Correlation of CD40 ligand and CXC ligand expression with inflammatory response and plaque properties in patients with coronary heart disease

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ABSTRACT

Objective: To study the correlation of CD40 ligand (CD40L) and CXC ligand (CXCL5) expression with inflammatory response and plaque properties in patients with coronary heart disease. Methods: Patients who were diagnosed with coronary heart disease in Xiantao First People’s Hospital in Hubei Province between February 2015 and April 2017 were selected as the CHD group of the study, and healthy volunteers who received physical examination during the same period were selected as the control group. Peripheral blood was collected to separate RNA, and the CD40L and CXCL5 expression were determined; peripheral blood was collected to separate serum, and the contents of inflammatory response indexes, lipid metabolism indexes and collagen metabolism indexes were determined. Results: CD40L and CXCL5 mRNA expression in peripheral blood of CHD group were significantly higher than those of control group; TNF-α, IFN-γ, IL-6, PCSK9, sdLDLC, ox-LDL, Gal-3, Lp-PLA2, ICTP, ADAMTS4, CatK and CyPA contents in serum of CHD group were significantly higher than those of control group whereas IL-10, TGF-β1, TIMP1 and TIMP2 contents were significantly lower than those of control group; CD40L and CXCL5 expression in peripheral blood were positively correlated with TNF-α, IFN-γ, IL-6, PCSK9, sdLDLC, ox-LDL, Gal-3, Lp-PLA2, ICTP, ADAMTS4, CatK and CyPA contents in serum, and negatively correlated with IL-10, TGF-β1, TIMP1 and TIMP2 contents. Conclusion: Abnormal high expression of CD40L and CXCL5 can aggravate the inflammatory response and reduce the plaque stability in patients with coronary heart disease.

1. Introduction

Coronary atherosclerotic heart disease, coronary heart disease for short, is a common disease of the cardiovascular system in our country, and its incidence has been rising year by year under the influence of heredity, environment, diet and other factors. The atheromatous plaque formation and property change in the coronary arteries are the pathological basis of the occurrence and development of the disease. This process involves the formation of foam cells, lipid deposition, fibrous cap degradation and so on[1,2]. In recent years, more and more studies have confirmed that inflammation is an important biological link throughout various pathological links of atherosclerosis, the activation of the inflammatory response is directly involved in the formation of foam cells and able to influence lipid deposition and fibrous cap degradation process, but the specific regulatory mechanism is still not clear. Chemokines are the molecules that play a key role in inflammatory response cascade activation and amplification, which can mediate inflammatory cell activation and infiltration by acting on receptors on the cell surface[3,4]. CD40 ligand (CD40L) and CXC ligand (CXCL5) are the important chemokines in the body[5-6], and we specifically analyzed the correlation of CD40 ligand (CD40L) and CXC ligand (CXCL5) expression with inflammatory response and plaque properties in patients with coronary heart disease in the following study.
2. Clinical information and research methods

2.1 General case information

Patients who were diagnosed with coronary heart disease in Xiantao First People’s Hospital in Hubei Province between February 2015 and April 2017 were selected as the CHD group of the study, all patients were diagnosed by coronary CTA or coronary angiography and without history of myocardial infarction attack, and the patients combined with autoimmune diseases or infectious diseases were excluded. Healthy volunteers who underwent physical examination during the same period were selected the control group. There were 105 cases in the CHD group, including 62 males and 43 females who were 42-62 years old; there were 65 cases in the control group, including 37 males and 28 females who were 40-64 years old. There was no significant difference in general data between the two groups (P>0.05).

2.2 Research methods

2.2.1 Peripheral blood index detection

3-5 mL of cubital venous blood was collected from the two groups of research subjects, joined by lymphocyte separation medium and centrifuged to separate the mononuclear cells suspended in the middle, the kit was used to extract the RNA in peripheral blood mononuclear cells for PCR reaction, and the reaction curve was referred to calculate the CD40L and CXCL5 mRNA expression.

2.2.2 Serum index detection

6-8 mL of cubital venous blood was collected from the two groups of research subjects, let stand for coagulation and centrifuged to separate upper clear serum, and enzyme-linked immunosorbent assay kit was used to determine serum TNF-α, IFN-γ, IL-6, IL-10, TGF-β1, PCSK9, sdLDLC, ox-LDL, Gal-3, Lp-PLA2, ICTP, ADAMTS4, CatK, CyPA and TIMP1 and TIMP2 contents.

2.3 Statistical methods

SPSS 20.0 was adopted for data input and analysis, analysis of measurement data between two groups was by t test and correlation analysis was by Pearson test. Differences were statistically significant if P<0.05.

3. Results

3.1 CD40 ligand and CXC ligand expression in peripheral blood

CD40L and CXCL5 mRNA expression in peripheral blood of CHD group were (2.41±0.42) and (2.88±0.38) respectively; CD40L and CXCL5 mRNA expression in peripheral blood of control group were (1.02±0.14) and (1.01±0.16) respectively. The t test analysis of the differences in CD40L and CXCL5 expression in peripheral blood between the two groups was as follows: CD40L and CXCL5 mRNA expression in peripheral blood of CHD group were significantly higher than those of control group.

3.2 Serum inflammatory response index contents

The t test analysis of the differences in serum inflammatory response indexes TNF-α, IFN-γ, IL-6, IL-10 and TGF-β1 between the two groups was as follows: TNF-α, IFN-γ and IL-6 contents in serum of CHD group were significantly higher than those of control group whereas IL-10 and TGF-β1 contents were significantly lower than those of control group. Pearson test analysis of the correlation of CD40L and CXCL5 with inflammatory response indexes was as follows: CD40L and CXCL5 expression in peripheral blood were positively correlated with TNF-α, IFN-γ and IL-6 contents in serum, and negatively correlated with IL-10 and TGF-β1 contents.

3.3 Serum lipid metabolism index contents

The t test analysis of the differences in serum lipid metabolism indexes PCSK9 (ng/mL), sdLDLC (pg/mL), ox-LDL (ng/mL), Gal-3 (pg/mL) and Lp-PLA2 (ng/mL) between the two groups was as follows: PCSK9, sdLDLC, ox-LDL, Gal-3 and Lp-PLA2 contents in serum of CHD group were significantly higher than those of control group. Pearson test analysis of the correlation of CD40L and CXCL5 with lipid metabolism indexes was as follows: CD40L and CXCL5 expression in peripheral blood were positively correlated with PCSK9, sdLDLC, ox-LDL, Gal-3 and Lp-PLA2 contents in serum.

Table 1.

Comparison of serum inflammatory response indexes between the two groups of subjects (ng/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>TNF-α</th>
<th>IFN-γ</th>
<th>IL-6</th>
<th>IL-10</th>
<th>TGF-β1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD group</td>
<td>105</td>
<td>126.6±16.5</td>
<td>65.9±7.9</td>
<td>114.7±15.3</td>
<td>60.7±8.9</td>
<td>68.6±8.9</td>
</tr>
<tr>
<td>Control group</td>
<td>65</td>
<td>76.1±9.5</td>
<td>28.5±4.1</td>
<td>50.4±7.9</td>
<td>113.6±14.8</td>
<td>129.5±17.8</td>
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<tr>
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</table>

Table 2.

Comparison of serum lipid metabolism indexes between the two groups of subjects.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>PCSK9</th>
<th>sdLDLC</th>
<th>ox-LDL</th>
<th>Gal-3</th>
<th>Lp-PLA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD group</td>
<td>105</td>
<td>18.9±2.2</td>
<td>6.5±0.9</td>
<td>548.6±71.4</td>
<td>65.9±8.9</td>
<td>203.5±31.8</td>
</tr>
<tr>
<td>Control group</td>
<td>65</td>
<td>11.4±1.9</td>
<td>3.3±0.6</td>
<td>305.7±41.8</td>
<td>20.3±3.6</td>
<td>85.6±11.5</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>&lt;0.05</td>
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</table>
atheromatous plaque formation cholesterol so as to induce foam cell formation and accelerate the which belongs to the ELR+CXC subfamily, has the glutamic acid fibrous cap degradation and other processes, and inflammation The pathologic process of coronary atherosclerosis in the course of 4. Discussion

The pathologic process of coronary atherosclerosis in the course of coronary heart disease involves foam cell formation, lipid deposition, fibrous cap degradation and other processes, and inflammation is an important biological link throughout these pathologic processes[7,8]. So in recent years, inflammatory response has become a hot topic in cardiovascular disease research. CD40L is a member of the tumor necrosis factor superfamily, which has the activity of chemokines, is mainly expressed on lymphocyte, macrophage and platelet surface, and can not only promote the activation of a variety of inflammatory cells, but also promote the platelet adhesion and thrombosis[9]. CXCL5 is a member of the CXC chemokine family, which belongs to the ELR+CXC subfamily, has the glutamic acid - leucine - arginine domain structure, and can directly increase the activity of macrophages and promote macrophage phagocytosis of cholesterol so as to induce foam cell formation and accelerate the atheromatous plaque formation[10]. In order to clarify the roles of above two kinds of chemokines in the occurrence and progression of coronary heart disease, we analyzed the CD40L and CXCL5 expression in peripheral blood of patients with coronary artery disease, and the results showed that CD40L and CXCL5 mRNA expression in peripheral blood of CHD group were significantly higher than those of control group. This indicates that the high expression of chemokines CD40L and CXCL5 in peripheral blood is closely related to the occurrence of CHD and the development of illness.

The activation of inflammatory response in patients with coronary heart disease will cause the changes in the contents of various inflammatory cytokines, including pro-inflammatory cytokines TNF-α, IFN-γ and IL-6 as well as anti-inflammatory cytokines IL-10 and TGF-β 1. TNF-α is secreted by activated mononuclear macrophage, which is not only related to the initiation and activation of inflammatory response, but also related to the formation of foam cells by macrophage phagocytosis of lipid[11]; IFN-γ is secreted by lymphocytes, mononuclear macrophages, endothelial cells and other types of cells, and has direct pro-inflammatory activity[12]; IL-6 has a variety of biological activities, which can not only mediate inflammation cascade activation, but also stimulate the proliferation of vascular smooth muscle cells and accelerate the formation of atherosclerotic plaques[13]. IL-10 and TGF-β 1 are the anti-inflammatory cytokines, the former can antagonize the activity of a variety of pro-inflammatory factors, and the latter can promote the secretion of extracellular matrix, reinforce the plaque fibrous cap and suppress the inflammatory response[14,15]. Analysis of the changes in above serum inflammatory response indexes in patients with coronary heart disease showed that serum TNF-α, IFN-γ and IL-6 contents of CHD group were significantly higher than those of control group whereas IL-10 and TGF-β 1 contents were significantly lower than those of control group. This indicates that the increase of pro-inflammatory factors and the decrease of anti-inflammatory factors are closely related to the occurrence of coronary heart disease. Further analysis of the correlation of CD40L and CXCL5 with inflammation indexes showed that CD40L and CXCL5 expression in peripheral blood of patients with CHD were positively correlated with ICTP, ADAMTS4, CatK and CyPA contents in serum, and negatively correlated with TIMP1 and TIMP2 contents.

3.4 Serum collagen metabolism index contents

The t test analysis of the differences in serum collagen metabolism indexes ICTP, ADAMTS4 (ng/mL), CatK (ng/mL), CyPA (ng/mL), TIMP1 (pg/mL) and TIMP2 (pg/mL) between the two groups was as follows: ICTP, ADAMTS4, CatK and CyPA contents in serum of CHD group were significantly higher than those of control group whereas TIMP1 and TIMP2 contents were significantly lower than those of control group. Pearson test analysis of the correlation of CD40L and CXCL5 with collagen metabolism indexes was as follows: CD40L and CXCL5 expression in peripheral blood were positively correlated with ICTP, ADAMTS4, CatK and CyPA contents in serum, and negatively correlated with TIMP1 and TIMP2 contents.

4. Discussion

Table 3.

Comparison of serum collagen metabolism indexes between the two groups of subjects.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>ICTP</th>
<th>ADAMTS4</th>
<th>CatK</th>
<th>CyPA</th>
<th>TIMP1</th>
<th>TIMP2</th>
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</thead>
<tbody>
<tr>
<td>CHD group</td>
<td>105</td>
<td>8.8±1.1</td>
<td>78.5±9.4</td>
<td>1.85±0.24</td>
<td>9.8±1.2</td>
<td>137.5±17.9</td>
<td>83.5±10.3</td>
</tr>
<tr>
<td>Control group</td>
<td>65</td>
<td>3.7±0.6</td>
<td>30.5±5.7</td>
<td>0.98±0.12</td>
<td>2.9±0.4</td>
<td>336.8±52.9</td>
<td>236.5±34.8</td>
</tr>
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Lipid is the important component within the coronary atherosclerotic plaque, and the phagocytosis of lipid by macrophages during inflammatory response activation is the initial link of atheromatous plaque formation, which will gradually progress to lipid plaque. LDLC is the main form of lipid in the coronary atherosclerotic plaque, and the contents of sdLDLC and ox-LDL are the most abundant[16]. PCSK9 is a proprotein convertase involved in LDL metabolism, which can cause low-density lipoprotein receptor degradation and inhibit the metabolism of LDL so as to cause LDL accumulation and participate in the formation of atherosclerotic plaque[17,18]; Gal-3 belongs to galectin family, which on the one hand, can be combined with the lipid modified by glycosylation end products and promote lipid deposition, and on the other hand, can enhance the LDL phagocytosis by macrophages, and promote the formation of atheromatous plaque[19]; Lp-PLA2 is involved in the regulation of ox-LDL and can hydrolyze ox-LDL and produce oxidative free fatty acid, which can promote the activation of macrophages and accelerate the process of atherosclerotic plaque. Analysis of the changes of above inflammatory response indicators in the serum of patients with coronary heart disease showed that PCSK9, sdLDLC, ox-LDL, Gal-3 and Lp-PLA2 contents in serum of CHD group were significantly higher than those
of control group. This indicates that the lipid metabolism disorder is closely related to the occurrence of coronary heart disease. Further analysis of the correlation of CD40L and CXCL5 with lipid metabolism indexes indicated that CD40L and CXCL5 expression in peripheral blood of patients with CHD were positively correlated with PCSK9, sdLDLC, ox-LDL, Gal-3 and Lp-PLA2 contents in serum. This indicates that the high expression of CD40L and CXCL5 in the course of coronary heart disease can affect the process of lipid metabolism to promote lipid deposition and atherosclerotic plaque formation.

After the formation of coronary atherosclerotic plaque, the decline in its stability is an important factor in the progress of the disease. The integrity of the fibrous cap of atheromatous plaque is directly related to the stability of the plaques, and the excessive activation of inflammation can increase the formation of a variety of proteases and degrade the collagen within the fibrous cap, which in turn causes the damage of fibrous cap integrity and the decrease of plaque stability. Type I collagen is the main collagen in the fibrous cap, which can be hydrolyzed under the action of ADAMTS4, CatK, CyPA and other proteases and produce the corresponding product ICTP hydrolyzed under the action of ADAMTS4, CatK, CyPA and other proteases and TIMP1 and TIMP2 are the inhibitors of proteases and can bind to proteases to inhibit the collagen hydrolysis[21,22]. Analysis of the change of the above collagen metabolism indexes in serum of patients with coronary heart disease showed that serum ICTP, ADAMTS4, CatK and CyPA contents of CHD group were significantly higher than those of control group whereas TIMP1 and TIMP2 contents were significantly lower than those of control group. This indicates that the collagen metabolism disorder is closely related to the occurrence of coronary heart disease. Further analysis of the correlation of CD40L and CXCL5 with collagen metabolism indexes indicated that CD40L and CXCL5 expression in peripheral blood were positively correlated with ICTP, ADAMTS4, CatK and CyPA contents in serum, and negatively correlated with TIMP1 and TIMP2 contents. This indicates that the high expression of CD40L and CXCL5 in the course of coronary heart disease can affect the collagen metabolism process and promote the degradation of collagen on the plaque surface to reduce the stability of the plaque.

To sum up, it can be concluded that the CD40L and CXCL5 expression are unusually high in patients with coronary heart disease; abnormally high expression of CD40L and CXCL5 can aggravate the inflammatory response and reduce the plaque stability in the course of coronary heart disease.

References


