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Review Article

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 (FcRys) on a variety of hematopoietic cells with different structures and different functions were defined by World Health Organisation (WHO).

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

Recently, intensive studies on Fcys 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 dysregulations of Fcys.

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

Introduction

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

Fc receptors are a group of integral membrane glycoproteins molecules presented on phagocytic cell surface mainly and such specialised molecules specifically recognise and bind to the Fc portion of the immunoglobulins molecules after triggered by various cellular immune effector functions, 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. Different class of Fc receptors have different specificity for a specific immunoglobulin binding [3-7].

Fc-gamma receptor (FcR γ) 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 Fc γ R was first described by Berken and Benacerraf [9]. Human Fc γ Rs are found to be distributed on many different kinds of cells and cell lines under the condition resting and activated [10,11].

Fc γ 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]. Fc γ 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].

Fc γ 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 Fc γ type I, Fc γ type II binds with low and medium affinity for monomeric IgG [14,15].

Fc γ 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 Fc γ type III) with Fc γ type IIIa and Fc γ type IIIb. Studies showed that Fc γ RIIIb 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 7,000 different types of diseases/disorders from the combination factors in the pathophysiological mechanism of genetics and environment 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 the dysregulations of Fc γ s.

The studies on Fc γ s have provided the understanding in disease mechanism it also provides the approaches for Rare disease therapies.

Characterisations of Fc γ s

Immune biological function of Fc γ Rs: Fc γ Rs are binding molecules on the surface of effector cells and soluble form in circulation reacting with the Fc part of the immunoglobulins or antibodies [19]. They play very important regulation roles 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 in activation and inhibition in health control [20–23].

In the normal conditions, Fc portion of monomer IgG does not bind to Fc receptors, only if Fab binds to foreign or auto-antigens or monomeric IgG aggregated and then it will trigger effector cells to destroy antibody-coated target cells through several immune processes such as the antibody-dependent cell mediated cytotoxicity (ADCC), Endocytosis, phagocytosis of immune complexes by effector cells, clearance of immune complexes, regulation of production of antibody by Fc γ Rs, biological substance release mediated by Fc γ Rs, and the regulation of cytokines mediated by Fc γ Rs [24–29].

The significances of Fc γ RIIA on megakaryocytic lineage of the platelets precursor cells

Fc γ 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 Fc γ type I or Fc γ type III with a variation of numbers of copies [15]. The presence of IgG Fc Receptors on platelets was demonstrated by Rosenfeld, et al. Such findings showed platelets are cells with immune functions [14].

Further studies revealed that Fc γ RIIA and Fc γ RIIC protein has activation biological functions through the immunoreceptor tyrosine-based activation motif (ITAMa), and in contrast, Fc γ RIIB protein has inhibition biological functions through the ITAMi [30]. Therefore, Fc γ R type IIA,B and C have been extensive studied due to their important immune-biological functions, particularly in platelet activation associated diseases/disorders.

An interesting study 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. It was presumable that Up-regulation of Fc γ Rs on or in platelet could be occurred at megakaryocyte/megakaryoblast level under the influence of cytokines which it would further exacerbate the pathological processes. Chong's group have characterised Fc γ RII on 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 a combination of techniques including immune-cytochemical staining, dual colour flow cytometry, immunoprecipitation from the protein level. Finally they studied mRNA expression of Fc γ R type II and their transcripts. Their results showed the presence of Fc γ R type IIA gene which is the Transmembrane (TM) exon [32–37].

Interestingly, they also found the presence of Fc γ R type IIA 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 summarised in Table 1.

The characterisation of Fc γ RIIA on cells of megakaryocytic lineage at protein and RNA levels enhanced the understanding of the pathophysiology in the Fc γ Rs regulation of the platelet activation associated diseases/disorders from the protein to RNA levels.

The significances of these studies were two fold; the first was the identification of the presence of Fc γ R type IIA on platelet and their precursor cells, megakaryocytes and megakaryoblasts from protein to molecular level. The transmembrane molecular of Fc γ R type IIA found on these

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

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]

cells have implied the pathophysiological mechanism in some platelet activation associated diseases/disorders because Fc γ R type IIA may play a physiological role from excessive binding and injurious effects of immune complexes such as in immune thrombocytopenia.

The second significance was that the sole type of the Fc γ RIIA 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 Fc γ Rs

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 [39-40]. Studies revealed that Fc γ s 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 [41-42].

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

Three types of the Fc γ RII (A,B and C) with low and medium affinity identified they 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].

Fc γ RIII also is a low and medium affinity receptor with A and B genes (Fc γ RIIIA and Fc γ RIIIB) identified also located on chromosome 1q23.3 on the FCGR2/3 locus [46,49].

Studies showed such genetic variations affecting immune functions, increasing individual's susceptibility and impacting therapeutical response of disorders/diseases [50-52]. Studies also showed that there are many different kinds of disorders/disease linked with such genetic variations associated dysfunctions of FcR γ s (gain or loss) with different consequences occurring with heterogeneity among different ethnic groups [53-55].

Some types of rare diseases associated with dysfunctions of Fc γ rs

Fc γ Rs in immunodeficiency: FcR γ s play roles in the regulatory functions in the immune system. Studies have showed Fc γ Rs mediated Ab-dependent enhancement (ADE) of HIV-1 infection in vitro in the conditions of dysfunctions will contribute to immune disorders such as immunodeficiency [56].

A study showed monoclonal antibodies to FcRI blocked antibody-dependent enhancement of HIV-1 infection and also they demonstrated CD4 molecule in antibody-enhanced HIV-1 infection was through FcR [57]. Evidence of antibody-dependent enhancement of human immunodeficiency virus type 1 (HIV-1) infection via Fc receptor was provided by a study [58]. Takeda, et al. demonstrated that serum from AIDS patients increased Fc γ R-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 conducted by Hussain, et al. showed that Fc γ R 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 Fc γ R type II and III on rectal epithelial cells it suggested the rate of HIV infection increased when cells encounter an antibody-coated virus [61].

Fc γ Rs in autoimmune associated Rare diseases: Fc γ Rs associated autoimmune disease is a disease caused by auto antibody or immune complexes leading to inflammation through FcR aggregation [62-64].

As discussed above, Fc γ Rs play bi-functional role by either activation or inhibition through different signalling mediated pathways. Immune Thrombocytopenia (ITP) is a representative example of the auto immune disease.

Studies indicated that many autoimmune diseases might be associated by impairment of the FcR regulation. Platelet activation causes severe or fatal cardiovascular consequences clinically. Data strongly demonstrated the evidences of the platelet activation associated diseases through Fc γ Rs dysfunctions.

The interaction of immune complexes with platelet Fc γ R type II due to the excessive binding of immune complexes leads to platelet activation, thrombosis or increased platelet consumption and thrombocytopenia in some clinical conditions.

Evidence showed that Fc γ Rs on platelets play role in the pathophysiology of Heparin-Induced Thrombocytopenia (HIT). An IgG heparin-dependent antibody is frequently demonstrated in patients with HIT and this antibody reacts with platelets in the presence of heparin and causes strong platelet aggregation. Evidence of the involvement of Fc γ R in HIT came from an interesting studies using of IV.3, a monoclonal antibody with specifically for Fc γ R 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 Fc γ RII and Fc γ RIII in a population study and they found three polymorphisms associated with systemic lupus erythematosus and lupus nephritis [66].

Another group studies demonstrated that Fc γ RIIb role in the regulation through the polymorphisms and dysfunction in the systemic lupus erythematosus as the autoimmune mechanism of disease. So they suggested such study can be an opportunities for therapeutic target [67].

Goulding, et al. investigated the Fc γ R on neutrophil signalling responses on patients with rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis in a comparison with healthy subjects, and their results suggested that cytosolic signalling of neutrophil Fc γ 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 Fc γ R polymorphism on KD and they suggested that the altered transcription or expression of FcR γ 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 [69]. Shrestha, et al. studies showed that the common variation of Fc γ R type IIA increased Kawasaki disease susceptibility and they suggested that Fc γ R IIIA variant is a determining factor for treatment response and implied KD pathogenesis and the IVIG anti-inflammatory mechanism [70].

Fc γ Rs in Malignant rare diseases: Evidences suggested some types of malignancies are involved in the mechanism of immune regulation through the Fc γ Rs [71].

Treffers, et al. investigated the role of regulation of the Fc γ RIIIb (CD16b) on solid cancer cells coated with antibody either trastuzumab (anti-HER2) or cetuximab (anti-EGFR) and their results showed the antibody-dependent cell mediated cytotoxicity was substantially enhanced after Fc γ RIIIb was blocked by anti-Fc γ RIIIb antibodies, indicated the negative regular role of Fc γ RIIIb [72].

Musolino, et al. studied the association of Fc γ R IIB polymorphisms with HER-2/neu-positive breast cancer therapy with a monoclonal antibody-trastuzumab through the antibody-dependent cell mediated cytotoxicity mediated by Fc γ RIIb 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 γ 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 Fc γ RIIA/Fc γ RIIIa polymorphisms can be used as the prognostic factors for disease progression in metastatic colorectal cancer treated with cetuximab plus irinotecan presumed through the process of antibody-dependent cell mediated cytotoxicity [74,75].

Studies on colorectal cancer associated with Fc γ R have been conducted. Calem group studied 74 patients with metastatic colorectal cancer and their results showed Fc γ RIIIa 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 Fc γ R in B-cell Chronic Lymphocytic Leukemia (CLL) and they found that Fc γ R expression was a bad prognostic factor, independent of age and sex, but correlated well with the tumor mass score [78]. However, Dornan, et al. results suggested that FCGR2A and FCGR3A polymorphisms did not significantly change the outcomes of relapsed or refractory CLL patients treated with fludarabine or the monoclonal antibody [79].

Therapeutic trials through the immune processes of Fc γ Rs on rare diseases

Advancing studies on genetic variations on Fc γ Rs increased the understanding of disease mechanism and translated such findings into clinical applications, such as in disease monitoring of therapeutic response and disease prognosis.

The therapeutic trials with monoclonal antibody in immune disorders were reported [80]. Bio-therapeutical monoclonal antibody against Fc γ R by the engineering approaches showed it is an effective through the immune processes of Fc γ R for many different kinds of diseases clinically [81].

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

An infusion of 3G8 (a monoclonal antibody specific against Fc γ RIII) was given to a patient with refractory idiopathic thrombocytopenia purpura. 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 Fc γ R-mediated phagocytosis.

Fc γ Rs 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.

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.

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.

The roles of Fc γ Rs in COVID-19 might be involved in the disease susceptibility and the potential therapeutical applications through the processes of Fc γ Rs might be helpful.

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 [87,88].

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.

In addition, thrombocytopenia is one of the clinical features of COVID-19 and it is reported to be associated to clinical severity of disease [89]. 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 Fc γ Rs.

Conclusions

Human immune includes cellular immune and humoral immune. Fc receptors play very important role by linking cellular and humoral immune in the homeostasis, regulation and host defence in the host defence and homeostasis in both of the adaptive and innate immune system. Fc γ R is the major type of the five Fc receptor classes found to be distributed

on different types of cells. Many immune diseases such as autoimmune disease, immune deficiencies and even cancers can be mediated by the dysregulated of Fc γ R.

The characterisation on Fc γ Rs from protein to molecular level has been intensively studied, particularly in their genetic variations associated with disease susceptibilities.

Advancing studies on Fc γ Rs have revealed mysteries of many different kinds of diseases in the understanding of the disease pathogenesis for clinical settings. Recently, the interests of therapeutical approaches for diseases through the immune processes of Fc γ Rs have been drawn.

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