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The role of Fc receptors in HIV infection and vaccine efficacy

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Abstract

Purpose of the review—In this review, the roles of Fc-gamma (Fcγ) receptor polymorphisms are discussed in regards to HIV-1 vaccine efficacy, HIV acquisition, and disease progression. In addition, the significance of the neonatal immunoglobulin G (IgG) Fc receptor and potential effects of the aggregated IgA Fc receptor (FcαR) are addressed.

Recent findings—Fc receptors undoubtedly play an important role in antibody-mediated action in HIV infection and vaccines. Several studies have determined an association between polymorphic variants of FcγRIIA and FcγRIIIA in the acquisition and progression of HIV-1 infection, and in responses to vaccination regimens. A rather complex relationship exists between the relative affinity of these molecules and their impact on HIV disease acquisition and progression and HIV vaccine efficacy.

Summary—The discrepancies between different investigations of the role of Fc receptor polymorphisms appear to derive from the complex nature of the Fc receptor functions including factors like epistatic interactions and the race, gender, age and relative risk behavior of the investigated individuals. Furthermore, Fc receptors in nonhuman primates (NHP), the key model to study an AIDS-like disease in an animal model, appear to be even more diverse than in humans, and the function of these proteins has not been extensively explored. Given the critical role of Fc receptors in antibody-mediated function in humans and NHP, more investigations are needed to fully understand and exploit these functions for vaccine design.

Keywords

Fc receptors; non-human primate; single nucleotide polymorphism; vaccine efficacy; FcRn

Introduction

In the seminal study by Hessel *et al*. in 2007 [1], the role of Fc receptors (FcR) for HIV-specific antibody function was demonstrated in the non-human primate (NHP) model. This study showed a dramatic decrease in the protection afforded by broadly neutralizing antibodies when the Fc-binding activity was engineered out. In addition, a recent study using

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Conflicts of interest
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mice expressing human FcγRs has also shown that broadly neutralizing hemagglutinin stalk-specific antibodies require interaction with activating FcγRs to provide protection against influenza [2]. Furthermore, the RV144 clinical trial in Thailand, which showed a modest protective effect, demonstrated that in the presence of low levels of HIV-specific plasma IgA, non-neutralizing IgG binding antibodies capable of antibody dependent cellular cytotoxicity [ADCC] were associated with a decreased risk of infection [3,4]. The function of FcR is, however, dependent on polymorphic allelic forms of these receptors. The importance of FcR polymorphisms in clinical outcome has been extensively documented in oncology where an increased relative affinity of the polymorphic Fc receptor allelic forms resulted in a more efficient immunologic control of cancers [5]. In this review, we will summarize the role of Fc-gamma receptor (FcγR) polymorphisms in vaccine efficacy and HIV acquisition/infection and disease progression. In addition, we will discuss the potential roles of the neonatal IgG Fc receptor (FcRn) and Fc-alpha receptor (FcαR) in HIV infection and vaccines.

Fc receptors

Antibodies mediate some of their effector activities via their Fc domains attaching to cellular receptors. Each subclass of antibody/immunoglobulin binds to different classes of receptors.

Fcγ receptors

Fcγ receptors (FcγR) are the cellular receptors which bind the crystallizable fragment or Fc region of IgG subtype antibodies, i.e. the base portion of the “Y”-shaped immunoglobulin monomer. FcR can be divided into two main types: activating and inhibitory. There are six different types of FcγR: FcγRI (CD64), FcγRIIA (CD32A), FcγRIIC (CD32C), FcγRIIIA (CD16A), FcγRIIIB (CD16B), which are all activating receptors, and FcγRIIB (CD32B), the only inhibitory receptor [6]. The activating receptors, with the exception of FcγRIIA, require association with a separate signaling protein, the γ-chain, in order for cell signaling to occur [7]. FcγRIIA and FcγRIIB have intrinsic signaling motifs, immunoreceptor tyrosine based activation motif (ITAM) or immunoreceptor tyrosine based inhibition motif (ITIM), respectively within their cytoplasmic tails. FcγR are expressed on most cells of the innate immune system (monocytes, macrophages, natural killer [NK] cells, neutrophils, and others) and on B cells, but not on T cells. NK cells typically express FcγRIIIA and in some individuals FcγRIIC [8,9]. FcγRIIB is predominantly expressed on neutrophils, eosinophils and B cells. FcγRIIA is the most widely expressed FcγR and is usually co-expressed with FcγRIIB, as this receptor regulates the immune response [10]. FcγRIIA and FcγRIIIA retain low affinity for monomeric IgG and preferentially bind to immune complexes [10]. FcγRI is the only high-affinity FcγR in that it can bind both monomeric antibodies and immune complexes. Upon ligation of the receptors with immune complexes, several effector functions can be elicited including ADCC, antibody dependent cellular phagocytosis (ADCP), and antibody dependent cellmediated virus inhibition (ADCVI).

Fcγ receptor single nucleotide polymorphisms (SNP)

Allelic variations in the form of a single nucleotide polymorphism (SNP) occur in FcγRIIA and FcγRIIIA, at positions 131 and 158, respectively. Human FcγRI is not polymorphic. These SNPs attain clinical and functional relevance, effecting IgG binding, immune effector

functions and responsiveness to biological medicines [11]. FcγRIIA has a polymorphic residue at position 131, either a histidine or an arginine (H131R). The presence of at least one H allele is required for binding to IgG2, and binding to IgG1 and IgG3 is higher compared to binding to receptors with R allele [12]. FcγRIIIA has a single nucleotide polymorphism at position 158 resulting in either a phenylalanine (F) or valine (V). The V allele has a greater affinity for IgG than the F allele, which has clinical implications in the monoclonal antibody therapy for B-cell lymphoma and other cancers [5]. The pathogenesis of infectious diseases can be modulated by these allelic variants. HIV disease progression, risk of infection and vaccine efficacy have been shown to be affected by these polymorphisms [13]. However, some study results appear contradictory or not replicated in various patient cohorts.

FcγRIIA and HIV

Several studies have investigated the role of FcγRIIA polymorphism in HIV infection, acquisition after vaccination, or disease progression. FcγRIIA genotype has been demonstrated to predict progression of HIV infection. Specifically, patients homozygous for the low binding allele, RR131, progressed to a $CD4^+$ cell count of <200 cells/mm^3 more rapidly than individuals homozygous for the high binding allele, HH131, or heterozygous for the two alleles (RH131). However, the same study also showed that individuals with the HH131 genotype were more likely to develop *pneumocystis jirovecci* pneumonia as AIDS-defining opportunistic disease [14]. Likewise, the HH131 genotype has been associated with increased risk of placental malaria in HIV–infected women [15] and other perinatal infections [16].

The presence of the H allele, either in the heterozygous RH131 or homozygous HH131 version, was associated with lower HIV replication in patients who mounted a robust anti-p24 IgG2 response after vaccination with a highly attenuated recombinant fowlpox virus vector expressing HIV Gag-Pol and interferon-gamma (IFN-γ)[17]. Moreover, individuals with HH131 genotype exhibited the highest ADCVI responses after vaccination with recombinant gp120 protein. The effect of the H allele was a dose-dependent, with RH131 having intermediate and RR131 the lowest ADCVI activity [18]. In contrast, other studies including the RV144 trial and VAX004 trials have not found an association of this allele with HIV infection or response to vaccination (poster 420, Kijak et al., CROI 2012 [19]).

FcγRIIIA and HIV-1

There is still some uncertainty regarding the role of FcγRIIIA in HIV-1 infection, disease progression, and vaccination. V158F polymorphism, which is caused by different isoforms with either a valine (V) or a phenylalanine (F) in amino acid position 158 of FcγRIIIA, results in different binding affinity to IgG1 and IgG3. Forthal *et al*. showed no effect of V158F polymorphism on HIV-1 disease progression in infected individuals in the Multicenter AIDS Cohort Study (MACS) [14]. However, they recapitulated findings of an association of V158F gene polymorphism and the development of Kaposi's sarcoma (KS) as AIDS-defining illness [14,20]. In contrast, Poonia *et al*. showed that the homozygous FcγRIIIA-VV158 genotype was associated with a higher rate of HIV disease progression [21]. While VV158 individuals were predominantly in the HIV progressor group, higher

frequencies of the V158 allele were also detected among all HIV infected patients compared to natural virus suppressors and uninfected controls. Conversely, the combination of FcγRIIIA-FF158 and FcγRIIA-RR131, i.e. double homozygosity for low activity alleles, was associated with HIV disease progression [22].

FcγRIIIA-V158 has been associated with acquisition of HIV infection after vaccination in different trials utilizing different vaccination regimens or vaccine modalities. After vaccination with recombinant gp120 (HIV-1 envelope glycoprotein) in the Vax004 trial, individuals with low sexual risk-behavior were found at enhanced infection risk when they were homozygous VV158, with even higher infection risk than in individuals with the FF or FV genotype and high behavioral risk. This increased risk based on the VV158 genotype also became apparent, although not significantly, in the placebo vaccinated group [19]. Testifying to the complicated nature of Fc receptor and immune-related gene loci attributing to HIV infection risk after vaccination, another analysis found no association between FcγRIIA-H131R or FcγRIIIA-V158F variants alone and risk of infection. However, when analyzed in combination with GM or KM alleles, genetic markers of immunoglobulin γ and κ-type light chains, respectively, an association was noted between the GM23+/- allele and the high affinity V158 allele. An association was lacking for GM or KM alleles alone and KM/Fc receptor combinations [22]. Extensive analysis of the RV144 trial, revealed that the vaccine more efficiently protected individuals with the FF158 genotype in regards to disease progression to a $CD4^+$ T cell count of <350 cells/μl, time to highly active antiretroviral therapy (HAART) initiation, or AIDS-defining illnesses. These modulatory effects were only significant in males (Poster 420, Kijak et al., CROI 2012). This gender bias observation correlates with the previous study showing an effect of the FcγRIIIA genotype on vaccination, compared to studies which could not replicate the effect, as the VAX004 trial was a male only cohort. Therefore these studies point to risks with both the low-binding and high binding alleles, depending on what other genetic factors and endpoints are considered.

Neonatal IgG Fc receptor in vaccination and infection

The neonatal IgG Fc receptor (FcRn) is a major histocompatibility complex (MHC) class I-like heterodimer composed of the ligand binding α-chain non-covalently associated to β-2-microglobulin, the signaling domain [23,24]. It is expressed in a variety of cells and tissues including the mucosal epithelial cell barriers in the intestine, the lung, and at the maternal-fetal barrier of the placental mucosal epithelium [25]. In early life, FcRn provides passive immunity to the fetus *in utero* via transfer of maternal IgG [26]. In adults, its function is to transport IgG across polarized epithelial cells and to rescue IgG and albumin from lysosomal degradation, contributing to the long plasma half-life of these proteins [27]. A unique feature of FcRn is the pH-dependent binding [28]. IgG is internalized into early endosomes, acidic intracellular compartments, in which FcRn binds to the Fc region of IgG. The FcRn-IgG complexes are transported from the apical cell membrane via recycling endosomes that bud and mature into secretory vesicles to the opposite baso-lateral side of the cell where FcRn releases IgG, mediated by the neutral pH at the plasma membrane [29].

As the neonatal IgG Fc receptor (FcRn) transports IgG in mucosal epithelia, fusion proteins were engineered to target antigens at mucosal surfaces, allowing transcytosis to the antigen

presenting cells (APCs) on the other side. Fusion proteins of HIV-Gag (p24) to the Fc region of IgG in the presence of the adjuvant CpG were administered to mice intranasally. This immunization regimen resulted in local and systemic immunity, including Gag-specific antibody responses in serum and at mucosal sites. In addition, durable memory responses were induced, such as antibody secreting plasma cells and IFNγ-producing T cells that provided protection against challenge with a recombinant vaccinia virus expressing HIV Gag protein [30].

FcRn has been attributed to facilitating sexual transmission of HIV-1 by enhancing transcytosis across cervico-vaginal, penile urethra, and intestinal epithelia. Anti-HIV-1-specific-IgG-complexed HIV-1 isolates showed enhanced transcytosis, augmented by the acidic pH of cervico-vaginal or seminal fluids, facilitating viral transmission to susceptible target cells in the mucosal tissue. The transcytosis was abrogated in FcRn-knockdown cells or when FcRn-IgG interaction was blocked. Strong binding antibodies resulted in a more FcRn-dependent transcytosis rendering the virus more infectious, while strong neutralizing antibodies reduced the infectivity of the transcytosed virus [31]. These investigations raise questions whether non-neutralizing, binding antibodies are at all beneficial for containment of viral spread, which is an issue that requires further exploration utilizing animal models.

FcαR and HIV

The role of IgA antibodies in HIV-1 vaccines remains subject to debate. The RV144 clinical trial indicated that augmented HIV-Env specific serum IgA levels correlated with decreased protection efficacy; however, mucosal IgA was not measured [3]. In a recent DNA-based vaccine study aimed at elucidating the role of mucosal IgA in vaccine efficacy, macaques receiving an additional mucosal adjuvant had a protection rate of 80% compared to 60% with the DNA vaccine only. Protected monkeys had increased levels of vaginal IgA, but a correlation with serum IgA was lacking. The greatest viremic control was achieved in monkeys with the highest levels of vaginal IgG and IgA. The authors concluded that vaginal IgA is protective against mucosal transmission and that mucosal sampling should be included in future clinical studies (oral abstract OA04.02, Hutnick *et al*., AIDS Vaccine 2013). In light of these findings a deeper understanding of the receptors for IgA is warranted in both humans and macaques.

FcαR has been shown to alternatively splice in both humans and macaques, with ten and six splice variants reported, respectively. In addition, a single nucleotide polymorphism (SNP) is present in the cytoplasmic domain of human FcαR (also known as CD89), resulting in either serine or glycine at position 248 (S248G). These alleles differ significantly in calcium mobilization, degranulation, and cytokine release. The G248 allele mediates interleukin-6 (IL-6) release independently of FcR γ-chain association, whereas the S248 allele cannot. Similar to some FcγR allelic forms, the G248 allele occurs enriched in systemic lupus erythematosus populations and therefore may contribute to the pro-inflammatory potential of IgA [32]. The role of FcαR in HIV-1 infection and vaccination remains unclear. Future studies may help examine whether FcαR are polymorphic in widely used NHP models and elucidate their role in HIV/SIV infection and vaccines.

Nonhuman primate studies of Fc receptors

NHP such as rhesus, pig-tailed and cynomolgus macaques are widely used in the pre-clinical evaluation of monoclonal antibodies and vaccine candidates. As NHP can be infected with pathogenic simian immunodeficiency virus (SIV), the simian equivalent for HIV, the SIV/NHP animal model is one of the most important research tools in the quest for an effective HIV-1 vaccine. As the effector functions of antibodies are mediated by FcR, the sequence and function of the receptors in NHP are of crucial importance to translate into optimized vaccine design by addressing efficient antibody production and function. FcγR in rhesus macaques are highly polymorphic, with three FcγRI, five FcγRIIA and three FcγRIIIA allelic variants being described in a small cohort of nine animals [33]. Another study identified different FcγRIIIA allelic variants in rhesus macaques. These allelic variants resulted in different outcomes after administration of an anti-CD20 antibody [34]. Sequences obtained from pig-tailed macaques confirmed a high degree of polymorphism in FcγRIIA, with eight distinct allelic variants identified [35]. These studies indicate that a more thorough investigation of the full range of FcR in different NHP species, utilizing larger cohorts from several breeding colonies, is warranted for a more accurate interpretation of vaccine and therapeutic antibody studies in NHP models.

As NHP are extensively used to study an AIDS-like disease in an animal model and/or serve as study subjects in preclinical AIDS vaccine trials, the diversity and function of FcR is currently being extensively investigated in a number of laboratories including our own. In light of the difficulty in eliciting broadly neutralizing antibodies, multiple laboratories are investigating the efficacy of antibodies that are specifically designed either in regards to their immunoglobulin class and/or their relative activity of the Fc domain and the antibody glycosylation pattern [36]. Passive immunization strategies in NHP are extensively performed to determine which characteristics of antibodies may yield the best possible outcome in low dose AIDS virus challenge studies [37].

Conclusions

While the clinical advantage of relative high affinity polymorphic forms of FcR has been extensively documented in oncology, the functions of these receptors appear to be by far more complex in HIV-infected individuals and vaccine trials. Reasons for this heterogenic outcome are likely multifarious; it is conceivable that the number of individuals investigated is still too low to determine a definitive conclusion. In addition, the particular circumstances of HIV-infected individuals or vaccinees may significantly influence whether the overall impact of the polymorphisms is more beneficial or not. While a relatively higher affinity will result in an increased efficacy, this could also mean that the overall immune activation is increased, which is not necessarily beneficial in HIV infection. A further complication is the observation that certain bacterial, viral and parasitic protozoal infectious agents may benefit from higher affinity polymorphic Fc receptors, and thus an increased pathogenicity may be observed in humans [14,15,20,38].

More detailed investigations are needed to fully appreciate the overall role of Fc receptors in HIV pathogenesis in humans and NHP. The ultimate goal should be to determine how this knowledge can be harnessed for optimal design of an effective HIV vaccine.

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Key points

1. Fc receptors play an important role in antibody-mediated action of HIV-specific antibodies.
2. As a consequence of the importance of Fc receptors in HIV antibody function, polymorphic allelic forms of FcγRIIA and FcγRIIIA with a higher affinity "should" be associated with a more benign disease course of HIV infection and/or more efficient vaccine protection. However, a conclusive result as to the relative role of polymorphic allelic variants of these receptors is still elusive.
3. Recent observations have shown that the neonatal IgG Fc receptor may enhance HIV-1 transcytosis across epithelial cells.