Immunoglobulin superfamily members encoded by viruses and their multiple roles in immune evasion

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Pathogens have developed a plethora of strategies to undermine host immune defenses in order to guarantee their survival. For large DNA viruses, these immune evasion mechanisms frequently rely on the expression of genes acquired from host genomes. Horizontally transferred genes include members of the immunoglobulin superfamily, whose products constitute the most diverse group of proteins of vertebrate genomes. Their promiscuous immunoglobulin domains, which comprise the building blocks of these molecules, are involved in a large variety of functions mediated by ligand-binding interactions. The flexible structural nature of the immunoglobulin domains makes them appealing targets for viral capture due to their capacity to generate high functional diversity. Here, we present an up-to-date review of immunoglobulin superfamily gene homologs encoded by herpesviruses, poxviruses, and adenoviruses, that include CD200, CD47, Fc receptors, interleukin-1 receptor 2, interleukin-18 binding protein, CD80, carcinoembryonic antigen-related cell adhesion molecules, and signaling lymphocyte activation molecules. We discuss their distinct structural attributes, binding properties, and functions, shaped by evolutionary pressures to disarm specific immune pathways. We include several novel genes identified from extensive genome database surveys. An understanding of the properties and modes of action of these viral proteins may guide the development of novel immune-modulatory therapeutic tools.

Keywords: Horizontal gene transfer · Immune evasion · Immunoglobulin superfamily · Large DNA viruses · Viral evolution

Introduction

The evolution of the immune system has led to the creation of complex defense mechanisms designed to efficiently control microbial pathogens such as viruses. In turn, viruses have been forced to develop specific tactics to circumvent host immune surveillance. Although RNA viruses adopted antigenic hypervariation as the principal mechanism of immune evasion, large DNA viruses have evolved strategies such as the expression of host gene homologs with immunomodulatory properties. During co-evolution, viruses frequently capture cellular genes by horizontal gene transfer, duplicate and modify them to either mimic or interfere with the original host function, or to perform new tasks. These host-derived viral genes, which can account for almost 30% of the coding potential of large DNA viruses, are predominantly implicated in immune defense, although they also participate in other processes such as apoptosis, cell cycle regulation, and/or metabolism [1–3].

A number of cellular homologs found in viruses come from genes encoding members of the immunoglobulin superfamily (IgSF). The IgSF is the largest family of glycoproteins with more
than 700 gene members in the human genome [4]. IgSF members share a structural domain of 70–100 amino acids, known as the immunoglobulin-like domain, which is named after the immunoglobulin or antibody molecules. These domains show the typical Ig-fold formed by seven or more beta strands arranged into two beta sheets [5]. Although there is a great diversity within this superfamily, based on the number of strands and sequence length, three principal classes of IgSF domains have been defined: the variable (or IgV) domain, and the constant (or IgC) domains, IgC1 and IgC2. IgV domains are composed by nine beta strands, resembling the antibody variable domains. However, these IgV domains do not present the sequence variability that characterizes the antibodies or the TcR, but instead they share similarity in the overall sequence. IgC domains, on the other hand, are shorter and usually constituted by seven strands, with the IgC2 domains displaying some sequence patterns characteristic of IgV domains [5]. The structure of the Ig domain is ideally shaped for ligand binding, accommodating broad amino acid sequence variability without changing the conserved structure, thus allowing a high degree of interaction specificity and diversity. IgSF members include cell–cell adhesion and cell-surface recognition molecules, which are pivotal elements of the immune response. Most IgSF molecules are localized at the cell-surface and contain an ectodomain, encompassing one or several Ig domains, a transmembrane region, and a cytoplasmic tail. Some members of the IgSF bear signaling motifs such as the immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibitory motif (ITIM) in the cytoplasmic regions, regulating key leukocyte functions. Additionally, soluble IgSF proteins also exist, arising from secreted isofoms or cell surface shedding, a number of which function as decoy receptors acting as molecular traps recognizing their ligands with high affinity and specificity, and thus preventing their binding to the natural receptor [6]. Due to all these characteristics, IgSF molecules represent excellent targets for viral gene capture to manipulate immune responses, and might therefore be regarded as an important source of viral genome evolution.

Bioinformatic analyses that aim to identify parent cellular genes are often complicated due to a high evolutionary rate of viral genomes resulting in a rapid sequence divergence between the viral protein and the original cellular counterpart. In addition, in many instances, amino acid conservation is only limited to specific domains essential to maintaining the structure or function of the original protein. In this review we performed an exhaustive search analysis of IgSF members present in the genomes of three families of double-stranded DNA viruses: herpesviruses, poxviruses, and adenoviruses. Due to length restrictions, viral homologs of host IgSF members (vIgSF) bearing Ig domains that do not constitute their amino-terminal functional domains (best exemplified by MHC class I related proteins) have not been included. To identify viral IgSF homologs, we used the NCBI’s blast tools blastp and DELTA-BLAST, entering as query sequences of human IgSF members to search in the database of herpesviral, poxviral, and adenoviral proteins [7]. The amino acid sequences of the viral proteins resulting from this search were aligned with the corresponding host protein sequences using BLAST-Global Align to directly calculate the amino acid identity percentages. In addition, we scrutinized through the bibliography previously reported viral IgSF homologs. Altogether, we present a compilation of a diversity of IgSF-derived molecules of eight different types: homologs of CD200, CD47, Fc receptors, interleukin-1 (IL-1) receptor 2 (IL-1R2), interleukin-18 (IL-18) binding protein (IL-18BP), CD80, carcinoembryonic antigen-related cell adhesion molecules (CEA-CAMS), and signaling lymphocyte activation molecules (SLAMs), some of which were newly uncovered here. We also discuss in this review the structure and the current understanding of the functions of these host-derived viral immunomodulatory proteins.

**CD200 homologs**

CD200 and its receptor, known as CD200 receptor (CD200R), are type I membrane glycoproteins containing two extracellular Ig domains, an N-terminal IgV domain responsible for ligand binding followed by an IgC2 domain [8, 9]. CD200 is broadly expressed on a wide variety of cell types, including neurons, epithelial cells, endothelial cells, and lymphocytes [8]. In contrast, CD200R is preferentially expressed on myeloid cells, but is also present on lymphocytes and NK cells [10–12]. CD200R functions as a coinhibitory receptor that, upon interaction with CD200, hinders myeloid cell function [13–15]. In addition, CD200 has also been demonstrated to downmodulate T- and NK-cell functions [16–18]. Several herpesviruses, poxviruses, and adenoviruses have captured CD200 (Table 1). It is quite remarkable that, while nearly all virus-encoded homologs of CD200 (vCD200) identified in herpesviruses possess the two Ig-like domains, adenoviral and poxviral CD200 orthologs bear only the IgV domain. Notably, a number of herpesvirus vCD200s have been shown to bind host CD200R, independently of the percentage of sequence identity in their N-terminal Ig domain with their host genes. For instance, one of the best-studied vCD200, the K14 gene of the Kaposi’s sarcoma-associated herpesvirus (KSHV), which encodes a protein showing a 44% amino acid sequence identity with the human CD200 in its N-terminal Ig domain, is able to interact with human CD200R with almost identical affinity and kinetics as CD200 (Fig. 1A). Consistent with these observations, K14 has been reported to diminish the activation of macrophages and other immune cells [11, 18–20]. Paradoxically, the rat cytomegalovirus (CMV) England isolate (RCMV-E) vCD200, e127, does not seem to alter myeloid cell activity in vitro or in vivo despite efficiently interacting with the rat CD200R [21]. As shown in Table 1, the sequence identity of the N-terminal Ig domain of all known poxvirus and adenovirus vCD200 with their host genes is relatively low (21–31%). Consequently, the only vCD200 studied in poxviruses, the myxoma virus (MV) M141R protein, does not bind to CD200R, although it has been documented to exert a potent immunosuppressive role [22, 23]. It is also worth mentioning that a number of vCD200s, such as the R15 protein of rhesus macaque rhadinovirus or the 141R protein of the Yaba-like disease poxvirus have been shown or predicted to be
| Virus     | Viral gene(s) | % aa identity | % aa identity | Protein structure | CD200R binding | Functions                                                                 | References          |
|-----------|---------------|---------------|---------------|-------------------|----------------|---------------------------------------------------------------------------|---------------------|
| **Herpesviruses** |               |               |               |                   |                |                                                                           |                     |
| Betaherpesviruses |               |               |               |                   |                |                                                                           |                     |
| HHV-6    | U85           | 22            | 23            | 1 IgV, 1 IgC2, 1 TM | Yes            |                                                                           | [11]                |
| HHV-7    | U85           | 22            | 22            | 1 IgV, 1 IgC2, 1 TM | Yes            |                                                                           | [11]                |
| RCMV-E   | e127          | 49            | 90            | 1 IgV, 1 IgC2, 1 TM | Yes            | No alteration of myeloid cell activity (in vitro or in vivo).              | [21, 68]            |
| EEHV-1   | EE22          | 23            | 18            | 1 IgV, 1 IgC2, 1 TM | n.t.           |                                                                           | [73]                |
| " EE23   | 21            | 15            | 1 IgV, 1 IgC2, no TM (s) | n.t. |                     |                                                                           |                     |
| " EE51   | 55            | 100           | 1 IgV, 1 IgC2, 1 TM | n.t. |                     |                                                                           | [73]                |
| EEHV-4   | E24B          | 22            | 8             | 1 IgC2, no TM (s) | n.t.           |                                                                           | [73]                |
| EEHV-5   | EE22          | 22            | 17            | 1 IgV, 1 IgC2, 1 TM | n.t.           |                                                                           | [73]                |
| " EE22A  | 24            | 21            | 1 IgV, 1 IgC2, 1 TM | n.t. |                     |                                                                           | [73]                |
| " EE23   | 23            | 17            | 1 IgV, 1 IgC2, no TM (s) | n.t. |                     |                                                                           | [73]                |
| " EE51   | 59            | 100           | 1 IgV, 1 IgC2, 1 TM | n.t. |                     |                                                                           | [73]                |
| **Gammaherpesviruses** |               |               |               |                   |                |                                                                           |                     |
| KSHV     | K14           | 28            | 44            | 1 IgV, 1 IgC2, 1 TM | Yes            | Downregulation of myeloid, NK, and T-cell activity. Reduction of cytokines (TNF-α, IL-8, CCL2, IFN-γ). Th1 response suppression. | [11, 18–20, 74]    |
| RRV      | R15           | 33            | 54            | 1 IgV, 1 IgC2, 1 TM (or s) | Yes            |                                                                           | [24, 75]            |
| BGHV-8   | E11           | 55            | 91            | 1 IgV, 1 IgC2, 1 TM | n.t.           |                                                                           | [76, 77]            |
| EHV-5    | E11           | 86            | 100           | 1 IgV, 1 IgC2, 1 TM | n.t.           |                                                                           | [78]                |
| **Poxviruses** |               |               |               |                   |                |                                                                           |                     |
| Capripoxviruses |           |               |               |                   |                |                                                                           |                     |
| GTPV     | GTPV131       | 19            | 31            | 1 IgV, 1 TM | n.t.           |                                                                           | [79]                |
| LSDV     | LW138         | 18            | 31            | 1 IgV, 1 TM | n.t.           |                                                                           | [19, 22, 79]        |
| SPPV     | SPPV_131      | 18            | 31            | 1 IgV, 1 TM | n.t.           |                                                                           | [19, 79]            |
| Cervidpoxviruses |         |               |               |                   |                |                                                                           |                     |
| DPV      | DPV153        | 18            | 24            | 1 IgV, 1 TM | n.t.           |                                                                           | [80]                |
| Leporipoxviruses |          |               |               |                   |                |                                                                           |                     |
| MV       | M141R         | 19            | 31            | 1 IgV, no TM (s), in virion | No            | In vivo downregulation of macrophage and T-cell activity. Reduction of cytokines (IFN-γ, TNF-α, G-CSF). Downregulation of NF-κB. Virulence factor. | [19, 22, 23, 81] |
| SFV      | S141R         | 17            | 21            | 1 IgV, 1 TM | n.t.           |                                                                           | [19, 22]            |
| Yatapoxviruses |          |               |               |                   |                |                                                                           |                     |
| TANV     | 141R          | 12            | 25            | 1 IgV, no TM (s) | n.t.           |                                                                           | [82]                |
| YLDV     | 141R          | 12            | 29            | 1 IgV, no TM (s) | n.t.           |                                                                           | [19, 22, 83]        |
| YMTV     | 141R          | 12            | 27            | 1 IgV, no TM (s) | n.t.           |                                                                           | [19, 84]            |

(Continued)
CD47 homologs

CD47 is a heavily glycosylated protein consisting of a single IgV domain followed by five transmembrane-spanning regions and a short cytoplasmic tail [25, 26]. CD47 recognizes with a high affinity the signal regulatory protein alpha (SIRPα), a cell surface receptor that contains three extracellular Ig domains and a long intracellular tail bearing four ITIMs. While CD47 is ubiquitously expressed, SIRPα is only found in myeloid-lineage cells such as dendritic cells and macrophages, and also in neurons [25, 26]. Engagement of SIRPs by CD47, which occurs through their N-terminal IgV domains, triggers inhibitory signals. Thus, among other functions, CD47 acts as a “don’t eat me” signal that prevents the phagocytosis of the CD47-expressing cell by delivering inhibitory signals to macrophages via SIRPs. In addition, CD47 can interact in cis with integrins, and in trans with thrombospondin, and, albeit with a lower affinity than SIRPα, binds to the activating molecule SIRPγ [25]. CD47 homologs (vCD47s) have been found exclusively in poxviruses (Table 2). All chor-dopoxviruses (poxviruses that infect vertebrates) except four genera (parapoxviruses, molluscipoxviruses, crocodylipoxviruses, and avipoxviruses) contain predicted vCD47s. Since the rest of chor-dopoxviruses diverged from these four poxvirus genera 249 000 years ago and began to separate between them 166 000 years ago, we hypothesize that CD47 was most likely captured between these two time points [27]. Interestingly, even though these CD47 poxviral homologs have a low amino acid sequence identity (18–29%) with respect to their host parent gene, all of them conserve the structure of CD47, retaining an N-terminal IgV domain, five transmembrane helices, and a short cytoplasmic tail. The structural conservation of vCD47s among such diverse poxvirus species points to their functional importance. To date, only two vCD47s have been functionally studied: the A38L gene of the vaccinia virus (VACV) and M128L gene of the MV [28, 29]. Although the binding of the two vCD47s to SIRPα has not yet been evaluated, in vivo analyses have shown that M128L contributes to impair macrophage activation and functions as a key virulence factor (Fig. 1B) [29]. This immune-modulatory role of M128L might, however, occur independently of SIRPα binding and, instead, be mediated by additional proteins that interact with the five-span transmembrane regions and/or the Ig domain, such as integrins [25].

FcyR homologs

The family of Fc receptors for IgG (FcyRs) is composed of type I transmembrane or glycosylphosphatidylinositol (GPI)-anchored glycoproteins containing two or three IgC2 domains in their extracellular region, which are responsible for binding the Fc region of the IgG, and ITAM or ITIM motifs in their cytoplasmic region [30]. The different FcyRs bind distinct IgG subclasses with varying affinity and specificity. The members of this family, which are expressed in several immune cell types, constitute a link between the innate and adaptive immune systems. FcyRs are implicated in the regulation of multiple immune responses, including phagocytosis by myeloid cells, antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells or macrophages, and the modulation of B-cell activity. Several herpesviruses encode cell surface glycoproteins with homology to the Fc of IgGs (vFcyRs) and accordingly, in the cases where it has been evaluated, they are capable of binding the Fc of IgGs, thus functioning as viral IgG Fc receptors. As
Figure 1. Homologs of IgSF host members encoded by herpesviruses, poxviruses, or adenoviruses. Each type of viral homologs is illustrated with one selected example (infected cell in the right panel); the corresponding host protein and its function is also shown (uninfected cell in the left panel). (A) vCD200: KSHV K14 mimics CD200, binding CD200R to inhibit myeloid cell functions, such as TNF-α and CSF1 secretion. (B) vCD47: MV M128L conserves the structure of CD47, but it is still unknown if it binds to SIRPs or other proteins. (C) vFcγR: HCMV UL119, a molecule that it is also present in the virion surface, binds to the Fc of all human IgGs, preventing their interaction with FcγRs of NK cells, and thus blocks ADCC. (D) vIL-1R2: VACV B15R, a soluble protein, binds specifically to IL-1β, hindering its interaction with cellular activating IL-1 receptors. (E) vIL-18BP: MOCV MC054L, both as a soluble protein or attached to the surface of the infected cell through glycosaminoglycans, binds to IL-18, precluding its interaction with cellular activating IL-18 receptors. (F) vCD80: instead of binding CD28 or CTLA4, EBV BARF1 is secreted and forms soluble hexamers that can attach up to three CSF1 dimers. (G) vSLAM: OMCMV A43 is shed and binds CD244, preventing its interaction with CD48.

shown in Table 3, all of them present low amino acid sequence identity compared with the host FcγRs. The first described vFcγR was the complex formed by gE and gI, two structural proteins encoded by the US8 and US7 genes, respectively, of the herpes simplex virus 1 (HSV-1). gE presents homology to the second Ig domain of host FcγR, being the Fc-binding unit of the complex. Although gE alone binds with low affinity to IgG, its interaction with the Fc region is much higher when associated with gI [31]. Recently, it has been demonstrated that gE/gI performs the clearance of antiviral IgGs and viral antigens from the surface of viral-infected cells and blocks ADCC antibody-dependent in vivo [32, 33]. vFcγRs have been also found in betaherpesviruses. For instance, human CMV (HCMV) encodes four vFcγRs containing a single Ig domain. In contrast with the inability of the rest...
### Table 2. CD47 homologs

| Virus       | Viral gene(s) | % aa identity protein | % aa identity IgV | Functions                                                                 | References |
|-------------|---------------|-----------------------|-------------------|---------------------------------------------------------------------------|------------|
| **Poxviruses** |               |                       |                   |                                                                           |            |
| **Orthopoxviruses** |   |               |                   |                                                                           |            |
| VACV        | A38L          | 24                    | 27                | Overexpression of A38L increase Ca\(^{2+}\) influx into cells. No virulence factor. | [28, 85]   |
| VARV        | A41L          | 25                    | 28                |                                                                           |            |
| ECTV        | EVM138        | 27                    | 30                |                                                                           | [86]       |
| CPXV        | CPXV175       | 24                    | 29                |                                                                           |            |
| MPV         | A40L          | 26                    | 28                |                                                                           |            |
| RFXV        | RFXV146       | 24                    | 28                |                                                                           | [87]       |
| CMLV        | CMLV158       | 26                    | 28                |                                                                           | [88]       |
| RCNV        | gp156         | 29                    | 34                |                                                                           | [89]       |
| SKPV        | gp159         | 27                    | 31                |                                                                           | [90]       |
| TATV        | 163           | 29                    | 30                |                                                                           |            |
| HSPV        | HSPV160       | 22                    | 27                |                                                                           | [91]       |
| VPXV        | gp159         | 25                    | 30                |                                                                           | [90]       |
| YKV         | YKV144        | 28                    | 31                |                                                                           | [67]       |
| **Capripoxviruses** |   |               |                   |                                                                           |            |
| GTPV        | GTPV123       | 21                    | 24                |                                                                           | [79]       |
| LSDV        | LW128         | 20                    | 23                |                                                                           | [79]       |
| SPPV        | SPPV_123      | 20                    | 25                |                                                                           | [79]       |
| **Cervidpoxviruses** |   |               |                   |                                                                           |            |
| DPV         | DPV139        | 22                    | 28                |                                                                           | [80]       |
| **Leporipoxviruses** |   |               |                   |                                                                           |            |
| MV          | M128L         | 22                    | 22                | Downregulation of macrophage activity. Virulence factor.                  | [29]       |
| **Suipoxviruses** |   |               |                   |                                                                           |            |
| SFV         | S128L         | 20                    | 22                |                                                                           | [92]       |
| **Yatapoxviruses** |   |               |                   |                                                                           |            |
| TANV        | 128L          | 20                    | 22                |                                                                           | [82]       |
| YLDV        | 128L          | 20                    | 22                |                                                                           | [83]       |
| YMTV        | 128L          | 18                    | 19                |                                                                           | [84]       |
| **Unclassified poxviruses** |   |               |                   |                                                                           |            |
| SQPV        | A38L          | 21                    | 26                |                                                                           | [94]       |
| COTV        | COTV146       | 18                    | 21                |                                                                           | [95]       |

\(^a\)Genes in bold encode proteins whose functions have been tested.

\(^b\)The percentage of amino acid (% aa) identity was calculated as in Table 1.

All the vCD47s conserve the structure of CD47: 1 IgV domain, 5 transmembrane domains, and a short cytoplasmic tail.

CMLV: camelpox virus; CPXV: cowpox virus; COTV: cowpox virus; DPV: deepopox virus; ECTV: ectromelia virus; GTPV: goatpox virus; HSPV: horsepox virus; LSDV: lumpy skin disease virus; MPV: monkeypox virus; RCNV: raccoonpox virus; RFXV: rabbitpox virus; SFV: shope fibroma virus; SKPV: skunkpox virus; SPPV: sheeppox virus; SWPV: swinepox virus; TANV: tanapox virus; TATV: taterapox virus; VARV: variola virus; VPXV: volepox virus; YKV: Yoka poxvirus; YLDV: Yaba-like disease virus; YMTV: Yaba monkey tumor virus.

of the vFcyRs characterized, including HSV-1 gE/gI incapable of recognizing IgG3, two of the HCMV FcyRs (UL119 and RL11) bind all human IgG subclasses (IgG1–IgG4; Fig. 1C) [31]. Moreover, these two HCMV proteins are also present in the virion. Interestingly, the gene m138 (fcr1) of the murine CMV (MCMV), whose deletion produces a strong attenuation of viral replication in vivo, encodes a vFcyR that, apart from binding IgG, affects the surface expression of CD80 and several NKG2D ligands in infected cells [34–36]. In fact, it has been shown that the MCMV attenuation observed in the absence of m138 is dependent on these latter activities of the viral protein rather than on its ability to bind IgG. Finally, our bioinformatic analysis suggests that the K1 protein of KSHV and its orthologs in macaque gammaherpesviruses are putative FcyR homologs. Indeed, the amino acid sequence identity of the K1 protein, compared to the host FcyRs, is slightly higher than those observed in alpha- and betaherpesviral vFcyRs.
| Virus       | Viral gene | % aa identity | Protein structure | Type of IgG binding | Functions                                                                                   | References |
|------------|------------|----------------|-------------------|---------------------|--------------------------------------------------------------------------------------------|------------|
| Herpesviruses |            |                |                   |                     |                                                                                            |            |
|            |            |                |                   |                     |                                                                                            |            |
| Alphaherpesviruses |        |                |                   |                     |                                                                                            |            |
| HSV-1       |            |                |                   |                     |                                                                                            |            |
|            |            |                |                   |                     |                                                                                            |            |
| US8 (gE)   | 16         | 1 IgV, 1 TM    |                   | Human IgG1, IgG2, IgG4 | Inhibition of some host FcGRs. Clearing antiviral IgGs and viral antigens from the cell surface. In vivo ADCC blocking. Enhancing viral cell-to-cell spread. | [32, 33]   |
| US7 (gI)   | 15         | no Ig, 1 TM    | heterodimers gE/gI |                     |                                                                                            |            |
| Betaherpesviruses |        |                |                   |                     |                                                                                            |            |
| HCMV        | UL119      | 19             | 1 IgC2, 1 TM, 1 ITIM, in virion | Human IgG1, IgG2, IgG3, IgG4 | Inhibition of most host FcGRs. Clearing antiviral IgGs and viral antigens from the cell surface. Blocking ADCC by NK cells. | [31, 96–98] |
|            | RL11       | 18             | 1 IgC2, 1 TM, homodimers, in virion | Human IgG1, IgG2, IgG3, IgG4, Rabbit and rat IgG. | Inhibition of most host FcGRs. Blocking ADCC by NK cells. | [31, 96, 97] |
|            | RL12       | 17             | 1 IgC2, 1 TM      | Human IgG1, IgG2, Rabbit IgG. |                                                                                           | [31]       |
|            | RL13       | 18             | 1 IgC2, 1 TM, in virion | Human IgG1, IgG2, Rabbit IgG. |                                                                                           | [31, 99]   |
| CCMV        | UL119      | 17             | 1 IgC2, 1 TM      | n.t.                 |                                                                                           |            |
| RhCMV       | UL119      | 15             | 1 IgC2, 1 TM      | n.t.                 |                                                                                           |            |
| GMCMV       | UL119      | 16             | 1 IgC2, 1 TM      | n.t.                 |                                                                                           |            |
| SMCMV       | UL119      | 16             | 1 IgC2, 1 TM      | n.t.                 |                                                                                           |            |
| OMCMV       | UL119      | 17             | 1 IgC2, 1 TM      | n.t.                 |                                                                                           |            |
| MCMV        | m138 (fcr1) | 15            | 3 IgC2s, 1 TM     | Mouse IgG.           | Crucial for in vivo virus replication. Cell surface downregulation of NKG2D ligands and B7-1. | [34–36]   |
| RCMV-E      | e138       | 16             | 3 IgC2s, no TM(s) | n.t.                 |                                                                                           | [100]      |
| RCMV-M      | r138       | 15             | 3 IgC2s, no TM(s) | n.t.                 |                                                                                           | [100]      |
| Gammaherpesviruses |      |                |                   |                     |                                                                                            |            |
| KSHV        | K1         | 20             | 2 IgC2, 1 TM, 1 ITAM | n.t.                 | Oncogenicity. Cell transformation. Induction of cellular cytokines. Enhancing lytic reactivation and/or replication. | [101, 102] |
| RRV         | R1         | 21             | 2 IgC2, 1 TM, 1–2 ITAMs | n.t.                 | Oncogenicity. Cell transformation.                                                          | [103]      |
**Table 3. Continued**

| Virus       | Viral gene | % aa identity protein | Protein structure | Type of IgG binding | Functions                      | References |
|-------------|------------|------------------------|-------------------|---------------------|--------------------------------|------------|
| MfRV        | JM2        | 20                     | 2 IgC2, 1 TM, 1–2 ITAMs | n.t.                |                                |            |
| MneRV-2     | N1         | 21                     | 2 IgC2, 1 TM, 1–2 ITAMs | n.t.                |                                |            |

*a* Genes in bold encode proteins whose functions and/or binding capacity have been tested.

*b* The percentage of amino acid (% aa) identity was calculated as in Table 1 for the different host FcGRs, selecting the maximum value.

*c* TM means “transmembrane domain”; s means “soluble”.

*d* n.t. means “not tested”.

*e* HSV-1 selected as a representative, as all Alphaherpesviruses have gE and all of them except Scutaviruses also have gl.

CCMV: chimpanzee CMV; GMCMV: green monkey CMV; MfRV: Macaca fuscata rhadinovirus; MneRV: Macaca nemestrina rhadinovirus; RCMV-M: rat CMV Maastricht isolate; RhCMV: rhesus macaque CMV; RRV: rhesus macaque rhadinovirus.

**IL-1R2 and IL-18BP homologs**

The IL-1R2 and the IL-18BP, two secreted proteins that bind cytokines of the IL-1 family, have been identified among poxviruses. Both cellular molecules act as decoy cytokine receptors with an anti-inflammatory role [37]. IL-1R2 is a type I cell surface protein with an extracellular region formed by three IgC2 domains, and a nonsignaling short cytoplasmic tail. It is released as a soluble form, generated by enzymatic cleavage or alternative splicing [6]. IL-1R2 downregulates IL-1 activity by binding to IL-1α and IL-1β. This receptor is expressed by a limited number of cell types, including neutrophils, monocytes, and B cells. Three poxvirus genera that infect mammals contain soluble versions of the IL-1R2 (vIL-1R2) that conserve the three Ig domains or have evolved to encode only two (Table 4). Interestingly, the vIL-1R2s of vaccinia, cowpox, and ectromelia virus bind to IL-1β, but not to IL-1α (Fig. 1D) [38, 39]. Thus far, only the role of the vIL-1R2 of VACV, B15R, has been analyzed in infected mice and shown to act as a virulence factor [38].

IL-18BP, on the other hand, is a constitutively secreted protein with only one IgC2 domain that binds to IL-18 with high affinity and blocks its interaction with the IL-18 receptor.

**Table 4. IL-1R2 homologs**

| Virus       | Viral gene | % aa identity protein | % aa identity N-term. IgC2 | Protein structure | IL-1β binding | Functions                      | References |
|-------------|------------|------------------------|-----------------------------|-------------------|---------------|--------------------------------|------------|
| Poxviruses  |            |                        |                             |                   |               |                                |            |
| **Orthopoxviruses** |            |                        |                             |                   |               |                                |            |
| VACV        | B15R       | 25                     | 33                          | 3 IgC2, no TM (s) | Yes           | Virulence factor. Inhibition of fever. | [38, 69, 70] |
| ECTV        | C9R        | 26                     | 36                          | 3 IgC2, no TM (s) | Yes           |                                | [39, 86]   |
| CPXV        | CPXV209    | 24                     | 33                          | 3 IgC2, no TM (s) | Yes           |                                | [38, 69]   |
| MPV         | B14R       | 25                     | 32                          | 3 IgC2, no TM (s) | n.t.          |                                | [104]      |
| RCVN        | gp188      | 24                     | 35                          | 3 IgC2, no TM (s) | n.t.          |                                | [89]       |
| SKPV        | gp192      | 26                     | 36                          | 3 IgC2, no TM (s) | n.t.          |                                | [90]       |
| TAVT        | 203        | 27                     | 35                          | 3 IgC2, no TM (s) | n.t.          |                                | [91]       |
| HSPV        | HSPV192    | 26                     | 34                          | 3 IgC2, no TM (s) | n.t.          |                                | [90]       |
| VPXV        | gp192      | 24                     | 32                          | 3 IgC2, no TM (s) | n.t.          |                                |            |
| **Capripoxviruses** |            |                        |                             |                   |               |                                |            |
| GTPV        | GTPV004    | 12                     | 26                          | 2 IgC2, no TM (s) | n.t.          |                                | [79]       |
| LSDV        | LW006      | 14                     | 22                          | 2 IgC2, no TM (s) | n.t.          |                                | [79]       |
| “           | LW013      | 19                     | 25                          | 2 IgC2, no TM (s) | n.t.          |                                | [79]       |
| SPPV        | SPPV04     | 12                     | 22                          | 2 IgC2, no TM (s) | n.t.          |                                | [79]       |
| **Cervidpoxviruses** |        |                        |                             |                   |               |                                |            |
| DPV         | DPV015     | 13                     | 24                          | 2 IgC2, no TM (s) | n.t.          |                                | [80]       |

*a* Genes in bold encode proteins whose functions and/or binding capacity have been tested.

*b* The percentage of amino acid (% aa) identity was calculated as in Table 1.

*c* TM means “transmembrane domain”; s means “soluble.”

*d* n.t. means “not tested.”

CPXV: cowpox virus; DPV: deerpox virus; ECTV: ectromelia virus; GTPV: goatpox virus; HSPV: horsepox virus; LSDV: lumpy skin disease virus; MPV: monkeypox virus; RCVN: raccoonpox virus; SKPV: skunkpox virus; SPPV: sheeppox virus; TAVT: taterapox virus; VPXV: volepox virus.
Table 5. IL-18BP homologs

| Virus       | Viral gene(s)<sup>a</sup> | % a.a identity<sup>b</sup> | IL-18 binding<sup>c</sup> | Functions                                                                 | References |
|-------------|---------------------------|---------------------------|---------------------------|---------------------------------------------------------------------------|------------|
| **Poxviruses**
| Orthopoxviruses          |                           |                           |                           |                                                                           |            |
| VACV        | vIL-18BP (C12L)           | 27                        | Yes                       | In vivo suppression of IFN-γ production and cytotoxic T-lymphocyte activity. In vivo inhibition of NK-cell cytotoxicity. Virulence factor. | [41, 105] |
| VARV        | D5L                       | 28                        | Yes                       | Suppression of NF-κB activation and IFN-γ production. In vivo inhibition of NK-cell cytotoxicity. | [106]      |
| ECTV        | EVM013                    | 25                        | Yes                       |                                                                           | [40, 86, 105] |
| CPXV        | CPXV024                   | 28                        | Yes                       |                                                                           | [105]      |
| MPV         | D6L                       | 30                        | n.t.                      |                                                                           | [104]      |
| RPXV        | RPXV009                   | 27                        | n.t.                      |                                                                           | [87]       |
| SKPV        | gp015                     | 26                        | n.t.                      |                                                                           | [90]       |
| TATV        | 017                       | 25                        | n.t.                      |                                                                           |            |
| HSPV        | HSPV019                   | 23                        | n.t.                      |                                                                           | [91]       |
| VPXV        | gp015                     | 22                        | n.t.                      |                                                                           | [90]       |
| YKV         | YKV006                    | 24                        | n.t.                      |                                                                           | [67]       |
| **Capripoxviruses**     |                           |                           |                           |                                                                           |            |
| GTPV        | GTPV012                   | 23                        | n.t.                      |                                                                           | [79]       |
| LSDV        | LW015                     | 23                        | n.t.                      |                                                                           | [79]       |
| SPPV        | SPPV12                    | 22                        | n.t.                      |                                                                           | [79]       |
| **Cervidpoxviruses**    |                           |                           |                           |                                                                           |            |
| DPV         | DPV021                    | 19                        | n.t.                      |                                                                           | [80]       |
| **Suipoxviruses**       |                           |                           |                           |                                                                           |            |
| SWPV        | SPV011                    | 22                        | n.t.                      |                                                                           | [93]       |
| **Yatapoxviruses**      |                           |                           |                           |                                                                           |            |
| TANV        | 14L                       | 24                        | n.t.                      |                                                                           | [82]       |
| YLDV        | 14L                       | 24                        | Yes                       |                                                                           | [83, 107] |
| YMTV        | 14L                       | 27                        | Yes                       | Partial inhibition of IFN-γ production.                                   | [84, 108] |
| **Molluscipoxvirus**    |                           |                           |                           |                                                                           |            |
| MOCV        | MC051L                    | 24                        | n.t.                      |                                                                           | [105, 109] |
| “           | MC0531                    | 33                        | Yes                       | Suppression of IFN-γ production.                                          | [105, 109] |
| “           | MC0541                    | 42                        | Yes                       | Suppression of IFN-γ production. Simultaneously binding to IL-18 and to glycosaminoglycans on the cell surface. | [42, 105, 109] |
| **Avipoxvirus**         |                           |                           |                           |                                                                           |            |
| CNPV        | CNPV100                   | 16                        | n.t.                      |                                                                           | [110]      |
| “           | CNPV284                   | 16                        | n.t.                      |                                                                           | [110]      |
| “           | CNPV289                   | 23                        | n.t.                      |                                                                           | [110]      |
| FPV         | FPV073                    | 21                        | n.t.                      |                                                                           | [111]      |
| “           | FPV0714                   | 21                        | n.t.                      |                                                                           | [111]      |
| TPKV        | gp048                     | 20                        | n.t.                      |                                                                           | [112]      |
| “           | gp156                     | 30                        | n.t.                      |                                                                           | [112]      |
| PGPV        | gp222                     | 23                        | n.t.                      |                                                                           | [113]      |
| PEPEV       | PEPV228                    | 22                        | n.t.                      |                                                                           | [113]      |

<sup>a</sup> Genes in bold encode proteins whose functions and/or binding capacity have been tested.

<sup>b</sup>The percentage of amino acid (% a.a) identity was calculated as in Table 1.

<sup>c</sup>n.t. means “not tested”.

All the vIL-18BPs are soluble forms with only one Ig domain.

CNPV: canarypox virus; CPXV: cowpox virus; DPV: deerpox virus; ECTV: ectromelia virus; FPV: fowlpox virus; GTPV: goatpox virus; HSPV: horsepox virus; LSDV: lumpy skin disease virus; MPV: monkeypox virus; PEPV: penguinpox virus; PGPV: pigeonpox virus; RPXV: rabbitpox virus; SKPV: skunkpox virus; SPPV: sheeppox virus; SWPV: swinepox virus; TANV: tanapox virus; TATV: taterapox virus; TPKV: turkeypox virus; VARV: variola virus; VPXV: volepox virus; YKV: Yoka poxvirus; YLDV: Yaba-like disease virus; YMTV: Yaba monkey tumor virus.
dampening IFN-γ production from T cells and macrophages [6]. Most chordopoxviruses, including viruses that infect birds, have one or more copies of IL-18BP homologs (vIL-18BPs). vIL-18BPs of the molluscum contagiosum virus (MOCV), vaccinia, and ectromelia viruses, in addition to binding to IL-18, have been proven to suppress IFN-γ production in vitro (Table 5). Moreover, the vIL-18BPs encoded by the latter two viruses have also been characterized in murine models of infection and have been shown to counteract the potent proinflammatory role of IL-18, thus promoting virulence [40, 41]. Additionally, MC054L, the secreted vIL18-BP of the MOCV, can bind to glycosaminoglycans and remain attached to the surface of the infected cell, maintaining its IL-18-binding capacity (Fig. 1E) [42].

**CD80 homologs**

CD80 (B7.1), the prototype of the B7 family, is expressed on activated antigen-presenting cells. Its natural ligands are the T cell cell-surface molecules CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4, CD152), which exert opposite regulatory roles, controlling T-cell activation and tolerance [43]. CD80, a type I transmembrane protein with an N-terminal IgV domain followed by an IgC2 domain, is found on the cell surface predominantly as a homodimer [44]. A CD80 homologous gene, named BARF1, is present in the genome of the human Epstein-Barr virus (EBV) and two other EBV-like gammaherpesviruses that infect macaques (rhesus lymphocryptovirus and cynomolgus lymphocryptovirus). The EBV BARF1 glycoprotein is a secreted molecule that shows a 23% amino acid identity with the human CD80 (rising to 32% in the IgV domain) and conserves the two Ig domains of CD80. However, in contrast to CD80, BARF1 forms hexamers and, instead of interacting with CD28 or CTLA4, binds to the colony-stimulating factor 1 (CSF1), a cytokine secreted by many cell types (Fig. 1F) [45, 46]. Each BARF1 hexameric ring is capable of interacting with three CSF1 dimers [47]. Binding of BARF1 to CSF1, which occurs through a binding site on CSF1 located away from its cognate receptor-binding site, induces a conformational change that blocks the interaction of the cytokine with its cognate receptor [48]. In this way, BARF1 hampers the different roles of CSF1, mainly inhibiting macrophage differentiation and function [49]. The importance of BARF1 has been assessed in vivo using the macaque model with rhesus lymphocryptovirus infections, showing that rhBARF1 is required for immune evasion [50]. Additionally, several reports indicate that BARF1 is involved in driving EBV-oncogenic effects [51].

**CEACAM homologs**

The CEACAM family of receptors is a group of structurally related cell-surface glycoproteins that encompasses nine members (CD150 [SLAMF1], CD48 [SLAMF2], CD229 [SLAMF3, LY9], CD244 [SLAMF4], CD84 [SLAMF5], CD352 [SLAMF6], CD319 [SLAMF7], CD353 [SLAMF8], and CD84-H1 [SLAMF9]) [56, 57]. They are differentially expressed by a wide range of hematopoietic cells, including B and T cells, NK cells, and myeloid cells [57, 58]. SLAM family receptors are type I transmembrane proteins, possessing an ectodomain composed of an N-terminal IgV domain followed by an IgC2 domain. Exceptions to this common structure are as follows: CD48, which is a GPI-anchored protein, and CD229, which displays an ectodomain formed by a tandem repeat of two IgV/IgC2-region sets of domains. In their cytoplasmic domains several members of this family contain one or more copies of the immunoreceptor tyrosine-based switch motif (ITSM) [56]. Typically, SLAMs are self-ligands. CD244 and CD48, however, do not follow this rule, participating in heterophilic interactions among themselves. SLAM engagement, which occurs through their N-terminal IgV domains, results in signaling transduction events that ultimately modulate (positively or negatively) multiple aspects of the innate and adaptive immune responses, such as cytokine production, cytotoxicity, or cell differentiation and proliferation [58, 59]. A number of SLAM homologs have been described or predicted in herpesviruses, poxviruses, and adenoviruses (vSLAMs; Table 6). The first vSLAM characterized was the soluble UL7
### Table 6. SLAM homologs

| Virus            | Viral gene(s) | Host SLAM homolog(s) | % aa identity protein | % aa identity IgV | Protein structure | SLAM ligand binding | Functions                                                                 | References |
|------------------|---------------|----------------------|-----------------------|------------------|------------------|-------------------|---------------------------------------------------------------------------|------------|
| **Herpesviruses**|               |                      |                       |                  |                  |                   |                                                                           |            |
| **Alphaherpesviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| ChHV-5 F-US1     | n.d.          | SLAM                 | 11                    | 17               | 1 IgV, 1 TM, long protein | n.t.              |                                                                           | [114]      |
| **Betaherpesviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| HCMV UL7         | L Y9          | 11                    | 23                    | 1 IgV, 1 TM (or s) | No               |                   | Mediation of adhesion to leukocytes. Downregulation of proinflammatory cytokines. | [60]       |
| CCMV UL7         | L Y9          | 11                    | 17                    | 1 IgV, 1 TM      | n.t.             |                   |                                                                           |            |
| RhCMV rhUL7      | L Y9          | 12                    | 15                    | 1 IgV, 1 TM      | n.t.             |                   |                                                                           |            |
| CyCMV UL7        | L Y9          | 12                    | 15                    | 1 IgV, 1 TM      | n.t.             |                   |                                                                           |            |
| SMCMV S1         | SLAMF6        | S1                   | 62                    | 97               | 1 IgV, 1 IgC2, 1 TM | SLAMF6           |                                                                           | [61]       |
| “                | CD48 S30      | S30                  | 28                    | 36               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           | [61]       |
| “                | CD48 S31      | S31                  | 20                    | 36               | 1 IgV, 1 IgC2, 1 stalk, 1 TM | n.t.             |                                                                           | [61]       |
| OMCMV A33        | L Y9          | 23                    | 80                    | 1 IgV, 1 IgC2, 1 TM (or s) | LY9             |                   |                                                                           | [61]       |
| “                | CD48 A43      | A43                  | 45                    | 90               | 1 IgV, 1 IgC2, 1 TM (or s) | CD244           |                                                                           | [61]       |
| “                | CD48 A44      | A44                  | 28                    | 34               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           | [61]       |
| “                | CD48 A45      | A45                  | 15                    | 24               | 1 IgV, 1 IgC2, 1 stalk, 1 TM | n.t.             |                                                                           | [61]       |
| EEHV-1A ES2      | CD48          | 18                    | 21                    | 1 IgV, no TM (s) | n.t.             |                   |                                                                           |            |
| EEHV-5 EE49B     | CD48          | 17                    | 22                    | 1 IgV, 1 TM      | n.t.             |                   |                                                                           |            |
| **Poxviruses**   |               |                      |                       |                  |                  |                   |                                                                           |            |
| **Molluscipoxvirus** |               |                      |                       |                  |                  |                   |                                                                           |            |
| MOCV MC002L      | SLAMF1        | 18                    | 20                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           | [62]       |
| “                | SLAMF1        | 15                    | 14                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           | [62]       |
| “                | SLAMF1        | 15                    | 15                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           | [62]       |
| **Unclassified poxviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| SQPV F5          | CD48          | 13                    | 19                    | 1 IgV, 1 TM      | n.t.             |                   |                                                                           | [94]       |
| **Adenoviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| **Mastadenoviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| HAdV-A E3 CR1-β  | n.d.          | SLAM                 | 20                    | 21               | 1 IgV, 1 IgC2, 1 TM | CD244           |                                                                           | [63]       |
| HAdV-F E3 CR1-β  | n.d.          | SLAM                 | 18                    | 18               | 1 IgV, 1 IgC2, 1 TM | CD244           |                                                                           | [63]       |
| HAdV-G E3       | n.d.          | SLAM                 | 15                    | 19               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| SAdV-A E3 CR1-β1 | n.d.          | SLAM                 | 16                    | 19               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| SAdV-B E3 CR1-α  | n.d.          | SLAM                 | 12                    | 15               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| SAdV-C E3 CR1-β  | n.d.          | SLAM                 | 14                    | 24               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| SAdV-19 E3 CR1-β | n.d.          | SLAM                 | 17                    | 21               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| SAdV-20 E3 CR1-β | n.d.          | SLAM                 | 17                    | 21               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| TSAdV-1 105R     | n.d.          | SLAM                 | 16                    | 25               | 1 IgV, no TM (s)   | n.t.             |                                                                           |            |
| BAdV-A E3 ORFA   | n.d.          | SLAM                 | 15                    | 15               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| EAdV-A E3 ORFA   | n.d.          | SLAM                 | 17                    | 20               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| EAdV-B hORF1     | n.d.          | SLAM                 | 15                    | 18               | 1 IgV, 1 IgC2, 1 TM | n.t.             |                                                                           |            |
| **Aviadenoviruses** |               |                      |                       |                  |                  |                   |                                                                           |            |
| FAdV-A ORF11     | CD48          | 21                    | 34                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           |            |
| FAdV-1 ORF11     | CD48          | 17                    | 34                    | 1 IgV, no TM (s) | n.t.             |                   |                                                                           |            |
| FAdV-D ORF11     | CD48          | 23                    | 38                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           |            |
| FAdV-E ORF11     | CD48          | 23                    | 41                    | 1 IgV, 1 IgC2, no TM (s) | n.t.             |                   |                                                                           |            |
| FAdV-6,7,8 ORF11 | CD48          | 27                    | 43                    | 1 IgV, 1 IgC2, 1 TM | n.t.             |                   |                                                                           |            |

(Continued)
Table 6. Continued

| Virus    | Viral gene(s)a | Host SLAM homologb | % aa identity proteinc | % aa identity IgVd | Protein structuree | SLAM ligand bindingf | Functions | References |
|----------|----------------|--------------------|------------------------|--------------------|--------------------|---------------------|-----------|-----------|
| TAdV-1   | ORF11          | CD48               | 14                     | 34                 | 1 IgV, no TM (s)   | n.t.                |           |           |
| TAdV-5   | ORF11          | CD48               | 25                     | 35                 | 1 IgV, 1 IgC2, no TM (s) | n.t.                |           |           |

a) Genes in bold encode proteins whose functions and/or binding capacity have been tested.
b) n.d. means “not determined”.
c) The percentage of amino acid (% aa) identity was calculated as in Table 1.
d) TM means “transmembrane domain”; s means “soluble”.
e) n.t. means “not tested”.
f) BAdV: bovine adenovirus; CCMV: chimpanzee CMV; ChHV: chelonid herpesvirus; CyCMV: cynomolgus macaque CMV; EAdV: equine adenovirus; EEHV: elephant endotheliotropic herpesvirus; FAdV: fowl aviadenovirus; RhCMV: rhesus macaque CMV; SAdV: simian adenovirus; SQPV: squirrelpox virus; TAdV: turkey aviadenovirus; TSAdV: tree shrew adenovirus.

Viral acquisition of novel genes by horizontal gene transfer from hosts

Horizontal gene transfer is a process through which genomes can acquire genetic material from distantly related organisms. This process provides genes with new functions, allowing viruses to enhance their adaption to the host environment. Given the strong evolutionary pressures that viruses encounter, as well as their genome size constraints, any superfluously incorporated genes that do not increase their fitness will be rapidly discarded. To date, however, the mechanisms of horizontal gene transfer to explain the origin of these viral genes remain poorly understood. Some viral captured genes conserve the intron structure of the parental host gene, suggesting that they were acquired by direct recombination between the viral and host genomes [64]. However, most viral homologs are intronless. Thus, it is believed that host genes can be incorporated into viral genomes already in a spliced form, as a cDNA copy, during co-infections with retroviruses, since DNA viruses do not have the capacity for reverse transcription [65]. While this latter hypothesis has been widely accepted, direct evidence supporting it has not been provided. Interestingly, we have recently proposed that large DNA viruses may exploit the L1-driven and Alu-aided retrocopy cellular machinery in order to facilitate the incorporation of host genes [66]. The occurrence of virally encoded cellular homologs, as previously shown by other authors [2], may result from either a unique transfer event or from multiple independent acquisition events at different times during viral evolution. This aspect is also reflected within the vlgsf molecules. A clear example of a single capture event is the case of CD47 in poxviruses, as vCD47 molecules have been detected in all poxviruses that infect mammals except in the more phylogenetically distant molluscipoxviruses and parapoxviruses [67]. Herpesviral homologs of CD200, on the other hand, probably stem from several independent insertions, as they are present in diverse unrelated herpesvirus species. For instance, a recent capture of CD200 in RCMV-E is the most parsimonious explanation of the existence of e127, a CD200 homolog absent from the rat CMV Maastricht isolate and the MCMV [68].
Viral homologs of host genes as a source of functional diversity

Once incorporated into the viral genome, host homologs will often mimic the effects of the original cellular ancestors. In this regard, functional mimicry is largely exhibited among the vIgSF molecules with assigned biological activities described in this review. Alternatively, they can evolve to generate related or completely new functions. Quite frequently, they may also suffer processes of gene duplication, with one of the copies usually maintaining the original function and the other(s) diverging and gaining new functional roles. Moreover, successive gene duplications can lead to multigene families. Evidence of gene duplication has been found in homologs of CD200, FcyR, IL-1R2, IL-18BP, and CD48 in several viral species (see examples in Tables 1, 3 and 6). The acquisition of new functions after gene duplication is likely favored in IgSF genes due to the moldable nature of the Ig domains, as proven by their extraordinary evolutionary expansion, generating one of the largest protein families in vertebrates.

It is evident that, over time, proteins encoded by captured genes have been meticulously crafted within the viral genomes in ingenious ways to gain distinctive structural and functional features in order to selectively target and disarm several immune pathways. In some instances, these changes have included substantial structural alterations, which frequently imply size reductions, usually through removal of superfluous regions (e.g. Ig domains not involved in ligand binding), or alternatively, by expanding particular segments of the proteins to meet specific functional requirements. A paradigmatic example of the generation of highly diverse structural variants is provided by the five homologs of CD48 found in the New World monkey CMVs [61]. Some of the vIgSF molecules have also been optimized to change their cellular localization or to form part of the virion particle, as demonstrated for a number of the herpesviral FcγR homologs or the CEACAM homolog UL1 of HCMV (Fig. 1C) [31, 54]. Notably, a large number of the described viral homologs are soluble versions of the homolog UL1 of HCMV (Fig. 1C) [31, 54]. Notably, a large number of the described viral homologs are soluble versions of the homologs due to the moldable nature of the Ig domains, as proven by their extraordinary evolutionary expansion, generating one of the largest protein families in vertebrates.

Viral decoy receptors can be secreted into the environment of the virus-infected cells, sequestering cytokines or blocking different target molecules. Two of the best examples of this type of secreted receptor are the VACV IL-1R2 homolog B15R and the MOCV IL-18BP homolog MC054L, which are able to bind and block the cytokines IL-1β and IL-18, respectively (Fig. 1D and E) [42, 69, 70]. Additionally, a different kind of viral decoy receptor comprised molecules lacking the relevant intracellular signaling motifs of their cellular ancestors, thus being able to block the transmission of biological responses when exposed at the surface of the infected cell. While not yet functionally studied, a number of vIgSF members could be also classified in this category, such as the SLAM family homologs possessing transmembrane regions but lacking the ITSM cytoplasmic signaling motifs [61]. In other instances, viral proteins are able to dramatically alter their ligand recognition, exhibiting higher affinity or broader, more limited, or completely different binding specificity. This latter case is well illustrated by the EBV protein BARF1, a homolog of CD80, which can bind to cytokine CSF1, instead of its natural T-cell ligands CD28 or CTLA4, resulting in the inhibition of macrophage differentiation and function, and thus contributing to EBV immune evasion (Fig. 1F) [48–51]. Finally, an intriguing aspect that also emerges from the study of these viral products is the fact that a number of them can perform the immunomodulatory function of the original host molecule without binding to the cognate cellular ligand/receptor, while others, despite retaining the binding specificity of the ancestor cellular protein, do not perform the expected biological function. These two cases are exemplified within the virally encoded CD200 homologs by the MV M141R and the RCMV-E e127, respectively [21–23].

Translating functional optimization by viral evolution to immune therapy

The fact that these virally encoded proteins have been functionally optimized through thousands or even millions of years of evolution by altering their ligand specificities and affinities in order to counteract specific immune processes, places them as promising immunomodulatory reagents for the development of novel immune suppressive therapeutic strategies to treat inflammatory disorders [71]. Indeed, these viral molecules can likely offer additional advantageous characteristicst, such as low immunogenicity and low toxicity. Thus far, no viral IgSF protein has entered clinical trials. However, the serine proteinase inhibitor 1 encoded by the MV has already been tested in a phase II study as an anti-inflammatory drug for arterial trauma [72]. As with any biological drug, it remains to be seen whether unexpected problems might appear when these proteins are tested in patients, such as allergic reactions, immunogenicity, and/or other unforeseen side effects. To circumvent some of these potential complications, an alternative approach would be to utilize not the viral protein itself, but rather the cellular protein mutated according to the structural-functional information extracted from the viral homolog, thereby creating a new generation of engineered biologics. In conclusion, the study of host-virus co-evolution holds hidden treasures for immunologists and clinicians, especially since the repertoire of novel viral gene products with immunomodulatory functions is quickly rising. Comprehensive mechanistic insights into how these proteins target the immune system will facilitate the development of novel therapeutic approaches.

Acknowledgments: This work was supported by grants from the Ministerio de Economía y Competitividad (MINECO, Spain; grant numbers SAF2014-55683 to A.A. and SAF2015-69829 to P.E.).
Conflict of interest: The authors declare no commercial or financial conflict of interest.

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Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity · CD200R: CD200 receptor · CEACAM: carcinoembryonic antigen-related cell adhesion molecule · CMV: cytomegalovirus · CSF1: colony-stimulating factor 1 · CTLA4: cytotoxic T-lymphocyte-associated protein 4 · EBV: Epstein-Barr virus · FcγR: Fc receptors for IgG · GPI: glycosylphosphatidylinositol · HAdV: human adenovirus · HCMV: human CMV · HSV-1: herpes simplex virus 1 · IgSF: immunoglobulin superfamily · IL-1: interleukin-1 · IL-18: interleukin-18 · IL-18BP: IL-18-binding protein · IL-1R2: interleukin-1 receptor 2 · ITAM: immunoreceptor tyrosine-based activation motif · ITIM: immunoreceptor tyrosine-based inhibitory motif · ITSM: immunoreceptor tyrosine-based switch motif · KSHV: Kaposi’s sarcoma-associated herpesvirus · MCMV: murine CMV · MOCV: molluscum contagiosum virus · MV: myxoma virus · OMCMV: owl monkey CMV · RCMV-E: rat CMV England isolate · SIRPa: signal regulatory protein alpha · SLAM: signaling lymphocyte activation molecule · SMCMV: squirrel monkey CMV · VACV: vaccinia virus

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Received: 7/2/2017
Revised: 11/3/2017
Accepted: 29/3/2017
Accepted article online: 6/4/2017

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