control group, circulating Th17 cells, circulating Th17 related cytokines (IL-17A, IL-6 and IL-23) and transcription factor RORγt levels in ACS group were significantly increased [13]. In this study, we found that serum levels of IL-17A increased significantly in patients with USAP, NSTEMI and STEMI, suggesting that increased serum IL-17A is associated with the pathogenesis of atherosclerotic CAD. In addition, there was a significant correlation between IL-17A and hs-CRP levels, which was consistent with previous studies.

HMGB1, as a non-chromosomal nuclear protein, has been confirmed as a novel pro-inflammatory factor involved in the pathogenesis of atherosclerosis [21-23]. Kalinina et al. [37] initially found that HMGB1 was abundantly expressed in atherosclerotic plaques derived from human autopsy specimens. Furthermore, Hu et al. [21] showed that serum HMGB1 levels were markedly increased in SAP and USAP patients, and HMGB1 was correlated with the severity of coronary artery stenosis in these patients, particularly in SAP patients, which suggested that increased serum HMGB1 level might be a novel predictor of adverse clinical outcomes of atherosclerotic CAD and was involved in the pathogenesis of atherosclerotic CAD. Recent researches have shown that the HMGB1/IL-17A axis is involved in the development of a variety of inflammatory diseases, including some cardiovascular diseases [27, 28]. A study using a model of liver I/R injury found increased expressions of HMGB1 and IL-17A in I/R injury, and inhibition of HMGB1 reduced the expression of IL-17A [27]. Recently, Zhu et al. [28] showed that the HMGB1 inhibitor glycyrrhizin markedly reduced the production of IL-17A and ameliorated myocardial I/R injury. Taken together, these findings suggested that HMGB1 can regulate the expression of IL-17A. In addition, studies have revealed that HMGB1 might regulate the expression of IL-17A via the PI3K/Akt pathway, which was also a common signaling pathway of HMGB1 and IL-17A [38-41]. In this study, we found that serum IL-17A levels were positively correlated with HMGB1 levels, which suggested that increased serum IL-17A is involved in the pathogenesis of atherosclerotic CAD accompanied with HMGB1. In addition, the HMGB1/IL-17A axis also plays an important role in atherosclerosis. Once released from a necrotic cell, apoptotic cell or macrophage, HMGB1 functions as a pro-inflammatory stimulus that upregulates TNF-α, IL-6, hs-CRP and macrophage inflammatory proteins (MIP-1α and MIP-1β) [19]. IL-17A and IL-17F also promote the release of cytokines (IL-6, TNF-α and IL-1β) and chemokines (Cxcl1 (KC/Groα), MCP-1 (Ccl2) and IL-8) from fibroblasts, endothelial cells and leukocytes and thus are considered to be pro-inflammatory [29, 30]. Thus, we suggest that HMGB1 and IL-17A may synergistically reinforce the inflammatory process involved in atherosclerotic CAD, in which the induction of expressions of relevant inflammatory cytokines is a common mechanism.

Due to the diversity of cell source and functions, IL-17A has been demonstrated to participate in multiple stages of atherosclerosis [10, 12, 16, 17, 32-34, 42]. Smith et al. [16] studied the ApoE-/- mouse model and revealed a pro-inflammatory function of IL-17A in the process of atherosclerosis by promoting the aggregation of mononuclear macrophages to the arterial wall. Eid et al. [12] revealed that IL-17A and IFN-γ synergistically induced vascular smooth muscle cells to produce pro-inflammatory factors and chemokines. Furthermore, Zhang et al. [32] investigated the relationship between serum IL-17A levels and platelet aggregation in patients with ACS and found that serum IL-17A and platelet aggregation levels were significantly increased in ACS compared with control group. In addition, there was a positive correlation between the two factors. A previous research [33] further confirmed that IL-17A promoted platelet activation and aggregation induced by ADP and accelerated thrombosis via the MAPK/Erk2 signaling pathway. Previous studies on specimens of human atherosclerotic plaques suggested that IL-17A could increase the plaque's vulnerability [15]. A prospective clinical study [34] observed the correlation between serum IL-17A levels and cardiovascular outcomes in patients with AMI, suggesting that serum levels of IL-17 were independently associated with the risk of all-cause death and recurrent myocardial infarction after two years in AMI patients. Several studies have also proposed that IL-17A participated in multiple stages of atherosclerotic CAD, including promoting arterial wall inflammation, increasing the plaque's vulnerability, maintaining a thrombus and resulting in the occurrence of complications of atherosclerosis. Our study revealed that IL-17A is an independent risk factor for CAD. Taken together, these studies further suggest that IL-17A is a potent pro-inflammatory factor and plays a key role in the development of atherosclerosis and its complications.

In conclusion, concerning the complex pathophysiological mechanism and adverse manifestations of atherosclerosis, several serum inflammatory biomarkers may provide prognostic value [2]. In the present study, serum IL-17A levels were positively correlated with HMGB1 levels, which suggested that increased serum IL-17A may be involved in the pathogenesis of atherosclerotic CAD accompanied by HMGB1. Besides, the HMGB1/IL-17A axis plays an important role in atherosclerosis and may be a novel therapeutic target of CAD. Furthermore, our study revealed that IL-17A is an independent risk factor for CAD, suggesting that IL-17A is a potent pro-inflammatory factor and plays a key role in the development of atherosclerosis and its complications. Thus, IL-17A may be a potential target for pharmacological intervention of atherosclerotic CAD.

Overall, our study enrolled only a small group of Chinese patients, and a future study with a large cohort is needed. The precise mechanisms underlying our observations and their clinical relevance require future elucidation. In addition, there are many risk factors for atherosclerotic CAD; however, we only analyzed a few typical risk factors in this study.

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Disclosure of conflict of interest

None.

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