Immune Senescence in Atherosclerosis

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Atherosclerosis is one of the main underlying causes of cardiovascular diseases (CVD). It is associated with chronic inflammation and intimal thickening as well as the involvement of multiple cell types including immune cells. The engagement of innate or adaptive immune response has either athero-protective or atherogenic properties in exacerbating or alleviating atherosclerosis. In atherosclerosis, the mechanism of action of immune cells, particularly monocytes, macrophages, dendritic cells, and B- and T-lymphocytes have been discussed. Immuno-senescence is associated with aging, viral infections, genetic predispositions, and hyperlipidemia, which contribute to atherosclerosis. Immune senescent cells secrete SASP that delays or accelerates atherosclerosis plaque growth and associated pathologies such as aneurysms and coronary artery disease. Senescent cells undergo cell cycle arrest, morphological changes, and phenotypic changes in terms of their abundances and secretome profile including cytokines, chemokines, matrix metalloproteases (MMPs) and Toll-like receptors (TLRs) expressions.

atherosclerosis immune cell senescence cardiovascular diseases cardiology

1. Pathophysiology of Atherosclerosis

Typically, the building blocks of atherosclerotic plaque are lipids, particularly low-density lipoprotein (LDLs), and leukocytes, especially monocytes. Initiation of atherosclerosis begins with aberrant endothelial cells coupled with augmented expression of surface adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin. Concomitantly, it was enhanced by proinflammatory cytokines and LDLs which promote monocytes infiltration into the tunica intima layer of blood vessels. LDLs are susceptible to oxidation due to enzymatic modification by lipoxygenases and myeloperoxidase or reactive oxygen species (ROS). The oxidized low-density lipoproteins (oxLDLs) are a damage-associated molecular pattern (DAMP) which are recognized by immune cells and activate the NFκB pathway to signal pro-inflammatory cytokines release including IL-1, TNF-α, and adhesion molecules (VCAM-1, E-selectin and ICAM-I) [1]. In addition, low shear stress contributed to turbulent blood flow as senescent endothelial cells diminish nitric oxide (NO) production, hence it fails to vasodilate the blood vessels [2]. With all stated conditions, endothelial cells and smooth muscle cells are activated and release monocyte-colony stimulating factors (M-CSF) that transform monocytes into macrophages. Macrophages engulf the oxLDL and transform into foam cells. The advancement of inflammation is reinforced with proinflammatory cytokines secreted by polymorphonuclear cells (PMN) including tumor necrosis alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) and interferon (IFN)-γ [3]. Platelet-derived growth factor (PDGF) acts as a mitogen for vascular smooth muscle cells (VSMCs) to proliferate and collagen production to build fibrous cap and encompass lipid core during the initial stage. In later stages of lesion progression, pre-existing

inflammation is further amplified by the aging of VSMCs with a necrotic core composed of cell debris and lipids enveloped within the fibrous cap. Eventually, VSMCs undergo apoptosis with significant fibrous cap thinning due to the degradation of collagen and extracellular matrix [4]. As a result of that, the atherosclerotic plaques lose their stability and rupture, causing platelet aggregation or even advancing to detrimental complications such as thrombosis [5].

2. The Immune System in Atherosclerosis

Monocytes and macrophages are vital in the formation of atherosclerotic plaque. Both TNF-α and IFN-γ are potent proinflammatory cytokines secreted by macrophages, natural killer (NK) cells, and T-cells. IL-12 and IL-18 have distinct functions in promoting IFN-γ gene transcription in primary human $CD4^+$ T cells. It was indicated that both AP-1 and STAT4 activations are needed for IL-12-dependent IFN-γ promoter activation, while IL-18 enhanced the AP-1 binding activity. Surprisingly, the synergy between IL-12 and IL-18 greatly enriched the IFN-γ production of $CD4^+$ T cells. The combined effect of both cytokines enhanced the AP-1 binding activity by 20-fold, but not by IL-12 administration alone [6][7][8]. In addition, IFN-γ also triggers macrophages and monocyte to secrete ROS thus leading to cellular oxidative stress. Simultaneously, monocyte chemoattractant protein-1 (MCP-1) is also secreted to attract other macrophages and metalloproteinases to disintegrate the fibrous cap of atherosclerotic plaque [9]. Neopterin [10] and IL-12 [11] are highly expressed in atherosclerotic plaque, which could be remarkable biomarkers for atherosclerosis and CVD detection. As atherosclerotic plaque progresses, neopterin expression is intensified considerably. A stable coronary artery disease (CAD) patient and a non-CAD patient showed minimal neopterin expression in their normal and non-stenotic coronary arteries. On the other hand, neopterin expression was demonstrated to heightened in both early and advanced atherosclerotic plaques and macrophage foam cells in the coronary arteries of stable and unstable CAD patients [10]. Young apoE-deficient mice injected with IL-12 daily exhibited higher levels of antioxidized LDL antibodies and more rapid atherosclerosis than controls injected with PBS only [12]. Nevertheless, targeting the gene encoding IL-12 or vaccines against IL-12 hinders early lesion development through plaque stabilization but is not shown in late lesions [13][14].

Dendritic cells (DCs) are the most potent antigen-presenting cells (APCs) in the cell-mediated immune response through upregulated-surface receptors that act as co-receptors in naïve T-cells activation with respective co-stimulatory molecules including major histocompatibility complex MHC I or II. OxLDLs are turned into foam cells through exophagy by mature DCs, which contribute to atherosclerotic plaque formation. The cells create a seal zone coupled with acidification and lysosomal secretion in the contact zone [15]. MyD88 gene is essential in the maturation of DCs through increased antigen-presenting ability and T-cells activation. Mature DCs induced the production of pro-inflammatory cytokines IFN-α and IFN-β, and chemotactic factors CCR5 and CCL5 are upregulated to exacerbate local inflammation by attracting monocytes and T-cells in atherosclerotic lesions [16]. Furthermore, DCs in aortic walls increase the production of TNF-α, IFN-γ, and collagenases MMP to degrade surrounding collagen and extracellular matrix and destabilize the fibrous cap [17].

T-cells consist of Th1, Th2, Th17, helper T cells, cytotoxic T-cells, and regulatory T-cells (T reg). They exert both proatherogenic and anti-atherosclerotic effects. In early lesions, the amount of $CD8^+$ T cells is little compared to

later lesions. Research showed that $CD8^+$ T cells have been shifted into the dominant type in later lesions [18]. The synergistic effect of IL-12 and IL-18 on IFN-γ secretion assists in the recruitment of macrophages and differentiation of naive T cells into cytotoxic cells. Macrophages produce MMPs that degrade extracellular matrix while cytotoxic T-cells are equipped with perforin to induce pore formation coupled with granzyme B to activate caspase which led to apoptosis in VSMCs. The synergistic effect of macrophages with cytotoxic T cells is sufficiently potent to disintegrate the fibrous cap. On contrary, Th2 cells act as modulators by negating the production of IFN-γ through the secretion of anti-inflammatory cytokines such as IL-4, IL-5, and IL-13 [19]. IL-4 and IL-13 suppress monocyte activities by impeding the production of inflammatory cytokines, IL-6, TNF-α, and IL-12 [20] and by rendering the secretion of IL-1R antagonists [21]. Although IL-4 and IL-13 are anti-inflammatory in nature, but they also significantly increase the expression of VCAM-1 on the surface of vascular endothelial cells, causing T-cells to adhere to them [22] to facilitate neovascularization [23]. In endothelial cells, IL-4 and IL-13 induce the synthesis of monocyte chemoattractant protein-1 [24], and both HUVEC and dermal microvascular endothelial cells respond to IL-13 [25]. In addition, the release of TNF-α and IL-4 can induce apoptosis of endothelial cells [26]. The profound cytokines from T reg cells are anti-inflammatory cytokines, IL-10 and TGF-β. IL-10 downregulated the expression of IFN-γ, henceforth refraining from monocyte or macrophage activation, releasing cytokine and the upregulation of costimulatory molecules [27][28]. Whereas TGF-β1 was shown to repress the stimulation of IL-1β and TNF-α induced VCAM-1 expression, thus eliciting an athero-protective effect [29][30].

B-cells are complementary to T-cells, having both pro-atherogenic and anti-atherosclerotic properties. There are two major subsets of B-cells, which include B1 cells and B2 cells. B1 cell subtypes are further divided into B1-a and B-1b cells. Both subtypes are considered athero-protective by activation of the humoral response against the presence of oxLDL to produce anti-oxLDL IgM antibodies. B1-derived IgM binds to epitopes on apoptotic cells, enabling them to be cleared more efficiently and reduce the inflammation [31] with the assistance of IL-5 which allows proper expansion and releasing antibodies to prevent foam cell formation [32]. However, derived-1a-derived innate response activator (IRA) releases granulocyte-macrophage colony-stimulating factor (GM-CSF) that acts as mitogen of Ly6Chi monocytes, thus aggravating atherosclerosis by inflammatory response [33][34]. A study has demonstrated that mice deficient in IRA B cells are secured against atherosclerosis [35]. In turn, B2 cells will further differentiate into marginal zone B MZ-B cells and follicular B Fol-B cells. Fol-B cells are the predominant B2 population that produces atherogenic IgG that triggers MHC-II expression, therefore recruiting $CD4^+$ T cells as well as upregulation of proinflammatory cytokines TNF-α, IL-1β, and chemokines MCP-1, henceforth exacerbating atherosclerosis [36]. Furthermore, it has been shown that Fol-B cells promote Th1 and secrete proinflammatory cytokines [37][38]. T follicular helper cells activate Fol-B cells, which differentiate into germinal center B (GC-B) cells that create GCs [37][38]. As a result of GC-B cells proliferation and affinity maturation, high-affinity antigen-specific IgG and IgE are produced [39]. It has been documented that Fol-B cells are proatherogenic, mainly by secretion of IgG and activating Th1 cells [37][38]. Moreover, the role of MZ-B cells and regulatory B cells in atherosclerosis remains obscure [36].

3. Immunosenescence in Atherosclerosis

Changes in the cellular and antibody-related immune response that occurs along with aging are termed 'immunosenescence' [37][38]. Immunosenescence has been reported to associate with several age-related pathologies [39]. The decline in immune protection leads to vulnerability to infections, autoimmune diseases, and low-grade chronic inflammation, specifically termed inflammaging [40][41]. Inflammaging is associated with impaired autophagy [40][42] and ubiquitination [40][43], overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [44], and release of senescence-associated secretory phenotype (SASP) factors [40][45]. Atherosclerosis is an aging-associated pathology that may be exacerbated by inflammaging [46]. Ideally immune cells function to eliminate senescent cells as part of a protective mechanism against inflammatory responses. However, senescent immune cells have impaired functions and result in the accumulation and persistence of SASP release, promoting aging and age-related diseases [47][48]. Senescent immune cells have been found in the vasculature wall, characterized by increased secretion of proinflammatory mediators from macrophages, DCs, and foam cells that aggravate the atherosclerotic plaque formation [49].

On the other hand, senescent immune cells may also contribute to reducing plaque growth and necrosis. The decline in senescent naive T- and B-lymphocytes with the reduced T-cell receptor (TCR) [50][51] and B-cell receptor (BCR) [35][51] repertoire weakens the adaptive immune response. Moreover, the decline in response for Toll-like receptors (TLR) stimulation upon ligand (antigen) binding by macrophages/monocytes and DCs impede intracellular signaling in inflammatory response activation [52][53][54]. In addition to that, the decline in phagocytic capacity, antigen-presenting, cytokine production, and chemotaxis ability of macrophages hampers its initiation of clonal T-cells proliferation, therefore attenuates the progression of plaque inflammation [37][38]. Senescent immune cells share features of damaged DNA, impaired gene and mitochondrial function [40][55], cell cycle and growth arrest [56], apoptotic resistance, and production of SASP as inflammatory mediators [40][50].

4. Regulation of Immune Cells Senescence in Atherosclerosis

4.1. Monocytes, Macrophages, and Foam Cells

All three subsets of monocytes, classical (CD14++CD16−), intermediate (CD14++CD16+) and non-classical (CD14+CD16++) are observed to exhibit hallmarks of senescence [57][58]. However, one of the three subsets of monocytes, non-classical (CD14+CD16++) is observed to be elevated and highly secrete IL-8 and TNF-α in the blood plasma of the elderly population [59][60]. Non-classical (CD14+CD16++) monocytes are stated to highly express membrane-bound IL-1α and have upregulated NF-kB signaling, which is reminiscent of the senescence feature, SASP. The accumulation of non-classical subset and $CD16^{+}$ monocytes in the elderly population is reported to cause atherosclerosis due to their SASP secretion. The non-classical subset is reported to have the least proliferative capacity than the other two subsets, shorter telomere length, and anti-apoptotic properties besides a high concentration of cellular and mitochondrial ROS. Besides TNF-α and IL-8 [61], SASPs secreted from non-classical monocytes include CCL3, CCL4, CCL5, IL-6, IL-1β [59][60]. It is the subset that expresses the highest level of membrane-bound IL-1α and causes upregulation of NF-kB activation which is then followed by intermediate and classical subsets [62].

Several studies stated, most CVD patients are detected with a high subpopulation of non-classical monocytes, CD14+CD16+. CD14+CD16+ monocytes are demonstrated to have upregulated phagocytic activity as well as TNF-α and IL-1β secretion [57][58]. A study revealed senescent CD14+CD16+ monocytes highly express proatherogenic chemokine receptors, CCR2, CCR5, CCR7, and CX3CR1 as well as endothelial adhesion molecules, VCAM-1 and ICAM-1 [61]. These particular subsets of monocytes are also stated to have increased endothelial adhesion capacity [63]. The deficiency of the mentioned subset of monocytes is shown to be associated with increased fibrous cap thickness [18][63]. Moreover, senescent monocytes highly secrete inflammatory chemokines and chemokine receptors by such as CCL-2, CCL-3, CCL-4 and CCR-2, CCR-5, CCR-7, and CX3CR-1 that act as chemo-attractants, contributing to atherosclerotic plaque development [49]. The intermediate (CD14++CD16+) subset of monocytes is shown to upregulate the expression of CD74, a surface marker that acts as a receptor for macrophage inhibitory factor (MIF) [64]. It enhances the MIF expression in macrophages [65] which in turn promotes chemokine, and CCL-2 secretion from the endothelial cells. It serves to upregulate monocyte-endothelial adhesion and monocyte arrest and chemotaxis [66].

Senescent monocytes also release SASPs to recruit more peripheral monocytes for chemotaxis, diapedesis, and transmigration via the endothelium into inflamed vascular sites [67]. This is enhanced by senescent vascular endothelial cells (VECs) that decline in their NO secretion leading to compromised vascular integrity and protective functionality. Moreover, senescent VECs increase their secretion of monocyte chemokine protein-1 (MCP-1) that in turn recruit more peripheral monocytes to the endothelium. This leads to the formation of foam cells at an elevated rate, accelerating atherosclerotic plaque progression which potentially causes acute coronary disease such as myocardial infarction (MI) [68]. In addition to that, Klotho protein involves in regulating oxidative stress by reducing the expression of TNF-α from monocytes/macrophages. It has been reported that in patients with atherosclerosis, Klotho protein expression was observed to be reduced [69]. However, its expression level from senescent monocytes/macrophages is unclear.

Macrophages are the most abundant immune cells within atherosclerotic plaque hence it is the major contributor to plaque formation and progression in terms of cholesterol efflux, inflammation, necrosis initiation, and ECM degradation. Aged macrophages were found to have low expression of TLRs for antigen presentation to the effector T-cells to initiate inflammatory responses [70][71]. In an ApoE$^{-/-}$ mice model study, macrophages TLR 9 deficiencies have reduced atherosclerotic lesion size and vascular inflammation due to low accumulation of macrophages and expression of VCAM-1, ICAM-1, TNF-α and MCP-1 at the atherosclerotic plaque site [72][73].

A study has supported that senescent macrophages have impaired cholesterol efflux due to the downregulation of *ABCA1* and *ABCG1* genes as well as enhanced macrophage polarization into pro-angiogenic and disease-promoting phenotype which promotes inflammation, thereby accelerating the formation of foam cells and plaque progression [71][74]. In addition, senescent macrophages are able to polarize into M1 phenotypes (which include highly expressed SASP factors such as TNF-α, IL-6, IL-1β, CCL2, and collagenase factor, MMP 9) that accelerate the atherosclerotic plaque progression [74].

There are three subtypes of macrophages present in atherosclerotic plaque: resident-like macrophages, inflammatory macrophages, and TREM^{hi} macrophages [75]. Cardiac resident-like macrophages achieve a steady state as one ages, thereby it is compensated by recruited macrophages. However, resident-like macrophages in atherosclerotic plaque are shown to express several senescence markers including CXCL4, CCR2, and CXC3R1 [76]. Inflammatory macrophages are able to secrete SASPs factors including IL-6, TNF, and chemokines (CXCL2, CCL2, CCL3, CCL4, CCL5, CXCL10) [75]. It also highly expresses costimulatory ligands, CD80 that enhance antigen presentation and T-cells recruitment and inflammatory secretion at the atherosclerotic plaque [77]. Foamy TREM^{hi} macrophages have high expression of surface glycoprotein, CD9 that activates (PI3K)/Akt/mTOR signaling pathway associated senescence which aggravates atherosclerotic plaque inflammation [77][78]. In addition, these foamy TREM^{hi} macrophages also highly expressed fatty-acid scavenger receptors (CD36), that accelerate foam cell formation and atherosclerotic plaque expansion in size [75][79]. M2 phenotype macrophages are observed within atherosclerotic plaque and are stated to enhance the plaque rupture due to MMP-9 release that degrades type IV collagen at the fibrous cap, leading to plaque rupture [80].

Interestingly, MicroRNA-33 (miR-33) is frequently found in aged macrophages. MiR-33 is an inhibitor for the cholesterol transporter, ABCA1 [74][81]. Several in vivo studies have proved that mice with knockout of the *miR-33* gene had high plasma HDL levels, reduced plaque size, and decreased inflammatory response [81][82][83][84]. Similarly, inhibition of miR-33 in aged macrophage culture has alleviated vascular endothelial cell proliferation [74]. In one pathogenic study, the upregulation of miR-33 was triggered by *Mycobacterium tuberculosis.* That led to impairment of cholesterol efflux because accumulated cholesterol within the infected macrophages serves to be the source of nutrient for the bacterium [85]. It can therefore be said that patients with comorbidity, especially with TB infection are at high risk for atherosclerosis. However, the exact role of miR-33 expression in senescent macrophages remains unclear.

Other interesting miRNA associated with atherosclerosis is miRNA-126a. It is expressed by senescent macrophage, which is also known as p16 (Ink4a)- and β-galactosidase positive (p16$^+$/β-gal$^+$) subset [86]. miR-126a is known to promote telomerase activation in senescent macrophages besides promoting increased SA-β-gal activity and expression of cell cycle inhibiting genes, p53 and p16. Upregulated expression of miR-126a can trigger SMAD family member 3 (Smad3), thereafter the downstream NF-kB pathway (Smad3/NF-κB signaling) will activate the telomerase and promote M2 to M1 macrophage polarization within atherosclerotic plaque. As stated earlier, the pro-inflammatory M1 phenotype macrophages promote atherosclerotic plaque development via its secretion of inflammatory mediators that in turn cause vascular endothelial inflammation [87].

The involvement of senescent macrophage in atherosclerosis is affirmed by its role in secreting MMPs to promote plaque instability, elastic fiber degradation and fibrous cap thinning, therefore, accelerate the lesion rupture and thrombosis [49][68][88]. The high expression of MMPs from senescent macrophages and foam cells cause ECM degradation at the atherosclerotic plaque site which leads to weakening of the vascular wall [88]. Moreover, heathy macrophages perform efferocytosis to engulf and clear the cell debris from apoptotic cells to reduce the atherosclerotic plaque burden [89]. However, senescent alveolar macrophages are reported to have reduced efferocytotic capacity that promote sustained inflammation at the atherosclerotic plaque site [90].

4.2. Dendritic Cells (DCs)

There is scarcity in evidence of DCs senescence associated with SASP release and its role in atherosclerosis. Nevertheless, aging is associated with a reduced capacity of DCs to bind with T-cells [91]. Age-related changes which cause dysregulation of the immune responses are believed to be one of the driving factors of chronic inflammation commonly associated with the elderly population [91][92]. These changes include a low number of peripheral DCs, reduced capacity for chemotaxis and phagocytosis as well as antigen presentation to the effector T-cells [93]. Studies have reported chronic inflammation that is paired with aging during the atherogenic response to be associated with the occurrence of CVD [94][95].

Elevated merocytic DCs subsets ($CD8\alpha^{-}CD11b^{-}$) are shown to be correlated with aging where they were shown to impair T-cell priming capacity due to low expression of MHC class 1 surface molecules [96]. Another two subsets of DCs; $CD11c^{+}$ $CD11b^{-}$ and $CD11c^{+}$ $CD11b^{+}$ are observed to be accumulated within the atherosclerotic plaque [97] [98]. These $CD11c^{+}$ $CD11b^{+}$ subset of DCs shown to have highly expressed of pro-inflammatory and pro-atherogenic mediators including CCL-2, IL-6, IL-1β. Besides that, high expression of CD36, TLR 2 and TLR4, IL-12, and IL-6 are associated with atherosclerotic plaque formation [99].

The population of $CD11c^{+}$ DC is seen to increase with age in a murine model study [100]. Studies showed that antigen presentation and T-cells priming declined in immuno-senescent DCs [101] and that could inhibit the atherosclerotic plaque progression. $CD11c^{+}$ DC which is predominantly found in atherosclerotic plaque secretes VCAM-1, CCL-2, and scavenger receptors, LOX-1, CD36, and CD205.

4.3. T-Lymphocytes

Senescent T-cells have been shown to have activated p38 mitogen-activated protein kinase (p38-MAPK) signaling pathway and expressed IL-18, IFN-γ, and CCR-7 that in turn increased the abundance of $CD4^{+}/CD8^{+}$ (TEMRA) cells. Many senescent TEMRA cells are found to be present within the atherosclerotic plaque [49][70][102][103]. The overactivation of the p38-MAPK signaling pathway triggers TCR signaling and IFN-γ expressions of T-cells that aggravates atherosclerotic plaque development [104].

Meanwhile, accumulation of differentiated $CD8^{+}CD28^{-}$ T-cell is observed in the elderly population with coronary atherosclerotic plaque [105]. The low expression of CD28 leads to defective T-cells function and responsiveness towards oxLDL antigen presentation by APCs. Moreover, senescent $CD4^{+}CD28^{-}$ T-cells are reported to be associated with IFN-γ secretion and this subset is found elevated in patients with unstable angina [105]. Senescent $CD4^{+}CD28^{-}$ T-cells are also observed to highly secrete CCR5, CCR7 and CXCR1 that promotes inflammation at the atherosclerotic plaque site [106].

4.4. B-Lymphocytes

Studies have shown that the late memory B-cell ($IgD^{-}/CD27^{-}$) subset expresses the highest level of SASP biomarkers which includes TNF-α, IL-6, and IL-8 and pro-inflammatory miRNAs (miR-155, miR-16, and miR-93)

[107]. MiR-155 promotes monocyte differentiation, and accelerates foam cell formation besides down-regulating NO synthase expression which leads to endothelial inflammation [108]. However, it is also capable to reduce oxLDL uptake by down-regulating CD36 and LOX-1 expression [109]. MiR-155 is more commonly detected in patients experiencing acute myocardial infarction and unstable angina than in patients experiencing ordinary chest pain syndrome. High miR-16 is detected in patients experiencing peripheral artery disease [110][111]. In contrast, there is research indicating that elevated miR-16 alleviates atherosclerotic progression as it inhibits pro-inflammatory cytokines, IL-6, and TNF-α release but enhances anti-inflammatory cytokines, IL-10 release from foam cells [111]. MiR-93 is reported to inhibit ABCA1 expression, hence it leads to impaired macrophage cholesterol efflux, promoting atherosclerosis progression [112].

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