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Prospects for engineering HIV-specific antibodies for enhanced effector function and half-life

Austin W. Boesch^a, Galit Alter^b, and Margaret E. Ackerman^{a,c}

^aThayer School of Engineering, Dartmouth College, Hanover, New Hampshire

^bRagon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Cambridge, Massachusetts

^cDepartment of Microbiology and Immunology, Geisel School of Medicine, Lebanon, New Hampshire, USA

Abstract

Purpose of review—A wealth of recent animal model data suggests that as exciting possibilities for the use of antibodies in passive immunotherapy strategies continue to develop, it will be important to broadly consider how antibodies achieve anti-HIV-1 effect *in vivo*.

Recent findings—Beyond neutralization breadth and potency, substantial evidence from natural infection, vaccination, and studies in animal models points to a critical role for antibody Fc receptor (FcR) engagement in reducing risk of infection, decreasing postinfection viremia, and delaying viral rebound. Supporting these findings in the setting of HIV, the clinical maturation of recombinant antibody therapeutics has reinforced the importance of Fc-driven activity *in vivo* across many disease settings, as well as opportunistically resulted in the development and exploration of a number of engineered Fc sequence and glycosylation variants that possess differential binding to FcRs. Exploiting these variants as tools, the individual and concerted effects of antibody effector functions such as antibody-dependent cellular cytotoxicity, antibody-dependent cell-mediated virus inhibition, phagocytosis, complement-dependent cytotoxicity, antibody half-life, and compartmentalization are now being explored. As exciting molecular therapies are advanced, these studies promise to provide insight into optimal in-vivo antibody activity profiles.

Summary—Careful consideration of recent progress in understanding protective antibody activities *in vivo* can point toward how tailoring antibody activity via Fc domain modification may enable optimization of HIV prevention and eradication strategies.

Keywords

antibody-dependent cellular cytotoxicity; antibody; effector function; immunoglobulin A; immunoglobulin G; subclass

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Correspondence to: Margaret E. Ackerman, PhD, Thayer School of Engineering, Dartmouth College, 14 Engineering Drive, Hanover, NH 03755, USA. Tel: +1 603 646 9922; fax: +1 603 646 3856; margaret.e.ackerman@dartmouth.edu.

Conflicts of interest

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INTRODUCTION

Over the past several years, evidence supporting the involvement of antibody interactions with Fc receptors (FcRs) in contributing to protection from HIV infection and in viral containment has accumulated from studies spanning nonhuman primate (NHP) and humanized mouse models to humans. These discoveries parallel recent work regarding antibody therapies in other disease settings and point toward the potential utility of tools and insights provided by study of diverse monoclonal antibodies (mAbs) for optimization of the broadly neutralizing HIV antibodies being explored in translational prevention and eradication strategies. This review will summarize recent studies of the role of antibody effector activity in the setting of HIV with the goal of connecting these findings to trends and tools in antibody therapeutics in order to promote efficient exploration of novel antibody-based prophylactic and eradication strategies.

TRENDS AND TOOLS FROM STUDIES OF THERAPEUTIC MONOCLONAL ANTIBODIES IN OTHER DISEASES

The relative maturity of efforts aimed at optimization of the hundreds of novel, biobetter, and engineered mAbs currently in preclinical and clinical development offers significant potential to accelerate and enhance efforts to utilize broadly neutralizing antibodies (bnAbs) in the setting of HIV prevention and therapy. Beyond providing an extensive and widely utilized modular toolkit of antibody Fc domain variants that permit tailored effector activity, newer tools for incorporation of toxic small molecules or fusion with enzymes capable of catalyzing their formation, and methods for the generation of unique antigen recognition topologies have all advanced over the previous year. Although these advances may likewise feed forward into antibody prevention and therapy in the setting of HIV, we will focus on more traditional aspects of Fc domain engineering in this review.

Over the past year, insights developed across the diverse disease settings impacted by therapeutic mAbs have reinforced findings from studies of HIV indicating the critical involvement of the antibody Fc domain in anti-HIV mAb activity *in vivo*. Effector functions have been identified as critical to the in-vivo activity of a number of neutralizing antibodies, such as the broadly cross-reactive stem-reactive antibodies to influenza's hemagglutinin [1[¶]] but perhaps more surprisingly, antibodies to anthrax toxin [2[¶]] and staphylococcal enterotoxin B [3[¶]], both secreted toxins. For each of these mAbs and others, protection *in vivo* was impacted by Fc domain substitution, FcR expression, or both. Even among the class of immunomodulatory antibodies such as anti-CTLA-4, previously thought to act by blocking cellular receptors, are now thought to rather rely on antibody-dependent cellular cytotoxicity (ADCC) and other effector functions *in vivo* (reviewed in [4[¶]]). Collectively, these studies suggest that careful dissection of in-vivo mechanism(s) of action has the potential to permit significant enhancement of antibody efficacy.

As an example of the apparent synergistic enhancement of antibody activity via optimization of both Fv and Fc toward potentiated activity *in vivo*, the glycoengineered successor to rituximab received breakthrough therapy designation this year, and is the first

glycoengineered antibody to be approved in the USA [5,6[¶]]. Similarly, the development path of the promising ZMapp antibody cocktail utilized in Ebola treatment was focused on optimizing cumulative in-vivo activity [7[¶]]. The resulting oligoclonal cocktail of plant-derived, glycovariant mAbs bolsters support for the use of antibody Fc-enhanced variants or glycoengineered antibodies in combination, and points toward an example of limitations in the utility of selection based on in-vitro neutralization potency, or even efficacy in small animal models, as these activities failed to strictly predict in-vivo efficacy in NHP. Collectively, these and other clinical developments over the past year point toward the wisdom of a more holistic view of antibody activity.

THE PROMISE OF ANTIBODY-BASED PREVENTION, THERAPY, AND ERADICATION STRATEGIES

The development of vectored immunoprophylaxis using andeno-associated virus vectors [8] or potentially other methods [9] provide the opportunity to circumvent classical vaccination and the expense and logistical challenges of passive immunization with neutralizing antibodies. Andeno-associated virus technology has previously demonstrated sustained protection in rhesus macaques [8] as well as in an Fc γ R humanized mouse model [10,11], and is now being explored clinically.

Furthermore, beyond prophylaxis efforts, the potential to use mAbs therapeutically has begun to be reevaluated with the latest generation of bnAbs. Although apparently less effective in humanized mice [12,13], recent studies of mAb therapy in infected rhesus macaques have demonstrated robust and relatively durable reduction of viral replication mediated by even single bnAbs [14,15]. Combinations of bnAbs and/or the combination of these mAbs with naturally raised polyclonal antibodies from the host have lead to remarkably durable viral suppression in both model systems [13,14,16^{¶¶}].

These observations have further fueled new efforts in the sphere of viral reservoir reduction/eradication. ‘Kick and kill’ studies evaluating reactivation of latent virus with a mixture of inducers are also beginning to utilize bnAbs as their cytotoxic or virostatic agent (recently reviewed in [17[¶]]). Using delayed viral rebound as a measure of reservoir size or maintenance, one such study in humanized mice observed that viral inducers in combination with a multi-epitopic antibody mixture could delay rebound viremia for more than 100 days, and that this effect was Fc dependent [18^{¶¶}].

Varied outcomes observed in these and other studies when antibodies with alternatively ablated or enhanced FcR binding were used, motivates Fc domain optimization in the context of these promising strategies. As an example, viral rebound kinetics were dramatically accelerated and sensitivity to plasma bnAb concentration significantly reduced for a mixture of three bnAbs with ablated FcR binding as compared with wild-type antibody. The bnAb cocktail with ablated Fc γ R binding permitted much more rapid rebound even at concentrations 50-fold higher than wild-type antibodies [18^{¶¶}].

Thus, beyond efforts aimed at optimization of neutralization breadth, potency, and limitations as to viral escape via Fv engineering, the next generation of mAbs used in

prophylactic and therapeutic approaches will likely benefit from programming isotype, subclass, amino acid, and glycan Fc variants with differential FcγR, complement, and/or neonatal FcR (FcRn) binding to fine tune effector function and compartmental biodistribution for optimal activity.

ROLE OF THE ANTIBODY Fc DOMAIN *IN VIVO*

The Fc domain serves as a handle by which the adaptive immune system can circulate and distribute pathogen-specific antibodies at sites of infection, and upon encountering antigen engage a spectrum of FcRs and effector mechanisms to drive clearance or trapping of infected cells and virions.

Immunoglobulin types

The capacity of a given antibody's Fc domain to mediate these activities depends critically on its isotype. Among these, we will focus on immunoglobulin A (IgA) and immunoglobulin G (IgG) (Fig. 1), as these isotypes have been those most widely utilized in achieving passive immunity, and they are prevalent in serum and at mucosal surfaces. Additionally, they comprise nature's best examples of passive transfer experiments, with IgG antibodies able to utilize the FcRn to achieve placental transport and IgA antibodies prevalent in breast milk and able to coat and protect mucosal surfaces in the gastrointestinal tract.

Antibody effector function: Fc receptors in mechanism of action

Dedicated FcR such as FcγR, FcαR, and Fcα/μR can recognize these isotypes and subclasses to varying extents and stimulate the potent protective activities of a suite of innate effector cells with varying outcomes (Fig. 2). A wealth of human genetic and in-vitro and in-vivo data points toward the critical role of these functions in antibody activity *in vivo* (recently reviewed in the setting of HIV [27] and other diseases [28]); further, the specific avoidance of these activities by various pathogens via the secretion of soluble FcR competitors, Fc proteases, and glycosidases is also prevalent [29]. In the case of HIV, Vpu was recently described to antagonize tetherin's ability to inhibit detachment of virus from infected cells making them more susceptible to ADCC [30[¶]], providing one such mechanism to escape from antibody effector function and innate immune surveillance.

Antibody transport: Fc receptors in biodistribution

Similarly, dedicated transporters for both IgA and IgG exist (Fig. 2). The polymeric immunoglobulin receptor functions as an epithelial IgA transporter, and the FcRn serves as the IgG transporter. Recent data suggest that this receptor can facilitate transport of opsonized HIV across an epithelial monolayer *in vitro* [31]; however, others have observed that FcRn traffics multivalent immune complexes to lysosomes for degradation [32]. Although further work investigating the potential role of FcRn in facilitating HIV transport in the setting of naturally raised antibodies is likely necessary, passive transfer of an mAb with enhanced pH-dependent FcRn binding in macaques indicated that the role of this receptor in biodistribution and half-life extension likely outweigh the potential role of facilitated invasion for neutralizing mAbs [33^{¶¶}].

RECENT EVIDENCE OF THE IMPORTANCE OF ANTIBODY EFFECTOR FUNCTION IN HIV

Results from studies in humans, NHP, and mouse models over the past year have provided strong support for the role that improving our understanding of anti-HIV antibody activities *in vivo* could have in the development of antibody-based prophylaxis and prevention.

Vaccination

Emerging evidence from previous human vaccine trials has pointed to a complex relationship between HIV-specific antibodies and risk of infection. Correlate analysis of the RV144 vaccine trial, in which a modest reduction in risk of infection was observed among vaccinees, suggested that specific qualitative features of the humoral response might be key to protective efficacy [34]. Supported by a subsequent sieve analysis of vaccine-mediated selective pressure on breakthrough viruses [35], these studies identified V2-specific Abs as a correlate of reduced risk of infection [36]. Opposing this protective association with IgG, increased levels of envelope-specific IgA antibodies were observed among infected vaccinees, and secondary analyses indicated that ADCC activity was associated with reduced risk of infection among individuals with lower IgA responses [36]. This year, a third qualitative correlate, envelope-specific IgG3 antibodies [37], additionally associated with potentiated and polyfunctional effector activity [38] was identified.

Interestingly, RV144 does not mark the first trial in which qualitative antibody features have been associated with protection. Previous analysis of the VAX004 trial, in which overall efficacy was not observed, nonetheless indicated that HIV-specific ADCC activity correlated inversely with infection risk [39]. However, this AIDSVAX B/E based recombinant protein-based regimen, most fully evaluated among VAX003 participants, induced an extremely robust IgG4 response, which was associated with reduced antibody effector function [38], suggestive of competition among HIV-specific antibodies with differing effector function capacities. This observation of a potentially functionally inhibitory antibody type was experimentally confirmed in depletion studies in which selective removal of IgG4 resulted in enhanced activity of the remaining polyclonal pool of antibodies [38].

Lastly, an intriguing host genetic correlate was also recently identified; namely, a premature stop codon variant of the FcγRIIc receptor occasionally found on natural killer (NK) cells and B cells [26] was associated with reduced risk of infection [40]. However, whether or how this polymorphism may hold mechanistic significance remains unclear. Nonetheless, diverse data from these clinical trials point toward antibody effector function as associated with risk of infection.

Chronic infection and exposed seronegatives

Qualitative antibody features have likewise continued to be investigated in chronically infected individuals: fine-tuning of IgG glycosylation and FcR binding has been associated with differential control of viral replication and modulation of antibody activity [41,42], and an investigation of longitudinal tuning of neutralization and functional activity demonstrated

a rapid decline in antibody-dependent cell-mediated virus inhibition activity that correlated with reduced HIV-specific IgG3, as total IgG titers and neutralization activity increased [43]. Additionally, although controversial, previous findings as to the presence of HIV-specific IgA among exposed uninfected individuals have been further supported in the past year. IgA responses specific to envelope were observed in the vaginal secretions of HIV-negative women participating in a microbicide trial [44] as well as in foreskin swabs from highly exposed seronegative men [45].

Nonhuman primate studies

In parallel, a number of vaccine regimens have been tested in NHPs that have demonstrated varying levels of protective efficacy and implicated antibody effector activities in reduced viremia or reduced risk of infection [46–49]. Consistent with the inability of nonfucosylated b12 to augment protection in a mucosal challenge experiment [50], a recent -nef immunization study suggested that NK cell recruitment to the genital mucosa was not involved in protection from a simian immunodeficiency virus vaginal challenge [51]. Rather, the authors identified reduction in recruitment of CD4⁺ T cells to the site of infection attributed to anti-inflammatory immune complex signaling via binding of gp41-specific Abs to FcγRIIb as possibly contributing to reduced risk of infection [51–53].

Several studies this year evaluated protection provided by passively transferred polyclonal antibodies. When highly functional but nonneutralizing antibodies from human controllers were transferred to rhesus macaques, no protection against high-dose simian/HIV (SHIV) challenge was observed [54]. Rather than conclusively demonstrating the inability of nonneutralizing antibodies to provide protection, this experiment may serve to highlight the significant challenges associated with passive transfer of polyclonal human Abs to macaques: no human IgG was observed at the mucosa at the time of challenge, only a single infusion of antibody could be performed, and the estimated dose of HIV-specific antibody was less than half the dose of b12 required to achieve protection in this model. In another study, SHIVIG, a polyclonal IgG preparation from rhesus with high-titer neutralizing antibodies, was evaluated for its ability to provide protection against low-dose intra-rectal heterologous challenge [55]. Although reduced peak viremia was observed at the highest antibody dose, a greater number of transmitted founder variants were observed at lower doses, suggestive of antibody-dependent enhancement.

Among passive transfer studies, an IgG1 Fc mutant with increased affinity to FcRn improved transcytosis across cellular monolayers *in vitro*, increased serum half-life three-fold, enhanced mucosal distribution and persistence of IgG in the rectum, and most importantly, demonstrated improved protection from SHIV intrarectal challenges [33]. In another study, combinations of neutralizing ($n=3$) or nonneutralizing ($n=2$) antibodies were formulated for topical vaginal application [56]. Although the neutralizing antibody combination provided protection from infection in two-thirds of animals, the nonneutralizing antibody panel reduced plasma viral load, but did not influence transmission. In an interesting isotype switch experiment, the neutralizing human antibody (HGN194) [57] was evaluated in intrarectally applied dIgA1, dIgA2, and IgG forms, and SHIV acquisition was compared [58]. In this study, the dIgA1 variant exhibited the greatest degree of protection,

and this activity was attributed to enhanced virion capture and inhibition of viral transcytosis *in vitro*.

Studies in mouse models

A humanized Fc γ R mouse model has been developed that has the extracellular domain of human Fc γ Rs, but retains the mouse intracellular signaling [59], which used in combination with antibody Fc panels has begun to accelerate the underlying mechanism(s) of protective FcR-based immunity. Conveniently, the model recapitulates human structural features, cellular expression patterns, and effector functions, and has been coupled to luciferase-based reporting of HIV entry [60]. Use of this model has allowed generalization of the role of FcR in bnAb activity *in vivo* [61^{***}]. In the entry model, the use of murine subclass switch variants of a panel of seven different and variably potent bnAbs, including those recognizing the CD4⁺ binding site, V1/V2, V3, and V3/CD4⁺ induced epitopes, was generated and evaluated for protective activity. In a concentration-dependent manner, all variants of the potentiated murine IgG2a subclass exhibited the ability to reduce viral entry relative to murine IgG1, and this effect was lost in the context of genetically Fc γ R-deficient mice, providing the most comprehensive evidence of the importance of Fc-effector function in the protective activity of bnAbs *in vivo* to date. Beyond this panel, comparison of a human IgG1 Fc point mutant with enhanced affinity to Fc γ RIIa and Fc γ RIIIa and somewhat impaired affinity to Fc γ RIIb displayed enhanced protection over native IgG1, which in turn displayed greater activity than an Fc γ R knockout mutant, providing not only further support for previous findings that Fc γ R engagement is critical for protection, but also more importantly, the first evidence that protection from infection can be improved by selectively engaging activating Fc γ Rs.

In the context of treatment, combinations of three bnAbs with either enhanced or reduced Fc γ R-binding were also evaluated for their effect on viral loads observed following infection in this study. Although the enhanced variant cocktail was able to substantially reduce viral load, the Fc γ R binding ablated antibody cocktail had a limited impact on viral load despite similar serum concentrations [61^{***}]. This result extends the observation that FcR interactions contribute to sustained viral suppression in the ‘kick and kill’ viral reactivation study conducted in this model described above [18^{***}].

FRONTIERS IN RESOLVING AND OPTIMIZING ANTI-HIV ACTIVITY VIA Fc ENGINEERING

Although a wealth of data published this year indicates the importance of antibody effector function *in vivo*, questions as to the optimal Fc profiles of therapeutic and prophylactic antibodies remain.

Immunoglobulin A: friend or foe?

As an abundant antibody in the mucosa, IgA antibodies are potentially strong candidates for HIV protection, driving effector responses such as phagocytosis, ADCC and cytokine release through Fc α R present on neutrophils, monocytes, eosinophils, and some macrophage and dendritic cells (Fig. 2). In some circumstances, they have demonstrated functional

advantages over IgG [62,63], particularly in the context of neutrophil activities. However, as described here, evidence in HIV is somewhat mixed, with both protective and nonprotective associations observed in humans, and limited exploration in passive transfer studies to date. Whether differences in the site of action/assessment, specificities, subclass, glycosylation, presence/absence of J chain, and secretory component or other factors will resolve these conflicting data remain to be determined. However, given the evidence outlined here supporting a protective role for IgA, further evaluation of systemic and mucosal IgA responses and of passive IgA transfer is imperative.

Fortunately, recent progress has been realized using antibody engineering and novel production methods to enable stable and functionally equivalent forms of mIgA [64], dIgA [65], sIgA [66], and a stabilized IgA2m(2) allotype [67]. These antibody variants may be useful for exploring the protective potential of IgA through systemic or mucosal passive immunization studies and gaining insight into their compartmental dissemination and effector functions. Given IgA-focused Fc engineering efforts have been minimal to date, there may also be significant opportunity to tune binding to the high-affinity FcαR and the less characterized FcαμR found on follicular dendritic cells, a subset of tonsillar B cells, and activated macrophages [68]. Lastly, because IgA is heavily glycosylated, clarifying potential lectin interactions on effector cells or mucosal surfaces could likewise prove valuable.

Engineering enhanced effector function

An ever expanding set of Fc variants exists, with recent developments in enhanced immunomodulation of FcγR2a versus FcγR2b [69], creation of soluble, self-assembling, hexameric IgG with increased complement-dependent cytotoxicity activity [22^{*}], asymmetric Fc engineering via Fc heterodimers [70], among many others. Exploring the effects of enhanced binding to FcγRs and FcRn can be achieved by antibody Fc amino acid mutations, glycosylation engineering strategies, or both, each with its own set of advantages and disadvantages in terms of suitability, availability, and risk of immunogenicity. Although both point-mutated and glycoengineered mAb variants have long development histories and clear activity advantages *in vitro* and often in animal models, their clinical evaluation history is relatively short, with point-mutated variants only reaching phase I/II evaluation in the last few years, and approval of the first glycoengineered variant achieved in 2014.

Resolution of available effectors and mechanisms

Although empirical approaches may be needed to ultimately define optimal Fc activity *in vivo*, continued study of the localization and activity levels of various effector cells likely offer clues. Such data may also be key to experimental interpretation, as the antibody preferences of different cell types sometimes conflict. For example, it was recently determined that engagement of FcγRIIIb impairs ADCC mediated by FcγRIIa on neutrophils [71]. Therefore, an explanation of the inability of non-fucosylated b12 to provide enhanced protection via its ability to better stimulate NK cells [50] could be that this glycoform is counterproductive to the activation of neutrophils, which are abundant at mucosal sites and in blood. Evaluating these factors in NHP will also present a nontrivial challenge, as the degree of conservation between antibody biology in NHP and humans is incompletely determined.

As therapeutic approaches gain traction, it will be important to be mindful of possible differences in desirable effector functions depending on clinical factors, as the capacity of innate effectors to function is clearly impacted by HIV infection and a host of other immunological parameters. It is possible that desirable antibody activities may differ in the setting of prevention from those effective in therapy. Further, there may be significant differences in the epitopes available for recognition on infectious viral particles, compared with infected cells, budding virus, or latent cells that have been reactivated. Targeting of human endogenous retro-virus glycoproteins present on the surface of HIV-infected cells serve as one striking recent example [72].

CONCLUSION

The relative maturity of efforts aimed at optimization of the hundreds of novel, biobetter, and engineered mAbs in preclinical and clinical development offers significant potential to accelerate and enhance efforts to utilize bnAbs in the setting of HIV prevention and therapy. Toward this end, insights developed across the diverse disease settings impacted by therapeutic mAbs have reinforced findings from studies of natural HIV infection, vaccination, and passive transfer studies in indicating the critical involvement of the antibody Fc domain in mAb activity *in vivo*. Engineering the antibody constant domain to better serve as a molecular beacon in directing mAb biodistribution and in recruiting the potent protective functions of innate immune effector mechanisms presents an opportunity to supplement the protection afforded by neutralizing antibodies, providing a complementary approach to improving HIV recognition and neutralization activity.

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KEY POINTS

- Effector functions mediated by the Fc domain are key to antibody activity *in vivo* across a wide spectrum of diseases and models.
- Fc domain engineering offers a suite of modifications to selectively enhance or reduce antibody activity and alter IgG biodistribution.
- Fc engineering can enhance the protection afforded by a neutralizing antibody in the macaque SHIV challenge model.
- Broadly neutralizing antibodies are generally dependent on their Fc domains for optimal activity in humanized mouse models of HIV entry and viral suppression.

FIGURE 1.

Structural diversity of IgG and IgA. Structurally, IgG (a) and IgA (b) differ in valency, size, and extent of glycosylation. (a) IgG antibodies may be further divided into four subclasses (recently reviewed in [19]). Structurally, the most notable distinction among subclasses is the significantly extended hinge of IgG3, which contains a variable number of repeating units. Other structural differences include the ability of IgG4 molecules to undergo Fab arm exchange, which results in naturally bispecific but functionally monovalent antibodies [20]; and among all subclasses, varying numbers and formation of disulfide bonds in the hinge region have been observed [21]. Although IgG has traditionally not been thought to oligomerize, recent evidence suggests otherwise, with observations of ordered IgG1 hexamers [22] and confirmation of covalent IgG2 dimers [23]. (b) IgA1 and IgA2 subclasses, whose prevalences vary among serum and various secretions, primarily differ structurally in terms of their hinge region, which is extended and extensively *O*-glycosylated in IgA1. Although this extension may offer advantages in accommodating bivalent antigen binding across greater physical distances, it is also thought to sensitize IgA1 to proteolytic degradation, and to be relatively rigid, potentially constraining the geometry of bivalent antigen binding. IgA molecules may be covalently dimerized via disulfide bond formation with the J chain, a 15 kDa immunoglobulin fold family protein that can also covalently polymerize immunoglobulin M. dIgA, dimeric IgA; IgA, immunoglobulin A; IgG, immunoglobulin G; dIgA, dimeric IgA; sIgA, secretory IgA; mIgA, monomeric IgA.

FIGURE 2.

Properties of FcR. (a) There are multiple FcγR receptors, including FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb found on a spectrum of effector cells including macrophages, neutrophils, NK cells, eosinophils, basophils, dendritic cells—all exhibiting differential receptor expression patterns and activity profiles. Each receptor and its allotypic variants have differential binding to IgGs based on subclass, glycosylation, and avidity. Beyond their structural and cellular diversity, functional relationships are complex as differential engagement between activating and inhibitory FcRs dictates their effector function [24], and certain receptors have additional roles in antigen presentation [25] and B-cell activation [26]. Cumulatively, they are responsible for mediating functions as diverse as ADCC, antibody-dependent cell-mediated virus inhibition, phagocytosis, complement-dependent cytotoxicity, and trapping in mucus. FcRn, the IgG transporter, binds to IgG in a pH-dependent manner to permit shuttling across epithelial boundaries via endosomal

trafficking. (b) IgA receptors include polymeric immunoglobulin receptor, FcαR, and Fcα/μR found on a number of cell types following binding of systemic dIgA, polymeric immunoglobulin receptor is cleaved at the apical membrane, leaving a fragment known as the SC bound. The resulting dIgA with the J chain and SC is known as secretory IgA, a hydrophilic and negatively charged molecule repelled by mucosal surfaces thought to act as a relatively passive pathogen trap. SC is thought to occlude FcαR binding, and thus partially account for the striking activity difference between plasma and mucosal IgA species. ADCC, antibody-dependent cellular cytotoxicity; FcR, Fc receptor; FDC, follicular dendritic cell; IgA, immunoglobulin A; IgG, immunoglobulin G; NK, natural killer; ORF, open reading frame; PMN, polymorphonuclear leukocyte; SC, secretory component.