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Review Article

Crosstalk between macrophage and T cell in atherosclerosis: Potential therapeutic targets for cardiovascular diseases

Meiying Song[a], Shixin Xu[b], Aiqin Zhong[c,*], Junping Zhang[d,**]

[a] Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China
[b] Medical Experiment Center, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300193, China
[c] Department of Emergency, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300193, China
[d] Department of cardiology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300192, China

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1. Introduction

As a chronic inflammatory disease mainly located in arteries, atherosclerosis is considered to be one of the leading causes of cardiovascular diseases and stroke globally. [1] In the whole process of plaque formation, macrophages and T cells are present at different lesional stages. As is known to all, macrophages and T cells could polarize and modify their phenotype and function under the regulation of different cytokines and growth factors. Up to now, several distinct phenotypes present in the atherosclerotic lesions have been described. The most “common” and extensively studied cell types in atherosclerosis include M1 and M2 macrophages as well as effector T(Teff) and regulatory T(Treg) cells. M1 macrophages are considered as pro-inflammatory cells. They may contribute to the formation of necrotic core and plaque destabilization, resulting in thrombotic event. [2] Conversely, M2 macrophages perform in an atheroprotective way by inhibiting inflammatory cell recruitment and tissue remodeling. [2] Treg cells protect against atherosclerosis, which control and limit the pro-inflammatory actions of Teff subsets in the plaque. [3] The interactions between pro- and anti-inflammatory subsets of macrophages and T cells are in a dynamic balance under physiological conditions. While in atherosclerosis, the balance is pathologically tipped to the inflammatory side. (Fig. 1).

We have reviewed advanced studies, which indicated that increasing protective subsets may benefit plaque stability or regression of atherosclerotic lesion as well as the prognosis of cardiovascular diseases. We highlight that some factors may affect the balance between the protective or harmful subsets of them. In response to distinct cellular metabolic condition and cell-cell interactions, macrophages and T cells could show pro- or anti-inflammatory capacities. There is multilayered crosstalk between macrophages and T cells in atherosclerosis, which could be potential targets for cardiovascular diseases.

Abbreviations: Teff, effector T; Treg, regulatory T; IL, interleukin; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; MerTK, Mer receptor tyrosine kinase; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor-α; PPAR, peroxisome proliferator-activated receptor; Th1, T helper type 1;IFN-γ, interferon-γ; FoxP3, fork-head box P3;ox-LDL, oxidized low-density lipoprotein; CAD, coronary artery disease; CCR5, C-C chemokine receptor type 5; AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; RALDH2, retinaldehyde dehydrogenase 2; RA, retinoic acid; IL-18Rα, IL-18 receptorα; VSMCs, vascular smooth muscle cells; PD-1, programmed death-1; HUVECs, human umbilical vein endothelial cells; DCs, dendritic cells; SIRPα, signal regulatory protein α;CD47, cluster of differentiation-47; apoB LPs, apolipoprotein-B-containing lipoproteins; FccR, Fc receptor.

* Correspondence to: A. Zhong, Department of Emergency, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300193, China.
** Correspondence to: J. Zhang, Department of cardiology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 An Shan Xi Road, Nan Kai District, Tianjin 300192, China.
E-mail addresses: zhongaiqinde@163.com (A. Zhong), tjzhtcm@163.com (J. Zhang).

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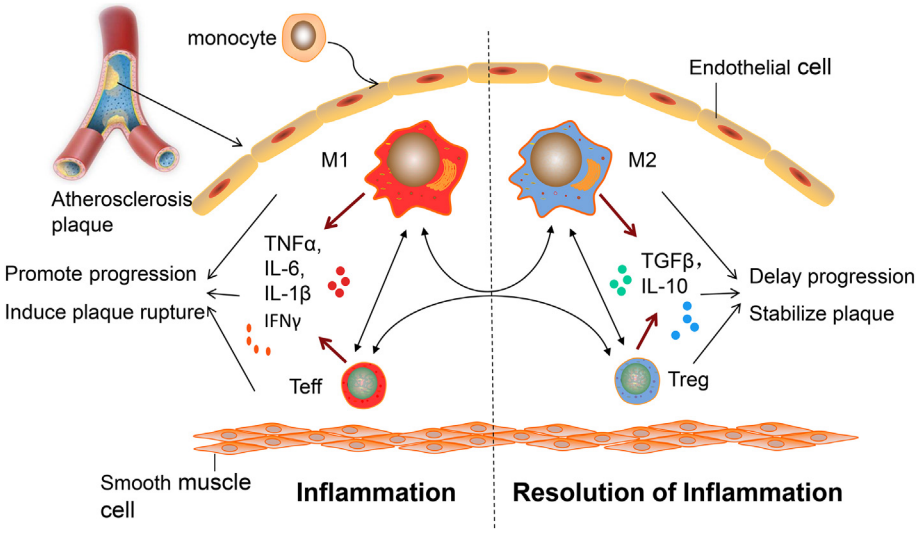

Fig. 1. Regulation and Impact of Innate-adaptive Immune Responses Related to Macrophages and T Cells in Atherosclerosis. There is a balance between pro-inflammatory response and inflammatory resolution in atherosclerotic plaques, which are reflected in the interaction of different functional phenotypes between macrophages and T cells. Teff cells as well as M1 macrophage promote the development of atherosclerosis by secreting pro-inflammatory cytokines, chemokines, and on the contrary, Treg cells and M2 macrophage suppress inflammation and promote phagocytosis to stabilize the plaque. Pro-inflammatory or anti-inflammatory T cell phenotypes can influence the balance of M1 and M2 phenotype of macrophage in plaque; meanwhile, resolving or inflammatory phenotypes of macrophage shift the local inflammatory condition to induce the change of T cell epigenetic phenotype.

2. Different functional phenotypes of macrophages in atherosclerosis

It was suggested by numerous reports that there could be multiple factors contributing to the different consequences of the macrophage functions. For instance, local environment [4], intracellular metabolic condition [5], gut microbiota metabolites [6] as well as genetic and epigenetic factors, such as non-coding RNAs [7]. In general, macrophages are generally categorized into two major sub-populations with different functions including classically activated M1 and alternatively activated M2, although M1 and M2 phenotype can't represent the final phenotypic subsets of macrophages. M2 macrophages can be further divided into four different subsets, consisting of M2a, M2b, M2c, and M2d, depending on the activating stimulus received. [8–10]

The M2a subset of macrophages could be triggered by interleukin (IL)-4, IL-13 and expresses mannose receptor in high level. These cells secrete anti-inflammatory cytokine like IL-10, transforming growth factor-β(TGF-β) and pro-fibrotic factors such as fibronectin which contribute to tissue remodeling. [8,10] M2b macrophages could be induced by immune complexes, Toll-like receptor (TLR) agonists or IL-1 receptor ligands. [8,10] M2c macrophages are induced by glucocorticoids and IL-10. These m2c macrophages express Mer receptor tyrosine kinase (MerTK) highly , which results in phagocytosis of apoptotic cells. [8,9] Finally, M2d macrophages are induced by TLR agonists through the adenosine receptor. These M2d macrophages are characterized by high levels of IL-10 and vascular endothelial growth factor (VEGF). [8,10]

In atherosclerosis, M1 macrophages secrete high levels of pro-inflammatory cytokines, including tumor necrosis factor-α(TNF-α), IL-1α, IL-1β, IL-6, IL-12, IL-18 and IL-23, which result in inflammatory cell recruitment into plaques and accelerate plaque progression [11]. In contrast, M2 macrophages have anti-inflammatory effects on atherosclerosis, which result in the regression of plaques, via reduction in the size of plaque, cholesterol content and inflammatory cell recruitment in plaques [12]. Moreover, recent studies have shown that M2 macrophages-mediated macro-calcification lead to plaque stability, while M1 macrophages promote micro-calcification progression, which is associated with plaque rupture [13].

Macrophage apoptosis is marked in all phases of atherosclerosis plaque development. For example, in the early stage of atherosclerosis lesion, macrophage apoptosis leads to the reduction of lesion areas by reducing the number of cells inside [14]. Furthermore, debris and apoptosis cells as well as impaired or dead cells can secrete pro-inflammatory factors, such as TNF-α, IL-1β, IL-6 and IL-8, and the production of TGF-β. This could induce further recruitment of monocytes and macrophages into plaques, promoting inflammatory response [15,16]. Mox macrophage is an emerging subset of macrophage. The investigators found that Mox macrophages comprise approximately 30% of all subsets of macrophages in advanced atherosclerosis plaques [17,18]. It has been investigated that there is a decreased number of macrophages in regressing plaques in mice, showing a certain preferences of phenotype shift of macrophages into M2-like phenotype, with an enrichment of M2-like macrophages [19].

Recent studies underlined the effects of transcription factors and nuclear receptors on macrophage phenotype. The expression of peroxisome proliferator-activated receptor(PPAR) was upregulated in M2 macrophages [20]. A recent study showed that dual PPAR-α& γ agonist can down-regulate pro-inflammatory M1 macrophages and up-regulate M2 macrophages in white adipose tissue of mice [21]. PPAR-γ induces polarization of macrophages to M2 phenotype by regulating macrophage lipid metabolism and inflammatory responses. M1 macrophages use glycolysis for energy generation while M2 macrophages prefer to fatty acid oxidation [22]. Activation of PPAR-γ or PPAR-δ pathways in M1 macrophages shifts lipid metabolism state to the oxidation of fatty acids and in turn contributes to the M2 phenotype. Similarly, activation of PPAR-γ pathways in high-risk plaques can effectively reduce plaque burden and inflammatory condition [23]. A recent study suggested that apoptosis cells co-cultured with macrophages could activate PPAR/LXR/ABCA1 pathway in macrophage on ABCA1/STAT6 pathway [24]. Considering the anti-atherogenic functions of PPAR on lesional macrophages and plaques. Future studies will attach more emphasis to the relating topic.

3. Imbalance of Teff cells and Treg cells in atherosclerosis

As discussed above about macrophages, complicated interactions between different subsets of $CD4^+$ T cells also play critical roles in atherosclerosis. Naïve $CD4^+$ T cells can differentiate into distinct cell subsets: Teff cells (T helper (Th1), Th2, and Th17) and Treg cells. [25] The most studied T helper cell subset is Th1. Th1 cells promote inflammatory cells recruitment into atherosclerotic lesions by secreting IFN-γ, which accelerate atherosclerotic lesion development and lead to lesion rupture [26]. Th17 cells secrete IL-17, IL-22, and IL-23, which have shown pro-inflammatory property in most studies [27]. Treg cells are characterized by the lineage specification transcription factor forkhead box P3 (FoxP3). They suppress inflammatory responses against atherosclerosis by producing anti-inflammatory cytokines IL-10 and TGF-β [3].

Studies demonstrate that the increased ratio of effector T cells to Treg cells promotes atherosclerosis. Increased Th17 and decreased Treg

were noted in patients with carotid artery plaques, and imbalance of Th17/Treg may contribute to unstable carotid atherosclerotic plaques [28]. The investigators showed that oxidized low-density lipoprotein (ox-LDL) induces Treg apoptosis and Th17 proliferation, which influence Th17/Treg balance in atherosclerosis [29]. Consistently, the ratio of Treg/Teff in the peripheral blood of coronary artery disease (CAD) patients is inversely correlated with inflammatory markers serum hs-CRP, suggesting that the ratio of Treg/Teff could be a potential marker to predict future cardiovascular events [30]. A recent study showed an increase in the number of Treg cells in coronary thrombi from CAD patients compared with the level in peripheral blood, suggesting that circulating Tregs may migrate to atherosclerotic lesions to mediate local inflammatory responses [31],besides, this could also be attributed to phenotypic plasticity of T cells. For studies concerned with atherosclerosis plaque stability, investigations have noted that a markedly lower level of Tregs in unstable atherosclerotic plaques compared with stable ones, suggesting that the reduction of anti-inflammatory cells in the setting of atherosclerosis might lead to plaque destabilization [32].

While the unbalance of Treg/Teff has been well characterized in atherosclerosis progression and plaque instability, the balance of these cells is more complicated than generally portrayed. The phenotypic plasticity of $CD4^+$ T cells is well established in prior decades. Adoptive transfer studies reveal that the functional phenotypes of T cells are not terminally differentiated population and can change into other subsets of T cells in response to environmental cues [25]. Tregs that express Th1 specific transcription factor T-bet retain their immunosuppressive functions, and this so called Th1-like Tregs in several pathological environments have been investigated in many recent reports [33].

Given the phenotypic plasticity of $CD4^+$ T cells, an adoptive-transfer study investigated that atherosclerosis-mediate inflammatory conditions contributed to Treg differentiation into Th1-like Treg phenotype [34], and the phenotype changes were not occurring in non-atherosclerosis C57BL/6 mice. Notably, Th1-like Treg cells show impaired anti-inflammatory functions in vitro and down-regulate Treg-associated genes expression. They fail to suppress Th-1-mediated arterial inflammatory and atherogenic immune responses in vivo [34].Consistent with this regard is a study that C—C chemokine receptor type 5(CCR5) and IFN-γ expressing $FoxP3^+$T-bet^+ T cells were shown to accumulate in aorta and para-aortic lymph nodes of $ApoE^{-/-}$ mice, investigators called as $CCR5^+$ Teff cells [35]. Furthermore, the gene expression profile of $CCR5^+$ Teff cells is like that expressed in Teff cells rather than Treg cells, and show impaired suppressive function in vitro. Adoptive-transfer of these $CCR5^+$ Teff cells promotes atherosclerosis markedly [35].

Homeostasis of T cells is regulated by several factors, the plasticity and stability of T cells leads to a more complex population of T cells but no more than pro-inflammatory and anti-inflammatory two cases. In conclusion, the balance of Teff/Treg cells is pathologically tipped to the inflammatory site in atherosclerosis.

4. Crosstalk between macrophage and T cell in atherosclerosis

In the past one decade, numerous experimental and clinical studies have established the important roles of some emerging targets in the development of atherosclerosis. They affect immune cells functional polarization by regulating cellular metabolic condition, secretion of cytokines as well as direct cell-cell interactions. The essential factors connecting macrophages and T cells are depicted in Fig. 2.

4.1. MicroRNA-33

MicroRNA-33(miR-33a and miR-33b), as an intronic miRNA which is co-expressed with the host gene SREBF1 and SREBF2, is associated with the regulation of cellular lipid metabolism, including cholesterol and fatty acid synthesis/uptake [36–38]. Increasing interests and debates were centered around the topic of how changes in the metabolism of immune cells influence their phenotypes. A few studies of miR-33 have focused on it. As one such study, increased expression of miR-33 was discovered in M1 macrophage. Furthermore, there is a markedly increased expression of M2 markers (Arg1, Mrc1, Fizz1) and reduced expression of M1 markers (Il6, Nos2, Il1b) when miR-33 was inhibited in cultured macrophages. The miR-33 inhibited macrophages are with higher expression and activity of AMPK (AMP-activated protein kinase) [39]. AMPK acts as the cellular energy sensor to promote ATP-producing pathways, such as fatty acid oxidation (FAO) [40]. Notably, when macrophages with anti-miR-33 treatment and naive T cells were co-cultured for 6 days, there was a significant increase in $FoxP3^+CD4^+$ Treg cells [39], indicating a link between miR-33-mediated metabolic shifts and innate-adaptive immunity in atherosclerosis.

As noted above, miR-33 promotes FAO by targeting AMPK, thereby induces macrophage pro-inflammatory phenotype. Interestingly, AMPK-dependent mechanism also showed an effect on the differentiation of $CD4^+$ T lymphocytes into Treg cells, where AMPK leads to decreased glucose transporter Glut1 and increased FAO [41]. Meanwhile, miR-33 inhibiting increases the expression of retinaldehyde dehydrogenase 2 (RALDH2) in macrophages [39]. RALDH2 is a key enzyme for generating retinoic acid (RA). RA has immune-regulatory properties. [42] Some studies revealed that functional maturation and specialization of immune cells are related to local RA levels. Notably, RA promotes conversion of naive T cells into Treg cells [43–45]. In addition, a lately study investigated that miR-33 regulate macrophage autophagy in AS by targeting key autophagy effectors and transcriptional regulators, which attenuate free cholesterol efflux processes. [46]

Up to now, inhibition of miR-33 has been demonstrated as protective against atherosclerosis. In models of atherosclerosis progression and regression, anti-miR-33 therapy significantly reduced atherosclerotic lesion size and increased plaque stability. [47–49] However, many additional miRNAs may be altered, [50] and further experiments are required to establish miR-33 targeting therapy in humans.

4.2. IL-37

IL-37, as an emerging therapeutic target for preventing and suppressing atherosclerosis, its anti-inflammatory properties were first revealed by a study. In this study, that transfection of human IL-37 in macrophages of mice contributed to suppression of pro-inflammatory cytokines induced by TLR was identified [51]. Over the past decade, a growing number of studies have confirmed and documented the protective effects of IL-37 on atherosclerosis by suppressing innate inflammation. In this context, a research revealed that IL-37 expression on macrophages reduces pro-inflammatory mediators' production and mRNA expression [52]. Moreover, human peripheral-derived monocytes stimulated with IL-37 and ox-LDL, show an attenuate induction of M1 cells and facilitated differentiation into M2 cells as supported by the up-regulation of M2 marker CD206 expression [53]. IL-37 acts as an inflammation inhibitor by binding to cell surface receptor IL-18 receptor α (IL-18Rα), and recruiting the orphan IL-1 receptor 8 (IL-1R8) afterwards. The interaction between IL-37, IL-18Rα and IL-1R8 triggers multiple anti-inflammatory responses, such as suppression of MAPK, NFκB, mTOR, TAK1, and activation of STAT3, Mer, PTEN [54–56].

In addition, some studies have offered comprehensive perspectives that this cytokine can regulate the atherosclerosis progression. For example, IL-37-treated $ApoE^{-/-}$ mice revealed a markedly decreased number of macrophages and $CD4^+$ T lymphocytes as well as increased vascular smooth muscle cells (VSMCs) and collagen in atherosclerotic plaques, leading to smaller lesion size and more stable plaques [57]. Moreover, IL-37 treatment results in decreased Th1 and Th17 cells as well as elevated Treg cells in vivo and in vitro, suggesting that the anti-inflammatory property of IL-37 in atherosclerosis is associated with distinct subsets of T cells. [57] This may be linked to the multiple signal events triggered by the interaction between IL-37, IL-18Rα and IL-1R8 mentioned above. Consistent with this concept, another study has

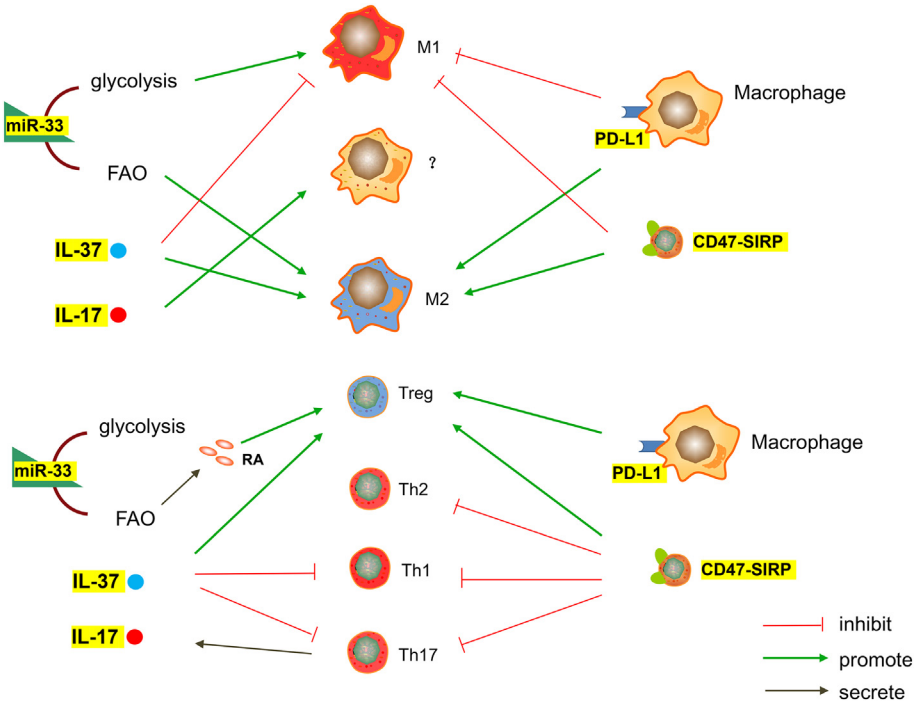

Fig. 2. Factors which affect the phenotype of macrophages and T cells. MiR-33 alter cellular metabolic by promoting FAO or glycolysis, which induces macrophages differentiate into M2 phenotype or M1 phenotype. FAO results in up-regulation of RA, which promotes the differentiation of Treg; Whether in vivo or vitro, IL-37 shows anti-inflammatory properties by suppressing lesion macrophage, inhibiting pro-inflammatory T cell phenotype (Th1, Th17) and mediating the differentiation of Treg; IL-17 is mainly secreted by Th17 cells, which may induce human monocyte-derived macrophages polarization into a new subset of macrophage distinct from others. The downregulation or silence of PD-L1 showed reduction M2 and Treg phenotypic expression as well as increased M1 marker. CD47-SIRPα are considered as atheroprotective, they promote the differentiation of M2 and Treg, and inhibit pro-inflammatory Teff cells.

identified that IL-37tg mice (transgenic mice expressing the human IL-37 genes) have lower levels of Th1 cells but higher levels of Th2 cells than ApoE$^{-/-}$ mice in plaque tissues. [58] To further investigate the effects of IL-37 on T cells in human, human CD4^{+} T cells were induced into different phenotypes (Th1, Th2, Th17, Treg phenotype) in vitro, then were co-cultured with IL-37. Decreased number of Th1 cells and increased number of Th2 cells were observed in the study [58].

Notably, in cardiovascular diseases, plasma IL-37 levels significantly increased in acute coronary syndrome patients compared to stable angina patients. [59] While another study indicates that atorvastatin may reduce increased the level of serum IL-37. [60] In the future, IL-37 need more in-depth study in the pathophysiological mechanisms.

4.3. IL-17

In the last few years, IL-17, as a marker of a novel T helper cell, Th17 cell, has received a lot of attention. Its physiologic and pathologic functions have been investigated in a variety of diseases, atherosclerosis included. Patients with atherosclerosis exhibit an increased level of IL-17 in circulation [61,62]. In addition, ApoE$^{-/-}$ mice showed reduced number of Tregs while the level of Th17 cells and IL-17 was increased [63]. These data suggest a close link between IL-17-mediated response and atherosclerosis in both human and mice. Notably, several studies have revealed a certain tendency of IL-17 in promoting atherosclerosis, while a few studies showed that IL-17 is atheroprotective [64,65].

The main source of IL-17 was identified as subsets of T lymphocyte cells: Th17 cells, γδ T cells, and CD8^{+} T cells [66]. IL-17 modulates other T helper cells through inducing the production of cytokines and chemokines [27]. In addition, the IL-17 producing Th17 cells can differentiate into other T-cell subsets, depending on the cytokine environment [66], which could be attributed to their phenotypic plasticity.

Macrophages are regulated by cytokines, such as IL-17, IL-17stimulates the secretion of pro-inflammatory cytokines [67]. Although there is still no enough evidence of whether IL-17 affect macrophage polarization, a few studies have shed light on it. A previous study investigated the expression of IL-17 receptor on primary murine macrophages from different anatomical compartments, and revealed that the highest expression on mucosal Ly6C^{hi} monocytes and “inflammatory” macrophages in steady-state non-inflammatory conditions [68]. Notably, human monocyte-derived macrophages treated with IL-17 induced a unique transcriptome pattern differ from any other macrophage polarization type [69]. IL-17-induced polarized macrophages showed upregulation of pro-inflammatory genes while a few pro-inflammatory genes such as CD40 were downregulated. Conversely, anti-inflammatory genes were upregulated, which were similar with anti-inflammatory M2 macrophages [69]. Moreover, in a recent study, macrophages treated with IL-17 were observed no increase in the expression of surface molecules related to M1, such as CD80 and CD86, or M2, such as CD36 or CD206 [67], suggesting that IL-17 does not induce macrophage into M1 or M2 phenotype. Moreover, the IL-17-induced macrophages expressed costimulatory molecules, which were similar to M1 [67].

Several therapies of IL-17 have made prominent progress. These primarily include anti-IL-17A monoclonal antibodies, secukinumab [70,71] and ixekizumab [72], and brodalumab [73], an anti-IL-17 receptor monoclonal antibody. These biological agents that target the IL-17 signaling pathway have currently been examined and approved for the treatment of moderate-to-severe atherosclerosis plaque.

4.4. PD-1/PD-L1

Programmed death-1(PD-1) acts as a co-inhibitory receptor, and participates in the transmission of the T cell co-stimulatory signal through binding with its ligand PD-L1 [74]. PD-1/PD-L1 pathway suppresses T cell activation and expansion [74]. In preclinical models, high PD-L1 expression in macrophages contained in patients with CAD suggested that it is upregulated in the inflammatory process associated with atherosclerotic evolution [75].

MiR-16 induces M1 polarization of mouse peritoneal macrophages from either the primary or M2-polarized state, indicated by the significant upregulation of M1 marker CD16/32, repression of M2 marker CD206 or Dectin-1, and increased secretion of M1 cytokine IL-12 or nitric oxide [76]. Notably, PD-L1 could be a potential target of miR-16, indicated by bioinformatics analysis. Meanwhile, the investigators found the downregulation of PD-L1 on macrophages, revealing that miR-16 acts by reducing PD-L1 on macrophages to promote macrophage phenotype shift from M2 to M1 [77]. In another study, peritoneal

macrophages from PD-1$^{-/-}$ mice in the presence of zymosan showed a significant increase of M1 marker (TNF-α, IL-6, MCP-1,IL-β, iNOS) whereas a decreasing tendency in the expression of M2 marker (CD206, Arg-1 and IL-10) [78]. Moreover, PD-L1 on bone marrow-derived macrophages promotes M2 polarization of macrophages accompanied with inhibited expression of pro-inflammation factors [78].

A few studies have revealed that PD-1/PD-L1 act as a bridge on the interaction of T cells with other cells, which may influence the polarization of T cells. For example, a study has revealed that PD-1/PD-L1 pathway plays a role in the in vivo plasticity of Th cells, resulting in conversion of Th1 cells to Treg type. [79] Another study provided evidence of increased differentiation and production of Th17 cells in PD1-knockout mice. [79] In addition, the investigators silenced PD-L1 on human umbilical vein endothelial cells (HUVECs) in ox-LDL states and then co-cultured with Treg cells. Notably, the anti-PD-L1 group shows significant reduction of the Treg phenotypic expression (CTLA-4, GITR), and Treg-associated cytokines secretion (IL-10 and TGF-β1) compared with impaired group. [80] These data revealed the property of PD-L1 on promoting Treg cells polarization.

Previous study found that the expression of PD-1 and PD-L1 is remarkably down-regulated on T cells in CAD patients than that of in healthy volunteers. [81] Surprisingly, the investigators observed three patients with advanced non-small-cell lung cancer who had significant improvement of complicated atherosclerotic plaques while receiving anti-PD-1 monoclonal antibody nivolumab treatment. [82] Further studies need to offer deeper insights into that PD-1 represents a strategy of immunotherapy for AS. But all in all, PD-1 will become a potential therapeutic target approach for AS in the future.

4.5. SIRPα/CD47

The spleen is an important secondary lymphoid organ, which combines the innate and adaptive immune systems. A range of immune cells, including monocytes, dendritic cells (DCs), B cells as well as T cells, going through the spleen, where they maintain a homeostasis state. When the homeostasis is broken, disorders in immune system may occur. In recent years, the vital role of the spleen in atherosclerosis has been documented [83,84]. Signal regulatory protein α (SIRPα) is found to be essential for steady-state homeostasis of T cells in spleen [85]. SIRPα is a transmembrane protein most expressed on monocytes, most subpopulations of macrophages, granulocytes as well as subsets of DCs [86,87].

A recent study showed smaller T zones in full-length of SIRPα protein ablated mice (Sirpα$^{-/-}$ mice).The absolute number of CD4^{+} T cells and CD8^{+} T cells significantly decreased in spleen [85,87]. In one study, the investigators found a significant increasing number of Th1, Th2, and Th17 subsets in the spleen of *C. albicans* infected CD47$^{-/-}$ mice compared with infected WT mice [88]. In this regard, another study found a significantly higher expression of CD47 in Treg of atopic dermatitis mice than normal controls. The investigators proposed that CD47high Treg cells are likely to induce Treg cells. [89] These data indicate that CD47 plays protective roles in inflammatory microenvironment by inhibiting pro-inflammatory Teff cells response and increasing immunosuppressive Treg cells response.

Impaired phagocytosis leads to an accumulation of apoptotic cells in advanced atherosclerosis plaques, which result in necrosis and inflammation of the plaques [90]. An advanced study has presented evidence that the lesional apoptotic macrophages express the “don't eat me” signal-CD47 and interacting with SIRPα. CD47 suppresses cell internalization by phagocytes [91]. Furthermore, the treatment of anti-CD47 showed significantly increased phagocytosis efficiency of M1 [92]. Notably, the disruption of CD47-SIRPα interactions can also change the phenotype of macrophages to M1 subtype in vivo [92]. An advanced study also indicates that SIRPα promotes macrophage M2 polarization as supported by the upregulation of M2 markers (IL10 and MR) [93]. In conclusion, SIRPα engages in complex pathological processes, including T cells homeostasis, phagocytosis and polarization of immune cells, and those are associated with atherosclerosis.

5. The relationship between macrophage and T cell in cardiovascular diseases

In atherosclerosis, apolipoprotein-B-containing lipoproteins (apoB LPs) are retained in the sub endothelial area of the arteries. [94,95] This entry and retention elicits local inflammation and promotes monocytes to migrate into lesional area, and triggers differentiation into M1 inflammatory phenotype. While M2 macrophages have been identified with atheroprotective effects. M2 macrophages inhibit inflammatory cell recruitment and repress pro-inflammatory cytokines production, due to the release of TGF-β and IL-10 correspondingly. M1 macrophages are enriched in rupture-susceptible shoulder regions whereas M2 are predominant in more stable plaque regions. [96] Inflammation in plaques is initiated by macrophage-mediated innate immune responses to modified lipoproteins. It is perpetuated by Th1 cells and Th17 cells as well as Th2 cells, which produce pro-inflammatory mediators such as IFN-γ and TNF [26]. Meanwhile, accompanied with the progressive decreasing in immunosuppress Treg cells, atherosclerotic plaques further progress [26]. In general, immune responses of T cells and macrophages commonly occur together in every stage of atherosclerosis, and the balance is pathologically tipped to the inflammatory side. The slow build-up of atherosclerotic plaques is asymptomatic, while the clinically high-risk plaques are characterized with large areas of necrosis and thinning of fibrous cap, which lead to plaque rupture or endothelial erosion and thus induce thrombus formation.

Vulnerable human plaques have higher Fc receptor (FccR) expression than the stable counterparts. Surprisingly, a recent study showed lower plaque burden in both carotid artery and descending aorta in Apoe$^{-/-}$FccRIIb$^{-/-}$ double knockout mice by inducing Treg/M2 polarization. [97] It indicates that anti-inflammatory immune skewing is atheroprotective with fibrous and histologically stable. In another study, miR-33 antagonism is atheroprotective partly by reducing plaque inflammation by promoting Treg/M2 macrophage polarization. [39] In addition, investigators delineate the temporal dynamics of immune cell accumulation following acute myocardial infarction. [98] While in another study, therapeutic Treg cell activation after myocardial infarction led to improved healing and survival by inducing M2 differentiation. [99] The crosstalk between Macrophage and T cell present themselves as a seamless state between anti- and pro-inflammation in cardiovascular diseases, and these data suggest that regulating the relationship between them could be a potential therapeutic target.

6. Conclusion

Clinical studies have revealed that several of the existing drugs have been used for the prevention of cardiovascular disease. For example, canakinumab (a therapeutic monoclonal antibody targeting IL-1β) group showed the significant decrease of the primary composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. However, it has indicated a significant increase in the risk of fatal infection in canakinumab group [100]. This suggests that immunotherapy is effective, but direct and one-sided immunosuppression can cause disorders in the immune system and attenuate host defense. In this perspective, some clinically approved drugs for cardiovascular disease with anti-inflammatory functions work by regulating differentiation of macrophage and T cell [101,102]. However, given their essential roles in host immunity, precise targeting at macrophage and T cell are clinically restricted. In general, it is believed that the shift into the inflammatory phenotype aggravates the atherosclerotic process. On the contrary, the anti-inflammatory direction can delay the progression of the lesion, which may be a new therapeutic target.

The roles of macrophages and T cells in atherosclerosis and plaque

stability were discussed in this review. Moreover, we also review recent studies on factors that influence both macrophage and T cell, including proteins, cytokines, chemokines and non-coding RNAs. They show anti- or pro inflammatory immune properties by regulating the differentiation of macrophage and T cell. Strategies targeting macrophage and T cell may provide specific and significant approaches for the prevention and treatment of atherosclerotic cardiovascular diseases. These factors associated with intracellular energy metabolism, secretion of cytokines as well as direct cell-cell interactions, may be considered as relevant hallmarks, emerging biomarkers and possible targets for prevention and therapy. Although the quantitative effect of the therapy on disease progression probably depends on the stages and severity of disease.

Furthermore, in this field the, major challenge is to explore more specific targets of individual interactions towards a more integrative and global investigation of how macrophage and T cell come together to influence the fate of atherosclerosis. Special attention is also supposed to be paid to the importance of the crosstalk between macrophage and T cell in diverse pathological progresses, such as cancer.

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Author agreement/declaration

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Conflict of interest

The authors declare that they have no competing interests.

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