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The Therapeutical Approaches for Rare Diseases through the Immune Processes of IgG Fc Receptors

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Abstract

Fc Receptor for Immunoglobulin G (IgG) is the major class among the five classes of Fc receptors including Fc Receptor for IgA, IgE, IgM and IgD. Three types (type I, II and III) of the Fc Receptors for Immunoglobulin G (FcRγs) on a variety of hematopoietic cells with different structures and different functions were defined by World Health Organisation (WHO).

FcRγs are a group of integral membrane glycoproteins surface molecules mainly on the surface of effector cells playing very important roles in host defence and regulation in both of the adaptive and innate immune system through signal transduction and other several biological processes after triggered by the immune reactions.

Rare diseases are a group of disorders/disorders occurring in a small percentage of the population commonly with the chronic phase and most of them are genetic based. Data suggested that there are some types of rare diseases/disorders such as auto-immune and immune-deficiency associated diseases and even some types of cancer associated with dysfunction of Fcγs.

Recently, intensive studies on Fcγs from the level of genetics increased the understanding in pathophysiological mechanism of some diseases. Such advances obtained provide the opportunities for the therapeutical approaches for rare diseases in some types involved in Fcγs dysregulations.

The aim of this review is to discuss the characterisation of Fcγs from genotype to phenotype and the Fcγs associated rare diseases including cancers from laboratory bench to clinical bedside.

***Keywords*:** *Extracorporeal membrane oxygenation; hemoptysis; acute respiratory distress syndrome; bronchial arteriography*

Introduction

Immunoglobulins or antibodies are the bi-functional molecules structurally featured with Fab (Fragment of Antigen Binding) and Fc (Fragment of Crystalised region) portions.

Fc receptors are a group of integral membrane glycoproteins molecules presented on phagocytic cell surface and they specifically recognise and bind to the Fc portion of the immunoglobulins molecules after triggered by various cellular immune effector functions and to destroy and eliminate the opsonized target through the important roles in host defence and immune regulation in activation and inhibition (gain and loss functions) (1, 2).

Five classes Fc receptors (Fc receptor for IgA, Fc receptor for IgD, Fc receptor for IgE, Fc receptor for IgG and Fc receptor for IgM) have

been classified based on the type of antibody. Different class of Fc receptors have different specificity for a particular immunoglobulin (3-7).

Fc-gamma receptor (FcRγ) is the major class among these five classes of Fc receptors and they are the members of immunoglobulin superfamily of genes. The nomenclature of Fc Receptors as defined by the world health organisation (WHO) in 1987 was described by Henry Metzger in 1990 (8).

The existence of FcγR was first described by Berken and Benacerraf (9). Human FcγRs are found to be distributed on many different kinds of cells and cell lines under the condition resting and activated (10,11).

Fcγ type I (also known as CD64) is an integral cell membrane protein with a molecular weight of 68-72kDa found on monocyte, macrophages and myeloid leukemia cell lines activated (12). Fcγ type I was first isolated from the monocytic cell line (U937) and display high affinity for monomeric IgG and showed preferential binding of IgG subclasses, in order of rank is IgG1=IgG3>IgG4; it does not react with IgG2 (13).

Fcγ type II (also known as CD32) is a 40kDa molecular weight glycoprotein which was initially isolated by affinity chromatography of a monocytic cell line-U937 cell lysates on IgG-Sepharose in 1982 (13). It was further characterised by a monoclonal antibody-IV.3. Unlike Fcγ type I, Fcγ type II binds with low and medium affinity for monomeric IgG (14, 15).

Fcγ type III (also known as CD16) is a 50-70kDa protein with low affinity distributed on neutrophils, macrophages and NK cells (10). It was originally identified by 3G8 (a monoclonal specifically against Fcγ type III). Studies showed that FcγRIIIb is an anchored molecule without the intracellular signalling motifs (16).

Rare disease is defined as a kind of diseases/disorders affecting a small population. It is estimated that there are more than 7000 different types of diseases/disorders from the combination pathophysiological mechanism of genetic and environmental factors or their interactions (17, 18). No worldwide accepted definition is available for rare diseases so far. It can be early life onset or later life onset. Studies showed that there are some types of rare diseases/disorders associated with Fcγs dysregulations.

The studies on Fcγs have provided the understanding in disease mechanism it also provides the approaches for rare disease therapies.

Characterisations of FcγRs

Immune biological Function of FcγRs

FcγRs are binding molecules on the surface of effector cells reacting with the Fc part of the immunoglobulins or antibodies (19). They play important regulation role in immune system between cellular and humoral immunity by enable antibodies to perform several biological functions, forming a link between specific antigen recognition and effector cells under the normal physiological conditions and the maintenance (homeostasis) of the balance between activation and inhibition of signals is crucial in health control (20-23).

In the normal conditions, the Fc portion of monomer IgG does not bone to Fc receptors on cell surface, only if Fab binds to foreign or auto-antigens or monomeric IgG become aggregated and then triggered effector cells to destroy antibody-coated target cells through the antibody-dependent cell mediated cytotoxicity (ADCC) (24), Endocytosis and phagocytosis of immune complexes by effector cells (25-27) and clearance of immune complexes, regulation of production of antibody by FcγRs (28), biological substance release medicated by FcγRs, regulation of cytokines mediated by FcγRs (29).

The significances of FcγRIIA on Megakarocytic lineage of the platelets precursor cells

Fcγ type II is a transmembrane protein and a polymorphic molecule distributed widely on hematopoietic cells such as monocyte, macrophages, neutrophils, B-lymphocyte either as a sole type or in a combination with Fcγ type I or Fcγ type III with a variation of numbers of copies (15). The identification of IgG Fc Receptors on platelets demonstrated by Rosenfeld et al showed platelets are cells

with immune functions, rather than they are only the debris of megakaryocytes as people thought before (14).

Molecular studies revealed that FcγRIIA and FcγRIIC proteins have activation biological functions through the immunoreceptor tyrosine-based activation motif (ITAMa), and in contrast, FcγRIIB protein has inhibit biological functions through the ITAMi (30). Such findings help to identify the subtype of FcγRs in different functions for example, FcγRIIA and FcγRIIC have activation function in contrast, FcγRIIC has inhibition function. Therefore, FcγR type II has been extensive studied due to their important immune-biological functions, particularly in platelet activation associated diseases.

An interesting study conducted by Chong group demonstrated that IV.3, the monoclonal antibody specific again IgG Fc receptor type II inhibited platelet aggregation induced by the sera from patients with heparin induced thrombocytopenia indicating that heparin induced thrombocytopenia is mediated by IgG Fc receptor mechanism (31).

Platelets are differentiated from its precursor cells-megakaryoblasts matured to megakaryocytes. Up-regulation of FcγRs on or in platelet which presumable occurs at megakaryocyte/megakaryoblast level under the influence of cytokines would further exacerbate the pathological processes. The characterisation of FcγRIIA on cells of megakaryocytic lineage at protein and RNA levels enhanced the understanding of the pathophysiology in the FcγRs regulation of the platelet activation associated diseases/disorders from the protein to RNA levels.

Chong et al studied human megakaryocytes isolated from bone marrow by using Magnetic Activated Cell Sorting (MACS), megakaryoblasts and megakaryoblastic cell lines (MEG-01 and UT-7) and by using other combinations techniques including immune-cytochemical staining, dual colour flow cytometry, immunoprecipitation and they have characterised the FcγR type II protein but not type I and III from these cells/cell lines studied. Finally they studied mRNA expression of FcγR type II and their transcripts. Their results showed the presence of FcγR type IIA gene which is the transmembrane (TM) exon (32-37).

Interestingly, they found the presence of FcγR type II from protein to mRNA level on the early haematopoietic progenitor cell stages, stem cell antigen (CD34)-expressing cell line (KG-1) and its less differentiated subline (KG-1a) (38) and as summerised in Table 1.

Cell types	IgG Fc Receptor subtypes IIA	References
Platelets	+	(14), (32-37)
Megakaryocytes	+	(33-37)
Megakaryocytic Cell Lines;	+	
MEG-01	+	(32-37)
UT-7	+	(33-37)
Hematopoietic Stem Cell Lines;	+	
KG-1	+	(38)
KG-1A	+	(38)

Table 1: *The identification of IgG Fc Receptor type IIA Megakaryocytic Lineage/cell lines*

The significances of these studies were two fold that the first was the identification of the presence of FcγR type IIa on platelet and their precursor cells, megakaryocytes and megakaryoblasts from protein to molecular level. The transmembrane molecular of FcγR type IIa found on these cells have implied the pathophysiological mechanism in some platelet activation diseases because FcγR type IIA gene product may play a physiological role as it can compete with the membrane-bound FcγR IIA for binding of IgG-containing immune complexes and thus protect these cells from excessive binding and injurious effects of immune complexes such as in immune thrombocytopenia.

The second significance was that the sole type of the FcγRIIa identified on these cells (megakaryocytes, megakaryoblasts and the CD34 expressing cell lines (KG-1 and KG-1a) can be used as an identification marker in hematopoietic lineage differentiation stage.

Genetic Variation of FcγRs

Studies revealed that Fcγs are composed of homologous immunoglobulin-like extracellular (EC) domains, divergent transmembrane (TM) and intracytoplasmic (IC) regions with different degree of heterogeneity on different cells with different coding gene variations were characterised. Multiple genetic variations including Single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) on low and medium affinity have been identified in the FCGR loci (39-42).

Three very similar genes (A, B and C) have been characterized for Fcγ type I by the gene cloning studies located on chromosome 1q21.2 (43-46). Six variants transcripts of the FcRγ type I were further identified (47).

FcγRII with low and medium affinity of the FcγRIIA, FcγRIIB FcγRIIC are encoded with the mRNA splice variants of FCGR2A, FCGR2B and the A and B recombination variant-FCGR2C of these three gene products with conserved extracellular domains located on chromosome 1q23.3 on the FCGR2/3 locus (48). FcγRIII is a also low and medium affinity receptor with A and B genes (FcγRIIIA and FcγRIIIB) identified also located on chromosome 1q23.3 on the FCGR2/3 locus (46,49)

Studies also proved such genetic variations affect immune functions and increase individual's susceptibility and impact therapeutical response of disorders/diseases (50-52). There are many different kinds of disorders/disease linked with such genetic variations associated dysfunctions of FcRγs (gain or loss) with different consequences occurring with heterogeneity among different ethnic groups (53-55).

Some Types of Rare Diseases Associated With Dysfunctions of FcγRs

FcγRs in Immunodeficiency

FcRγs paly roles in regulatory functions in the immune system. Studies have showed FcγRs mediated Ab-dependent enhancement (ADE) of HIV-1 infection in vitro in the conditions of activation or inhibition will contribute to immune disorders such as immunodeficiency (56).

A study showed monoclonal antibodies to FcRI for immunoglobulin G blocked antibody-dependent enhancement of HIV-1 infection and also they demonstrate CD4 molecule in antibody-enhanced HIV-1 infection was through FcR (57).

Takeda et al provided the evidence of antibody-dependent enhancement of human immunodeficiency virus type 1 (HIV-1) infection via Fc receptor (58).

Takeda et al demonstrated that serum from AIDS patients increased FcγR-dependent HIV infection of monocytes and their data also suggested the rate of HIV infection increases when cells encounter an antibody-coated virus and they also found that HIV-1 infection of monocyte and macrophages could be increased by the viral antibody (59, 60).

Another study by Hussain et al showed that FcγR type II and III were present on human rectal epithelial cells. So they suggested that rectal transmission of HIV may be mediated by HIV antibody complexes binding to FcγR type II and III on rectal epithelial cells it suggested the rate of HIV infection increased when cells encounter an antibody-coated virus (61).

FcγRs in autoimmune Rare diseases

FcγRs associated autoimmune disease is a disease caused by auto antibody or immune complexes leading to inflammation through FcR aggregation (62-64).

FcγRs play bi-functional role by either activation or inhibition through different signalling medicated pathways. Immune thrombocytopenia (ITP) is a representative example of the auto immune disease.

Studies indicated that many human autoimmune diseases might be associated by impairment of the FcR regulatory system. Platelet activation causes severe or fatal cardiovascular consequences clinically. Data strongly demonstrated the evidences of the platelet activation associated diseases through FcγRs dysfunctions.

The interaction of immune complexes with platelet FcγR type II due to the excessive binding of immune complexes leads to platelet activation and thrombosis or increased platelet clearance and thrombocytopenia in some clinical conditions.

FcγRs on platelets play role in the pathophysiology of Heparin-Induced Thrombocytopenia (HIT). An IgG heparin-dependent antibody is frequently demonstrated in patients with HIT, this antibody reacts with platelets in the presence of heparin and causes strong platelet aggregation. Evidence of the involvement of FcγR in HIT came from an interesting studies using of IV.3, a monoclonal antibody with specifically for FcγR type II and their results showed IV.3 strongly inhibited the heparin-dependent platelet aggregation induced by patient sera with heparin induced thrombocytopenia indicating that heparin induced thrombocytopenia is mediated by IgG Fc receptor mechanism (65).

Su., *et al.* investigated the relevant and function of genetic variations of FcγRII and FcγRIII in a population study and they found three polymorphisms associated with systemic lupus erythematosus and lupus nephritis (66).

Another group studies demonstrated that FcγRIIb role in the regulation through the polymorphisms and dysfunction in the systemic lupus erythematosus as the autoimmune mechanism of disease. They suggested such study can be an opportunities for therapeutic target (67).

Goulding et al investigated the Neutrophil Fc gamma receptor signalling responses on patients with definite rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis in a comparison with healthy subjects, and their results suggested that neutrophil Fcy R cytosolic signalling of neutrophil Fcy R in active RA rheumatoid arthritis was impaired (68).

Kawasaki Disease (KD) is rare disease characterised with vascular inflammation involved multi-tissues/organs, particularly leading to coronary artery lesions and genetic variation contributes to autoimmune diseases. Biezeveld., *et al*. studied FcγR polymorphism on KD and they suggested that the altered transcription or expression of FcgR on specific cell types of the immune system may play a role in susceptibility and treatment success but at different level from the functional polymorphism by their study (69).

Shrestha., *et al*. studies showed that the common variation of FcγR type IIA is associated with increased Kawasaki disease susceptibility and the FcγR IIIA variant is a determining factor for treatment response and implied KD pathogenesis and the IVIG anti-inflammatory mechanism (70).

FcγRs in Malignant rare diseases

Evidences suggested at least some types of malignancies are involved in the mechanism of immune regulation through the FcγRs (71).

Treffers., *et al*. investigated the role of regulation of the FcγRIIIb (CD16b) on solid cancer cells coated with antibody either trastuzumab (anti-HER2) or cetuximab (anti-EGFR and their results showed the ADCC was substantially enhanced after FcγRIIIb was blocked by anti- FcγRIIIb antibodies, indicated the negative regular role of FcγRIIIb (72).

Musolino., *et al*. studied the association of FcγR IIb polymorphis with HER-2/neu-positive breast cancer therapy with a monoclonal antibody-trastuzumab through the ADCC mediated by FcγR IIb and they found RIIIa-158 V/V genotype significantly correlated with objective response rate and progression-free survival they also found a trend significance in objective response rate and progression-free survival for the Fc gamma RIIa-131 H/H genotype (73).

Cancer immune therapies through the immune processes have been further studied by several groups and their results showed that

combined FcγRIIa/FcγRIIIa polymorphisms are prognostic factors for disease progression in metastatic colorectal cancer treated with cetuximab plus irinotecan presumed through the process of ADCC (74,75).

Several studies on colorectal cancer have been conducted. Calemma group studied 74 patients with metastatic colorectal cancer and their results showed FcγR IIIa polymorphisms were significantly associated with response to anti-EGFR-based therapy in 49/74 patients (76).

Zhang., et al. data suggested that FCGR2A-H131R and FCGR3A-V158F polymorphisms may be useful as the molecular markers to predict clinical outcome in patients with metastatic colorectal cancer treated with cetuximab (77).

Schranz and Graf studied the prognostic significance of the expression of FcγR in B-cell Chronic Lymphocytic Leukemia (CLL) and they found that FcγR expression was a bad prognostic factor, independent of age and sex, but correlated well with the tumour mass score (78).

Dornan et al results suggested that FCGR2A and FCGR3A polymorphisms did not significantly change the outcomes of relapsed or refractory chronic lymphocytic leukemia (CLL) patients treated with fludarabine or the monoclonal antibody (79).

Therapeutic trials through the immune processes of FcγRs on Rare Diseases

Advancing studies on genetic variations on FcγRs increased the understanding of disease mechanism and translated to clinical applications, such as in disease monitoring of therapeutic response and disease prognosis.

The therapeutic trials with monoclonal antibody in immune disorders were reported. Biotherapeutical monoclonal antibody against FcγR by the engineering approaches showed it is an effective through the immune processes of FcγR for many different kinds of diseases clinically (80,81).

Intravenous gamma immunoglobulin (IVIG) has been used to treat some kinds of immune mediated rare diseases successfully for several mechanisms, One of the application mechanisms of Immunoglobulin therapy in such diseases is to block, or to compete the binding with immune complexes on effector cells and to mediate Fc receptor on effector cell surface to regulate immune responses, particularly in immune thrombocytopenic purpure (82,83).

An infusion of 3G8 (a monoclonal antibody specific against FcγRIII) was given to s patient with refractory idiopathic thrombocytopenia purpure. It resulted in a dramatic rise the platelet count, which reached normal level for two weeks (84). The clinical effect was assumed to have been brought about, in part by a modulation of mononuclear phagocytic function, particularly by inhibiting of FcγR-mediated phagocytosis.

FcγRs and Coronavirus Disease 2019

Beyond the rare diseases reviewed above, the roles of immune regulations and the therapeutical approaches for Coronavirus disease 2019 (COVID-19) through IgG Fc receptors is worth to be discussed here.

COVID-19 is declared March 2020 by the World Health Organization (WHO) as a pandemic infectious disease characterised with severe acute respiratory syndrome. No specific and effective cure to kill the virus is available so far. It is expected that clinical vaccination trail for COVID-19 will be completed later this year or early next year.

It is assumable that dysfunction in immune host defence, humoral and cellular immunity linking and regulation, genetic variations resulting in increased diseases susceptibility, poor response to therapies, the diseases severity and mortality might be involved in the pathogenesis of the COVID-19.

Studies showed the infection of SARS-CoV-2 enter host cells through the receptor of angiotensin-converting enzyme (ACE2) (85,86). In addition, Studies from Takeda et al suggested possible mechanism of COVID-19 possible through antibody-dependent enhancement

(ADE) (59). ADE has been showed in several viral infections through the pathway of promoting viral cellular uptake of infectious virus–antibody complexes following their interaction with Fc receptors.

Thrombocytopenia is one of the clinical features of COVID-19 and it is reported to be associated to clinical severity of disease (87). There are several possibilities resulting in thrombocytopenia including increase destruction of platelets due to the coagulation status, decreased production of platelets due to therapies. One of the mechanisms of thrombocytopenia could be due to immune mechanism mediated by FcγRs.

Immunotherapy with immune IgG collected from patients recovered COVID-19 combined with antiviral drugs could be an alternative treatment against COVID-19 although some clinical practical issues need to be solved and procedures need to be improved (88,89).

No doubt, further studies will be conducted in the future to investigate the possibility of therapeutical approaches for COVID-19 such as to block and neutralise viral activity and to regulate the cytokine storm though the immune processes and the genetic variation through FcR can be used as one of the treatments. As other diseases, genetic variation is associated with the susceptibility, clinical severity and mortality of the COVID-19. It has been noted that there were some COVID-19 cases reported to be reinfected in couple of month time.

Conclusions

Human immune includes cellular immune and humoral immune. Many immune diseases can be mediated by either cellular immune or humoral immune. Fc receptors play very important role by linking cellular and humoral immune in the homeostasis, regulation and host defence. FcR is the major type of the five Fc receptor classes. Diseases/disorders occur if dysregulated. Advancing studies have revealed mysteries of many different kinds of diseases in the understanding of the pathogenesis and helping in clinical therapies.

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