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The Role of Fcγ Receptors in Myocardial Diseases and Atherosclerosis

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Abstract

Myocardial diseases and atherosclerosis are widely considered to be an immune mediated process. Fcγ receptors (FcγRs) contribute to the regulation of immune and inflammatory responses and have been implicated in human cardiovascular lesions. Major cell types involved in the pathogenesis of the diseases express FcγRs and their ligands such as immune complexes and C-reactive protein have been shown to activate FcγRs signal pathway. This review summarizes recent significant progress addressing the various roles of FcγRs in the disease pathogenesis which comes from the studies of FcγRs deficient animal models, clinical investigations and in vitro molecular and cellular studies. These new findings help us appreciate the emerging role of FcγRs in cardiovascular diseases, and suggest FcγRs as a potential therapeutic target for the diseases.

Keywords: Myocarditis; Cardiomyopathies; Myocardial diseases; Atherosclerosis; Fcγ receptors; C-reactive protein

Introduction

It is well established that myocardial diseases and atherosclerosis are inflammatory diseases of the myocardium and the wall of large- and medium-sized arteries where both innate and adaptive immunity response play a pivotal role in the initiation, growth and progress of the lesions [1]. The receptors for the Fc region of IgG (FcγRs) are members of the immunoglobulin gene 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 myocardial diseases and atherosclerosis. Systemic autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome, are characterized by accelerated cardiovascular diseases partly due to the presence of autoantibodies and autoantigens, and the subsequent formation of immune complexes [3,4]. For example, several autoantibodies such as those directed against oxidized low-density lipoprotein (ox-LDL) and heat shock proteins have been detected in atherosclerotic lesions [5-8]. Immune complexes may form between these antigens and autoantibodies and promote the progression of the disease via FcγRs cross-linkage and activation and complement activation [9]. In addition, C-reactive protein, a crucial mediator of cardiovascular disease, elicits a wide array of harmful effects in a majority of cell types involved in the disease pathogenesis, mostly mediated via Fcγ receptor-dependent pathways [10]. In this review we will summarize recent studies addressing the multifaceted roles of FcγRs in cardiovascular diseases.

The Family of Fcγ Receptors

Most Fcγ receptors 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 (ITAMs), 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 (ITIM) contained in its cytoplasmic region [2]. Immunoreceptor signals must be approximately transduced and regulated to achieve effective immunity while controlling inflammation and autoimmunity. It is generally held that processes are mediated by the interplay of distinct activation and inhibitory receptors via ITAMs and ITIM. Crosslinking 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 coexpressed with activated FcγRs of varying affinities and isotype specificities on inflammatory effector cells such as mast cells, 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 thresholds for cell activation and thus generates a well-balanced immune response [14].

Although humans and mice 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 FcγRs between humans and mice is shown in table 1 [2,11,12].

Theoretical Backgrounds of FcγR System in Myocardial Diseases

Immunoglobulin therapy has been used for the treatment of primary and secondary antibody deficiency for more than 25 years. It is a safe preparation with no long-term side effect. Although the mode of action remains unknown, the drug is thought to have potent immunomodulating and anti-inflammatory actions. Recently we have found that immunoglobulin treatment is beneficial upon myocardial diseases. In basic aspects, immunoglobulin therapy for experimental myocarditis has been found to be effective not only by the Fab portion

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	Mouse				Human					
FcγR	FcγRI	FcγRIIRB	FcγRIII	FcγRIV	FcγRIA	FcγRIIA	FcγRIIB	FcγRIIC	FcγRIII A	FcγRIIIB
Signalling pathways	ITAM FcR-γ	ITAM	ITAM FcR-γ	ITAM FcR-γ	ITAM FcR-γ	ITAM	ITAM	ITAM	ITAM FcR-γ	
affinity	High	Low	Low	Low	High	Low	Low	Low	Low	Low
monocytes/macrophages	+	+	+	+	+	+	+	−	+	−
Neutrophils	+	+	+	+	+	+	+	−	−	+
Dentritic cells	+	+	+	−	+	+	+	−	+	−
B cells	−	+	−	−	−	−	+	−	−	−
Mast cells	−	−	−	−	−	−	+	−	−	+

Table 1: Comparison of FcγR between humans and mice.

for anti-pathogen effects but by the Fc portion for anti-inflammatory effects. Immunohistochemical analysis showed that therapy with intact immunoglobulin, but not $F(ab')_2$ fragments, suppressed dendritic cell (DC) expression. An *in vitro* study showed that intact immunoglobulin, but not $F(ab')_2$ Fragments, suppressed the lipopolysaccharide-induced interleukin-1β production associated with the down regulation of CD32 antigen (Fcγ receptor II) expression. Thus, intact immunoglobulin therapy markedly suppressed myocarditis as a result of Fc receptor-mediated anti-inflammatory action, and the suppression of the disease was associated with the suppression of DCs, ie, the suppression of the initial antigen-priming process in experimental giant cell myocarditis [15]. Altogether, FcγRIIB-mediated inhibitory action is highly involved [16]. In clinical aspects, the effect of immunoglobulin administration for fulminant myocarditis and acute dilated cardiomyopathy was investigated. Immunoglobulin administration was very useful for the treatment of such patients. That is, the drug showed the potential beneficial effects against active myocardial damage with myocardial dysfunction, and the left ventricular ejection fraction of the patients was recovered by the treatment associated with reduced cytokine expressions. Accordingly, immunoglobulin treatment for patients with heart failure appears to be novel and effective treatment strategies in view of anti-inflammatory, anti-cytokine and anti-pathogen effects.

Atherogenic Effects of Fcγ Receptors

FcγRs are expressed not only by many immune cells such as dendritic cells, macrophages, monocytes, neutrophils, mast cells and B cells [2,17], but also by platelet, endothelial cells and vascular smooth muscle cells [2,18,19].

Macrophage-derived foam cells are important constituents of atheromatous lesions. Treatment of monocytes with LDL immune complexes containing intact anti-LDL could dramatically increase the ability of these cells to subsequently bind and take up LDL, whereas aggregated LDL or immune complexes of LDL prepared with $F(ab')_2$ fragments of anti-LDL had no significant effect [20]. These results suggest that the formation and interaction of immune complexes of LDL with FcγRs 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 FcγRI or FcγRII, and this was accompanied by an apparent impairment of LDL degradation through using bispecific antibodies consisting of anti-LDL monoclonal antibodies conjugated to anti-Fcγ receptor monoclonal antibodies [21]. Further study confirmed that the uptake of LDL immune complexes by macrophages predominantly through FcγRI led to the transformation of macrophages into foam cells [22]. In addition, HDL inhibits the uptake of modified LDL by macrophages, likely through interfering with CD36 and FcγRI expression [23]. Notably, enhanced CD36 expression in monocytes has been proposed to link autoimmunity and atherosclerosis [24].

Human macrophages are efficiently activated by LDL-IC mediated by FcγR, as reflected by the release of IL-1β and TNFα and the accumulation of oxygen active radicals [25]. A subsequent study showed that these effects were due to FcγRI mediated activation of the mitogen-activated protein (MAP) kinase signaling pathway, thus leading to macrophage activation [26]. Moreover, LDL-ICs localized in atherosclerotic lesions induce macrophage MMP-1 secretion by cross-linking FcγRI and FcγRII and stimulating a protein kinase C-dependent MAP kinase pathway [27]. The survival and proliferation of macrophages play a critical role in the pathogenesis of vascular inflammation [28-30]. OxLDL-IgG ICs promote the survival of monocytes by cross-linking FcγRI with ensuing activation of Akt-dependent survival signaling [31]. On the other hand, Luo et al. recently reported that FcγR activation through cross-linking stimulated macrophage proliferation via the activation of the ERK1/2 signaling pathway and the subsequent transcriptional activation of cyclin D1 expression [32]. These results imply that activation of FcγR on macrophages may exert a mitogenic effect similar to growth factors and consequently stimulate macrophage proliferation.

Endothelial cells also express FcγRs and are crucially involved in atherosclerosis [18,33]. Sumiyoshi et al. 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 $\gamma^{-/-}$ (knockout) mice [34]. FcγR also mediated monocyte adhesion to oxLDL-IC deposited on endothelium and the subsequent release of chemokine [35]. Thus, the interaction between FcγRs and oxLDL-IC may be another mechanism for vascular endothelial cell injury that could contribute to the progression of atherosclerosis. A recent study demonstrated that eNOS antagonism by CRP or immune complex is mediated by the coupling of FcγRI to FcγRIIB and the subsequent activation of Src kinase and SH2 domain-containing instills 5'-phosphatase 1. Therefore, FcγRI and FcγRIIB may constitute novel therapeutic targets for preventing endothelial dysfunction in inflammatory or immune complex-mediated conditions [36].

Increased platelet expression of FcγRIIa may contribute to greater platelet reactivity and has been associated with a greater risk of subsequent cardiovascular events [37,38]. IFNγ selectively upregulated the expression of FcγRIIa by cells exhibiting characteristics of megakaryocytes [39]. Konishi et al. demonstrated that FcγRs played a pivotal role in the initiation and generation of neointimal hyperplasia after balloon injury in mice deficient in FcγRs through the activation of platelets by collagen [40]. They further confirmed that collagen-induced activation of platelets through FcγRs aggravated the extension of myocardial ischemia-reperfusion injury [41].

Potential Role of Fcγ Recepotrs in Atherosclerosis

FcγRs have been detected in human atherosclerotic lesions using immunocytochemical techniques [10], which suggests a potential role for Fcγ receptors in the formation of arterial lesions and adds

further support to the hypothesis that FcγRs engage immune complexes during atherogenesis. Indeed, immunoglobulin treatment reduced atherosclerosis in apoE knockout mice [42,43] and the anti-atherosclerotic effects of immunoglobulin have been attributed to FcγR mediated anti-inflammatory and immunomodulating actions [43].

A number of *in vivo* studies in FcγR genetically altered mice have been reported. FcγR deficiency conferred the protection against the development of atherosclerosis in double-knockout mice which were derived from crossing apolipoprotein E-deficient mice (apoE$^{-/-}$) with γ chain-deficient mice$^{-/-}$ [44]. In particular, apoE$^{-/-}$γ$^{-/-}$ mice demonstrated a reduced size of atherosclerotic lesions along the aorta compared with their corresponding apoE$^{-/-}$ controls. Furthermore, the macrophage and T-cell content, the expression of monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), RANTES (regulated on activated normal T-cell expressed and secreted) and the activation of nuclear factor-κB (NF-κB) in aortic lesions from apoE$^{-/-}$γ$^{-/-}$ mice were all significantly reduced compared to apoE$^{-/-}$ mice. Interestingly, the FcγRI and FcγRIII of apoE$^{-/-}$γ$^{-/-}$ mice were not functional, while the 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. further evaluated the role of the inhibitory FcγRIIB in atherosclerosis in a hypercholesterolemic LDLR deficient mice model transplanted with FcγRIIB deficient bone marrow cells [45]. 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. Therefore, it appears that FcγRIIB deficiency might promote 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 pro-inflammatory cytokines in the aorta [46]. Moreover, recently Kelly et al. found that arterial lesion formation was dramatically decreased at a relatively later stage of atherogenesis in FcγRIII$^{-/-}$ LDLR$^{-/-}$ mice compared with LDLR$^{-/-}$ controls, which was associated with increased production of IL-10 by an expansion of CD4^{+} T-cells and upregulated IgG1 and IgG2c titers to oxLDL [47]. Collectively, these new results suggest that antibodies against atherosclerosis-associated antigens partially protect against atherosclerosis by conveying inhibitory signals through the FcγRIIb that downregulates pro-inflammatory signaling via other immune receptors.

Accumulating evidence based on epidemiological studies has shown that FcγRs are associated with a variety of atherosclerotic and thrombotic disorders. The association between FcγRs polymorphisms and coronary atherosclerosis (CAD) was firstly reported by Gavasso et al. who genotyped FcγRIIA-R/H131, FcγRIIIB-Na1/Na2 and FcγRIIIA-F/V158 polymorphisms in 882 patients undergoing diagnostic coronary angiography, and found that FcγRIIIA-F/V158 polymorphisms were linked to a strong protective effect because patients homozygous for the FcγRIIIA-V158 allele had a significantly reduced risk of CAD [48]. Later studies confirmed that FcγRIIA-R/H131 polymorphisms might not be an independent risk indicator of coronary artery disease, including patients with acute coronary syndrome (ACS) [49-53]. However, a recent study demonstrated a genetic association of FcγRIIa R/R131 genotype with a more frequent occurrence of ACS [54]. In addition, the FcγRIIA-R/H131 genotype was shown to be associated with endothelial dysfunction, advanced peripheral atherosclerosis and carotid artery intima-media thickness [55-57].

Macrophages play a crucial role in the development of vascular lesions in atherogenesis. Soluble FcγRIIIa derived from macrophages (S FcrR IIIa^{MΦ}) is present in the plasma. The level of sFcγRIIIa^{MΦ} was associated with the severity of coronary atherosclerosis in CAD patients and positively correlated with LDL-cholesterol to HDL-cholesterol ratios, but negatively correlated with HDL-cholesterol level [58]. Moreover, sFcγRIIIa^{MΦ} level 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 to HDL-cholesterol ratios, and family history of atherosclerotic diseases in subjects undergoing an annual medical checkup [59]. These findings indicate that the macrophages are activated during the process of atherosclerosis, and sFcγRIIIa^{MΦ} might serve as a novel biomarker for atherosclerosis. Pfeiffer et al. performed quantitative flow cytometry to measure the expression of FcγRI and FcγRIIA on peripheral monocytes in patients with severe atherosclerosis, and found that the expression of FcγRIIA on peripheral monocytes was significantly decreased in patients with clinical atherosclerosis compared to control subjects and it was positively correlated with serum HDL-cholesterol levels [60]. Base on these data, the expression of FcγRIIA 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 FcγRIIA crosslinking have been shown to activate platelets via tyrosine kinase Syk signaling pathway [61]. Calverley et al. showed that the expression of FcγRIIA on platelet surface was increased in patients with an acute coronary or cerebrovascular event, and patients with diabetes mellitus or uremia [37,38]. Therefore, increased platelet FcγRIIA expression may also contribute to increased risk of atherothrombotic events.

Fcγ Receptors and C-Reactive Protein

Although the binding of C-reactive protein to FcγRs is still under debate [62-64], a research group has recently provided the quantitative characterization of C-reactive protein binding to FcγRs by using ultrasensitive confocal imaging analysis [65-67]. Another study also presented structural and functional evidence for the involvement of pentraxins, including serum amyloid P component and C-reactive protein, in the activation of FcγRs [68]. Mineo et al. [69] examined the mechanisms of CRP actions on endothelium by testing the hypothesis that CRP attenuates endothelial NO synthase (eNOS) activation *in vitro*. The investigators found that CRP-induced declines in NO production promote monocyte adhesion to endothelium. They further investigated the role of Fcγ receptors, which display high affinity for CRP and modulate CRP actions. They found that, in FcγRIIB$^{+/+}$ mice, CRP blunts acetylcholine-induced increases in carotid artery vascular conductance, and that, in contrast, CRP enhances acetylcholine responses in FcγRIIB$^{-/-}$ mice. They concluded that FcγRIIB mediates CRP inhibition of eNOS.

At first glance their results appear to be contradictory to previous reports by our own group [15,16] by Gill et al. [70] In our study, not only FcγRIIB-mediated inhibitory effect on experimental autoimmune myocarditis in rats [15] but FcγRIIB-mediated antiatherosclerotic effect in apolipoprotein E-deficient mice [16] were demonstrated, using immunoglobulin preparations. Gill et al. [70] demonstrated the targeting effect of immunoglobulin on adhesion molecules using ischemia reperfusion model in cats, suggesting the down regulation of adhesion molecules via Fc receptors.

The fact that FcγRIIB mediates CRP inhibition of eNOS, resulting in endothelial dysfunction, is not necessarily in contradiction to aforementioned studies from different groups. The precise effect of FcγRIIB on cardiovascular inflammatory cascades may depend on experimental models. Such opposite activatory and inhibitory actions of FcγRIIB against inflammation may occur depending on the dose used and the experimental conditions. In fact, there are FcγRIIA, an activatory receptor, and FcγRIIB, an inhibitory receptor in humans, but only FcγRIIB has been identified in mice (Table 1).

Mineo et al. also explored the fact that FcγRIIB is expressed in human endothelial cells and in mouse endothelium. It is well known that CRP levels are strongly correlated with increased risk for cardiovascular inflammatory diseases [71,72]. Taken together, they proposed a CRP-modulating novel therapy by FcγRIIB for preventing cardiovascular complications in multiple inflammatory and autoimmune disorders. 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 FcγR-dependent pathways [10,73].

Several studies have indicated that C-reactive protein binds to FcγRI and FcγRII in monocytes [74-76]. C-reactive protein stimulates the expression of MMP-1 [77], MMP-9 [78], receptor for advanced glycation end products (RAGE) and its inflammatory ligand AGE [79], decreases interleukin-10 secretion [80], induces high-mobility group box-1 protein release [81] through FcγRs in monocytes/macrophages. C-reactive protein also promotes macrophage colony-stimulating factor release [82], which promotes macrophage proliferation, and CC chemokine receptor 2 expression via FcγRs [83], leading to the accumulation of monocytes in the atherogenic arterial wall. Moreover, C-reactive protein promotes oxidized LDL uptake via FcγRs which contribute to foam cell formation *in vitro* and *in vivo* [84,85].

C-reactive protein binds and interacts with FcγRI and FcγRII in endothelial cells [86], which induces endothelial cell apoptosis [78], promotes monocyte-endothelial cell adhesion [18], inhibits eNOS activity [69], and uncouples eNOS [87]. FcγRs also mediates C-reactive protein-induced reactive oxygen species generation and tissue factor expression *in vitro* and *in vivo* [19,88,89]. Notably, a recent study found that exaggerated neointima formation in human C-reactive protein transgenic mice depended on the presence of FcγRI [90].

Summary

Immune responses participate in every phase of myocardial diseases and atherosclerosis. FcγRs play crucial role in regulating a multitude of innate and adaptive immune responses. Findings obtained in FcγR knockout mouse models have been invaluable to decipher the role of FcγRs in the disease pathogenesis. Nevertheless, due to the differences of FcγRs in both species, the future challenge is to develop novel humanized models to elucidate the pathophysiological role of the different classes of human FcγRs.

Undoubtedly, a deeper understanding of the role of FcγRs will help design new strategy for the prevention and treatment of cardiovascular diseases, widely used for treating cardiovascular diseases, inhibit FcγRs signaling by disrupting membrane rafts to decrease the release of inflammatory mediators by monocyte/macrophage [91]. Therefore, targeting FcγRs will open new opportunities for the prevention and therapy, although the development and application of intravenous immunoglobulin, engineered Fcγ fragments, monoclonal anti-FcγR antibodies in vivo presents formidable technical challenges.

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