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REVIEW

CMV-encoded Fcγ receptors: modulators at the interface of innate and adaptive immunity

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Abstract The constant region of IgG antibodies mediates antiviral activities upon engaging host Fcγ receptors (FcγRs) expressed by a variety of immune cells, such as antibody-dependent cellullar cytotoxcity (ADCC) executed by natural killer (NK)cells. Human cytomegalovirus (HCMV) is unique among viruses by encoding also an array of several Fcγ-binding glycoproteins with cell surface disposition and concomitant incorporation into the virion. Evidence is increasing that the virus-encoded Fcγ receptors differ in their Fcγ binding mode but effectively operate as adversaries of host FcγRs since they are able to prevent IgG-mediated triggering of activating host FcγRs, i.e., FcγRI, FcγRIIA, and FcγRIIIA. Here we discuss virus-encoded FcγRs as the first known HCMV inhibitors of IgG-mediated immunity which could account for the limited efficacy of HCMV hyperimmune globulin in clinical settings. A better understanding of their molecular mode of action opens up new perspectives for improving IgG therapies against HCMV disease.

Keywords FcγRs · Immune evasion · Cytomegalovirus · IgG · ADCC

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Human cytomegalovirus

Cytomegaloviruses (CMVs) are prototypical members of the β-subgroup of the herpesvirus family with a relatively broad tropism for many cell types and tissues. Due to millions of years of co-evolution and co-speciation, all CMVs exhibit a close adaptation to their individual host. The best studied CMVs are the members infecting humans (HCMV), chimpanzee (CCMV), *Mus musculus* (MCMV), rhesus monkeys (RhCMV), *Rattus norvegicus* (RCMV), and guinea pigs (GPCMV). HCMV has the largest genome of all human pathogenic herpesviruses encompassing two covalently linked unique segments (large, L, and small, S), U_L and U_S [1]. Endowed with double-stranded DNA genomes of approximately 235 kbp, traditional estimates of the coding capacity of CMVs varied between 166 to more than 200 open reading frames (ORFs) [2, 3]. However, in a recent study, unexpectedly more than 750 HCMV translational products could be detected [4]. A further hallmark of the HCMV genome is the presence of 12 multigene families that probably arose by gene duplication during virus evolution. As all herpesviruses, CMVs form enveloped virions and establish a lifelong infection with alternating phases of active replication and latency [5]. HCMV infection is highly prevalent in all human populations reaching seroprevalence rates of 50–99 %. While passing asymptomatic and mostly unnoticed in immunocompetent individuals, HCMV infection in immunocompromised individuals or newborn infants leads to massive tissue damage and often life-threatening disease manifestations [6]. However, HCMV-induced health impairment may not only be restricted to immunocompromised individuals since the infection has been also linked to further acquired disorders such as arteriosclerosis and vascular disease, immune aging [7, 8], and certain types of tumors [9].

Primary CMV infection leads to disseminated replication in multiple organs including the liver, spleen, lungs, kidney, and

bone marrow before it is controlled and eventually terminated by well-orchestrated innate and adaptive immune responses. Primary immune reaction starts with the induction of innate responses comprising type I interferons (IFN) and activation of natural killer (NK) cells. Next, adaptive immune responses are initiated among which $CD8^+$ and $CD4^+$ T cells are essential for protection from primary and also recurrent MCMV infection [10, 11]. B-cell-dependent immunity plays a decisive role in the containment and control of recurrent infection [12]. Despite of successful termination of primary infection, CMVs invariably establish latent infection in certain cell types including $CD34^+$ hematopoietic stem cells, from which periodic reactivation consistently occurs. Additional experimental and clinical findings suggest that humoral immunity to CMV has a protective potential. In the murine system, adoptive transfer of immune serum to naïve Rag1−/− (T and B cell deficient) mice was sufficient for effective MCMV control after challenge [13]. On the other hand, CMVs must deal with adaptive immune pressure since they replicate predominantly in the presence of primed immune responses. To dampen antiviral immunity and promote CMV persistence and replication, a very large proportion of the CMV genome is employed in manipulating immune responses [14–16]. In this way, CMV has learned to target those immunological pathways and mechanisms that mediate the most critical antiviral effects, e.g., $CD8^+$ T cells, natural killer cells, interferons, and antibodies.

IgG antiviral effector functions

Immunoglobulins are essential mediators of the humoral immune system recognizing invading pathogens like bacteria or viruses. Immunoglobulin G (IgG) is the most abundant immunoglobulin subclass in serum and mediates immunological memory [17, 18]. Most of the antiviral IgG effector responses require the fragment crystallizable (Fc) part of the IgG molecule, Fcγ, which is designed to interact with a variety of soluble and cell-bound ligands. While a majority of IgG effector functions are both fragment antigen binding (Fab)- and Fcγ-dependent as further outlined below, neutralization of virions or toxins can be reached in a solely Fab-dependent but Fcγ-independent manner [19]. Crucial interaction partners of Fcγ are the C1q component of the complement system, and distinct classes of cellular receptors, e.g., the FcγRs (canonical or type I Fc receptors) and CD23 as well as DC-SIGN (CD209) (type II Fc receptors) [19–21]. Binding of C1q to opsonizing IgG leads to complement-dependent cytotoxicity of virally infected cells or virolysis, i.e., destruction of the viral particle [19]. The FcγRs connect the innate and the adaptive arm of the immune system and humoral and cell-mediated immunity, conferring FcγR central roles in the execution of immune responses [22]. Interaction of antigen-bound IgG with activatory FcγRs results in phagocytosis of immune complexes and opsonized pathogens, antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells or macrophages, and the release of inflammatory cytokines, chemokines, or superoxide radicals [23]. Binding of IgG to the only known inhibitory FcγR, FcγRIIB, leads to anti-inflammatory responses and downregulation of B cell activation [20, 24, 25]. The glycan structure of IgG is of critical importance for the immune response elicited via FcγRs. Certain modifications on the IgG glycan such as galactosylated IgG1 is associated with anti-inflammatory responses [26].

Diversity of host FcγRs

Ligands, expression pattern, and function of human FcγRs

Canonical FcγRs belong to the immunoglobulin receptor superfamily and constitute critical receptors of immune cell activation and deactivation that recognize Fcγ domains in an open conformation (reviewed in Pincetic et al. [21]). Due to their broad expression pattern, they mediate a large variety of pleiotropic immune effector functions upon triggering by IgG-composed immune complexes. Specifically, they mediate the clearance of pathogens and antigens, regulate many inflammatory effector mechanisms including cytokine production, induce destruction of target cells by ADCC, and control antibody production and the initiation of anti-inflammatory pathways [23, 27, 28]. While Fcγ is thought to be the prime ligand of FcγRs, other soluble factors of the innate immune system are also known to be recognized and bound by FcγRs. These ligands mainly belong to the family of pentraxins, e.g., human C-reactive protein (CRP), serum amyloid P (SAP), and pentraxin 3 (PTX3) [29, 30]. It is not excluded that pentraxins may compete with IgG for binding to FcγRs due to overlapping binding sites on FcγRs [31], thereby potentially interfering with IgG-mediated responses.

In humans, FcγRs are encoded by six genes clustered in close proximity on chromosome 1–FCGR1A, FCGR2A, FCGR2B, FCGR2C, FCGR3A, and FCGR3B. The FCGR2C gene resulted from a crossover between FCGR2A and FCGR2B [32, 33]. Some of the human FcγRs exist in different allelic variants that exhibit remarkably variable characteristics regarding IgG subclass affinity and immune cell activation (see Table 1). Such allelic variants are known as FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA, and FcγRIIIB [20, 34–38]. Most immune cell types co-express different types of FcγRs, albeit at different levels (see Table 2). FcγRI is mainly expressed on monocytes, macrophages, dendritic cell (DC), mast cells, eosinophils, and basophils and is inducible on neutrophils [39]. Moreover, FcγRI expression is strongly inducible by IFN-γ [40]. FcγRIIA is predominantly expressed on myeloid cells and mast cells. Interestingly, FcγRIIA is the only FcγR expressed at high levels by

Table 1 Human FcγRs, their allelic variants, and their binding affinities for various human IgG subclasses (adapted from Guilliams et al. 2014 [35])

Alleles	FcγRI	FcγRIIA H131	FcγRIIA R131	FcγRIIB I232	FcγRIIB T232	FcγRIIC Q13 Stop13		FcγRIIIA V158	FcγRIIIA F158	FcγRIIIB NA1, NA2, SH	FcRn
IgG1	++++ $6x10^7$	+++ $5x10^6$	+++ $3x10^6$	++ $1x10^5$	++ $1x10^5$	++ $1x10^5$	-	++ $2x10^5$	++ $1x10^5$	++ $2x10^5$	++++ $8x10^7$
IgG2	-	++ $4x10^5$	++ $1x10^5$	+ $2x10^4$	+ $2x10^4$	+ $2x10^4$	-	+ $7x10^4$	+ $3x10^4$	-	++++ $5x10^7$
IgG3	++++ $6x10^7$	++ $9x10^5$	++ $9x10^5$	++ $2x10^5$	++ $2x10^5$	++ $2x10^5$	-	++++ $1x10^7$	+++ $8x10^6$	+++ $1x10^6$	++++ $3x10^7$
IgG4	++++ $3x10^7$	++ $2x10^5$	++ $2x10^5$	++ $2x10^5$	++ $2x10^5$	++ $2x10^5$	-	++ $2x10^5$	++ $2x10^5$	-	++++ $2x10^7$

- No binding
\+ binding affinity $2x10^4 - 7x10^4$
++ binding affinity $1x10^5 - 9x10^5$
+++ binding affinity $1x10^6 - 8x10^6$
++++ binding affinity $1x10^7 - 8x10^7$

Shown FcγR variants correspond to gene polymorphisms depicted either by the amino acid position in the protein and the respective substitution (e.g., FcγRIIA H131 or FcγRIIA R131) or by the name of the allele (e.g., FcγRIIIB NA1, FcγRIIIB NA2, or FcγRIIIB SH). Indicated values correspond to the affinities of various human FcγRs for different IgG subclasses. Human FcγRs are classified into low-affinity FcγRs (+) and high-affinity FcγRs (++++). Minus sign indicates no binding. Affinity values are represented in M^{-1} unit

platelets [36]. FcγRIIB has a prominent inhibitory role for circulating B cells [41], which express also FcγR-like receptors, FCRL1-6, as a separate class of surface receptors modulating their function [42]. Other immune cells found to express inhibitory FcγRIIB are basophils [43] and NK cells [44], but not mast cells [45]. Furthermore, FcγRIIB is expressed by smaller subpopulations of monocytes [46], neutrophils, as well by macrophages and DCs [41]. FcγRIIC is only expressed in about 20 % of humans due to a stop codon at position 13, but if expressed, it is regularly found on NK cells, monocytes, and neutrophils [44, 47]. FcγRIIIA is present on NK cells, monocytes, and macrophages, whereas glycosylphosphatidyl-inositol (GPI)-anchored FcγRIIIB is expressed mainly on neutrophils and a subset of basophils [48]. FcγR expression is critically modulated by cytokines [36, 49, 50]. For example, the cytokine transforming growth factor ß1 (TGF-ß1) is an immunosuppressive cytokine that reduces the expression of the FcγR-associated common γ-chain and thereby also reduces the surface expression of the activating FcγRs FcγRI and FcγRIII, while FcγRIIA seems to be unaffected. In this way, TGF-β1 may dampen inflammation [50].

In contrast to the above mentioned FcγRs, the neonatal FcR (FcRn) encoded by the FCGRT gene is not expressed on immune cells but certain epithelial cells and able to bind monomeric IgG with very high affinity [51] (see Table 1). The FcRn structure is similar to MHC class I molecules and allows for the association with β_2m [51, 52]. FcRn expressed by syncytiotrophoblasts of the placenta mediates transport of maternal IgG to the fetus and thus controls maternal passive immunity [53] (Table 2). In addition, FcRn binds IgG at the intestinal lumen of mucosal surfaces at a slightly acidic pH and ensures efficient unidirectional transport to the basolateral side and thus controls IgG turnover [53]. Circumstantial evidence was provided supporting a significant protective role of FcRn in simian immunodeficiency virus infection [54].

Table 2 Expression patterns of human FcγRs and FcRn on different cell types

	FcγRI	FcγRIIB	FcγRIIB	FcγRIIC[b]	FcγRIIIA	FcγRIIIB	FcRn
T cells	–	–	–	–	–	–	
B cells	–	–	++	–	–	–	
NK cells	–	–	–[a]	+	++	–	
Macrophages	+	+++	++	+	+	–	+
Monocytes	Inducible	+++	+	+	++	–	+
Dendritic cells	+	++	+	–	–	–	+
Neutrophils	Inducible	+++	+	+	–	++	+
Eosinophils	Inducible	++	Uncertain	–	–	Uncertain	–
Basophils	–	++	++	–	–	+	–
Mast cells	Inducible	++	Uncertain	–	Uncertain	Uncertain	Not tested
Endothelium	–	–	–	–	–		+
Intestinal epithelium	–	–	–	–	–	–	+
Syncytiotrophoblasts	–	–	–	–	–		+
Platelets	–	+++	–	–	–	–	

Adapted from Nimmerjahn and Ravetch, Guilliams et al., Hogarth and Pietersz, Bruhns, Van der Heijden et al., and Ko et al. [27, 35, 36, 38, 44, 54]

[a] Detectable in Fcgr2c-Stop persons

[b] Detectable in Fcgr2c-ORF persons

Besides the canonical FcγRs that bind Fcγ in an open conformation in a 1:1 stoichiometry, type II Fc receptors that include CD23 and DC-SIGN recognize Fcγ in a closed conformation with a 2:1 stoichiometry (reviewed in Pincetic et al. [21]).

Structure of FcγRs

Canonical type I FcγRs are glycoproteins belonging to the fast expanding IgG superfamily. They are composed of an α-subunit responsible for ligand binding (e.g., Fcγ) that contains two or three C2-type extracellular domains (Ig-binding domains) depending on the FcγR type, a transmembrane domain, and an intracellular tail that may contain signaling motifs (see Fig. 1) [23, 27, 55]. The human FcγRs are all type 1 transmembrane proteins, with the exception of the GPI-anchored FcγRIIIB [48]. FcγRI is the only human FcγR possessing a unique additional third Ig-like domain (D3) that may contribute to its high-affinity Fcγ binding [39, 42], although domains 1 and 2 are sufficient to

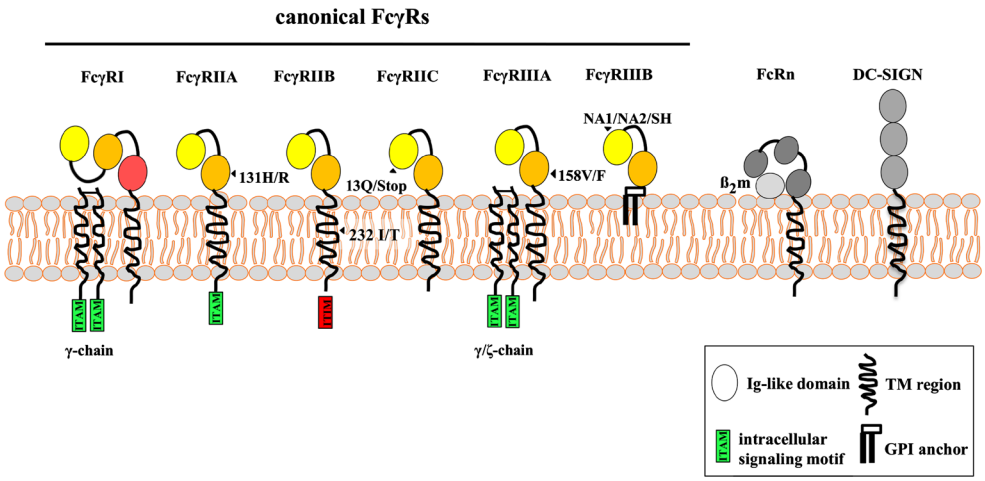

Fig. 1 Structural composition of human FcRs. Canonical FcγRs contain two or three immunoglobulin-like domains in their extracellular parts to bind IgG. Signal transduction upon receptor activation occurs via immuno-tyrosine-based-activating motifs (ITAM, indicated in *green*) usually in combination with the ITAM-containing, dimeric subunit, the common γ-chain, or immuno-tyrosine-based inhibitory motifs (ITIM, indicated in *red*). The family of human FcγRs comprises several activating members (FcγRI, FcγRIIA, FcγRIIIA) but only one inhibitory FcγR (FcγRIIB). Human FcγRs are shown color-coded based on their sequence relatedness. The neonatal FcR (FcRn) is structurally related to MHC-class I molecules and is able to transport and recycle IgG and thereby increases IgG half-life. DC-SIGN (dendritic-cell-specific intercellular adhesion molecule-3-grabbing non-integrin) is a C-type lectin receptor expressed by macrophages and dendritic cells. It is known to bind directly to C1q and Fcγ in a closed conformation

retain a weaker affinity for IgG [56]. Atomic-level structural data are available for the ectodomains D1 and D2 of FcγRIIA, FcγRIIB, and FcγRIII [57–59]. Both domains are each arranged in an identical immunoglobulin fold building a sandwich of two β-sheets. Moderate flexibility at the domain interface might allow the interdomain angle to vary slightly [55]. Host FcγRs bind Fcγ with 1:1 stoichiometry in an asymmetric manner, contacting residues in the C_H2 domain and in the C_H1-C_H2 hinge which connects the Fab to Fcγ [59]. The cross-linking of FcγRI-bound antibodies by multivalent antigens or the recognition of preformed immune complexes by FcγRII or FcγRIII results in clustering of the FcγR and triggering a variety of effector mechanisms [55].

In some FcγRs, the α-subunit is associated with a signaling adaptor molecule, the common γ-chain or CD3ζ. The common γ-chain and CD3ζ are dimeric signaling adaptors, containing immunoreceptor tyrosine-based activation motifs (ITAM) (Fig. 1) [42]. In contrast, FcγRIIA, FcγRIIC, and FcγRIIB have integrated activating or inhibitory signaling motifs in their own cytoplasmic tails [23, 36]. FcγRIIB is further unique because it is the only known inhibitory FcγR containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) [27, 60].

IgG features influencing ligand binding

Canonical FcγRs are characterized with regard to their binding affinity toward Fcγ into high-affinity and low-affinity receptors (see Table 1). High-affinity Fcγ receptors include FcγRI and the neonatal Fc receptor (FcRn). They are not only able to bind aggregated IgG, i.e., immune complexes, but also recognize equally well monomeric IgG. This implies that such FcγRs are easily saturated with "non-immune" IgG [61]. In contrast, low-affinity FcγRs, e.g., FcγRII and FcγRIII, preferentially bind IgG complexes, although low-affinity receptors may also be associated with monomeric IgG, which is referred to as "cytophilic" IgG and discussed as an inhibitory modulating ligand for $FcγRIII^+$ NK cells [61]. Curiously, the inhibitory FcγRIIB shows the lowest IgG affinity from all low-affinity receptors [37, 39]. In general, the human FcγRs bind to monomeric IgG of the subclasses IgG1, IgG3, and IgG4, albeit with clearly different affinities and with remarkable differences in binding affinities regarding distinct allelic variants of FcγRs. The IgG2 subclass is only poorly recognized by any canonical FcγR (see Table 1).

Binding of IgG to canonical FcγRs and downstream receptor activation is further tightly controlled by the presence and biochemical subcomposition of biantennary N-linked glycans conjugated to amino acid Asn297 in the C_H2 domain of IgG, which is highly conserved between all IgG subclasses and strongly influences the structural framework of Fcγ [20, 62]. For instance, defucosylation showed enhanced binding to FcγRIIIA, thereby increasing NK-cell-mediated ADCC up to 50-fold [63–66]. Conversely, unglycosylated IgG is not able to bind to FcγRs [67]. In conjunction with the remarkable structural diversity of the protein backbone of the IgG subclasses, the Fcγ domain thus takes a considerable heterogenic shape resulting in numerous Fcγ overall structures which could perhaps widely differ in their interaction with canonical and non-canonical Fc receptors.

Microbial Fcγ-binding proteins

To avoid the powerful effector functions mediated by IgG, various pathogens evolved specific immune evasion strategies. Some of these mechanisms interfere with the function of host FcγRs by competing with their ability to bind IgG, e.g., protein A (*Staphylococcus aureus*), protein G (*Streptococcus* sp.) [68], and the Phage-encoded protein TspB from *Neisseria meningitides* [69]. Several viruses from the herpesvirus family [70–77] and the core protein of hepatitis C [78] were also found to express Fcγ-binding proteins in virus-infected cells and as structural proteins incorporated into virus particles. In this respect, according to current knowledge, HCMV is provided with the most extensive genetic repertoire of independently acting viral FcγRs (vFcγRs). Notably, HCMV has been shown to encode quite a number of IgG-Fc-interacting proteins, i.e., vFcγR gp34 (*RL11*) [71, 72], vFcγR gp68 (*UL119–UL118*) [71], and another identified Fc-binding protein encoded by the gene *RL13* [70]. Furthermore, a fourth vFcγR, *RL12*, has been recently identified [70, 79] (see Table 3). Three out of four known vFcγRs belong to the *RL11* multigene family of HCMV comprising 14 individual members which are characterized by the RL11D or CR1 domain in their luminal part [1, 2]. The *RL11* gene family is supposed to have arisen by gene duplication before diverged by selection forces during the evolution process of primate CMVs [2]. The RL11D domain includes a characteristic key motif [1] as CXX (NQEKTY) $\times_{4–6}$ (YFLI) NX (ST) XXXXGXY (alternative residues given in brackets) consisting of a region of variable length formed around three conserved amino acid residues and including potential N-linked glycosylation sites. The HCMV FcγR genes are all transcribed with a relatively delayed kinetics during the protracted viral replication cycle reaching abundant protein amounts in the late phase of infection [71]. Isolated expression of their products proved that each molecule has intrinsic Fcγ binding capabilities. All the HCMV Fcγ-binding proteins readily reach the cell surface, thus constituting genuine FcγRs [70, 79, 80] (see Fig. 2). For comparison, we will also briefly discuss relevant aspects of other herpesvirus-encoded vFcγRs, i.e., the first-described gE/gI-Fcγ receptor complex of herpes simplex virus 1 (HSV-1) [73] and the

Table 3 Various herpesvirus-encoded FcγRs and their IgG binding capacities

	Virus	IgG binding	Interface for IgG binding	Stoichiometry	Literature
gp34/*RL11*	HCMV	Human IgG1, IgG2, IgG3, IgG4, Rabbit IgG, Rat IgG	nd	nd	Atalay et al. 2002; Sprague et al. 2008
gp68/*UL119–118*	HCMV	Human IgG1, IgG2, IgG3, IgG4	C_H2-C_H3	2:1	Atalay et al. 2002; Sprague et al. 2008
gpRL13/*RL13*	HCMV	Human IgG1, IgG2, Rabbit IgG	nd	nd	Cortese et al. 2012
gp95/*RL12*	HCMV	Human IgG1, IgG2, Rabbit IgG	Lower hinge C_H2-C_H3	nd	Cortese et al. 2012; Mercé-Maldonado and Hengel, unpublished
fcr-1/*m138*	MCMV	Mouse IgG	Ig-1	nd	Thäle et al. 1994; Lenac et al. 2006
gE-gI/*US7-US8*	HSV	IgG4> IgG1>or=IgG2; does not bind IgG3	C_H2-C_H3	2:1	Johansson et al. 1989, 1994; Chapman et al. 1999; Sprague et al. 2004

nd not determined

mouse cytomegalovirus (MCMV) Fc-binding protein m138 (fcr-1) [74, 76] (Table 4).

Herpesviral-encoded vFcγRs

HCMV vFcγR gp34 (RL11/TRL11)

The HCMV-encoded FcγR gp34 [71, 72] is a single-chain type 1 transmembrane glycoprotein transcribed from the *RL11* gene and its duplication, *TRL11*, which is present only in the UL*b*' negative HCMV laboratory strains Towne and AD169varATCC [81]. Like all other HCMV vFcγRs, *RL11* is dispensable for viral replication in vitro [71, 72]. gp34 consists of 234 aa with a N-terminal signal peptide and an extracellular region with three N-glycosylation sites, a transmembrane domain, and a C-terminal cytoplasmic tail of 31 aa.

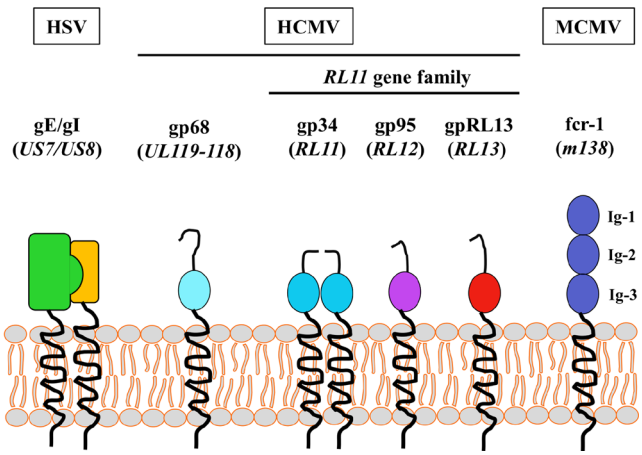

Fig. 2 Structural composition of herpesviral FcγRs. In herpes simplex virus (HSV) infection, the two glycoproteins gE and gI encoded by the genes *US7* and *US8* form a heterodimeric receptor complex acting as a FcγR. Unlike gE, the protein gI itself is not able to interact with IgG. In human cytomegalovirus (HCMV), there were four independent FcγRs identified: gp68, encoded by *UL119-118*; gp34, encoded by *RL11*; gp95, encoded by *RL12*; and gpRL13, encoded by *RL13*. In mouse cytomegalovirus (MCMV), there is one vFcγR identified, *m138*-encoded fcr-1

The cytoplasmic tail contains a dileucine consensus motif (DXXXLL, where X is unknown) indicating a potential function in intracellular targeting of the protein to the endocytic route [71]. The glycoprotein gp34 is synthesized with early and late kinetics reaching continuously increasing levels during the course of HCMV replication. Analysis of purified soluble gp34 (aa 24–182) revealed that a large majority of the protein forms dimers of an apparent molecular mass of 60 kDa [75]. Thus, a disulfide-linked gp34 homodimer [gp34 (24–182) contains five cysteins] may be present in the non-reducing environment of the extracellular milieu when the intact protein is present at the cell surface. Its ability to bind to the Fcγ fragment of IgG comprises not only all human IgG subclasses (IgG1, IgG2, IgG3 and IgG4) but also rabbit IgG and also, to a lesser extent, rat IgG (see Table 3) [71]. Importantly, gp34 as well as HCMV vFcγR gp68 exhibit a glycan-independent binding mode to Fcγ [75], implying that their binding characteristics must fundamentally differ from host FcγRs.

HCMV vFcγR gp68 (UL119–118)

Like gp34, the vFcγR gp68 is composed of a single-chain type 1 transmembrane glycoprotein that is transcribed from the spliced mRNA encoded by the open reading frames *UL119* and *UL118* [71]. The resulting protein consists of 347 aa and has been detected as a structural component in preparations of purified virions [82]. The gp68 polypeptide includes a N-terminal signal peptide followed by the extracellular region predicted to form a single immunoglobulin superfamily (IgSF)-like domain, residues 71–289 of which were demonstrated to be required for Fcγ binding [75]. The luminal domain of gp68 is joined by a transmembrane domain and a C-terminal cytoplasmic tail displaying a potential intracytoplasmic immunoreceptor tyrosine-based-like inhibition motif (consensus sequence I/V/L/SxYxxL). gp68 undergoes extensive glycan modification: the ectodomain exhibits 12 putative N-glycosylation sites and 8 putative O-glycosylation sites, most of

Table 4 Overview of known functions mediated by herpesviral FcγRs

	Features and functions	Literature
HCMV gp34	− Dispensable for HCMV replication in vitro − Impairs IgG-mediated FcγRI, FcγRIIA, and FcγRIIIA activation − Impairs ADCC by NK cells	Atalay et al. 2002; Corrales-Aguilar et al. 2014
HCMV gp68	− Dispensable for HCMV replication in vitro − High-affinity binding of Fcγ − Impairs IgG-mediated FcγRI, FcγRIIA, and FcγRIIIA activation − Impairs ADCC by NK cells	Atalay et al. 2002; Sprague et al. 2008; Corrales-Aguilar et al. 2014
HCMV gpRL13	− Dispensable for HCMV replication in vitro − Rapidly mutated upon in vitro propagation of HCMV isolates	Stanton et al. 2010; Dargan et al. 2010
HCMV gp95	− Dispensable for HCMV replication in vitro − Impairs Fcγr activation	Mercé-Maldonado and Hengel, unpublished observations
MCMV fcr-1	− Dispensable for MCMV replication in vitro − *m138* gene deletion results in strong attenuation in vivo − Downmodulates MULT-1 and H60 − Interferes with clathrin-dependent endocytosis − Downmodulates RAE-1ε − Downregulates the B7-1 co-stimulatory molecule CD80	Crnkovic-Mertens et al. 1998; Lenac et al. 2006; Arapovic et al. 2009; Mintern et al. 2006
HSV gE-gI	− Protects HSV-infected cells from ADCC − Protects cells from complement attack − Impairs IgG-mediated FcγRIIA and FcγRIIIA activation − Cell-to-cell spread	Dubin et al. 1991; Johnson et al. 1988; Nagashunmugam et al. 1998; Corrales-Aguilar et al. 2014; Dingwell et al. 1994

which are obviously used thus increasing the molecular weight of the 33-kDa protein backbone to an 68-kDa endoglycosidase-H-sensitive intermediate which matures further to more than 100 kDa weighing endoglycosidase-H-resistant forms [71]. The vFcγR gp68 is co-expressed with vFcγR gp34 and synthesized during the early and late phases of the HCMV replication cycle [71]. Although it has not yet been possible to obtain a crystal structure for HCMV vFcγR gp68, at least detailed biochemical evidence was generated of how HCMV FcγR gp68 recognizes Fcγ. Gel filtration and biosensor binding experiments revealed that, unlike host FcγRs but similar to the HSV-1 Fc receptor gE-gI, gp68 binds to the C_H2-C_H3 interdomain interface of the Fcγ dimer with high affinity in the nanomolar range and a 2:1 stoichiometry [75]. gp68 binds to all human IgG subclasses, i.e., IgG1, IgG2, IgG3, and IgG4 (see Table 3) [71].

HCMV RL13-encoded vFcγR

Only recently, a third vFcγRs was identified also belonging to the *RL11* gene family of HCMV which is expressed by *RL13*, a member of a restricted set of hypervariable genes found in the HCMV genome [70]. The ORF *RL13* is present in all primary isolates of HCMV, but it is very rapidly mutated when HCMV is adapted to cell culture growth, indicating that the intact RL13 glycoprotein (gpRL13) is detrimental to virus replication in various types of cells including fibroblasts and endothelial and epithelial cells [83]. This unique feature of gpRL13 selects for truncated and defect versions of the protein in HCMV strains propagated in cell culture [83–85]. The primary translation product of *RL13* is predicted to result into a 35-kDa protein backbone which is subjected to extensive glycosylation [86]. The glycoproteins found in RL13-transfected cells exhibit a molecular weight of approximately 100 and 55 kDa [70]. The glycosylated protein was found in the envelope of HCMV at relatively high densities and on the surface of transfected cells [86]. In its C-terminal cytoplasmic tail, gpRL13 harbors a YxxL endocytic motif which was shown to mediate the internalization of the Fcγ ligand [70]. RL13 displays a selective preference for IgG binding to the human IgG1 and IgG2 subclasses while ignoring IgG3 and IgG4 (see Table 3) [70]. Rough mutational analysis of the RL13 extracellular region revealed that the putative Ig-like region including further membrane-proximal sequences was required for IgG binding [70].

HCMV RL12-encoded vFcγR

A fourth recently discovered HCMV vFcγR is encoded by *RL12*, a further *RL11* gene family member [70] and thus displaying the same basic molecular architecture as the other type 1 transmembrane glycoproteins of HCMV which represent vFcγRs. According to its *RL13* relatedness, it is predicted to contain one IgSF-like domain in its extracellular domain, followed by a transmembrane domain and a C-terminal cytoplasmic tail, altogether yielding a molecular backbone of approximately 45–48 kDa, depending on the HCMV strain. Predictions for N- and O-linked glycans confirm the presence of numerous putative sites throughout the sequence resulting in a high molecular weight of about 95 kDa prior to endoglycosidase H treatment. The *RL12* sequence is, in contrast to gp34 and gp68, but similarly as noted for *RL13*, remarkably divergent among various HCMV strains. gp95

selectively binds only to monomeric human IgG1 and IgG2 but does not recognize IgG3 and IgG4 (see Table 3) [70].

MCMV vFcγR m138 (fcr-1)

So far, only one MCMV-encoded vFcγR could be identified which is transcribed from the early gene *m-138*/fcr-1 [76]. However, this vFcγR allowed a detailed analysis not only in vitro but also in infected mice and may thus exemplify the exciting and indispensable potential of vFcγRs for cytomegalovirus fitness in vivo. The MCMV-encoded vFcγR was identified as a 569 aa type 1 transmembrane glycoprotein of 65 kDa that is further processed into a highly glycosylated form of 105 kDa detected on the plasma membrane of MCMV-infected cells [74] (Fig. 2). Deletion of this gene from the MCMV genome resulted in a dramatic virus attenuation in vivo irrespective of the presence of B cells and antibodies, demonstrating that the observed alleviation of MCMV replication in mice was not only dependent on the m138/fcr-1 property to bind IgG [87], but rather suggested the existence of further dominant targets of m138/fcr-1 (see Table 3). fcr-1 is predicted to preserve three FcγR-related putative IgSF-like domains termed Ig1, Ig2, and Ig3, displaying a relatively low but still significant sequence homology with IgSF domains of murine cellular FcγRs CD16/FcγRIII and CD32/FcγRII, reaching 17 % identity and 24 % similarity, and are adjacent to a top N-glycan-rich stabilizing domain [74]. m138/fcr-1 not only binds to Fcγ but was also shown to impair NK cell functions by downmodulation of the NKG2D ligands MULT-1, H60, and RAE-ε [74, 88] as well as the B7-1 molecule CD80 [89], readily explaining the strong attenuation of replication in mice upon deletion of the *m138* gene [87]. The same N-terminal part of the m138/fcr-1 ectodomain, Ig1, which is sufficient for MULT-1 function, is also needed to complex with the Fc part of IgG. In fact, soluble Fc fragments of IgG are able to inhibit fcr-1-mediated downmodulation of MULT-1, presumably by competing for the binding to the same fcr-1 domain [74]. In conclusion, *m138*/fcr-1 represents an excitingly versatile CMV inhibitor which simultaneously interacts with IgG as well as NKG2D and T cell ligands to counteract several concurrent immune responses.

HSV vFcγR complex gE/gI

The herpes simplex virus (HSV)-expressed vFcγR consisting of the virion structural proteins gE and gI represents the first described herpesviral vFcγR [90–92]. The glycoproteins gE and gI are transcribed from the HSV genes *US7* and *US8*, respectively. They are both displayed on the surface of infected cells and are also incorporated into the virus envelope [73, 93, 94] (Fig. 2). gE shows slight sequence homologies to the second Ig domain of host FcγRs [93]. The glycoprotein gE but not gI shows Fc binding function when expressed alone [73]. Specifically, gE is able to bind weakly aggregated IgG with low affinity, while when acting in conjunction with gI, the gE/gI complex is able to recognize also monomeric IgG with high affinities. Biochemical and ultra-structural analyses of gE-gI binding to Fcγ revealed that gE-gI interacts with the Fcγ C_H2-C_H3 interdomain junction with a stoichiometry of two molecules of gE-gI per Fcγ [95]. In contrast to the HCMV vFcγRs, it binds human IgG1, IgG2, and IgG4, but it is surprisingly not able to recognize IgG3 (Table 3) [96]. Studies with HSV-1 have demonstrated that simultaneous binding of human anti-HSV IgG to a HSV antigen with its Fab arms and to gE-gI with its Fcγ region, a phenomenon referred to as "antibody bipolar bridging," protects the virion and infected cells from IgG-mediated immune responses [73], i.e., gE and gI cooperate to protect infected cells from ADCC [112, 113].

Singular Fcγ binding modalities

Sequence alignments of cellular FcγRs revealed that they do not share obvious structural commonalities with HCMV or bacterial FcγRs. While all FcγR structures consistently bind Fcγ, a range of observations indicate that they indeed differ in their individual binding mode. These differences may be crucial for the immune effector functions executed by host FcγRs on the one hand and antagonistic consequences of microbial FcγRs on the other hand. While all canonical host FcγRs bind IgG molecules in the upper hinge region between the Fab arms and the C_H2 domain of the Fc part [59, 97], some of the herpesviral FcγRs are known to approach other contact sites on the antibody, e.g., the C_H2-C_H3 interdomain interface (see Table 3). This binding site was mapped for the HCMV-encoded vFcγR gp68 as well as the HSV FcγR gE [75]. Surprisingly, experiments with mutated IgG variants indicated that the precise binding sites are nevertheless not congruent [75]. Moreover, there is an additional clear difference between both FcγRs: the heterodimeric receptor complex gE/gI binds IgG only at slightly basic pH values in the extracellular milieu but not at acidic pH (e.g., in the endosomes upon internalization). In contrast, gp68 IgG-Fc binding is stable at pH values from pH 5.6 to pH 8.1 [75]. Another significant hint is provided by the fact that HCMV FcγRs and HSV gE differ in their potential to bind to IgG subclasses (see Table 3). While gp34 and gp68 bind all human IgG subclasses, the HSV gE FcγR fails to recognize IgG3 [71]. Similar differences extend to the HCMV vFcγR encoded by the HCMV genes *RL13* and *RL12* which only bind to IgG1 and IgG2, but not to IgG3 and IgG4 [70]. Such a preference in IgG subclass binding contrasts also with all human activating FcγRs (with the exception that FcγRI does not bind IgG2) [35–37]. Last but not least, host and the HCMV FcγRs gp34 and gp68 seem to differ regarding the conformational requirements of the Fcγ

ligand. This notion was deduced from the observation that N-linked glycosylation leading to an open conformation is mandatory for the recognition by human FcγRs, while the HCMV-encoded FcγR gp68 and HSV gE/gI readily recognize and bind deglycosylated IgG in a closed configuration [75].

HCMV vFcγRs gp34 and gp68 inhibit activation of FcγRI, FcγRIIA, and FcγRIIIA

Cytomegaloviruses frequently reactivate or super-infect successfully CMV-infected hosts in the presence of high levels of CMV-specific IgG [98–100], suggesting that HCMV must have mechanisms to circumvent the antiviral effect of nevertheless protective antibodies. Despite the evidently different Fcγ binding modes between HCMV FcγRs and host FcγRs as outlined above, a systematic study was pursued to assess the potential interferences between both types of Fcγ binding devices [80]. The methodological basis of this comprehensive approach was provided by a newly developed BW5147 hybridoma-based FcγR activation assay which allows precise quantitative measurement of FcγR responses in vitro [101]. This procedure identified various members of the human FcγR family, i.e., FcγRI/CD64, FcγRIIA/CD32A, and FcγRIIIA/CD16A, to be targeted by the HCMV FcγRs gp34 and gp68 acting as effective antagonists of Fcγ ligand induced receptor responses [80]. The functional impact of both antagonists was first demonstrated by comparing gp34- and gp68-deficient HCMV mutants derived from various HCMV strains with wild-type viruses and *RL11* and *UL119–118* gene-revertant mutants, respectively, using polyclonal human HCMV-IgG preparations. Primary human FcγRIII/CD16$^+$ NK cells precisely traced the results obtained before with FcγRIII expressing BW5147 reporter cells, confirming the predictive value of the innovative surrogate test.

Next, the findings were verified by gain-of-function experiments based on humanized monoclonal antibodies (e.g., trastuzumab and rituximab) and isotypes thereof allowing testing of different IgG subclasses in the presence of ectopically expressed gp34 and gp68. The humanized monoclonal antibodies also facilitated surface immune-precipitation studies to show that both HCMV-encoded Fcγ binding proteins possess the capacity to bind tightly to trastuzumab when fixing its antigen, HER2, on the plasma membrane. This result demonstrated simultaneous linkage of immune IgG with antigen and the HCMV inhibitors on the plasma membrane (see Fig. 3), compatible with the model of "antibody bipolar bridging" which was suggested for HSV gE/gI [73, 95].

Favorably, the BW5147 test system allowed a direct functional comparison of the established HSV gE/gI inhibitor with the HCMV candidates, gp34 and gp68. In relation to HSV gE, both gp34 and gp68 demonstrated at least equivalent if not superior forces to impair FcγRIIIA and FcγRIIA-mediated responses. Unexpectedly and

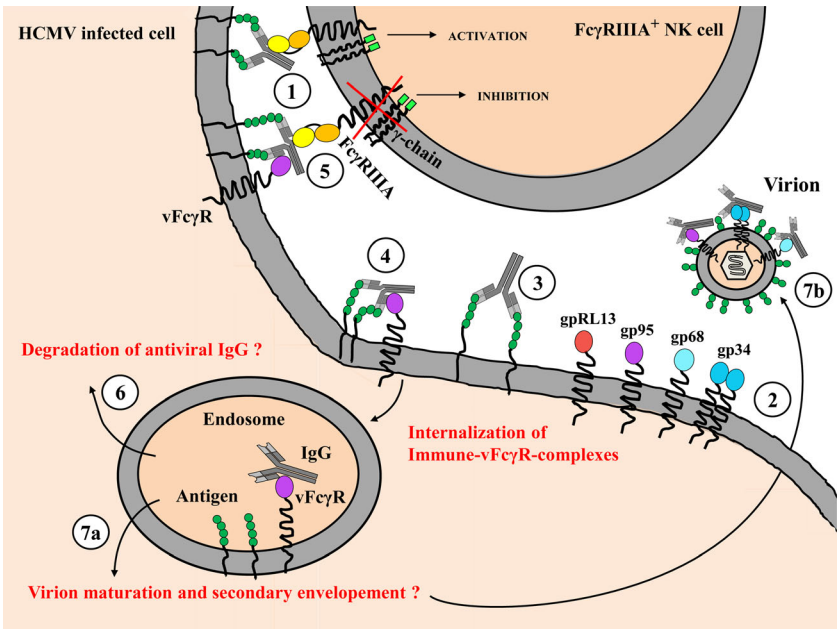

Fig. 3 Scenarios of interference of HCMV encoded FcγRs with antiviral IgG and host FcγR activation. State 1: Upon opsonization of viral antigen on the cell surface, IgG is competent to activate host FcγRs, e.g., FcγRIIIA (CD16) on NK cells, leading to immune effector cell responses (e.g., antibody-dependent cellular cytotoxicity (ADCC)). State 2: HCMV expresses four viral FcγRs with cell surface disposition, i.e., gp34, gp68, gp95, and gpRL13. Immune IgG bound to viral antigen on the cell surface (state 3) is recognized by a HCMV FcγR (state 4) forming ternary heterocomplexes, preventing the activation of host FcγRs (state 5). HCMV vFcγRs may internalize bound IgG from the cell surface and transport IgG to endolysosomal compartments for subsequent degradation of IgG (state 6) or incorporation of IgG into viral progeny at sites of virion maturation and secondary envelopment (state 7a) before vFcγR containing HCMV particles are released from infected cells (state 7b)

contrasting with both HCMV vFcγRs, HSV gE enhanced rather than weakened FcγRI triggering. This finding warrants further experiments exploring to which end IgG-coated HSV-infected cells can stimulate FcγRI bearing immune cells. Another difference between gE/gI and HCMV vFcγRs is the preference for varying IgG subclasses. HSV gE/gI does not bind to IgG3 [90] which differs from the other subclasses by its unique extended hinge region [97]. Unlike gE, both of the HCMV vFcγRs were able to efficiently block IgG3 immune complexes [80], corresponding to the fact that HCMV-specific IgG responses are constituted primarily by IgG1 and IgG3 antibodies [102, 103].

Which HCMV antigens are exposed on the plasma membrane of infected target cells and recognized by cytotoxic IgG triggering ADCC and further FcγR-mediated responses? It was demonstrated that HCMV antigens eliciting efficient ADCC responses become exposed only in the late phase of the replication cycle on the cell surface, while IgG-opsonized cells arrested in the early phase constituted only very poor target cells [80]. This observation suggests (i) that structural HCMV glycoproteins known to become exposed on the cell surface as the HCMV replication cycle progresses, e.g., gB [67], gH [68], and UL128 [69], are prime candidate targets of relevant IgG and (ii) that the expression kinetics of the HCMV FcγRs has closely adapted to the abundance of surface resident HCMV antigens yielding maximal levels in the late phase of infection [71].

Do HCMV FcγRs affect IgG and complement mediated virion neutralization?

gE/gI complexes are constitutively incorporated into HSV virions. There is evidence that gE/gI protect viral particles from virolysis, i.e., neutralization by immune IgG and complement [73, 94, 104]. Likewise, the FcγRs gp68 and gp34 were found in HCMV virions ([82] and unpublished data). These features of the prototypic vFcγR prompted us to test equivalent functions of the HCMV vFcγRs. Interestingly, gp34 as well as gp68 did not affect the potency of polyclonal or monoclonal neutralizing IgG, independent on the presence of complement (Henrike Reinhard, Hartmut Hengel, unpublished data). The fact that HCMV virion entry was insensitive to the vFcγRs in the presence of HCMV immune IgG in fibroblast as well as endothelial cell cultures indicates that the two known routes of HCMV entry, i.e., via gH-gL-gO and via the pentameric gH-gL-UL128-131 complex [105], cannot be affected by Fcγ domains bound to the vFcγRs but only by the Fab part of IgG bound to the relevant virion glycoproteins. Furthermore, gp68 and gp34 did not influence complement-mediated cell lysis when tested in the context of HCMV-infected cells (Eugenia Corrales-Aguilar, Hartmut Hengel, unpublished data). The lack of lysis in HCMV-infected fibroblasts can be explained by findings of Spiller et al. [106], demonstrating that transcription of CD46 and CD55, two complement control proteins (CCPs), is drastically upregulated during HCMV infection. These two CCPs prevent the activation of the C3 convertase; thus, complement-mediated lysis of cells is abolished.

Implications for immunotherapy

Virus-specific hyperimmune globulins from human donors are often used to treat or prevent threatening virus infections. Traditionally, neutralizing IgG is considered to be the primary correlate of seroprotection. In many afflicted tissues, however, HCMV is known to spread intracellularly (e.g., via infected endothelial cells and leukocytes) and via cell to cell, i.e., without diffusing to the extracellular space as a cell-free virion [70], thus avoiding virion neutralization by antibodies. Given such a scenario, non-neutralizing but FcγR-activating and particularly ADCC-inducing IgG is plausible to represent an effective component of humoral immunity against HCMV. Several findings are compatible with this notion. Only recently, a novel phenotype of human NK cells transcriptionally deficient for the FcR signaling transmembrane adaptor γ chain (Fig. 1) has been identified which instead expresses CD3ζ [107], another signaling adaptor associated with FcγRIII/CD16 containing even three ITAM motifs at fairly high levels. This NK cell population was characterized to exhibit a reduced natural cytotoxicity via the NK cell receptors NKp46 and NKp30 but a remarkably vigorous responsiveness via CD16/FcγRIII [108]. Even more excitingly, this NK cell phenotype (g^- NK cells) was associated with prior HCMV infection and confirmed to have clearly enhanced ADCC capabilities compared to conventional NK cells [108]. Independently, $NKG2C^{high}$ $CD57^{high}$ NK cells which are expanded by HCMV in vivo and in vitro [109, 110] were demonstrated to act as prominent effectors of ADCC against HCMV [111], which is tempting to speculate that the HCMV-imprinted NK cell populations g^- NK cells and $NKG2C^{high}$ $CD57^{high}$ may overlap. Combining these findings, ADCC-inducing IgG is plausible to represent a primary effective component of humoral immunity, which becomes only secondary attenuated by gp34 and gp68. Both immunoevasins could thus contribute to the disappointingly poor therapeutic performance of HCMV-specific hyperimmune globulin observed in a variety of clinical settings [112–115] since they enable HCMV to evade from IgG effector responses and take direct proviral effects in scenarios of post-acute and recurrent infection when HCMV-IgG antibodies are present at higher concentrations [116]. In this context, it is worth mentioning that the optimal range of gp34- and gp68-mediated IgG inhibition is below the HCMV-IgG serum concentration of humans. Replicating mainly at organ sites with IgG concentrations that are lower than those in the serum, it is thus

conceivable that the inhibitory effects detected in vitro are indeed physiologically relevant. These insights offer new perspectives to improve the efficacy of HCMV-specific IgGs. One conceivable approach could aim at an enrichment of gp34- and gp68-specific IgG within HCMV hyperimmune globulin preparations since those antibodies should override the inhibitory effect of the HCMV vFcγRs and strongly enhance immune cell signaling via host FcγRs.

Further perspectives and open questions

A newly established murine BW 5147 reporter cell based methodology has provided evidence that the vFcγRs gp34 and gp68 possess a broad immune evasion potential by impairing the activation of all canonical activating human FcγRs, i.e., FcγRI, FcγRIIA, and FcγRIIIA [80]. Since the predictions of the reporter cell assays were accurately verified by the subsequently demonstrated attenuation of ADCC responses of analyzed FcγRIII$^+$ human NK cells [80], further ramifications of gp34 and gp68 on HCMV immune responses mediated by FcγRI$^+$ and FcγRIIA$^+$ cells are plausible to assume. The mechanistic insight into the inhibition process of gp34 and gp68 is still at the very beginning. We showed that HCMV gp34 and gp68 are able to form ternary heterocomplexes on the surface of infected cells containing IgG, the IgG-bound antigen, and the vFcγR, suggesting a molecular configuration compatible with the requirements of the concept of "bipolar bridging" [73, 95]. While the Bjorkman laboratory has demonstrated on the ultra-structural level that the architecture of the prototypical HSV FcγR gE/gI-IgG complex allows indeed bipolar bridging of IgG [95], additional interaction models may be required for the HCMV FcγRs—merely due to the fact that at least four different HCMV binding proteins are competitively expressed on the surface of HCMV-infected cells. The immunological selection pressure may support their functional diversification rather than molecular redundancy in their protein-protein interactions. The presence of independent but functionally related immunoevasins jointly targeting immune control mechanism is a characteristic feature of cytomegalovirus evasion from CD8$^+$ T cell responses by manipulating the MHC I pathway of antigen presentation or from NK cells by preventing activating NK receptor interactions [14, 117–121]. Nevertheless, combined removal of gp34 as well as gp68 inhibitors from the surface of HCMV infected cells reveals hardly additive or even synergistic effects [80], suggesting that these two factors do not act in an obvious cooperative manner and leaves an open question if removal of additional HCMV vFcγRs will have additive or synergistic effects. Furthermore, it will be interesting to test if HCMV vFcγRs are also able to act in a cis-inhibiting manner when HCMV is infecting myelomonocytic target cells bearing host FcγRs.

Recently, Manley et al. [122] showed that MSL-109, a neutralizing human monoclonal IgG isolated from a CMV seropositive individual that recognizes the viral glycoprotein H (gH), is selectively taken up by infected cells and incorporated into assembling virions. However, HCMV progeny generated in the presence of MSL-109 acquires rapid resistance. Their data showed facilitation of a MSL-109-resistant virus infection of naive cells by a model in which the Fcγ domain of virus-attached MSL-109 aids to the entry of the virus. The authors suggested that the role of the Fcγ domain may be twofold—first, in the uptake of the antibody into infected cells to generate resistance and, second, the subsequent infection of naive cells by resistant virus. Yet, the precise mechanism of how this resistant virus enters cells and the role the Fc domain plays in mediating this process remain still unclear. The antibody uptake into HCMV-infected cells and transportation to sites of virion membrane assembly and maturation may be explained by a possible Fcγ-mediated interaction through the HCMV vFcγRs (see Fig. 3). For example, gp34 may mediate this IgG uptake since its cytoplasmic tail contains a dileucine consensus motif (DXXXLL, where X is unknown) indicating a potential function in intracellular targeting of the protein to the endocytic route [71, 123]. Taken together, HCMV FcγRs could thus be implicated in further host FcγR-independent mechanism of evasion from antiviral IgG and support Fcγ exploitation to promote HCMV entry and dissemination.

Lastly, all of the HCMV FcγRs may fulfill further Fcγ independently executed proviral functions. This is exemplified by the impressive multitasking abilities of the MCMV *m138*/fcr-1 molecule which downregulates the NKG2D ligands MULT-1, H60, and RAE-ε [74, 88] as well as the B7-1 molecule CD80 [89] beyond its Fcγ binding activity.

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