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Function of CD147 in atherosclerosis and atherothrombosis

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Abstract

CD147, a member of the immunoglobulin super family, is a well-known potent inducer of extracellular matrix metalloproteinases. Studies show that CD147 is upregulated in inflammatory diseases. Atherosclerosis is a chronic inflammatory disease of the artery wall. Further understanding of the functions of CD147 in atherosclerosis and atherothrombosis may provide a new strategy for preventing and treating cardiovascular disease. In this review, we discuss how CD147 contributes to atherosclerosis and atherothrombosis.

Keywords

CD147; Atherosclerosis; Atherothrombosis

Introduction

Atherosclerosis is a known inflammatory disease. Therefore, investigation of the key inflammatory mechanism involved in atherogenesis is crucial for designing therapeutic strategies targeting cardiovascular disease.

CD147, also known as extracellular matrix metalloproteinase (EMMPRIN) or basigin [1], is a member of the immunoglobulin super family and expressed at varying levels in many cell types, including hematopoietic, epithelial, and endothelial (ECs) cells and leukocytes [2–4]. The protein was originally discovered on the surface of solid tumor cells [5] and found to induce the expression of various matrix metalloproteinases (MMPs) in adjacent fibroblasts [6] by homotypic interactions with other CD147 molecules.

Overexpression of CD147 has been observed in inflammatory disease, such as lung inflammatory disease [7, 8], rheumatoid arthritis [9–13], systemic lupus erythematosus [14], and ischemic injury [19, 20] and significant amount of evidence has highlighted the potential effects of CD147 in atherosclerosis [15–18]. In vitro data show that pro-atherogenic stimuli, such as low -density lipoproteins (LDLs), C-reaction protein (CRP),

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Disclosures

None.

advanced glycation end-products, and high glucose levels, can stimulate CD147 expression in inflammatory cells [37–39]. Anti-atherogenic drugs, such as fluvastatin can inhibit CD147 expression in macrophages [39]. Oxidized LDLs can upregulate CD147 expression and soluble CD147 (sCD147) release in human coronary artery smooth muscle cells [40]. CD147 expression is also significantly upregulated in activated ECs. All of these findings suggest that CD147 performs an important function in atherosclerosis. In this review, we summarize the multiple functions of CD147 in atherosclerosis and atherothrombosis.

Structure and receptors of CD147

The CD147 gene is located on chromosome 19 p13.3 and encodes a 29 KD protein. It usually occurs between the 35th and 65th KD migrations on SDS-PAGE, depending on the degree of glycosylation [21–23]. The protein consists of two C2-like immunoglobulin extracellular domains, a transmembrane, and a short cytoplasmatic domain [24–26]. Treatment with endoglycosidase F leads to a mobility shift from approximately 58 KD to 28 KD, thereby suggesting that the majority of CD147 glycosylation events is N-linked [21]. A distinct CD147 transcript that encodes for three Ig domains has been identified; this transcript has been shown to be responsible for homophilic CD147 interaction [27].

CD147, as a transmembrane protein, interacts with several other proteins, such as integrins [29], CD98 [30], CyPA [31], CyPB [32], CyP60 [33], caveolin-1 [34], MMP-1 [35], and the proton-coupled transporters of monocarboxylates (MCT-1 and MCT-4) [36]. It can also form oligomerization [28]. Proline 180 and glycine 181 residues in the extracellular domain of CD147 are important to CypA-induced signaling events involving mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF- κ B), which may participate in many biological functions in atherosclerosis, including activation, migration, and proliferation of atherosclerosis-related cells and regulation of various proinflammatory cytokines.

The function of CD147 in atherosclerosis and atherothrombosis

CD147 is minimally expressed in normal vessels, but its expression increases following inflammation and vascular injury. Increased expression of CD147 is detected in human atherosclerotic plaques, localized predominantly in regions rich in macrophages, SMCs, and MMP-9-positive cells [15, 43]. Kim [44] et al. reported that CD147 and its receptor, CyPA, are co-expressed in EC layers facing the lumen as well as macrophage-rich areas. Clinical data show that elevated levels of CD147 in platelets, monocytes, and granulocytes in circulation, as well as higher levels of sCD147 in plasma, are observed in patients with coronary artery disease (CAD). Levels of CD147 expression in platelets appear to correlate with the extent of CAD [45]. These findings suggest that CD147 may contribute significantly to the pathological processes of atherosclerosis and atherothrombosis. Below, we discuss the cell-specific functions of CD147 in atherosclerotic disease.

Roles of platelet CD147

Platelet activation contributes to the pathogenesis of atherosclerosis and thrombosis. Although the function of CD147 in platelets remains unclear, several evidences have established as lines. First, CD147 expression in platelets occurs in an activation-dependent

manner. CD147 is localized in the open canalicular system and α -granules of platelets and transferred to the external surface of cells following stimulation of the platelets. Resting platelets show low surface expression of CD147, which is upregulated by various platelet stimuli (e.g., thrombin, ADP, and collagen) [46]. Second, CD147 can interact with homophilic proteins and perform an important function in platelet activation and recruitment. Binding of recombinant soluble CD147 to platelets induces platelet degranulation with enhanced surface expression of CD40L and P-selectin. Third, CD147 expression in platelets can promote NF- κ B-dependent inflammatory processes in monocytes. Incubation of platelets with monocytes leads to NF- κ B dependent induction of inflammatory cytokines (e.g., IL-6 and TNF- α) and MMP-9 in monocytes via CD147. Pretreatment with CD147 siRNA or blocking antibody reduces this effect [46]. Moreover, pro-atherogenic factors can stimulate platelet CD147 expression and sCD147 release. Ox-LDL is involved in initiation of atherosclerotic lesions, inducing not only foam cell formation and vascular endothelial damage but also platelet interaction during with circulation. Yang et al. [47] found that ox-LDL stimulates platelet CD147 expression and sCD147 release via binding to LOX-1 and that HDL inhibits this effect.

Besides functioning as a signaling receptor, CD147 also functions as an adhesion receptor through homotypic interaction with other CD147 molecules and the platelet collagen receptor glycoprotein VI (GPVI). Seizer et al. [48] observed that activated platelets show significantly enhanced rolling in immobilized CD147-Fc and that blockage of CD147–GPVI interaction using CD147 or GPVI blocking antibodies greatly reduces rolling; these findings indicate that the platelets may come into contact with and bind to the CD147 expression surface. Findings are further supported by the observation that CD147–GPVI binding is involved in platelet-monocyte interactions in vivo, which augment monocyte recruitment to the vascular wall [49].

Effects of CD147 on inflammatory cells

CD147 performs multiple functions in interactions between platelets, leukocytes, and ECs as well as monocyte differentiation (Figure 1). Inflammation cell migration and differentiation are pivotal steps in the early phases of atherosclerosis. CD147 expression has been shown to be induced in activated leukocytes, such as neutrophils, lymphocytes, and monocytes [50]. Its function may be correlated with the inflammatory response in atherosclerosis. Damsker et al. [10] demonstrated that proinflammatory leukocytes, specifically neutrophils, monocytes, and activated CD4 (+) T-cells, lose their ability to migrate in response to cyclophilin A in vitro when treated with anti-CD147 monoclonal antibody.

(1) Neutrophils

Recent evidence has emerged to suggest an important function of neutrophils in the initial phase of atherosclerosis in mice. Early neutrophil inflammatory signals trigger intimal recruitment of monocytes, which differentiate into macrophages and internalize native and modified LDL, thereby leading to foam cell formation [51]. The functions of CD147 in neutrophils have recently been explored. First, CD147 is associated with neutrophil proinflammatory characteristics. Blockage by CD147 siRNA or anti-CD147 antibody in vitro can decrease MMP production and inhibit neutrophil chemotaxis [53, 54]. Second,

CD147 contributes to neutrophil recruitment to inflammatory tissues. Kato et al. [52] found that CD147^{-/-} neutrophils exhibit reduced binding to E-selectin and E-selectin-dependent adherence to human umbilical vein endothelial cells (HUVECs). As a physiological ligand for E-selectin, CD147 is responsible for neutrophil recruitment in renal ischemia/reperfusion in vivo. In an acute myocardial infarction model, Seizer et al. [46] found that neutrophil recruitment into the infarct border zone is significantly reduced in CD147^{+/-} mice and anti-CD147 mAb-treated mice; similarly, macrophage recruitment is significantly reduced in CD147^{+/-} mice and anti-CD147 mAb-treated mice. Many other in vivo studies show that blocking CD147 can reduce tissue inflammation. Arora et al. [55] found that blocking cyclophilin-CD147 interactions by targeting CD147 (using anti-CD147 Ab) or cyclophilin (using a non-immunosuppressive cyclosporine A analog) reduces tissue neutrophilia by up to 50% with a concurrent decrease in tissue pathology using a mouse model of acute lung injury. All of these data show that CD147 mediates neutrophil adhesion and infiltration into acute inflammatory sites and reveals the vital functions of CD147 in the initial phase of atherosclerosis.

(2) Monocytes/macrophages

The functions of CD147 in monocytes and macrophages has been recently studied. First, CD147 expression is upregulated in monocytes as it is stimulated by atherogenic proinflammatory cytokines accompanied with increased MMP expression [15]. Second, CD147 mediates monocyte chemotaxis and adhesion. In vitro research has shown that treatment with CyPA (an important ligand of CD147) induces monocyte chemotaxis and promotes monocyte rolling and adhesion to HUVECs under flow conditions but that these effects are inhibited by an anti-CD147 antibody [56]. Moreover, CD147 is required for induction of MMP9 and MT1-MMP on monocytes. MT1-MMP has recently been reported to facilitate monocyte migration through activated ECs in vitro [57]. Thus, CD147 mediates monocyte migration into the subendothelial space by regulating MT1-MMP expression.

After settling under the endothelium, monocytes differentiate into macrophages that endocytose lipids and further differentiate into foam cells. Foam cell formation is a key mechanism in atherosclerosis. Advanced atherosclerotic plaques that tend to rupture are rich in activated macrophages and foam cells. Increased expression of CD147 is reported when monocytes are differentiated into macrophages [9, 43]. Overexpression of CD147 and release of its ligand CyPA during foam cell development originates not only from monocytes/macrophages but also from CD34⁺ progenitor cells. CD147 appears to regulate not only MMPs on foam cells but also a broader spectrum of inflammatory proteins, such as M-CSF. Blockage of CD147 hinders these effects [58]. Therefore, CD147 contributes to inflammatory processes within plaques and aggravates atherosclerotic process.

(3) T-cells

The innate response initiated by activation of monocytes/macrophages in the vessel wall followed by more specific adaptive responses is mediated by T- and B-cells [59, 60].

Although, the actual and complex mechanism of CD147 in T-cells has yet to be completely understood, there are several evidences about the role of CD147 as lines. First, CD147 is

strongly upregulated in CD4⁺ and CD8⁺ T-cells once T-cells are activated [61]. Up-regulation occurs when T-cells are activated through their TCR or by mitogens, such as phytohemagglutinin (PHA). CD147-dependent T-cell activation occurs at the level of antigen presenting cells rather than actual T-cells, which may be attributable to the function of CD147 as an adhesion molecule [62, 63, 23]. Second, CD147 exerts both positive and negative effects on T-cell biology. The functions of CD147 on lymphocyte activation and cell adhesion regulation may be determined by its different bioactive epitopes [64]. Blocking of CD147 with an antibody could block several aspects of T-cell activity, such as proliferation and cytotoxicity to human neurons, in vitro [65]. CD147, via selective inhibition of specific downstream elements of the Vav1/Rac1 route, also contributes to the negative regulation of T-cell responses [66].

All T-cell subsets (e.g., CD4⁺, CD8⁺, TCRγδ⁺, and NKT cells) have been observed in both human and murine atherosclerotic plaques [67]. Different T-cell subsets perform different functions in atherosclerosis. Among CD4⁺ T-cells, T-helper type 1 (THP1) cells are pro-atherogenic and secrete CD40L, TNF-α, and interferon-γ. These events result in pro-atherogenic sequelae and plaque instability. Huang et al. [68] found that CD147 expression is upregulated in phorbol-12-myristate-13-acetate (PMA)-induced THP1 cells. CD147 is also highly expressed in the cell surface of human regulatory T-cells (Tregs), which are athero-protective [69]. Thus, further studies must be developed to clarify the functions of CD147 on T-cell subsets and atherosclerosis.

Effects of CD147 on endothelial cells

Endothelial cells (ECs) perform a key function in the onset and progression of atherosclerosis. Once injured, the endothelium becomes dysfunctional by releasing less nitric Oxide (NO) and losing its endothelium-dependent vasodilation function, thereby advancing platelet aggregation and promoting adhesion molecule expression. The functions of CD147 in EC have been studied, although the details remain unclear.

First, CD147 expression is significantly upregulated in activated ECs [70]. CD147 induces activated EC proliferation, survival, migration, and MMP secretion. Regenerative ECs settle at sites where atheromas grow to repair the vascular wall but they do not possess all of the properties of normal ECs. For example, these ECs lack the Gi-dependent signaling pathway [71]. The Gi-α subunit is a heterotrimeric G protein subunit that inhibits cAMP production from ATP. Several Gi types have been uncovered, including Gia1, Gia2, Gia3, and Gia4. The Gi signaling pathway triggers arterial relaxation by stimulating endothelial production of NO, vasodilatory arachidonic acid metabolites, and endothelium-derived hyperpolarizing factor. Many leukocytes and lipids deposit under the dysfunctional endothelium to initiate atherogenesis.

Second, angiogenesis is a process also found in advanced atherosclerotic plaques and believed to promote plaque destabilization [72]. CD147 mediates angiogenesis. Research shows that inhibition of CD147 by siRNA leads to significantly decreased angiogenesis in vitro. In a murine B16 melanoma model, silencing of CD147 expression results in the reduced capability of tumor cells to metastasize to draining lymph nodes. CD147

knockdown also decreases VEGF expression in vivo accompanied by reduced blood vessel formation [73].

Effects of CD147 on vascular smooth muscle cells

An important feature of atherosclerosis is thickening of the arterial wall. Vascular smooth muscle cells (VSMCs) accumulate in plaques and contribute to the formation of complicated atheromas. CD147 is important for VSMC multiplication because the protein can induce MMP expression, ECM degradation, and plaque instability. Research reveals that IL-18 and CD147 can mutually stimulate each other's expression and secretion from VSMCs via oxidative stress and phosphatidylinositol 3-kinase (PI3K)-Akt-ERK signaling; IL-8 can also stimulate SMC migration in a CD147-dependent manner. Blockage of IL-18 and CD147 cross-regulation can inhibit SMC migration [74].

Effects of CD147 on the generation of reactive oxygen species

Growing evidence suggests that reactive oxygen species (ROS) are involved in the pathogenesis and progression of atherosclerotic diseases. First, the initial phase of atherosclerosis is sustained by oxidation of LDL cholesterol (ox-LDL) particles, which is taken up by monocyte-macrophages. Ox-LDL depends on the ROS produced by blood cells and resident cells of the artery wall. Increased ROS production is known to impair endothelial and vascular smooth muscle cell functions, thereby contributing to the development of atherosclerosis. In an acute myocardial infarction model, Seizer et al. revealed the decreased presence of 3-nitrotyrosine residues as a measure of oxidative stress in anti-CD147-treated mice compared with corresponding controls via analysis of the left freewall of infarcted ventricles 24 h after ischemia and reperfusion [56]. The exact and complex mechanism of ROS controlled by CD147 has yet to be completely elucidated.

Signaling pathways mediated by CD147 in atherosclerosis and atherothrombosis

In atherosclerosis and atherothrombosis, CD147 mediates a variety of signaling pathways, including NF- κ B, MAPK, and JAK/STAT, to regulate various pathological processes (Figure 2).

NF- κ B is a critical regulator of innate and adaptive immunity and regulates many key inflammatory genes linked to atherosclerosis, such as those of IL-6 and TNF- α . Many studies show that CD147 induces inflammatory activation via the NF- κ B signaling pathway. EMMPRIN-Fc treatment leads to activation of MMP-9, which is hindered by inhibition of the IKK complex. CD147 expression in platelet surfaces can stimulate NF- κ B-driven pathways, such as MMP and cytokine induction, in monocytes [46]. Yuan et al. [75] also found that CD147-ERK-NF- κ B cascade may be the main signaling pathway for CyPA in monocytes/macrophages. CD147 regulates more NF- κ B-related inflammatory cellular activities (e.g., IL-6 and TNF- α) than MMP activity alone. Therefore, CD147 performs multiple functions in regulating inflammatory genes linked to atherosclerosis.

MAPK (ERK1/2) induces several pathological processes of atherosclerosis, such as EC injury, chemotactic migration, leukocyte adhesion, atherosclerosis-related cell proliferation, foam cell formation, and MMP secretion. MAPK (JNK2) and MAPK (p38) contribute to the formation of foam cells and proliferation of VSMCs [76]. In response to various stimuli, CD147 can activate all three MAPK signaling pathways by interaction with CyPA, which appears to be extensively linked to the inflammatory response [77–79].

CD147 is known to be involved in the JAK/STAT pathway, which participates in atherosclerosis development [80]. JAK/STAT is an important signaling pathway that regulates initiation/progression of atherosclerosis and remodeling in response to injury. JAK/STAT activation has been observed in atherosclerotic lesions and vascular cells incubated with cytokines, angiotensin II, and lipids [81].

CD147 may be involved in many other signaling pathways during atherosclerosis development. More studies are needed to fully understand the specific mechanisms linking CD147 to atherogenesis.

Role of CD147 in atherothrombosis

When the thinned out fibrous cap disrupts and exposes the subendothelial, highly thrombogenic layer to the circulation; or the superficial erosion of the fibrous cap caused the plaque rupture, It makes a transition from a chronic phase to an acute event, i.e., acute coronary syndromes or cerebrovascular accidents. The vulnerability of plaques is substantially determined by the activity of MMP and inflammatory cells. When the plaque is ruptured, platelets participate in thrombosis. Yong et al. found that only platelet CD147 expression and not monocyte, granulocyte, or soluble CD147 levels is higher in the coronary circulation of stable coronary disease patients and that upregulation of CD147 expression is independent of shear stress [82]. Nevertheless, CD147 expression in monocytes is significantly upregulated in acute myocardial infarction (AMI) compared with that in chronic stable angina; increased expression of MT1-MMP and MMP-9 activity in the plasma, which are normalized after successful therapy, may also be observed [42]. Consequently, CD147 expression performs a particularly important function in unstable CAD.

Perspective

Evidence to substantiate the functions of CD147 in atherosclerosis and atherothrombosis highlights the important role of CD147 in vascular diseases. First, CD147 expression in both circulating platelets and monocytes and plasma levels of soluble CD147 are significantly elevated in patients with acute vascular events, such as AMI and ischemic stroke. Increased CD147 levels in the circulation may serve as a marker of inflammation and predictor of high risk of acute vascular events. Second, increased CD147 expression can induce activation and recruitment of platelets and leukocytes and promote production of various proinflammatory mediators. CD147 may be a promising therapeutic target for treating atherosclerosis and atherothrombosis. CD147-blocking antibodies, antagonistic peptides [83], and siRNA have been used in animal models to reduce tissue inflammation. CD147^{+/-} mice and mAb anti-CD147-treated WT-mice are largely protected from myocardial I/R injury [56]. Anti-CD147

treatment can also reduce LPS-induced lung inflammation [55]. Similarly, monocytes pretreated with CD147 siRNA show not only reduced recruitment to carotid artery injuries but also lower levels of monocyte–platelet aggregation in the circulation. Moreover, the HAb18G/CD147 antagonistic peptide AP-9 can alleviate progressive joint destruction of rheumatoid arthritis by reducing MMP production and the invasive potential of synoviocytes. Therefore, CD147 provides new opportunities with which to advance vascular disease therapy.

Conclusion

Increased CD147 expression has been implicated in atherosclerosis and atherothrombosis. However, because of its pleiotropic and multiple effects, many other specific mechanisms and biological functions through which CD147 participates in atherosclerosis and atherothrombosis remain unclear. More studies are needed to evaluate the functions and therapeutic potential of CD147 in atherosclerosis and atherothrombosis.

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Figure 1.

Function of CD147 in interactions between endothelial cells, platelets and leukocytes as well as monocyte differentiation. IL-6: interleukin-6; TNF-α: Tumor necrosis factor-α; MT1-MMP: Membrane-type matrix metalloproteinase-1 MMP-9:matrix metalloprotein 9; CypA: cyclophilin A; GPVI glycoprotein VI

Figure 2.

Various signaling pathways that CD147 mediates. CD147 mediates a variety of signaling pathways involving mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF- κ B) and JAK/STAT to regulate various pathological processes in atherosclerosis and atherothrombosis. IL-6: interleukin- 6; TNF- α : Tumor necrosis factor- α ; MMPs: matrix metalloproteins.