Minireview

The role of Fcγ receptors in atherosclerosis

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Abstract

Atherosclerosis is widely considered to be an immune-mediated process. Fcγ receptors (FcγRs) contribute to the regulation of a multitude of immune and inflammatory responses and are implicated in human atherosclerotic lesions. Major cell types involved in the pathogenesis of atherosclerosis express FcγRs and their proatherogenic ligands such as immune complexes and C-reactive protein, which act to activate FcγR signaling pathways. This review summarizes recent significant progress addressing the multifaceted roles of FcγRs in atherogenesis which comes from the studies of FcγR-deficient animal models, clinical investigations and *in vitro* molecular and cellular studies. These new findings help us appreciate the emerging role of FcγRs in atherosclerosis, and suggest FcγRs as a potential therapeutic target for atherosclerosis.

Keywords: atherosclerosis, Fc γ receptors, immune complexes, C-reactive protein

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Introduction

It is well established that atherosclerosis is a chronic inflammatory disease of the wall of large- and medium-sized arteries where both innate and adaptive immunity responses play a pivotal role in the initiation, growth and rupture of atherosclerotic plaques.[1] The receptors for the Fc region of IgG (FcγRs) are members of the Ig superfamily and are widely expressed in the hematopoietic system where they regulate the immune and inflammatory responses.[2] Increasing lines of evidence suggest that FcγRs are implicated in the pathogenesis of atherosclerosis. Systemic autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome, are characterized by accelerated atherosclerosis partly due to the presence of autoantibodies and autoantigens, and the subsequent formation of immune complexes (ICs).[3,4] Moreover, several autoantibodies such as those directed against oxidized low-density lipoprotein (oxLDL) and heat shock proteins have been detected in atherosclerotic lesions.[5–8] ICs may form between these antigens and autoantibodies that promote the progression of atherosclerosis via FcγR cross-linkage and activation as well as complement activation.[9] In addition, C-reactive protein (CRP), a crucial mediator of cardiovascular disease, elicits a wide array of proatherogenic effects in a majority of cell types involved in atherogenesis, mostly mediated via FcγR-dependent pathways.[10] In this review, we summarize recent studies addressing the multifaceted roles of FcγRs in atherosclerosis.

The family of FcγRs

Most FcγRs are activating receptors and consist of the high-affinity receptor FcγRI and a family of low-affinity receptors, including FcγRIIA, FcγRIIC, FcγRIIIA and FcγRIIIB in humans, and FcγRIII and FcγRIV in mice.[11] Activated FcγRs result in the phosphorylation of immunoreceptor tyrosine-based activating motifs, leading to the activation of the signaling molecule SYK and the initiation of the downstream signaling cascade. FcγRIIB is conserved in mice and humans and is the only known inhibitory FcγR which transmits inhibitory signals through an immunoreceptor tyrosine-based inhibitory motif contained in its cytoplasmic region.[2] Cross-linking of activated FcγRs results in pathogen clearance by antibody-dependent cellular cytotoxicity, degranulation and phagocytosis, as well as the release of cytokines and other inflammatory mediators. FcγRIIB is co-expressed with activated FcγRs on inflammatory effector cells such as neutrophils and macrophages and negatively regulates activating signals delivered by these receptors.[12,13] Thus, the family of FcγRs provides a prime example of how simultaneous triggering of activating and inhibitory signaling pathways sets the threshold for cell activation to maintain a well-balanced immune response.[14]

Although human and mouse have orthologous FcγRs and, in both species, most of the corresponding genes are clustered in close proximity to each other in syntenic regions on chromosome 1,[12] the human FcγR system is more complex,

and the comparison of Fc γRs between human and mouse is shown in Table 1.[2,11,12]

Proatherogenic effects of Fc γRs

Fc γRs are expressed not only by immune cells such as dendritic cells, macrophages, monocytes, neutrophils, mast cells and B-cells,[2,15] but also by platelets, endothelial cells and vascular smooth muscle cells,[2,16,17] Although B-cells, dendritic cells, mast cells and neutrophils express significant amounts of Fc γRs and have been shown to play a role in atherosclerosis, there are few investigations into the contribution to atherosclerosis of Fc γRs expressed in these cells. This review focuses on the proatherogenic effects of monocytes/macrophages and vascular cells via Fc γR-dependent pathways.

Macrophage-derived foam cells are important constituents of atheromatous lesions. In addition to the scavenger receptor pathway, the uptake of immune-complexed lipoproteins through Fc γRs represents another pathway of macrophage foam cell development. Treatment of monocytes with LDL-ICs containing intact anti-LDL antibody could dramatically increase the ability of these cells to subsequently bind and take up LDL, whereas aggregated LDL or ICs of LDL prepared with F(ab')2 fragments of anti-LDL antibody had no significant effect.[18] These results suggest that the formation and interaction of ICs of LDL with Fc γRs on monocytic cells is involved in the generation of macrophage-derived foam cells. Indeed, foam cell development of monocytes was enhanced by targeting LDL aggregates to Fc γRI or Fc γRII, and this was accompanied by an apparent impairment of LDL degradation through using bispecific antibodies consisting of anti-LDL monoclonal antibodies conjugated to anti-Fc γR monoclonal antibodies.[19] Further study confirmed that the uptake of LDL ICs by macrophages predominantly through Fc γRI led to the transformation of macrophages into foam cells.[20] In addition, high-density lipoprotein (HDL) inhibits the uptake of modified LDL by macrophages, likely through interfering with CD36 and Fc γRI expression.[21] Notably, enhanced CD36 expression in monocytes has been proposed to link autoimmunity and atherosclerosis.[22]

Human macrophages are efficiently activated by LDL-ICs mediated by Fc γRs, as reflected by the release of interleukin-1β (IL-1β) and tumor necrosis factor-α and the accumulation of oxygen active radicals.[23] A subsequent study showed that these effects were due to Fc γRI-mediated activation of the mitogen-activated protein kinase signaling pathway, thus leading to macrophage activation.[24] Moreover, LDL-ICs localized in atherosclerotic lesions induced macrophage matrix metalloproteinase-1 (MMP-1) secretion by cross-linking Fc γRI with Fc γRII.[25] The survival and proliferation of macrophages play a critical role in the pathogenesis of vascular inflammation.[26–28] oxLDL–IgG ICs promote the survival of monocytes by cross-linking Fc γRI with ensuing activation of Akt-dependent survival signaling.[29] On the other hand, Luo *et al*.[30] recently reported that Fc γR activation through cross-linking stimulated macrophage proliferation via the activation of ERK1/2 signaling pathway and the subsequent transcriptional activation of cyclin D1 expression. These results imply that the activation of Fc γR on macrophages may exert a mitogenic effect similar to growth factors and consequently stimulate macrophage proliferation. Taken together, it is clear that the Fc γR-mediated immune reaction induces a variety of metabolic and functional changes in macrophages which are likely to contribute, directly or indirectly, to endothelial damage and the accumulation of macrophages in human atherosclerotic lesions.

Endothelial cells also express Fc γRs and are crucially involved in atherosclerosis.[16,31] Sumiyoshi *et al*.[32] were the first to show that the deletion of the FcR γ chain preserves the endothelial function and attenuates oxidative stress induced by hypercholesterolaemia in FcR $\gamma^{-/-}$ mice. Fc γR also mediated monocyte adhesion to oxLDL-IC deposited on endothelium and the subsequent release of chemokines.[33] Thus, the interaction between Fc γRs and oxLDL-IC may be another mechanism responsible for vascular endothelial cell injury that could contribute to the progression of atherosclerosis. A recent study demonstrated that endothelial nitric oxide synthase (eNOS) antagonism by CRP or ICs is mediated by the coupling of Fc γRI to Fc γRIIB and the subsequent activation of Src kinase and SH2 domain-containing inositol 5′-phosphatase 1. Therefore, Fc γRI and Fc γRIIB emerge as novel therapeutic targets for preventing endothelial dysfunction in inflammatory or IC-mediated conditions.[34]

Table 1 Comparison of Fc γRs between human and mouse

	Mouse				Human					
	Fc γRI	**Fc γRIIB**	**Fc γRIII**	**Fc γRIV**	**Fc γRIA**	**Fc γRIIA**	**Fc γRIIB**	**Fc γRIIC**	**Fc γRIIIA**	**Fc γRIIIB**
Signaling pathways	ITAM FcR-γ	ITIM	ITAM FcR-γ	ITAM FcR-γ	ITAM FcR-γ	ITAM	ITIM	ITAM	ITAM FcR-γ	
Affinity	High	Low	Low	Low	High	Low	Low	Low	Low	Low
Monocytes/ macrophages	+	+	+	+	+	+	+	−	+	−
Neutrophils	+	+	+	+	+	+	+	−	−	+
Dentritic cells	+	+	+	−	+	+	+	−	+	−
B-cells	−	+	−	−	−	−	+	−	−	−
Mast cells	−	−	−	−	−	−	+	−	−	+
Fc γR variants	None				Fc γRIIA-R/H131		Fc γRIIB-I/T232		Fc γRIIIA-F/V158 Fc γRIIIB-Na1/Na2	
IgG isotype	IgG1 IgG2a IgG2b IgG3				IgG1 IgG2 IgG3 IgG4					

Fc γR, Fc γ receptor; ITAM, immunoreceptor tyrosine-based activating motif; ITIM, immunoreceptor tyrosine-based inhibitory motif

Increased platelet expression of FcγRIIa may contribute to greater platelet reactivity and has been associated with a high risk of subsequent cardiovascular events.[35,36] Interferon-γ selectively upregulated the expression of FcγRIIa in cells exhibiting the characteristics of megakaryocytes.[37] Konishi *et al*.[38] demonstrated that FcγRs played a pivotal role in the initiation and generation of neointimal hyperplasia after balloon injury in FcγR-deficient mice through the activation of platelets by collagen. They further confirmed that collagen-induced activation of platelets through FcγRs aggravated the extension of myocardial ischemia–reperfusion injury.[39]

Potential role of FcγRs in atherosclerosis: insight from animal models

FcγRs have been detected in human atherosclerotic lesions using immunocytochemical techniques,[10] which suggests a potential role for FcγRs in the formation of arterial lesions and provides further support to the hypothesis that FcγRs engage ICs during atherogenesis. Indeed, Ig treatment reduced atherosclerosis in apoE knockout mice,[40,41] and the antiatherosclerotic effects of Ig have been attributed to FcγR-mediated anti-inflammatory and immunomodulatory actions.[41]

A number of *in vivo* studies in FcγR genetically altered mice have been reported (Table 2). FcγR deficiency conferred protection against the development of atherosclerosis in apoE$^{-/-}$ $\gamma^{-/-}$ double knockout mice.[42,43] In particular, apoE$^{-/-}$ $\gamma^{-/-}$ mice demonstrated a reduced size of atherosclerotic lesions along the aorta compared with their corresponding apoE $^{-/-}$ controls. Furthermore, the macrophage and T-cell contents, the expression of monocyte chemoattractant protein-1, intercellular adhesion molecule-1, regulated on activated normal T-cell expressed and secreted and the activation of nuclear factor-κB in aortic lesions from apoE$^{-/-}$ $\gamma^{-/-}$ mice were significantly reduced compared with apoE$^{-/-}$controls. Interestingly, FcγRI and FcγRIII of apoE$^{-/-}$ $\gamma^{-/-}$ mice did not function, while FcγRIIB expression was upregulated in the aorta. Thus, in addition to the deficiency of activating FcγRI and FcγRIIIA, the upregulation of inhibitory FcγRIIB might provide an alternative explanation for the atheroprotection. Zhao *et al*.[44] further evaluated the role of the inhibitory FcγRIIB in atherosclerosis in a hypercholesterolemic low-density lipoprotein receptor (LDL-R)-deficient mice model transplanted with FcγRIIB-deficient bone marrow cells. They observed that the plaque area in the descending aorta was significantly larger in mice transplanted with FcγRIIB-deficient bone marrow cells than in mice transplanted with control normal bone marrow cells. However, no differences in plasma cholesterol or triglyceride concentrations between the two groups were found. Moreover, FcγRIIB deficiency resulted in amplified splenocyte proliferative response to Con A stimulation, enhanced expression of major histocompatibility complex class II on B-cells, and enlarged amount of CD25 + CD4 T-cells and B-cells in the spleen. Therefore, it appears that FcγRIIB deficiency promotes atherogenesis by inducing an imbalance of stimulatory and inhibitory immune cells. A very recent study reported that male apoE$^{-/-}$FcγRIIb$^{-/-}$ mice developed exacerbated atherosclerosis that was independent of lipid levels, and was characterized by increased antibody titers to modified LDL and proinflammatory cytokines in the aorta.[45] Moreover, Kelly *et al*.[46] found that arterial lesion formation was dramatically decreased at the advanced stage of atherogenesis in FcγRIII$^{-/-}$LDLR$^{-/-}$ mice compared with LDLR$^{-/-}$ controls, and this was associated with increased production of IL-10 by an expansion of CD4 + T-cells and upregulated IgG1 and IgG2c titers to oxLDL. Collectively, these new results suggest that antibodies against atherosclerosis-associated antigens partially protect against atherosclerosis by conveying inhibitory signals through FcγRIIb that downregulates proinflammatory signaling via other immune receptors.

FcγR polymorphisms and expression in the vascular atherosclerotic disease: insight from clinical studies

Accumulating evidence based on epidemiological studies has shown that FcγRs are associated with a variety of atherosclerotic and thrombotic disorders (summarized in

Table 2 Atherosclerosis studies on genetic manipulation of FcγRs in the mouse model

Mouse model	Plasma lipids	Lesion size	Cellular composition	Cytokines	Immune response	Ref.
apoE$^{-/-}$ $\gamma^{-/-}$	↔	↓	Lesion: macrophages↓ T-cells↓	Lesion: MCP-1↓ ICAM-1↓RANTES↓	IC-induced NF-κB activation↓	42
LDLR$^{-/-}$+FcγRIIB$^{-/-}$BMT	↔	↑	Spleen:CD4$^+$CD25$^+$T-cells↑ B-cells↑	Plasma: IL-10↑IL-4↑ IL-5↑	Splenocyte proliferative response↑ anti-oxLDL IgG2a/c↑	44
apoE$^{-/-}$ FcγRIIb $^{-/-}$	↔	↑	Lesion: macrophages ↔ T-cells↑	Lesion: IL-1β↑TNFα↑ IL-17A↑IL-23↑	B-cell responses to modified LDL↑	45
LDLR$^{-/-}$FcγRIII$^{-/-}$	TC↑	↓	Lesion: macrophages↓ T-cells↑	Lesion, plasma, spleen: IL-10↑ IFN-γ↑	anti-oxLDL IgG1, IgG2c↑	46

IFN-γ, interferon-γ; TNFα, tumor necrosis factor-α; oxLDL, oxidized LDL; ICAM-1, intercellular adhesion molecule-1; RANTES, regulated on activated normal T-cell expressed and secreted; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; BMT, bone marrow transplantation; TC, total cholesterol; ↑, increase; ↓, decrease; ↔, none

Table 3 Association of Fc γR polymorphisms with coronary artery disease

Fc γR alleles	Study population	Number studied	Association	Ref.
Fc γRIIA-R/H131 Fc γRIIIB-Na1/Na2 Fc γRIIIA-F/V158	Caucasian	882 patients with CAG, 96 controls	No association with CAD; Fc γRIIA and Fc γRIIIB genotypes; Fc γRIIIA-V/V158 protective against CAD	47
Fc γRIIA-R/H131	Caucasian	MONICA: 527 patients with a history of MI, 527 controls LURIC: 2227 patients with CAD, 1032 controls	No association	48
Fc γRIIA-R/H131	German	2391 patients with CAG, 510 controls	No association	49
Fc γRIIA-R/H131	Caucasian	506 patients with acute MI, 468 controls	No association with risk of MI	50
Fc γRIIA-R/H131	Australia	66 patients with SAP, 105 patients with UAP	No association	51
Fc γRIIA-R/H131	German	701 patients with ACS, 467 patients with SAP, 684 controls	Fc γRIIA-R/R131 associated with ACS	53

CAG, coronary angiography; SAP, stable angina pectoris; UAP, unstable angina pectoris; CAD, coronary artery disease; MI, myocardial infarction; ACS, acute coronary syndrome

Table 3). The association between Fc γR polymorphisms and coronary atherosclerosis (CAD) was first reported by Gavasso *et al.*,[47] who genotyped Fc γRIIA-R/H131, Fc γRIIIB-Na1/Na2 and Fc γRIIIA-F/V158 polymorphisms in 882 patients undergoing diagnostic coronary angiography, and found that Fc γRIIIA-F/V158 polymorphisms were linked to a strong protective effect because patients homozygous for the Fc γRIIIA-V158 allele had a significantly reduced risk of CAD. Later studies confirmed that Fc γRIIA-R/H131 polymorphism is not an independent risk indicator of coronary artery disease, including patients with acute coronary syndrome (ACS).[48–52] However, a recent study demonstrated a genetic association of Fc γRIIa R/R131 genotype with a more frequent occurrence of ACS.[53] In addition, the Fc γRIIA-R/H131 genotype was shown to be associated with endothelial dysfunction, advanced peripheral atherosclerosis and carotid artery intima-media thickness.[54–56]

Macrophages play a crucial role in the development of vascular lesions in atherogenesis. Soluble Fc γRIIIa$^{M\Phi}$ derived from macrophages is present in the plasma. The level of sFc γRIIIa$^{M\Phi}$ was associated with the severity of coronary atherosclerosis in CAD patients and positively correlated with LDL-cholesterol/HDL-cholesterol ratio, but was negatively correlated with HDL-cholesterol level.[57] Moreover, sFc γRIIIa$^{M\Phi}$ concentration in the plasma was correlated with carotid maximum intima-media thickness and a number of risk factors for atherosclerosis, such as aging, current smoking, diabetes, hypertension, LDL-cholesterol/HDL-cholesterol ratio and family history of atherosclerotic diseases.[58] These findings indicate that the macrophages are activated during the process of atherosclerosis, and sFc γRIIIa$^{M\Phi}$ serves as a novel biomarker for atherosclerosis. Pfeiffer *et al.*[59] performed quantitative flow cytometry to measure the expression of Fc γRI and Fc γRIIA on peripheral monocytes in patients with severe atherosclerosis, and found that the expression of Fc γRIIA on peripheral monocytes was significantly decreased in patients with clinical atherosclerosis compared with control subjects and it was positively correlated with serum HDL-cholesterol concentrations. Based on these data, the expression of Fc γRIIA may be proposed as a marker for assessing relative risk of atherosclerotic disease.

Collagen-mediated platelet activation contributes significantly to coronary and cerebrovascular thrombus formation associated with atherosclerotic plaque destabilization. Both collagen and Fc γRIIA cross-linking have been shown to activate platelets via the tyrosine kinase Syk signaling pathway.[60] Calverley and co-workers[35,36] showed that the expression of Fc γRIIA on platelet surface was increased in patients with acute coronary or cerebrovascular events, and patients with diabetes mellitus or uremia. Therefore, increased platelet Fc γRIIA expression may also contribute to increased risk of atherothrombotic events.

The interaction of Fc γRs with CRP in atherosclerosis

Although the binding of CRP to Fc γRs is still under debate,[61–63] a research group has recently provided the quantitative characterization of CRP binding to Fc γRs by using ultrasensitive confocal imaging analysis.[64–66] Another study also presented structural and functional evidence for the involvement of pentraxins, including serum amyloid P component and CRP, in the activation of Fc γRs.[67] While there is an ongoing debate whether CRP participates actively in atherogenesis or is merely an innocent bystander, growing amounts of data have shown that CRP elicits a proinflammatory and proatherogenic role, ranging from fatty streak formation to clinical events, mostly mediated via Fc γR-dependent pathways.[10,68]

Several studies have indicated that CRP binds to Fc γRI and Fc γRII in monocytes.[69–71] CRP stimulates the expression of MMP-1,[72] MMP-9,[73] receptor for advanced glycation end products and its inflammatory ligand AGE,[74]

decreases IL-10 secretion,[75] and induces high-mobility group box-1 protein release[76] through FcγRs in monocytes/macrophages. CRP also promotes macrophage colony-stimulating factor release[77] and CC chemokine receptor 2 expression via FcγRs,[78] leading to the accumulation of monocytes in the atherogenic arterial wall. Moreover, CRP promotes oxidized LDL uptake via FcγRs which contribute to foam cell formation *in vitro* and *in vivo*.[79,80]

CRP binds and interacts with FcγRI and FcγRII in endothelial cells,[81] which induces endothelial cell apoptosis,[73] promotes monocyte–endothelial cell adhesion,[16] inhibits eNOS activity,[82] and uncouples eNOS.[83] FcγRs also mediates CRP-induced reactive oxygen species generation and tissue factor expression *in vitro* and *in vivo*.[17,84,85] Notably, a recent study found that exaggerated neointima formation in human CRP transgenic mice depended on the presence of FcγRI.[86]

Perspectives

Immune responses participate in every phase of atherosclerosis and FcγRs play a crucial role in regulating a multitude of innate and adaptive immune responses.[87,88] Accumulating body of evidences have suggested the role of FcγRs in the development of atherosclerosis and a summary of the potential cellular effects of FcγRs in atherosclerosis is presented in Figure 1. The new findings based on FcγR knockout mouse models have provided valuable information to decipher the role of FcγRs in atherosclerosis in human. Nevertheless, due to the differences of FcγRs in human and mouse, the future challenge is to develop novel humanized models to elucidate the pathophysiological role of the different classes of human FcγRs in atherogenesis.

Undoubtedly, a deeper understanding of the role of FcγRs in atherosclerosis will help design a new strategy for the prevention and treatment of atherosclerosis. Statins, widely used for treating atherosclerosis, inhibit FcγR signaling by disrupting membrane rafts to decrease the release of inflammatory mediators by monocyte/macrophage.[89] Therefore, targeting FcγRs will open up new opportunities for atherosclerosis prevention and therapy, although the development and application of intravenous Ig, engineered Fcγ fragments and monoclonal anti-FcγR antibodies *in vivo* presents formidable technical challenges.

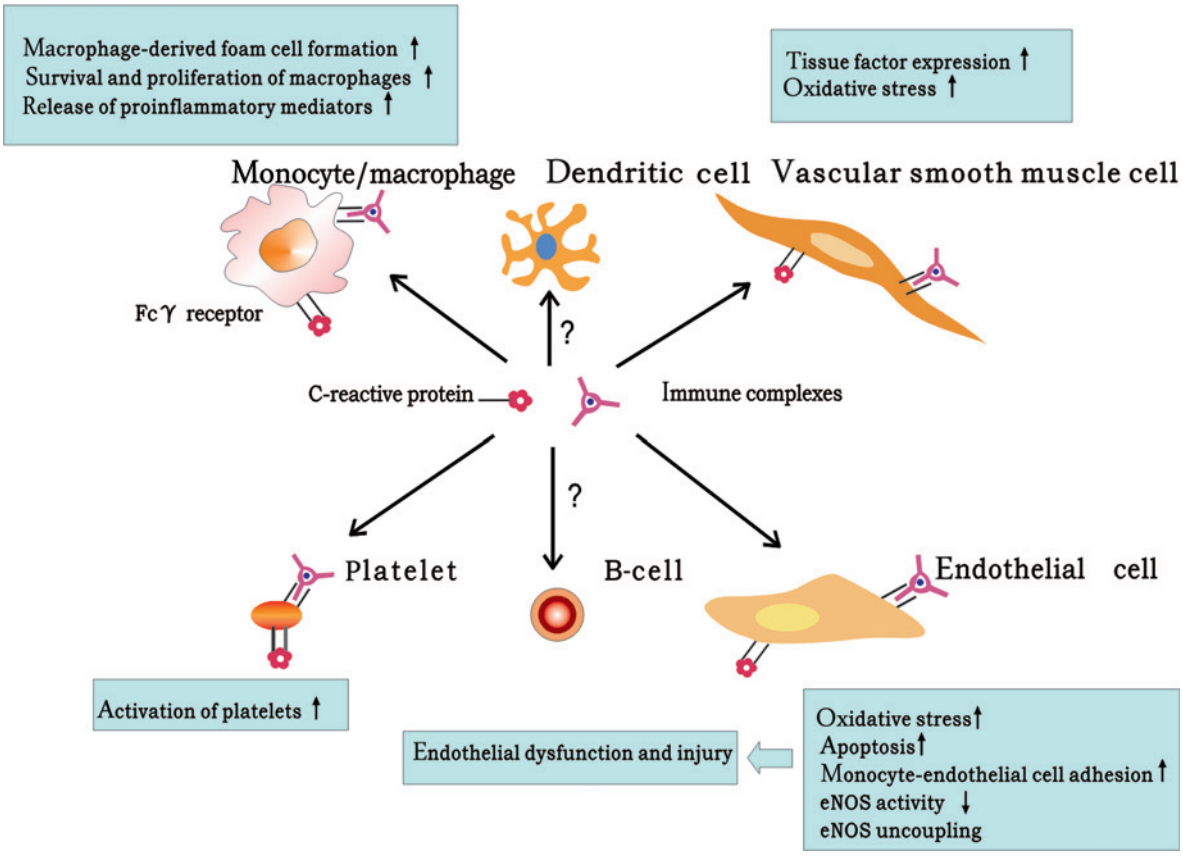

Figure 1 The potential cellular effects mediated by Fcγ receptors (FcγR) in atherosclerosis. The interaction of Fcγ receptors with immune complexes or C-reactive protein induces a series of proatherogenic pathological reactions. FcγR-mediated macrophage activation promotes survival and proliferation of macrophages, increases macrophage-derived foam cell formation and enhances release of proinflammatory mediators, e.g. IL-1β, TNFα, MMP1, MMP10, leading to the accumulation of macrophages in human atherosclerotic lesions and vulnerable plaque. On the other hand, FcγR-mediated immune reaction results in endothelial dysfunction, including eNOS uncoupling, eNOS activity inhibition, excessive oxidative stress, endothelial cell apoptosis and adhesion augmentation and induces tissue factor expression and activation of platelets, which are associated with an increased risk of cardiovascular events. Dendritic cells and B-cells are also implicated in the development of atherosclerosis. Potential antiatherosclerotic mechanisms mediated by FcγRs in these cells remain to be elucidated. Moreover, FcγRIIB alleviates arterial lesion progression in animal models although the molecular mechanisms have not been fully understood. IL-1β, interleukin-1β; TNFα, tumor necrosis factor-α; MMP, matrix metalloproteinase; eNOS, endothelial nitric oxide synthase. (A color version of this figure is available in the online journal)

Finally, optimizing antibody activity by enhancing the interaction with the inhibitory FcγRs, or blocking antibody binding to the stimulatory FcγRs, might represent novel immunotherapeutic approaches for atherosclerosis.

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