Original Article
Characteristics of immunogenic and tolerogenic dendritic cells within the arterial wall in atherosclerosis and in vitro

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Abstract: Aim: To investigate the characteristic of mature dendritic cell (mDC) and tolerogenic dendritic cell (TDC) in human lower limb atherosclerosis occlusion syndrome (ASO) and diabetic foot and in vitro. Methods: 58 human ASO and diabetic foot arterial specimens were collected from surgical operation and autopsy. Immunohistochemical and Western blotting method were used to examine the distribution and the content of CD83 and CD1a positive reaction mDC and CD11b and DC-SIGN positive reaction TDC. Furthermore, bone marrow-derived DCs were induced by rmGM-CSF and rmIL-4 in the presence or absence of LPS in vitro. The percent of CD11c+CD11b+TDC and CD11c+CD83+mDC were analyzed by flow cytometry. The effects of TDC and mDC on T lymphocytes were analyzed by the IL-17 level, the percent of Th17, and IL-17 mRNA expression. Results: Immunogenicity mDC was heavily found in intima plaque and around the small vessel of adventitia on artherosclerosis aorta of lesion group, and was positively correlated to the progress of the disease. However, there were low expression of TDC and was negatively correlated to the progress of the disease. Meanwhile, we found that there is a close relationship between high glucose and disease progression. TDC expressed high levels of IL-10 and TGF-β1 and down-regulated the percent of CD4+IL-17+Th17, IL-17 mRNA and the level of IL-17 in vitro. Conclusion: TDC and mDC are assembled in the process of ASO, and the progression of the disease might be aggravated by DC-maturation. High glucose might closely relate to the progression of atherosclerosis.

Keywords: Dendritic cells, lower limb atherosclerosis occlusion syndrome, diabetic foot, immune response, tolerogenicity, immunogenicity

Introduction
Atherosclerosis is a chronic inflammatory vessel disease characterized by early endothelial dysfunction [1]. In response to endothelial activation, monocytes and T-cells mediate the progression of atherosclerosis [2]. Furthermore, auto-antigens like oxidized LDL (oxLDL), heat shock proteins (HSPs) HSP 60/65, or cross-reactions with foreign antigens contribute to atherosclerotic disease progression. Immune cells such as T cells, dendritic cells (DCs), macrophages, and mast cells are recruited from the blood stream into atherosclerotic lesions, and they are responsible for the progression and destabilization of atherosclerotic plaques. Transmigration of T cells into atherosclerotic lesions is an early event in atherosclerosis, and there they modulate inflammation by the secretion of Th1- or Th2-cytokines.

DCs are a specific type of leukocytes able to alert the immune system to the presence of antigens, infections and inflammatory mediators [3]. In recent years the impact of DCs on the initiation and progression of atherosclerosis has been evaluated. They play a central role in the initiation of both innate and adaptive immune responses. Mature dendritic cells (mDC) are professional antigen-presenting cells, which activate T cells against certain plaque antigens, thereby enhancing inflammation in atherosclerosis. MDC plays a crucial role in the inflammatory process within atherosclerotic lesions by stimulation of effector T cells, which can contribute to plaque instability [4]. Toler-
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genic DCs (TDC) would be an invaluable tool for therapy of allograft rejection, autoimmune diseases, or allergy. CD11b+ TDC could induce CD4+ T cells to differentiate into antigen-induced Tregs in orally tolerized mice with collagen induced arthritis (CIA), and at least in part because of its ability to suppress Th17 differentiation [5]. TDC exhibit regulatory capacities in regulatory T cells (Tregs) induction also based on the secretion of anti-inflammatory cytokines, such as IL-10 or TGF-β, and the expression of toll-like receptor 2 (TLR-2) and indoleamine 2, 3-dioxygenase (IDO) [6, 7].

DCs are normal residents of non-diseased healthy arteries where they are found predominantly in the intima and at the boundary between the media and adventitia [8]. The number of DCs present in the arterial intima increase as lesions progress through the stages of intimal thickening, fatty streak formation and the development of an atheromatous plaque [9], so that there are significantly higher DC numbers in advanced plaques relative to early lesions. DCs are also more abundant in rupture-prone unstable areas of atherosclerotic plaques [10]. Co-localisation of DCs and T cells has been observed within human lesions, particularly in areas containing inflammatory infiltrates associated with neovascularisation and around the vasa vasorum in the adventitia [11]. Similarly, in areas of unstable plaque, the detection of CD83 (a maturation marker) and CCL21 positive DCs in areas also enriched in CD40L+ T cells, suggests that DCs prime lesion T cells for an immunostimulatory response [12]. In the same study, unstable plaques from patients with ischemic symptoms were found to express relatively higher mRNA levels of CD83, CD86, CCL19 and CCL21 than asymptomatic subjects, all indicators of DC maturation [12].

Diabetic foot problems are a common complication of diabetes [13]. Hyperglycaemia is the hallmark of diabetes and is a major independent risk factor for diabetic macrovascular disease, playing a key pathogenic role in the development of diabetes-associated atherosclerosis. However, a clear causative role for hyperglycaemia has not been established. Recent studies in animal models indicate that glucose may play a role in diabetes-accelerated atherosclerosis by promoting pro-inflammatory responses in monocytes and macrophages. Recent studies have demonstrated that DCs in the subendothelial space of the aorta can also efficiently accumulate lipids and differentiate into foam cells, thereby contributing to the initiation and further progression of atherosclerosis.

Lower extremity atherosclerosis is a risk factor for diabetic foot disease. Lower extremity atherosclerosis, as a kind of common major vascular complications in diabetic patients, plays an important role in the incidence of diabetic foot disease [14].

Atherosclerosis can cause stenosis or obstruction, causing insufficient blood supply to the extremities, thereby causing ischemic ulcers, local infection and microcirculation [15]. Meanwhile limb peripheral neuropathy have resulted in weakening or loss of protective sensation and foot biomechanics change, can easily cause damage to mechanical or temperature, once the damaged legs end microcirculation will make it not easy to repair. Also it is not easy to control the infection, and finally developed into gangrene.

Both hyperglycaemia and dendritic cells (DCs) play causative roles in atherosclerosis. However, whether they interact in atherosclerosis remains uncertain [16]. Currently little is known about the direct interaction of TDC and mDC in ASO and diabetic foot disease. To investigate the potential association of TDC and mDC in human ASO and diabetic foot disease, Immunohistochemical and Western blotting method were used to examine the distribution and the content of CD83 and CD1a positive reaction mDC and CD11b and DC-SIGN positive reaction TDC. The aim of this study is to investigate the TDC and mDC on the differentiation of Th17 cells in vitro and characterize the impact of TDC and mDC in human lower limb atherosclerosis occlusion syndrome (ASO) and diabetic foot, and investigate the relation of high glucose to the progression of atherosclerosis.

Materials and methods

Animals

7-8 week old C57/6 mice were purchased from Anhui Medical University. The experimental protocols adopted in this study were approved by our institutional review board.
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Clinical data

Patients presenting at the Provincial hospital affiliated to Anhui medical university vascular surgery between July 2008 and June 2013 with suspected or established lower limb atherosclerosis occlusion syndrome and diabetic foot were recruited for the study. Fifty-eight human arterial specimens were collected from surgical operation and autopsy (18 people with diabetic foot ulceration, the other 30 cases of lower limb artery lesions clearly without diabetic were set to lower limb atherosclerosis occlusion syndrome (ASO) group and 10 people without obvious morphosis change were assigned as normal group) participated in the study. All of the human arterial specimens had informed consents from patients and were approved by the Ethics Review Committee for human Experimentation of Provincial hospital affiliated to Anhui medical university vascular surgery (Hefei, China). Paraffin sections were made routinely. Each study patients completed a standardized questionnaire about previous and present illness and smoking status. Clinical data were recorded and are listed in Table 1.

Reagents

Recombinant murine granulocyte/macrophage colony-stimulating factor (rmGM-CSF) and recombinant murine interleukin-4 (rmIL-4) were purchased from Peprotech. Lipopolysaccharide (LPS) was purchased from Sigma-Aldrich, St. Louis, MO. Anti-mouse FITC-CD11b, PE-CD11c, FITC-CD11c, PE-CD83, FITC-CD4 and PE-IL-17 antibodies their respective control IgGs were purchased from BioLegend. ELISA kits for IL-17, IL-10 and TGF-β1 were purchased from Research & Development (R&D) Co., Ltd. (US). Rabbit anti-CD11b antibody (ab133571) was obtained from Abcom; Rabbit anti-IDO antibody (bs-2379R) and Rabbit anti-DC-SIGN (bs-2557R) were obtained from Bios (Beijing, China); Rabbit anti-CD83 (LS-C176864) antibody was obtained from LSBio. All of the antibodies were applicable to Immunohistochemistry.

Immunohistochemistry

Paraffin sections were made routinely. Immunohistochemical method was used to examine the distribution of CD83, CD1a, CD11b and DC-SIGN positive reaction dendritic cells (DC).

Immunohistochemical (IHC) streptavidin-peroxidase (SP) staining was performed by the avidin-biotin peroxidase complex method according to the procedures provided by the kit [17]. In brief, deparaffinized 5-mm-thick tissue section was placed in a microwave oven in 10 mM citrate buffer (pH6.0) for 10 min for antigen retrieval. After issue sections were blocked with 0.3% hydrogen peroxidase in phosphate-buffered saline for 10 min at room temperature, each section was incubated overnight at 4°C with primary antibodies for CD83, CD1a, CD11b and DC-SIGN (1:200 dilutions).

Images were obtained using a Nikon video microscope (MicroscopyU Nikon, Tallahassee, Florida, USA), and a quantitative analysis was carried out using the Image-Pro Plus software (Media Cybernetics, nRockville, Maryland, USA) to quantify staining in five random fields per slide. The relative intensity of CD83, CD1a, CD11b and DC-SIGN staining was quantified according to the optical density values.

### Table 1. Clinical data

<table>
<thead>
<tr>
<th>Item</th>
<th>Normal</th>
<th>ASO</th>
<th>Diabetic foot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.34 ± 12.37</td>
<td>64.23 ± 10.65</td>
<td>66.35 ± 12.48</td>
</tr>
<tr>
<td>Sex, male</td>
<td>6/10</td>
<td>18/30</td>
<td>10/18</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2/10</td>
<td>22/30</td>
<td>15/18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0/10</td>
<td>22/30</td>
<td>18/18</td>
</tr>
<tr>
<td>Smoking</td>
<td>4/10</td>
<td>17/30</td>
<td>5/18</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3/10</td>
<td>24/30</td>
<td>7/18</td>
</tr>
<tr>
<td>Laboratory examination (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>4.35 ± 0.56</td>
<td>5.10 ± 1.02</td>
<td>6.04 ± 0.47</td>
</tr>
<tr>
<td>TG</td>
<td>1.17 ± 0.39</td>
<td>1.56 ± 0.37</td>
<td>2.35 ± 0.78</td>
</tr>
<tr>
<td>HDLC</td>
<td>1.32 ± 0.48</td>
<td>1.08 ± 0.31**</td>
<td>0.94 ± 0.47**</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.86 ± 0.77</td>
<td>3.41 ± 0.88</td>
<td>3.63 ± 0.45</td>
</tr>
<tr>
<td>FBG</td>
<td>4.92 ± 0.45</td>
<td>5.13 ± 1.21*</td>
<td>12.73 ± 4.68</td>
</tr>
</tbody>
</table>

TC total cholesterol, TG triglyceride, HDLC high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, FBG fasting blood glucose. *P < 0.05; **P < 0.01 versus Normal control; *P < 0.05; **P < 0.01 versus ASO patient group.
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Western blotting

Vessel wall were lysed by RIPA-buffer, and the protein levels were measured by using a BCA protein assay kit. Protein extracts (10 μg) were separated with 10% SDS-PAGE, transferred to a nitrocellulose membrane by electrotransfer (200 V for 90 min) and blocked with 5% nonfat milk for 2 h at room temperature. Then the membranes incubated with primary antibodies of rabbit monoclonal anti-CD83, CD1a, CD11b and DC-SIGN (1:200 dilutions) at 4°C overnight. The antigen-antibody complex was visualized using anti-rabbit IgG horseradish peroxidase with a dilution of 1:40000 and an enhanced chemiluminescence detection system (ECL-Pierce, Invitrogen; USA).

Quantitative analysis of the Western blots by densitometry was carried out using a computerized densitometer (Image J Launcher, Broken Symmetry Software). All values were normalized to the β-actin loading control.

Generation of bone marrow-derived dendritic cells

DCs were generated from the monocyte culture according to the procedure described previously [18]. Bone marrow cells were cultured in a six-well plate using RPMI 1640 medium supplemented with 10% FCS (Gibco Co. USA), 1% penicillin/streptomycin, rmGM-CSF (20 ng/ml), and rmIL-4 (20 ng/ml) (PeproTech, San Diego, CA). After 4 hours of culture, non-adherent cells were removed. On day 7 of the culture, non-adherent and loosely adherent DC were harvested and analyzed by flow cytometry to assess the immature DCs (iDCs or TDC) phenotype. Control mDC were activated using LPS (100 ng/ml) in the last 48-hour culture. Supernatants were collected to measure IL-10 and TGF-β1.

Assay and purification of bone marrow-derived CD11c⁺CD11b⁺TDC and CD11c⁺CD83⁺mDC by flow cytometry

At day 7 of the mouse DCs culture, TDC was characterized by CD11c and CD11b, and the maturation status was analyzed by CD11c and CD83 expression using flow cytometry analysis as described previously [18]. Briefly, DCs (1 × 10⁶) suspension 200 μl and the combinations of FITC-CD11b, PE-CD11c and FITC-CD11c, PE-CD83 antibody 1 μl were added into each fluorescence-activated cell sorting tube, respectively. The samples were mixed gently, incubated for 20 minutes at 4°C, and then analyzed by flow cytometer. Bone marrow CD11c⁺CD11b⁺TDC and CD11c⁺CD83⁺mDC were analyzed and purified by fluorescence-activated cell sorting (FACSaRIA II, Becton Dickinson). The purity of the sorted DCs was > 99%. Data was analyzed by Flow Jo7.6.1 analysis software.

Assay of suppression of TDC and mDC on Th17 cells in vitro

To examine the suppressive activity of TDC and the stimulative activity of mDC in vitro, a Transwell system was used. Briefly, these experiments were performed in 24-well Transwell plates (0.8-mm pore size membrane, Corning, Acton, MA); splenic T cells from C57/6 mice were isolated and seeded to the upper compartment of the chamber, while TDC or mDC were seeded to the lower compartment. The ratio of TDC to T cells is 1:10. After 48 hours in culture, T cells in the upper compartment were harvested and re-stimulated with PMA (5 μg/ml) and ionomycin (5 μg/ml) for 5 hours and BFA (10 μg/ml) for 4 hours. Th17 (CD4⁺/IL-17⁺ T cells) were determined by flow cytometry. The expression of IL-17 mRNA in T cells was analyzed by RT-PCR as the method described in the followed. And the cells supernatants were collected for IL-17 measurement by ELISA.

RT-PCR analysis

The total RNA of T lymphocytes was extracted using Trizol reagent according to the manufacturer’s instructions. RNA samples were quantified by absorbance at 260 nm. The RNA was reverse-transcribed and RT-PCR was performed in a final reaction volume of 50 μL using iCycler 480 Probes Master (Roche Diagnostics, Indianapolis, IN). Each sample was analyzed in triplicate. Cycling conditions consisted of an initial denaturation of 95°C for 5 minutes, followed by 38 cycles with 95°C melting (30 s), 57°C annealing (30 s), and 72°C extension (30 s). Primer sequences were as follows: IL-17 (up-stream 5’-CCAGGGAGAGCTTCA TCTGT-3’, down-stream 5’-AGGAG TCCTTGGCCTCAG T-3’); GAPDH (upstream 5’-GGTGAAGGTCGGTGTGAA CG-3’, down-stream 5’-CTCGCTCCTGGAAGATGGTG-3’) were used together as normal genes for the experiment. Amplicon sizes were verified by electrophoresis on a 2% agarose gel after ethidium bromide staining [19].
Figure 1. Attenuated TDC in vessel wall of ASO and diabetic foot patients compared to healthy person (200 ×). A. Representative images of CD11b-expressing TDC (left) and DC-SIGN-expressing TDC (right) in the vessel wall of healthy person. B. Representative images of CD11b-expressing TDC (left) and DC-SIGN-expressing TDC (right) in the vessel wall of ASO patients. C. Representative images of CD11b-expressing TDC (left) and DC-SIGN-expressing TDC (right) in the vessel wall of diabetic foot patients.
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Figure 2. Increased mDC in vessel wall of ASO and diabetic foot patients compared to healthy person (200 ×). A. Representative images of the expression of CD1a in mDC (left) and the expression of CD83 in mDC (right) in healthy human vascular wall. B. Representative images of the expression of CD1a in mDC (left) and the expression of CD83 in mDC (right) in ASO patients vascular wall. C. Representative images of the expression of CD1a in mDC (left) and the expression of CD83 in mDC (right) in diabetic foot patients vascular wall.
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Cytokines secretion

TDC, mDC and T cell which cocultured with DCs supernatants were collected, and the levels of IL-10, TGF-β1 and IL-17 in supernatants were measured using ELISA kits. Briefly, DCs supernatants 40 ul were seeded into 96-well culture plates, which were bagged with IL-10, TGF-β1 or IL-17. These 96-well culture plates were incubated for 2 hours and then were seeded goat-anti- mouse IgG-HRP 100 ml (1:400). And after 1 hour of incubating, O-phenylenediamine was added into each well. One hour later, H₂SO₄ (2 mol/l) 50 ml suspended the reaction. Optical density (OD) values were measured at 450 nm using an Automatic Microplate Reader (BLx808; Bio-Tek, Winooski, VT, USA). The OD measured in the standard supernatants, diluted serially, and the arbitrary units each exhibited good linear correlation at all determinations (R = 0.99; data not shown).

Statistical analysis

All data were expressed as mean ± standard deviation (S.D.). The data were analyzed by SPSS version 11.5 statistical package. Differences between groups were evaluated by one-way ANOVA. P values less than 0.05 were considered statistically significant.

Results

Expression of CD11b and DC-SIGN positive TDC in vessel wall of ASO and diabetic foot patients

To estimate the distribution of TDC in ASO and diabetic foot patient, the expression of the CD11b and DC-SIGN were analyzed. Immunohistochemical results showed that comparing healthy person vessel wall, there were had TDC gathered in the ASO and diabetic foot patient. Compared with ASO patient, there are significantly low expressions of CD11b and DC-SIGN in diabetic foot patient (Figure 1). Meanwhile, TDC were mainly found in intima plaque and around the small vessel of adventitia on atherosclerosis aorta of lesion group. Next, we investigated the expression of CD11b and DC-SIGN used the method of Western blotting, and Western blotting showed the same result as the Immunohistochemical (Figure 3A, 3B).

Expression of CD83 and CD1a mDC in vessel wall of ASO and diabetic foot patients

As we knew that CD83 and CD1a were the specificity marker of the mDC. Next, we investigated the expression of CD83 and CD1a in ASO and diabetic foot patient. Immunohistochemical results showed that compared to the healthy person vessel wall, there were had obviously largely amount of mDC gathered in the ASO and diabetic foot patient. Meanwhile, compared to ASO patient, there are significantly heavily expressions of CD83 and CD1a in diabetic foot patient (Figure 2). mDC were mainly located in intima plaque and around the small vessel of adventitia on atherosclerosis aorta of lesion group.
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group, which expressed at the same location as TDC. Western blotting was used to detected the content of CD83 and CD1a proteins, and results were the same as Immunohistochemical results, and there were had lager amount of CD-83 and CD1a mDC gathered as the progress of the disease (Figure 3A, 3C).

DCs derived from bone marrow were induced successfully and expressed high levels of IL-10 and TGF-β1

Bone marrow cells were cultured and stimulated by rmGM-CSF and rmIL-4 for seven days. Results showed that the percent of CD11c⁺CD11b⁺TDC and CD11c⁺CD83⁺mDC in bone marrow cells induced by rmGM-CSF and rmIL-4 was approximately 41.5% and 60.1%, separately (Figure 4A). In order to get high purity of DCs, CD11c⁺CD11b⁺TDC and CD11c⁺CD83⁺mDC were purified by fluorescence- activated cell sorting, and the purity of the CD11b⁺F4/80⁺ TDC was about 99.3% (data were not showed). Then the purified CD11c⁺CD11b⁺TDC and CD11c⁺CD83⁺mDC were induced for the subsequent experiment. Meanwhile, compared with LPS induced mDC, TDC secreted significantly high levels of IL-10 and TGF-β1 (Figure 4B).

TDC inhibited the functions of Th17 cells while mDC promoted the differentiation of Th17 cells in vitro

To investigate the role of TDC and mDC on Th17 cells, T cells were re-stimulated with PMA, Ion and BFA in the co-culture system of TDC and T lymphocytes. Results showed that compared with LPS induced mDC, the percentage of CD4⁺IL-17⁺Th17 cells were significantly decreased (Figure 5A, 5B). The expression of IL-17 mRNA was analyzed by RT-PCR, and results showed that the expression of IL-17 mRNA in T cells was down-regulated compared with mDC groups (Figure 5C, 5D). Additional, compared with
mDC group, the level of IL-17 in T cells supernatants was decreased in the co-culture system (Figure 5E). These results demonstrated that TDC inhibited the functions of Th17 cells in vitro while mDC promoted the proliferation of Th17 cells.

**Discussion**

Th17 has been assumed as an important effector T cell subset involved in atherosclerosis disease development, and IL-17 secreted by Th17 has also been considered as an important pro-inflammatory cytokine [20, 21]. Many of evidences have supported the role of IL-17 in the pathogenesis of atherosclerosis [22]. In atherosclerosis, CD4+ T cells subsets with regulatory capacity, such as Th2 cells and Tregs, were functionally impaired, which allowing Th17 to evolve and progress into chronic inflammation [23]. In this study, compared to LPS-induced mDC, induced TDC expressed high levels of IL-10 and TGF-β1 and down-regulated the percent of CD4+IL-17+ Th17, IL-17 mRNA and the level of IL-17 in co-cultured system in vitro.

Results suggesting that TDC showed a tolerogenic capacity while mDC showed an immunogenic capacity.
Inflammation plays an important role in plaque destabilization, and the presence of immune cells in atherosclerotic plaques was shown to be a major contributing factor for their progression and destabilization leading to plaque rupture and acute ischemic syndromes [24]. In this study, we described in cross-sections of ASO and diabetic foot patient plaques as an accumulation of DCs in vulnerable plaques of vessel wall, suggesting that their presence might be associated with plaque destabilization. Additionally, we showed a decrease of TDC in the diabetic foot patient plaques when compared with ASO patient plaques. And compared to ASO patient plaques, diabetic foot patient showed a increased of mDC, suggesting that TDC and mDC were assembled in the process of ASO and diabetic foot, and the progression of the disease might be aggravated by DC-maturation. In this study, to the best of our knowledge, we show for the first time that numbers of plaque-migrated mDC inversely correlate with recruited TDC in the inflammatory ASO and diabetic foot patient plaques. Moreover, the emergence of mDC and TDC directly correlated with the progress of the disease.

From the clinical data of the patients we could find a significantly increased of FBG in diabetic foot patient. High sugar can inhibit eNOS synthase and increased reactive oxygen products, especially through the inhibition of superoxide anion $O_2^-$-based anti-atherosclerotic NO production, thereby stimulating vascular smooth muscle cells in and promoting atherosclerosis in the arterial wall happen easily. High glucose can also increase the expression of the scavenger receptors SR-A, CD36 and LOX-1, which can increase the oxLDL-uptake capacity of DCs. High glucose induces a proinflammatory cytokine profile (IL-6 and IL-12) in human DCs, leading to DCs maturation [25]. That is to say, elevated glucose can increase the expression of mDC, thereby contributing to diabetes and its related disease atherosclerosis. These results support the hypothesis that atherosclerosis is aggravated by hyperglycaemia-induced DCs activation, and high glucose might closely relate to the progression of atherosclerosis.

Atherosclerosis is complex inflammatory disease with many factors involved in disease initiation, progression and regression. Dendritic cells, though only a minor cell population within the body, have been implicated in all stages of the disease and have demonstrated both pro- and anti-atherogenic involvement [26]. Increasing evidence of the involvement of DCs in atherosclerosis regression indicate they are a good candidate as a target in the development of therapies to reduce atherosclerotic burden. It can be speculated that inhibit the activation of the DCs and increase abundance of TDC might be an efficient method to treatment the disease of atherosclerosis.

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Disclosure of conflict of interest

None.

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