A REVIEW ON CD88-EXPRESSING IMMUNE CELLS AND THEIR INFLUENCE ON ATHEROSCLEROSIS

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Abstract

CD88, which stands for "Cluster of Differentiation 88," is also known as C5aR, which stands for "Complement 5a receptor." This complement receptor has 7 transmembrane domains and is found on various cell types, including monocytes, macrophages, dendritic cells, epithelial cells, adipocytes, and endothelial cells. Atherosclerosis is a condition associated with chronic inflammation of the arterial walls. It's marked by lipid retention and building, monocyte and T lymphocyte recruitment into the intima, foam cell generation, smooth muscle cell proliferation, and collagen and protein accumulation. C5a has been found in a wide range of atherosclerotic lesions, from fatty streaks to advanced plaques. The expression of CD88 has been linked to both proatherogenic and antiatherogenic effects in atherosclerosis. Initial activities of C5a in atherosclerosis include chemotaxis, oxidative burst, and vascular adhesion molecule activation. CD88 expression has also been linked to the formation of atherosclerosis plaques via adaptive immune cell activation. Regulation and effector functions require ligand-receptor binding (C5a-C5aR) in the pathogenesis of atherosclerosis. CD88 expression has been linked to all stages of atherosclerosis. Myeloid cells have been identified to express CD88, which is responsible for many of C5a's biological properties. During atherogenesis, macrophages and dendritic cells are two important antigen presentation cells (APCs) that carry and display the CD88 surface marker. The proliferation and division of CD4+ T helper cells are controlled by macrophages, dendritic cells, and mast cells, which are also responsible for the release of both proatherogenic and antiatherogenic cytokines. However, there is no evidence that naive CD4+ T helper cells express CD88 from any of the research that has been done. Since CD88 is expressed by a wide variety of immune cells in atherosclerotic plaques, including macrophages, dendritic cells, T lymphocytes, and B lymphocytes, this review will focus on the influence of CD88-expressing immune cells in atherosclerosis formation.

Keywords: CD88; C5a; $CD4^+$ T cell; Macrophages; Dendritic cell

Introduction

Dental Complement 5a receptor (C5aR), widely known as CD88, is a 7T-spanning, G-protein-coupled receptor (GPCR) expressed on the surface of both myeloid and non-myeloid cells (1). CD88 can be expressed by a variety of immune cell types, including monocytes, macrophages, neutrophils, activated mast cells, and dendritic cells (DCs), among others. Platelets, microvascular endothelial cells, adipocytes, kidney epithelial cells, cardiac myocytes, vascular smooth muscle cells, astrocytes, microglia, and neurons are all examples of non-immune cells that express CD88 (2). The well-known complement ligand C5a communicates with the CD88 protein to mediate several biological processes (3, 4). There is mounting evidence that the complement activation product C5a can have either a beneficial or detrimental effect on the progression of atherosclerosis and other inflammatory illnesses. Recent research suggests that C5a plays a part in the development of atherosclerosis. These findings suggest that, depending on the stage of development, C5a can either promote or prevent the progression of atherosclerosis (5, 6).

The role of CD88 in the initiation and progression of atherosclerosis has been established for over two decades, with prior discoveries indicating that genetic deletion of CD88 or blocking the CD88-induced signaling cascade limits the growth of atherosclerotic plaques (7). CD88 has a vital function in several stages of the atherogenesis process, making it one of the most critical molecules in the progression of atherosclerosis (6). C5L2, which is a less potent C5a receptor, competed with C5aR for C5a binding, and the relative amount of C5a occupancy at each receptor determined whether the result was pro-inflammatory or anti-inflammatory (8). This

review will focus on the involvement of CD88-expressing immune cells in the initiation and progression of atherosclerosis as a disease.

CD88 structure, ligands, and functions

C5aR (CD88) is a 46 kDa seven-transmembrane (7TM) receptor present in a variety of cell types (9). CD88 belongs to the G-protein-coupled receptors (GPCR) family, which also encompasses olfactory receptors and orphan receptors with similar structures and signalling functions. C5aR (CD88) is a 350-amino-acid protein that contains one glycosylated asparagine at position 5. Further tyrosine sulfation occurs post-translationally at sites 11 and 14 (10). The initial structural investigation of C5aR revealed key biochemical information that would allow the development of antibodies and synthetic inhibitors to these receptors, which bind C5a with high affinity and initiate a G-protein-dependent cascade of cell responses. Several investigations have demonstrated the key structures required for C5aR ligand binding (1, 10).

Nuclear magnetic resonance (NMR) spectroscopy revealed that CD88 is composed of four helices linked together by loops (11, 12). Disulfide bonds link the helical structures together, making the molecule extremely resistant to oxidative degradation. CD88 is composed of an external N-terminus, seven TM-helices, and an intracellular C-terminus that are all connected by loops (Figure 1). The C5aR amino acid sequences have potential glycosylation sites with aspartate and tyrosine residues at the N-terminus. C5aR signaling is mediated by these amino acids involved in ligand binding. Genetically, CD88 genes are located at chromosome 19, q13.33, and are typical of the chemo-attractant receptor gene family. They are encoded in a two-exon structure, with 50 untranslated regions and an initiating codon in the first exon and the rest of the coding sequence and 30 untranslated regions in the second (13).

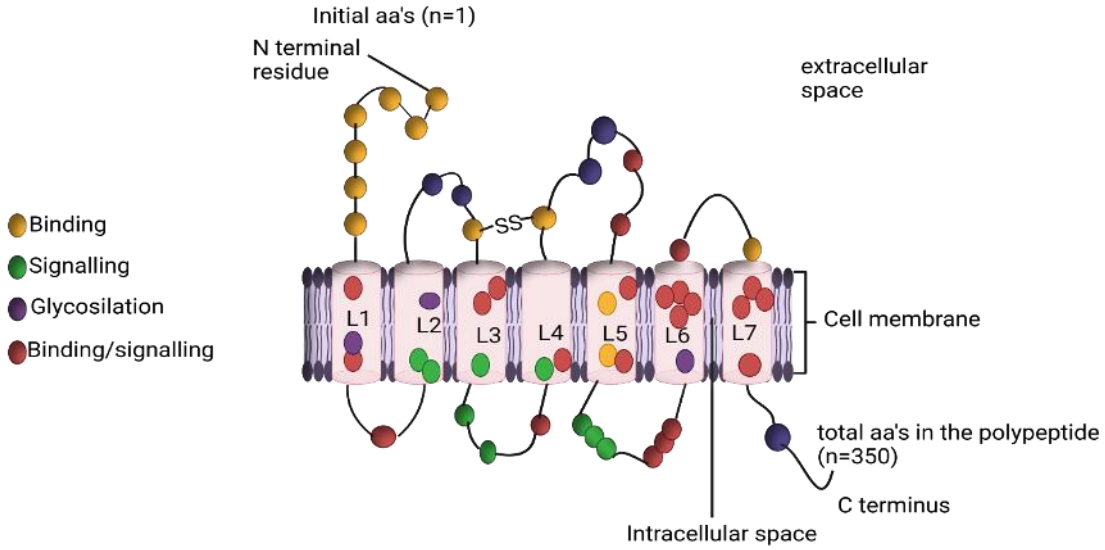

Figure 1: C5aR comprises 350 aas from the N terminal to the C terminal through 1-7 membrane loops. The ligand-binding sites at the N terminal residue extruded from the first loop within the extracellular space were depicted in this figure. The aa's residues have a signaling role in loops 3 and 5, while the glycosylation function can be performed by the aa's residues nearly throughout the loops. An additional set of possibly critical binding or signaling aa's residues is also shown. Modified from Kohidai, L. (2008)

C5a and C5a desArg have been found as ligands for C5aR, with a relatively high affinity for C5a but a 10–100-fold lower affinity for C5a des Arg (13). The C5aR comprises two different C5a binding sites that are separate from one another. The acidic N-terminus of C5aR interacts first with C5a's basic core, which is rich in aspartates. The agonistic C-terminus of C5a binds to a binding pocket created by hydrophobic transmembrane domain residues and charged extracellular loop residues at the base (1). Another intracellular component that binds to the C-terminus of active C5aR is the Wiskott-Aldrich syndrome protein (WASP), a multifunctional protein that alters actin dynamics and may play a role in C5a-dependent chemotaxis (10).

C5a has now been identified as a pleiotropic molecule that regulates the activity of a variety of cell types and performs a variety of biological functions (14). C5a acts as a chemo-attractant and increases the production of pro-inflammatory cytokines by interacting with C5aR expressed by myeloid cells (15), which is tied to the pathophysiology of atherosclerosis. C5a stimulates calcium signaling, degranulation, cytokine production, and chemotaxis in a variety of cells that populate the intima of the artery wall through the expression of CD88 on the surface of these cells (12). There is a relationship between increased CD88 expression and the development of inflammatory illnesses like atherosclerosis (4).

Atherosclerosis

Atherosclerosis is the most common cause of cardiovascular disease, which is the leading cause of death around the world. Atherosclerosis is a chronic inflammatory disease of the blood vessels caused by both atheroprotective and proatherogenic immune responses (15, 17). It is well-known that atherosclerosis is a protracted, complex, step-by-step process that is defined by an inflammatory response of the artery wall due to lipid retention and accumulation (18). Hyperlipidaemia and lipid intimal deposition in the arteries initiates the process of atherosclerotic plaque development (16). Depending on the kind of arterial wall involved, atherosclerosis can induce coronary heart disease, chronic kidney illness, carotid artery disease, or peripheral artery disease. According to increasing evidence, it is predicted that atherosclerosis, a major non-communicable disease, will continue to pose the greatest threat to global health and socioeconomic sectors until 2030.

Hypercholesterolemia, diabetes, hypertension, gender, and cigarette smoking are all risk factors for atherosclerosis (19). There are cells, lipids, connective-tissue elements, and detritus in an atherosclerotic lesion. The most prevalent cellular elements of atheroma are blood-borne inflammatory and immunological cells, followed by vascular smooth muscle cells and endothelial cells (20). An essential role for cellular immunity appears to be played in the pathophysiology of atherosclerotic plaque development through the recruitment, activation, and proliferation of immune cells, such as monocytes, macrophages, DCs, and T lymphocytes.

All the degenerative diseases, including atherosclerosis, rheumatoid arthritis, diabetes mellitus, aging, and cancer, are associated with lipoprotein levels, particularly low-density lipoprotein (LDL). LDL is well-known for playing a critical role in the development and progression of this degenerative diseases (21). The oxidation of this low-density lipoprotein (oxLDL) is an important step in the progression of atherosclerotic plaques (22). Oxidative alterations of LDL modify its structure, allowing the new conformation of LDL to be identified and taken up by scavenger receptors (SRs) on macrophages and smooth muscle cells (SMCs) before the production of foam cells, which suggests the onset of atherosclerosis (23).

Utilizing reliable mouse models, researchers were able to better comprehend the mechanism of atherosclerosis plaque formation (24, 25). When it comes to atherosclerosis, wild-type mice are rather resistant; therefore, genetic alteration is typically required to make them more susceptible (24). In atherosclerosis research, mice lacking either apolipoprotein E or the LDL receptor are two of the most often used models (23). Both the ApoE–/– and LDLr–/– strains are dyslipidaemic, putting them at risk for atherosclerosis due to reduced lipoprotein production and metabolism (23). Unlike LDLr-/- mice, which develop severe atherosclerosis only after consuming an atherogenic diet, ApoE/ mice form atherosclerotic plaques on their own, without the need for dietary intervention (25).

The role of CD88 in atherosclerosis

C5aR (CD88) are abundantly expressed in innate and adaptive immune cells (16). Using CD88 as a marker, it was demonstrated that C5a cholesterol clefts and necrotic cell debris were found in lipid-rich atherosclerotic lesions, confirming the presence of CD88 (6). C5a has been found in a variety of atherosclerotic lesions ranging from a fatty strike to advanced plaques, but not in healthy arteries (3). A persistent inflammatory condition such as atherosclerosis is indicated by the presence of inflammatory monocyte-derived cells, mast cells, and T lymphocytes in the intima (26). According to a recent study (4), NK and NKT cells express C5aR constitutively in steady-state settings, at least at the mRNA level, indicating that NK expression of CD88 plays a role in the early stages of atherosclerosis (27). CD88 is expressed by neutrophils and mast cells, which have been associated with the latter stages of atherosclerosis (28). During the early stages of atherosclerosis, inflammatory cells such as macrophages communicate immunological signals to the adaptive immune system by expressing CD88 and binding the C5a ligand (17).

One of C5a's biological activities includes the attraction of monocytes to the atherosclerotic environment, and its expression on myeloid cells has been shown (4). Intimal immune cells that populate the arterial wall play important roles in atherosclerosis development (1, 4) and have been reported to express C5aR in multiple investigations. Several studies on animals show that C5aR expression is a key factor in the development of atherosclerosis, but other data seems to contradict this. Atherosclerosis development in mouse models of atherosclerosis is reduced when the C5a ligand or its receptor C5aR (CD88) is suppressed (7). Cholesterol-fed rabbits with the C5a inhibitor K-76COONa were less likely to develop atherosclerotic lesions, as it suppressed C5aR expression (6). Since K-76COONa is known to have anti-complement activity, perhaps by preventing the activation of the C5-C5aR binding that chemotaxis the immune cells into the intima, persistent suppression by this novel inhibitor may have negatively impacted the rabbit's immunity.

Atherosclerosis-related factors such as macrophages are known to express C5aR or CD88, which binds to the C5a ligand to conduct a variety of biological tasks that may be proatherogenic or antiatherogenic (Figure 2). Many investigations have found that simply linking C5a to the C5aR found in immune cells within atherosclerotic lesions has a proatherogenic effect, and this has been demonstrated in various research (6, 29). To change the atherogenic habitat, C5a acts as a chemoattractant for monocytes, T lymphocytes, and mast cells. The synthesis of proatherogenic and antiatherogenic cytokines,

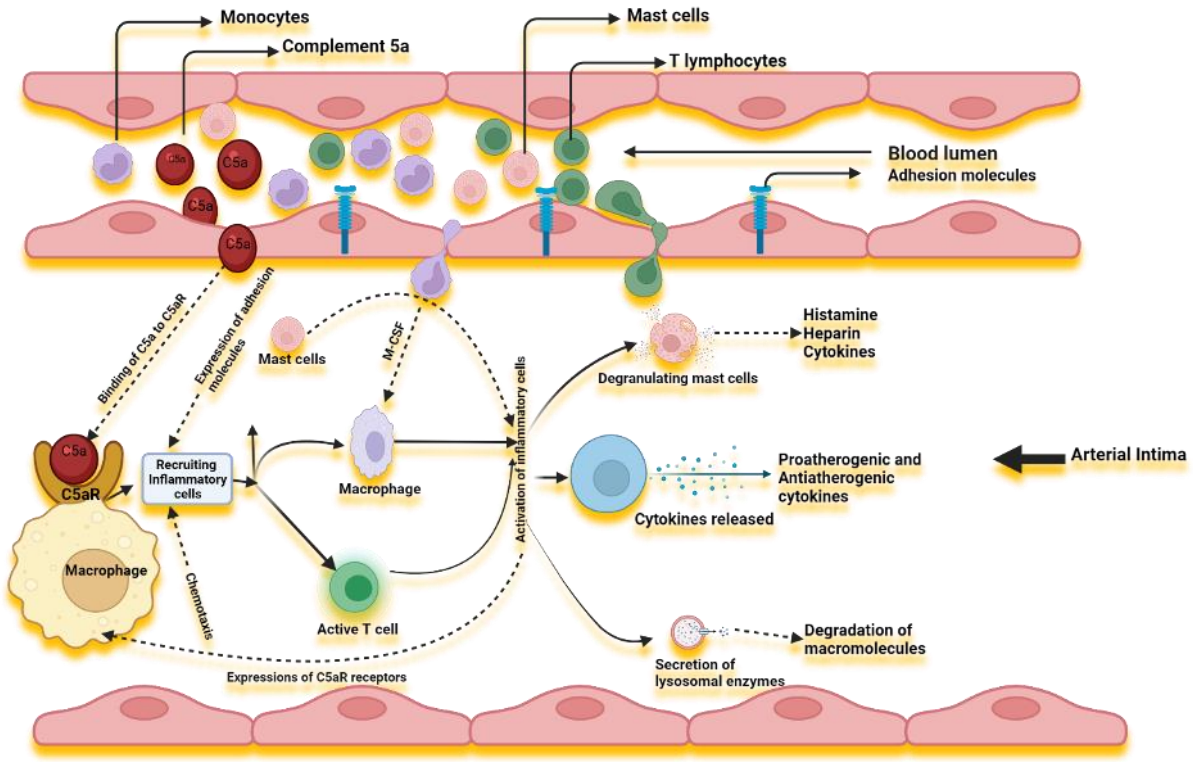

Figure 2: The C5a binding to macrophage-produced C5aR causes inflammatory responses in atherosclerosis. Chemotactically, the binding of C5a to its receptor draws monocytes, T lymphocytes, and mast cells from the bloodstream to the artery intima. Once there, these cells are activated, which leads to the production of cytokines, the expression of C5aR, the proliferation of T cells, and the degranulation of mast cells

expression of related receptors, macrophage secretion of lysosomal enzymes, T lymphocyte proliferation, and mast cell degranulation are all driven by C5a's direct stimulation of inflammatory cells (3).

Influence of immune cells expressing CD88 to atherosclerosis – Macrophages, Dendritic cells (DC's), T lymphocytes (Th1, Th2, Tregs, Th17, Th9), B lymphocytes

Macrophages are not the only kind of cell found in atherosclerotic lesions; other immune cells such as DCs and T lymphocytes also contribute to atherosclerosis. Atherosclerosis is a chronic inflammatory disease of the artery wall that is primarily caused by myeloid cells from the innate immune system. Adaptive immune cells are not essentially involved in the initial stage of the development of atherosclerosis, but they are significantly important in the disease's progression and consequences. The anti- and pro-atherogenic processes are driven by T and B lymphocytes, which are prevalent in both mouse and human atherosclerotic plaques (16, 30). C5aRs are found in both innate and adaptive immune cells, and they bind to the ligand C5a to cause a range of biological consequences. Studies in humans and experimental animals are increasingly implicating the C5a-C5aR axis in atherosclerosis (3). Atherosclerosis-prone animals' atherosclerotic plaque development is significantly reduced when C5aRs are either absent or blocked (3).

The macrophages are huge mononuclear phagocytic cells found in nearly all human and animal tissues (31), performing a variety of functions, one of which is phagocytosis. In addition to phagocytosis, they play a crucial role in innate immunity (31) and help launch adaptive immunity by attracting other immune cells such as NK cells, T cells, and B cells (27). Macrophages are key players in the proinflammatory process, causing inflammation and bolstering the immune system (32). Macrophages can decrease immune responses by producing cytokines, which have an anti-inflammatory effect. As the most common immune cell in atherosclerotic lesions, macrophages are implicated in all stages of atherosclerosis, including the onset and progression of advanced atherosclerosis (18). Macrophages also encourage the creation of intricate and unstable plaques by maintaining a pro-inflammatory microenvironment. Tissue repair and remodeling, as well as plaque stability, are all supported by anti-inflammatory macrophages (33). Based on their role in inflammatory reactions, macrophages are divided into two phenotypes: M1-proinflammatory and M2-antiinflammatory (34). M1 macrophages promote while M2 macrophages hinder atherogenesis (32, 34).

Macrophages are very important in atherosclerosis (33, 35). They derive from circulating monocytes after being stimulated by a monocyte colony-stimulating factor (36). Early in atherosclerosis, the conversion of monocytes to

macrophages and the modification of LDL in the arterial wall are essential. When monocyte-derived macrophages take up modified LDL, they transform into fat-loaded macrophages that dwell in the arterial wall, exacerbating the local inflammatory response and promoting the progression of atherosclerotic plaque. Leukocytes cannot adhere to endothelial cells under normal conditions, but during the early stages of atherosclerosis, oxLDL causes endothelial cells to express certain adhesion molecules on their surfaces, such as E-selectin, P-selectin, VCAM-1, and ICAM-1 that bind to diverse receptors on the surface of leukocytes (19, 37). Also, the main thing that makes monocytes move into the intima is monocyte chemo-attractant protein-1 (38). During atherogenesis, monocytes multiply and travel into the intima, where they become macrophages and absorb lipoproteins, forming foam cells (39, 40). Intimal monocyte colony-stimulating factors promote the maturation of blood monocytes into macrophages (36, 39).

Foam cells are formed from atherosclerotic artery macrophages during a multi-step transformation process, and these cells are crucial to atherogenesis (Figure 3). The artery wall increases LDL oxidation by a variety of mechanisms involving enzymes or free radicals such as superoxide, hydrogen peroxide, and nitric oxide (40). Excessive oxidative stress causes LDL modification, resulting in signals detected by pattern recognition receptors, such as the CD36 receptor on macrophage immune cells, which recognizes LDL oxidation-specific epitopes (40). Scavenger receptors like CD36 are present on macrophages, and they can recognize and internalize oxidized LDL (Figure 3). macrophages generate several pro-inflammatory mediators in response to the interaction with oxLDL, leading to persistent inflammation response. Monocytes are drawn to the intima by chemokines, such as CX3CL1 and CCL2, that are created during the inflammatory phase (41). Foam cells produce inflammatory cytokines and chemokines, which cause the upregulation of endothelial cell adhesion molecules and the continued build-up of leukocytes in the intima. This event causes an increase in the local inflammatory response in the intima (41).

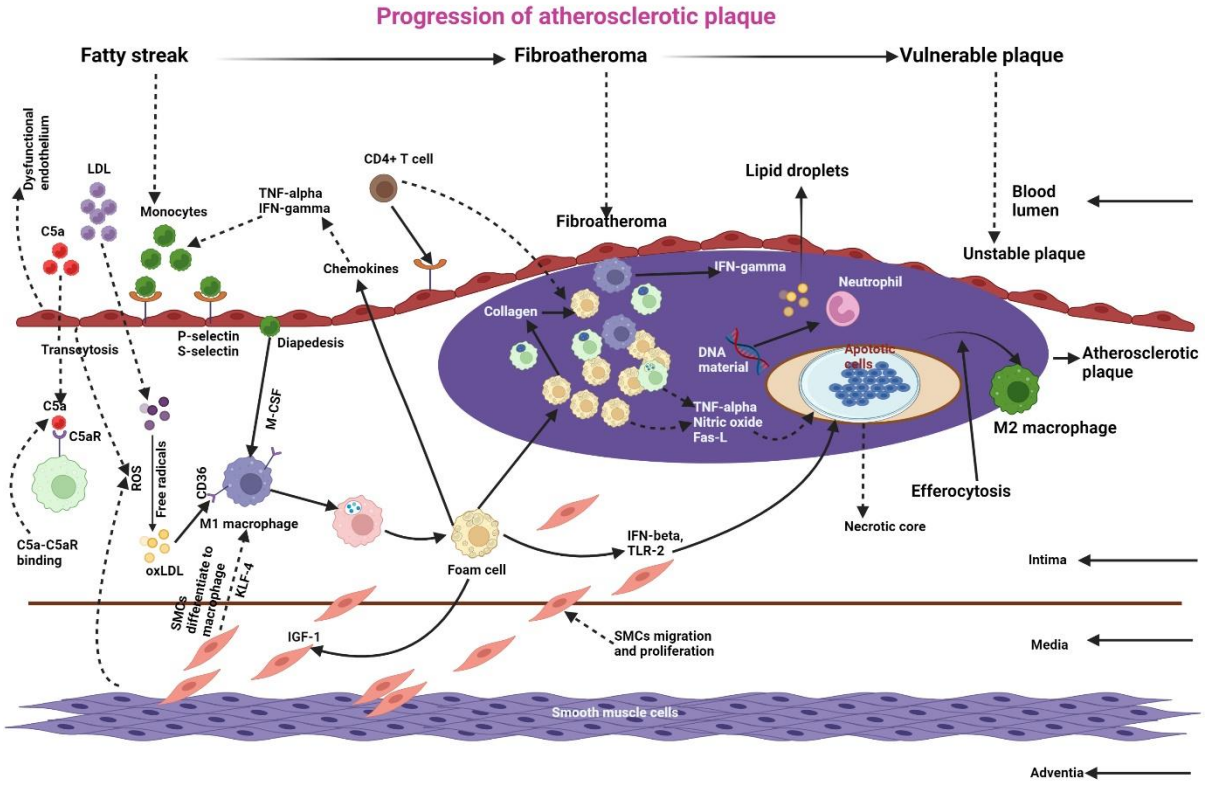

Figure 3: C5a is a chemotactic molecule that can only bind to the C5aR on CD88-expressing immune cells like macrophages as indicated in this figure. The binding of C5a-C5aR expressing macrophage triggers their participation in the progression of atherosclerosis from fatty streak to unstable plaque through fibroatheroma. Subendothelial cell space or transcytosis allows LDL to enter the intima. A faulty endothelial cell and SMCs oxidized LDL in the intima by producing ROS, a reactive oxygen species (ROS). Adhesion molecules like P and S selectin attract monocytes into the intima. M-CSF helps monocytes become macrophages. Macrophages absorb oxLDL via CD36 and transform into foam cells, which contribute to the pro-inflammatory environment by producing chemokines that recruit more monocytes. Foam cells released IGF-1, causing SMCs to multiply and migrate into the intima. A dead foam cell's lipids and DNA attract neutrophils. Pro-inflammatory cytokines generated by macrophages and neutrophils inflame advanced atherosclerotic plaques. Macrophages cause the release of IFN-γ from T-cells, which increases inflammation and activates endothelial cells, which then attract more monocytes to the site of inflammation

Macrophages can synthesize and secrete C5, which suggests that they could serve as local sources of C5a production during atherogenesis (42). Inflammatory cells are recruited and activated, cytokines and chemokines are produced, and granule-based enzymes are released when macrophages express CD88 during atherogenesis (3, 7). Its ligand C5a has proinflammatory effects when it interacts with its receptors in atherosclerotic lesions, which can be generated by macrophages during atherogenesis ([13, 6]). This interaction affects the formation of plaques as well as their stability and ability to break. According to (43), immunizing monocytes with peptides positioned at the C5aR's N-terminus reduces monocyte differentiation into macrophages, resulting in a reduction in early atherosclerotic plaque development. Macrophages, endothelial cells, smooth muscle cells, and mast cells all express C5a receptors. Inflammatory chemo-attractant C5a is recognized by C5aR-expressing macrophages, which attract leukocytes to the atherosclerotic plaques. As atherosclerosis develops, C5aR-expressing macrophages stimulate the endothelium to produce and release a wide spectrum of pro-inflammatory and anti-inflammatory molecules, which in turn causes the atherosclerotic plaque to become more unstable. It has been proven that macrophages have a role in the development of atherosclerosis and the breakdown of atherosclerotic plaques in both *in vitro* and *in vivo* contexts and this immune cell expresses C5aR at a higher level than other cells (3, 39).

DCs are adaptive immune activators seen in both normal and atherosclerotic artery walls (44, 45). Due to their many roles, including lipid uptake, antigen presentation, efferocytosis, and inflammation resolution, DCs have recently been shown to have a functional role in all stages of atherosclerosis (44). The number of DCs increases during the early phases of atherosclerotic lesions (45). There are several possible explanations for this, including the activation of improved differentiation of quiescent DCs precursors that pre-exist in the subendothelial layer and are likely to have developed from embryonic stages, or the migration of monocytes and DC precursors from the bloodstream into the intima. For DCs to enter the intima, chemotactic stimuli and adhesion molecules are required (46). In addition, G-CSF stimulates monocytes to grow into DCs in endothelial tissue, and G-CSF is known to be regulated by C5a binding to its receptor C5aR or CD88 (44). DCs help makes early foam cells, regulate lipid metabolism, and control T-cell responses (Figure 4). Unlike macrophages, most DCs in atherosclerotic lesions do not convert into foam cells (45). The interaction between DCs and oxLDL results in an increase in proatherogenic cytokines like IL-6 and IL-13, whereas IL-10, is downregulated. This increases pro-inflammatory cytokines in DCs.

Chemokines, adhesion molecules, and VCAM-1 all help DCs bulk up in the intima of the artery. DCs adhesion to endothelial cells is increased by oxLDL in vitro (46). In the intima of the artery, damage-associated molecular patterns and pathogen-associated molecular patterns arising from microorganisms can activate and mature immature DCs (45, 46). TLR4, which is involved in the onset and progression of atherosclerosis, is one of the numerous receptors via which DCs receive signals (47). TLR4 expression by DCs during atherogenesis detected changed autoantigen, triggering a signaling cascade (47, 48). TLR4 and C5aR interplay in DCs during atherogenesis is the subject of a recent study, which could lead to the discovery of a new research focus on the pathogenesis of atherosclerosis (49). Direct communication between DCs and B cells in atherosclerotic plaques has been established (45). This interaction may lead to the generation of antibodies, thus more research on this aspect is warranted. CD88, a chemo-attractant for B-lymphocytes, is also expressed by DCs in the plaque.

Atherosclerosis is caused by an inflammatory process in the intima of an artery (40). Prior research on atherosclerosis has focused on innate immunity rather than immune-mediated inflammation (50). Pathophysiology of atherosclerosis may be especially interested in the complement system and toll-like receptors (TLRs), as well as how they work together (50). However, immune responses to plaque antigens have just recently been shown to diminish inflammation. These responses are heavily reliant on T cells (27). Activation of pro-inflammatory Th1 and NKT cells in response to self-antigens in the plaque can promote disease development, but activation of anti-inflammatory regulatory T cells can prevent disease progression (51). CD4+ T cells are a broad group of lymphocytes that can both promote and inhibit inflammation (Figure 5). Though CD88 has been discovered on human and mouse inactivated T cells by some researchers, others have not, or have only detected it in specific subsets, on lymphocytes (6, 13). The expression of C5aR in CD4+ Th cells, whether naive or activated, has not been demonstrated in vitro or in vivo (4). Furthermore, the modulation of adaptive immune responses has been associated with C5aR signaling. Several studies show that APCs use C5a to control T cell proliferation and differentiation (4, 6, 12-13). T-box expressed in T cells (T-bet) and the signal transducer and activator of transcription 4 (STAT4) are two transcription factors that promote Th1 cell maturation in naive CD4+ T cells produced by antigen-presenting cells (Figure 5). T-bet deficiency in Lldr/ mice reduces atherosclerosis, proving that Th1 cells are pro-atherogenic (52). Th1 cells release pro-inflammatory cytokines including IFN-γ and TNF-α (53).

Th2 cells are a CD4+ T cell subset that primarily interacts with B cells (54). Th2 cells seem to have a more complicated role in atherosclerosis than Th1 cells because they have both pro-and anti-atherogenic effects (20). By inducing the expression of T-box expressed in T cells GATA-3 and STAT4, IL-4 induces Th2 cell differentiation (Figure 5). Antiatherogenic cytokines like IL-5, IL-10, IL-13,

and IL-25 are released by activated Th2 cells, while proatherogenic cytokines like IL-4 and IL-9 are released by active Th2 cells (55). IL-5 protects against atherosclerosis

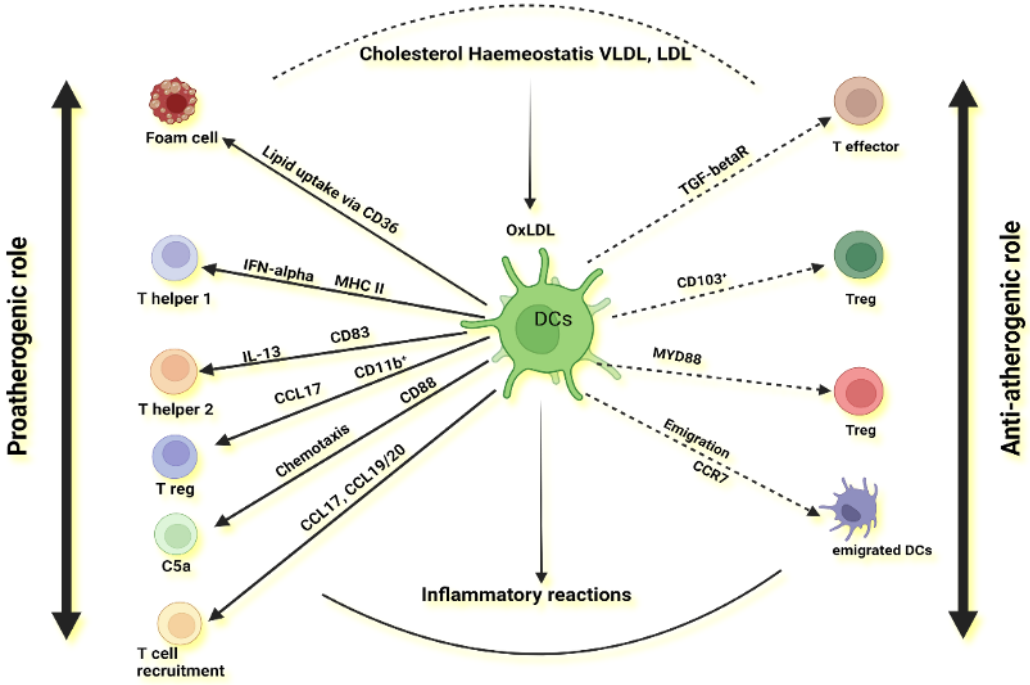

Figure 4: Proatherogenic DCs and antiproliferative DCs are prevalent in atherosclerotic lesions portrayed in the figure. Initially, DCs can devour lipids and resemble foam cells, indicating early plaque development. By reducing VLDL and LDL (low-density lipoprotein) levels, DCs help to keep cholesterol levels in check (LDL). It is conceivable for CCR7-dependent DCs to emigrate from atherosclerotic plaques. T lymphocytes may be attracted to the inflamed vessel wall by DCs using CCL17, CCL19, or CCL20. In atherosclerosis, TGF-type II receptor stimulation in DCs stops the proinflammatory T-cell activity. TLR adaptor MyD88 is required in DCs for Treg-mediated atherosclerosis control. The activation of Th1 cell responses and the release of interferon (IFN) by the Major Histocompatibility Complex II promotes atherosclerosis in DCs. CD11b+ DCs that express CCL17 inhibit Treg responses, resulting in atherosclerosis. CD103-positive DCs stimulate Treg responses and protect against atherosclerosis. C5a chemoattracts leukocytes when oxLDL interacts with DCs, causing atherosclerosis to develop. In addition, when oxLDL and DCs interact, DCs release IL-13, which increases the production of Th2 cytokines that promote atherosclerosis. Adapted and modified from (Zernecke, 2015)

in hypercholesterolemic mice (56). IL-33, another cytokine that can trigger Th2 responses, has been shown to protect ApoE-/- mice from developing atherosclerosis (57).

Tregs can control the priming and execution of T effector responses by preventing effector T-cell activation by direct contact or suppressing APCs (58). Tregs are essential for regulating immune effector responses and maintaining self-tolerance (59). ApoE-/- mice also had fewer Tregs in the spleen and a lower Treg suppressive function than age-matched control mice (60). For the development of atherosclerosis, the balance between different T-cell subsets is crucial (61). ApoE-/- mice have higher levels of Th17 cytokines and decreased Treg numbers and TGF- secretion when compared to wild-type mice (62). Overall, data suggest that immunological tolerance, as mediated by Treg, is hampered in atherosclerosis (51, 60). Tregs appear to protect against atherosclerosis in mouse studies. Treg cell depletion also implies that Treg cells protect against atherosclerosis (63). Reduced Treg levels cause a significant worsening of atherosclerosis in mice. This was investigated in mice models lacking CD80/86, CD28, or ICOS, as well as mice treated with CD25-neutralizing antibodies (64).

Th17's exact role in human atherosclerosis is uncertain and controversia (65). The role of IL-17 in atherosclerosis has been investigated in numerous mouse models, with inconsistent results, with pro-and anti-atherogenic effects attributed to Th17 (66). Th17 cells can trigger both pro-inflammatory and anti-inflammatory immune responses depending on the environment and the condition (65). Th17 cells generate TNF-, IL-6, IL-10, IL-17F, IL-21, IL-22, and IL-23 in addition to the hallmark cytokine IL-17A (also known as IL 17). ROR- γt, ROR- α, and STAT-3 are nuclear receptors that distinguish Th17 cells from naive Th cells (Figure 4). In mice, TGF-, IL-6, and IL-23 are essential for Th17 differentiation, whereas IL1- appears to be important for human Th17 development. Th17 development and maintenance necessitate cytokines such as IL-21 and IL-23. TGF- does not directly promote Th17 development, rather it does so through inhibiting

transcription factors that promote Th1 and Th2 differentiation. STAT-3, which is essential for the production and function of the transcription factor ROR-γt, is activated by IL-6 (Figure 5).

T helper 9 (Th9) cells, which release large amounts of interleukin-9 (IL-9), play a role in several autoimmune disorders and inflammation (67). Combining IL-4 and TGF- induces a Th9 phenotype in CD4+ cells (Figure 5). After rIL-9 injection, treatment with IL-9 mAb dramatically reduced plaque size, suggesting that Th9 cells and IL-9 play a pathogenic role in atherosclerosis (68). Th9 cells have been found in plaques and are thought to serve an anti-atherogenic role (30).

B cells are lymphocytes that make antibodies and emit cytokines, which are important in both innate and adaptive immunity. The presence of both pro-and anti-atherogenic features in both intimal and adventitial B cells has been discovered to play a role in atherogenesis (54). Atherosclerosis appears to be promoted by B2 B cells whereas it appears to be slowed by B1 B cells, which may be due to the secretion of interleukin (IL)-10. B cells have emerged as essential immune cells in the regulation of atherosclerosis. In atherosclerotic lesions, B cells are less numerous than T cells, but they do exist (69). The fact that some IgM and IgG species protect against atherosclerosis supports the idea that B cells play an atheroprotective role (54). Anti-oxLDL IgM antibodies may protect against atherosclerosis by binding to oxLDL and thereby reducing oxLDL absorption by macrophages and the formation of foam cells (70). In mouse atherosclerotic lesions, B-cells can be seen in both early and advanced stages, whereas they can only be found in advanced stages in human lesions (71). B-cells play a critical role in both humoral and adaptive immune responses. Antigen presentation and cytokine synthesis by B-cells govern T-cell activation and antibody production. Although the link between B-cell-produced autoantibodies and atherosclerosis was recognized decades ago, the molecular processes by which B-cells contribute to atherosclerosis remain unexplained. B-cells have recently been discovered to serve a pro-atherogenic role (54), calling into question the previously held belief that B-cells were atheroprotective.

Leukocyte recruitment to tissues, which is a crucial stage in the inflammatory response, requires leukocyte binding and extravasation in the vasculature. C5a's B cell-directed chemotactic activity may aid researchers in better understanding the mechanisms of B lymphocyte recruitment to inflamed tissues, which could lead to new insights into the pathophysiology of inflammatory disorders such as atherosclerosis.

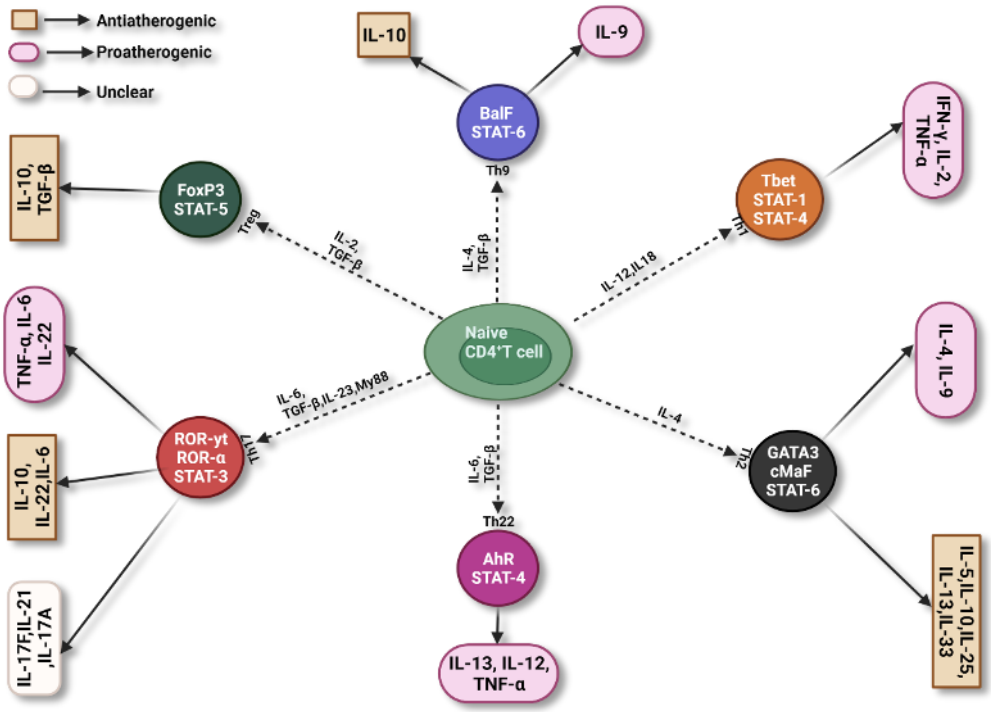

Figure 5: The effect of innate immune cell mediators, especially macrophages, on CD4+ T cell maturation in atherogenesis. When immune cells like macrophages express C5a-C5aR, they trigger the differentiation of naive CD4+ T cells into diverse T helper cell subsets, which in turn releases multiple cytokines that drive the development of atherosclerosis. Many different cytokines contribute to the development of inflammation by releasing more proatherogenic cytokines. Mature T cells secrete a variety of cytokines, some of which have antiatherogenic activities. Th17 secreted IL-6, a pro-and anti-atherosclerotic cytokine. Although the functions of IL-17A, IL-17F, and IL-21 produced by the Th17 subgroup are unknown, it is presumed that IL-22 has an antiatherogenic role during the process of

atherogenesis

Naive and memory B-lymphocytes, however, displayed very minimal C5aR expression that was sufficient to elicit an in vitro response to recombinant C5a. Meanwhile, the role of the B reg and B10 subgroups in the control of atherosclerosis remains uncertain. Another important function of B cells, aside from antibody production and cytokine release, is to enhance T-cell-mediated responses. For example, they can behave as APCs, which transmit co-stimulatory signals to T cells, in which B cells can chemoattract and activate T cells during atherogenesis by expressing the CD88 antigen.

Trends for the future

Complement components can be triggered by a variety of events in atherosclerotic lesions, and evidence is mounting suggesting the C5aR is active within atherosclerotic plaques. Atherosclerotic plaques may be prevented from forming through complement activation's removal of dead cells and cell debris, but there are multiple studies in animals that contradict this theory. Activation of complement components, notably C5a, is assumed to have a pro-inflammatory effect; nevertheless, C5a's active activity has been shown to have an anti-inflammatory effect as well. C5a's function in the plaque's terminal end, and maybe its part in plaque rupture, is a big advance, even though it has been connected to the formation and progression of atherosclerotic plaques. Furthermore, several immunohistochemical studies have found that activated C5a is more common in unstable than stable atherosclerotic lesions, implying that C5a is involved in plaque stability. To determine their roles in atherosclerosis pathogenesis, more study is needed in the future to classify diverse macrophage populations based on their morphological and functional characteristics based on the overexpression or downregulation of CD88 during atherogenesis. The identification of components of the complement system that could be exploited as therapeutic targets for the prevention and/or treatment of atherosclerosis will require more investigation. The need to concentrate efforts on understanding the precise involvement of the Th17 subgroup in the atherogenic context was also essential at this point. It is necessary to determine if CD88 is increased or downregulated when there is an equilibrium balance between T cell subsets to conduct further research.

Conclusion

This review looked at the involvement of C5aR (or CD88) in the pathophysiology of atherosclerosis, with an emphasis on their role in leukocyte recruitment, foam cell formation, and cytokines production in the development of atherosclerosis. C5aR expression primarily regulates leukocyte chemotaxis to the intima of the artery wall, where they consume oxLDL and generate foam cells, which are important in the progression of atherosclerosis plaques. While the exact significance of the C5a-C5aR interaction in atherosclerosis is still being researched, new studies reveal that it is a significant element in the initiation and progression of atherosclerotic lesions. As a result, inhibiting C5a synthesis or blocking C5a receptors is an intriguing target for fighting this disease.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Rafeezul Mohamed and Muhammad Amir Yunus designed the conceptual framework, and Hayatuddeen Muhammad Rumah drafted the review manuscript.

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