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Subversion of cytokine networks by virally encoded decoy receptors

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Summary

During the course of evolution, viruses have captured or created a diverse array of open reading frames that encode for proteins that serve to evade and sabotage the host innate and adaptive immune responses, which would otherwise lead to their elimination. These viral genomes are some of the best textbooks of immunology ever written. The established arsenal of immunomodulatory proteins encoded by viruses is large and growing and includes specificities for virtually all known inflammatory pathways and targets. The focus of this review is on herpes and poxvirus-encoded cytokine and chemokine binding proteins that serve to undermine the coordination of host immune surveillance. Structural and mechanistic studies of these decoy receptors have provided a wealth of information, not only about viral pathogenesis but also about the inner workings of cytokine signaling networks.

Keywords

immune evasion; viral mimicry; decoy receptor; pro-inflammatory cytokines; poxvirus; herpesvirus; structural immunology

Introduction

Good artists copy, great artists steal. -Pablo Picasso

Viruses have evolved a myriad of strategies to elude innate and adaptive immune responses. Common targets of many viruses are cytokines, extracellular signaling molecules that serve as key regulators of the immune response against invading pathogens. Cytokine activity is marshaled early against the initial stages of viral infection and is an essential component of host defense (1). In the majority of cases, cytokine-mediated responses can account for the complete clearance of viral infection (2). Most of the damage inflicted on virally infected cells is the result of activities initiated by pro-inflammatory cytokines such as the interferons (IFNs), interleukin-1 (IL-1), IL-12, IL-18, tumor necrosis factor (TNF), as well as a number of chemokines (3, 4). Not surprisingly, these agents are favored targets for viral subterfuge, and most viruses have developed strategies for modulating cytokine signaling in infected cells (5–7).

During the course of evolution, viruses have captured the genetic information necessary to produce their own versions of cytokines. Stolen host genes are particularly prevalent among the large DNA viruses, which devote significant parts of their genome to immune evasion

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strategies. For example, viruses encode their own versions of IL-10 (8–10), which inhibits monocyte/macrophage and neutrophil cytokine production, IL-6, which inhibits TNF and IL-1 production by macrophages (11), IL-17, which can costimulate T-cell proliferation (12), and a myriad of chemokines that control leukocyte trafficking and pro-inflammatory cytokine synthesis (13, 14). These viral proteins often deviate in sequence from host proteins of related function, because viruses alter pirated genes to create new functional properties. For example, although cellular IL-10 can costimulate thymocyte and mast cell proliferation as well as B-cell major histocompatibility complex (MHC) class II expression, Epstein-Barr virus (EBV)-encoded IL-10 cannot. This difference maps to a single amino acid substitution (9). In a similar fashion, viral IL-6 has altered its cytokine receptor contact sites to enhance its complementarity with the gp130 receptor (15, 16). Another example is the vaccinia-encoded protein A39R that binds to and activates host PlexinC1 in a similar fashion as the semaphorin sema7a, albeit with higher affinity (17, 18). Viruses also use membrane-spanning cytokine receptors, often with modified signaling properties. There are examples of virally encoded receptors that do not signal, that signal constitutively, or that differentially signal due to alterations in their cytokine binding profiles. Stolen host chemokine receptors are a frequent platform for this type of viral chicanery (19).

A common strategy of immune evasion employed by large DNA viruses is to produce soluble proteins that can sequester pro-inflammatory cytokines, thereby blocking their function (5, 6, 20, 21). These decoy receptors are the focus of this review and are most frequently encoded by pox and herpesviruses, whose complete genomes can encode for 100–200 open reading frames (ORFs), with as much as half dedicated to host manipulation (22, 23). Frequently, these viral decoy receptors correspond to soluble versions of their cellular counterparts. For example, orthopoxviruses secrete a soluble IL-1-binding protein with high sequence similarity to the ectodomains of mammalian IL-1 receptors (24). Orthopoxviruses also encode IFN γ decoy receptors that are clearly related to host IFN γ receptors but differ from the transmembrane receptors by virtue of a unique C-terminal region and their ability to bind IFN γ from multiple species with high affinity (25). Viruses also appear adept at stealing host proteins and altering their functional targets. For example, most poxviruses encode a protein that acts as a potent decoy receptor for type-I IFNs (26, 27). It turns out that this protein is far more related in sequence to cellular IL-1 receptors (and viral IL-1 decoy receptors) than it is to IFN α/β receptors produced by mammals. Occasionally the origin and evolution of a viral decoy receptor is unclear, as there appears to be no host or viral protein with sequence or structural similarity. This is particularly common for pathogen-encoded chemokine decoy receptors and is readily understandable when one considers the complexity of engineering a secreted variant of a G-protein coupled receptor (GPCR).

Subversion of the chemokine system

Initially identified by their prominent role in leukocyte trafficking in the context of inflammation, it was subsequently shown that chemokines have a broad range of functions including angiogenesis, lymphoid tissue development, wound healing, and metastasis. The role of chemokines in orchestrating the antiviral response is also well-established. One of the hallmarks of chemokine function is the establishment of concentration gradients that guide immune responder cells toward sites of infection (28). Chemokines are secreted from both endothelial and extravascular cells and are then retained at the cell surface primarily by interacting with cell surface glycosaminoglycans (GAGs). It is believed that under physiological conditions chemokines are presented to chemokine receptors on leukocytes as ligands immobilized to a solid phase via interaction with GAGs (29, 30). Chemokines bind seven-transmembrane pass GPCRs and stimulate a complex array of signaling pathways that regulate chemotaxis among other phenomena (28, 31–34). The secretion of specific

chemokines is coordinated with the differential expression of chemokine receptors on different cell types to determine which leukocytes migrate during inflammation (4). There are at least 45 known chemokines and 18 GPCRs, with the ligands organized into four families, designated CC, CXC, CX3C, and C based on the placement of N-terminal cysteine residues. Chemokine family members adopt a highly conserved overall structure despite the fact that they display low sequence identity to one another and have a wide variety of signaling properties (28).

The importance of chemokines in the context of viral infection is further emphasized by the discovery that viruses have evolved strategies to modulate host chemokine signaling networks (19). For example, Kaposi's sarcoma-associated herpesvirus (HHV8) encodes a chemokine antagonist related to CC-chemokines that has been shown to bind to multiple CC chemokine receptors to block function (35), and a clinical strain of human cytomegalovirus (HCMV) encodes a micro-RNA that targets the CC-chemokine RANTES (36). Viruses also encode for seven transmembrane chemokine receptors that are structurally similar to host GPCRs and have been shown to signal constitutively or sequester chemokines without signaling in virally infected cells. An example of this is the constitutively active HHV8 GPCR that signals to induce cell proliferation (37). The chemokine network is so crucial to the clearance of pathogens that a wide variety of agents are known to encode for secreted chemokine-binding proteins with anti-inflammatory activity, including the helminth parasite *Schistosoma mansoni* (38) and bloodsucking ticks (39). Herpes and poxviruses also encode an array of different chemokine decoy receptors with diverse chemokine-binding and functional activities, including the capacity to block receptor interactions and disrupt chemokine gradients (Figs 1 and 2).

Herpesvirus-encoded chemokine decoy receptors

The first chemokine-binding protein identified in a herpesvirus is encoded by the M3 ORF of γ -herpesvirus68 (γ HV68), a rodent pathogen related to Kaposi's sarcoma-associated herpesvirus (HHV8) (40, 41). M3 is a high affinity chemokine decoy receptor, capable of promiscuous binding to all four families of chemotactic cytokines. Indeed, all CC, C, and CX₃X chemokines tested to date bind with nanomolar or better affinities, as do a subset of CXC-chemokines. Chemokines sequestered by M3 are disabled from mediating leukocyte chemotaxis as well as intracellular calcium signaling. M3 has shown efficacy in several inflammatory models including vascular injury, allograft transplantation, tumor rejection, and allergen-induced asthma (42–45). In addition, studies using M3 as a transgene within β -islet cells indicate that it is capable of providing resistance to insulinitis (46).

Alexander *et al.* (47) solved the crystal structure of M3 both alone and in complex with the CC-chemokine macrophage chemotactic protein-1 (MCP-1) (CCL2). The structure showed that M3 is a two β -sandwich domain protein that forms a tightly packed anti-parallel homodimer. As can be seen in Figs 1 and 2, two MCP-1 molecules bind independently into two niches located at distal ends of M3. The N-terminal domain (NTD) of M3 is highly acidic, and loops protruding from it engage a basic patch located in the N-loop and 40s loop region of MCP-1. The binding cleft created by the M3 C-terminal domain (CTD) engages the N-terminal region of MCP-1, including the disulphide bond invariantly found in all chemokines. One of the more striking features of the M3/MCP-1 complex is the engagement of chemokine residues previously implicated as essential for binding CCR2, a GPCR specific for MCP-1. Thus, despite the lack of any sequence similarity with GPCRs, M3 acts to sequester chemokines in a competitive manner through structural mimicry of host chemokine receptors (47). However, unlike host chemokine receptors, M3 is capable of binding a remarkably diverse array of different chemokines. A follow-up study examined the structure of M3 in complex with the chemokine lymphotactin (XCL1), where the decoy receptor engages similar structural regions of the chemokine (N-term, N-loop, and 40s-loop)

that share little sequence identity with other high affinity ligands (48). Promiscuous chemokine binding by M3 appears to be facilitated by structural reorganization of contact loops and individual domains of the M3 dimer that are reminiscent of the binding of diverse antigens by antibodies. These structures teach us that the M3 CTD recognizes conserved chemokine features associated with GPCR binding, while the acidic NTD reconfigures to engage diverse basic GAG-binding regions found in nearly all chemokines (Fig. 2A). Indeed, the electrostatic complementation of acidic M3 with basic chemokines results in an extremely fast on-rate for complex formation. Cellular assays support the structural information and show that M3 is capable of disrupting the interaction of chemokines with both GPCRs and GAGs (48).

In addition to M3 encoded by γ HV68, chemokine binding proteins have also been found in α - and β -herpesviruses. Glycoprotein G (gG) encoded by α -herpesviruses is found in the viral envelope and can be secreted following proteolytic cleavage of its C-terminal transmembrane domain. gG has no sequence similarity to any known host proteins or to any previously characterized chemokine binding proteins. The gG proteins in some α -herpesviruses including equine herpesviruses 1 and 3, and bovine herpesvirus 1 and 5 have been shown to bind chemokines spanning the CC, CXC, and C classes (49). Functional data indicate that binding of these gG decoy receptors to a chemokine inhibits both receptor and GAG interactions. Additionally, these proteins may be able to function in their membrane-bound form as well. The gG proteins encoded by human α -herpesviruses 1 and 2 (HSV-1 and HSV-2) have also been shown to bind to the CC and CXC classes of chemokines. However, in sharp contrast to studies with gG encoded by equine and bovine α -herpesviruses, data suggests that HSV gG binds to chemokines via the GAG-binding region and can enhance receptor binding and chemotaxis, perhaps to recruit cells pertinent to viral infection or spread (50).

HCMV is a member of the β -herpesvirus family and encodes a chemokine-binding protein termed pUL21.5. This decoy receptor appears to have exquisite specificity for the human chemokine RANTES (CCL5), binding with approximately 320 pM affinity and effectively blocking chemokine receptor binding (51). As CCL5 is important for T-cell recruitment and activation, the production of this decoy suggests an important role of adaptive immunity in the control of HCMV infection (52). Interestingly, the mRNA encoding pUL21.5 is incorporated into HCMV virions, suggesting that the decoy receptor can be produced and secreted by newly infected cells prior to the transcriptional activation of the viral genome (53).

Poxviral CKBPs

Members of the orthopoxvirus and leporipoxvirus genera encode multiple chemokine decoy receptors with diverse functional properties. The first group of these proteins that was characterized has been termed viral chemokine binding proteins (vCKBPs) but also has gone by the family names T1/35kDa and vCCI. vCKBPs appear to bind selectively to CC-chemokines with generally high affinity (0.03–100 nM) and block their interaction with cellular receptors (54–56). These abundantly secreted glycoproteins are typically expressed early during viral infection and are conserved in many viral species, including cowpox, ectromelia, variola, rabbitpox, myxoma, and some strains of vaccinia (57, 58).

The structures of several CKBPs have been described. In 1999, Carfi *et al.* (59) published the high-resolution structure of cowpox vCCI, revealing a single β -sandwich domain annotated with several large loops and connecting helices. The surface of β -sheet I is covered by some of the larger loops, while β -sheet II is more surface exposed and contains a patch of negatively charged residues. The structure of a second vCKBP, EVM1 from ectromelia virus, was reported by Arnold *et al.* (60) and established the general folding

characteristics of the vCKBP family, with EVM1 exhibiting an RMSD of 2.0 Å with cowpox vCCI over 220 amino acids. The same solvent inaccessible β -sheet I was observed, as was the solvent exposed and negatively charged patch on β -sheet II. Mutational studies established that the binding site for chemokines is localized to a cluster of five residues on the face of β -sheet II and the adjoining β 2– β 4 flexible loop. Structurally, it is curious to note that the NTD of M3 is similar to these vCKBPs. Although EVM1 shares only 4% sequence identity with the M3 NTD, the two structures align with an RMSD of 3.3 Å over 199 residues (60).

A more precise understanding of chemokine binding by vCKBPs came from the NMR solution studies of Zhang *et al.* (61), who determined the structure of rabbitpox vCCI in complex with human MIP-1 β (CCL4). The decoy receptor was found to bind chemokines with a 1:1 stoichiometry, primarily engaging the same regions recognized by the M3 decoy (N-term, N-loop, and 40s-loop). These structural studies are supported by chemokine mutations that indicate that many vCKBPs act as competitive inhibitors, binding many of the same residues used to engage host signaling receptors (56, 62, 63). Interestingly, several key residues implicated in chemokine GAG interactions are not apparently necessary for vCKBP sequestration, although as seen in Fig. 2B, the chemokine footprint shows that some GAG binding residues are indeed contacted.

The A41 and E163 chemokine-binding proteins

Two additional poxvirus-encoded proteins that are distantly related to the vCKBP family were structurally and functionally characterized in 2008. The structure of vaccinia virus A41 was solved at 1.9 Å resolution and revealed a very similar topology to that of the vCKBPs, despite sharing only ~20% sequence identity (64). The protein was shown to bind to the chemokines CCL21, CCL25, CCL26, and CCL28, with affinities of between ~10–100 nM. In contrast to the vCKBPs discussed above, however, A41 does not block chemokine receptor binding and thereby chemotaxis. Instead, A41 appears to interact with the GAG recognition regions of chemokines, as binding is inhibited in a dose-dependent manner by heparin. Studies of the related ectromelia virus encoded protein E163 indicate that it interacts with the same set of CC-chemokines that A41 binds, although high affinity engagement of CCL24, CCL27, CXCL12 α , CXCL12 β , and CXCL14 was also reported (65). Chemokine mutational analysis was used to demonstrate that E163 binds directly to the GAG recognition regions of chemokines, and like A41, the E163 decoy receptor is ineffective in blocking chemotaxis. However, in addition to blocking chemokine-GAG interactions, the study by Ruiz-Arguello *et al.* (65) reported that the decoy receptor itself can associate GAGs with high-affinity. Thus, it appears that A41 and E163 modulate the chemokine network primarily through the disruption of chemokine gradients rather than the competitive inhibition of chemokine receptor binding (Fig. 1).

SECRET domain chemokine decoy receptors

In 2006, Alejo *et al.* (66) reported the discovery of yet another family of poxvirus-encoded chemokine decoy receptors termed SECRET domains (smallpox virus-encoded chemokine receptor). First identified in the C-terminal region of the variola virus encoded TNF decoy receptor CrmB (see below), sequence analysis suggested that a similar ~160 residue domain is present in cowpox and monkeypox CrmB as well as cowpox and ectromelia CrmD. ORFs encoding SECRET domains alone have also been found in a number of poxviruses, with cowpox strains encoding at least three of them, termed SECRET-containing proteins (SCP1-3). Chemokine-binding studies of the SECRET domains from variola CrmB, ectromelia CrmD, and SCPs from cowpox and ectromelia suggest that all of these decoy receptors bind a similar set of chemokines with approximately 0.3–30 nM affinities, including CCL25, CCL27, CCL28, CXCL11, CXCL12 β , CXCL13, and CXCL14. Further,

the binding of SECRET domains to the murine chemokine CCL25 was shown to block chemotaxis, suggesting that the function of these proteins may be more similar to the vCKBPs discussed above rather than A41 and E163 proteins that block only chemokine GAG interactions.

In 2010, Antonets *et al.* (67) reported a computational modeling study of the variola CrmB SECRET domain, suggesting that it will adopt a fold related to that seen for vCKBPs, despite having only ~15% sequence identity to the family. Soon afterwards, Xue *et al.* (68) reported the structure of the SECRET domain of ectromelia CrmD both alone and in complex with human CX3CL1. In contrast to other characterized ligands, CX3CL1 binds CrmD with only micromolar affinity and an extremely fast off-rate with interactions that are readily disrupted by the presence of heparin. As predicted, the overall topology of the SECRET domain is very similar to vCCI, EVM1, and A41, being composed of a sandwich of two anti-parallel β -sheets (I and II). There are significant differences in the structures however. For example, there are no flanking helices in the SECRET domain and one of the larger loops (7–9 loop) that normally limits the solvent accessibility of the β -sheet I in vCCI, EVM1, and A41 has instead become incorporated as strand 8 of β -sheet II. Most importantly, structure of the SECRET domain in complex with CX3CL1 shows that this chemokine binds the opposite face of the decoy receptor β -sandwich, on β -sheet II, as compared to the binding demonstrated for vCKBPs (Figs 1 and 2). The binding footprint of the decoy receptor on CX3CL1 is predominantly localized to the basic charged GAG-binding region near 40s-loop, with limited structural contact with the receptor binding N-term or N-loop regions. The reason for these variations in chemokine sequestration by the SECRET domain relative to vCKBPs is not entirely clear, and neither is the binding mechanism for other chemokines that bind the SECRET domain with considerably higher affinity than CX3CL1.

Targeting TNF

TNFs are powerful instigators of inflammation and play a significant role in the clearance of viral infections. Produced by many cell types such as macrophages and T cells, the pro-inflammatory effects of TNF are also involved in autoimmune disorders such as rheumatoid arthritis, Crohn's disease, and graft versus host disease (69). TNF α is a constitutive homotrimer that exerts its effects by signaling through two members of the TNF receptor (TNFR) superfamily, TNFR1 (p55/p60) and TNFR2 (p75/p80). TNFRs are found on almost every cell type with the exception of naive T cells and red blood cells. Signals are transduced when three receptors bind to a TNF α trimer, one at each monomer-monomer interface. Downstream signaling effects vary depending on the TNFR being engaged. While signaling through TNFR1 can activate apoptosis, it also triggers the activation of the nuclear factor- κ B (NF- κ B), activator protein-1 (AP-1), and mitogen-associated protein kinase (MAPK) pathways. These signaling events activate cellular responses such as the induction of reactive oxygen species and the production of more cytokines and chemokines. Signaling through TNFR2 can activate similar pathways, but it does not have the same ability to induce apoptosis (70). TNF- β , or lymphotoxin- α (LT- α), is a closely related member of the TNF superfamily that is produced by activated B and T lymphocytes and has similar activities to TNF- α . Like TNF- α , LT- α signals through TNFR1 and TNFR2 and is involved in the regulation of various cellular processes including proliferation, differentiation, apoptosis, lipid metabolism, coagulation, and neurotransmission. LT- α is secreted as a soluble homotrimer, or it can form heterotrimers with lymphotoxin- β , which effectively anchors it to the cell surface. The differences in the biological activity between TNF- α and LT- α appear to be due to differential binding to target cells (71).

Both herpes and poxviruses are known to block TNF signaling pathways, targeting a number of different control points (72). For example, most poxviruses encode for a protein termed CrmA that can potently inhibit the caspase 8 enzyme, an important downstream component in the triggering of apoptosis (73). Herpesviruses also encode inhibitors of caspase 8, such as HHV8 vFLIP, and HCMV UL36, both of which inhibit the pre-oligomerization of pro-caspase 8 and thus a polarization of the cell towards apoptosis (74, 75). EBV encodes the six-transmembrane protein LMP1 that mediates signaling through the TNF/CD40 pathway to drive cell proliferation as opposed to apoptosis, and BZLF1 that inhibits TNFR1 expression through effects on cellular C/EBP proteins (76–78). In this review, we focus on what is known about the arsenal of decoy receptors for TNF family ligands have been identified in poxviruses (Fig. 3).

Poxvirus-encoded TNF decoy receptors

Poxviruses encode multiple TNF decoy receptor variants that are secreted during viral infection (79, 80). The first of these proteins was identified in Shope fibroma virus based on sequence conservation of multiple cysteine-rich domains (CRDs) located at the N-terminus of both the viral and host signaling receptors (81). Referred to as cytokine response modifiers in orthopoxviruses (Crms), the cowpox virus strain GRI encodes a total of four Crm paralogues (CrmB, CrmC, CrmD, and CrmE), while some vaccinia strains do not encode any. Variola and monkeypox viruses encode only CrmB, while ectromelia encodes only CrmD (82–85). CrmB and CrmD both have four CRDs as well as the C-terminal chemokine-binding SECRET domain as discussed above, while CrmC and CrmE appear to contain only three TNFR-related CRDs. The Leporipoxvirus encoded TNF decoy receptor, T2, has similar features as CrmB and CrmD, although chemokine-binding of the C-terminal domain has not yet been established. These viral TNF decoy receptors share 30–50% sequence similarity with the N-terminal CRDs of mammalian TNFRs (84).

While most mammalian TNFRs exhibit species-specific ligand recognition, the Crm decoy receptors display remarkable ligand-binding promiscuity, which likely contributes to the ability of a given orthopoxvirus to infect a variety of hosts. For example, CrmB and CrmD can bind and potently inhibit human, mouse, and rat TNF α as well as human LT α (Fig. 3). CrmE can bind human, mouse, and rat TNF α , neutralizing the effects of human TNF α most effectively, although it does not bind to LT α . While quantitative single-site binding affinities for the Crm proteins binding to TNF ligands are not currently available, qualitative avidity measurements and functional assays suggest that the viral decoy receptors can readily outcompete TNFR1/2 binding (82–86). Indeed, ectromelia engineered to lack CrmD is severely attenuated in the mousepox model of infection, with the observed median lethal dose increased by six orders of magnitude. Further, a massive inflammatory response was observed at the site of infection of the CrmD knock-out virus that was not seen when CrmD was present, providing an excellent illustration for how efficient this decoy is at controlling inflammation (87).

The binding of TNF α and LT α to TNFR2 and TNFR1 have been well characterized structurally (88, 89). As shown in Fig. 3, the signaling receptors triangulate around the constitutively trimeric ligands, embedding into niches at the monomer interfaces of the cytokine. Interestingly, the ectodomains of the TNFR receptors do not appear to make any lateral contact with one another in the assembled hetero-hexameric complex. The interactions of TNF ligands and their receptors have been argued to be mediated primarily by two regions on the TNFRs: the 50s loop, which engages a conserved hydrophobic patch on the ligand surface, and the 90s loop, which mediates non-conserved interactions that may modulate ligand-binding specificity (90). In 2007, Graham *et al.* (91) determined the structure of CrmE encoded by vaccinia virus. The structure of unliganded CrmE closely resembles the TNFRs and shares 30% sequence identity over CRDs 1–3 with human

TNFR2. However, there are some unique elements to the CrmE structure including an unusual CRD3 that contains two disulfide bonds in the A module, but only one in the B module that appears to allow for a more open conformation of the decoy receptors C-terminal region. CrmE conserves the structure of the 50s-loop with human TNFR1 and TNFR2, but the 90s-loop region appears to be completely distinct in sequence and structure (92). Differences such as these may account for the significantly increased breadth of ligand binding specificity exhibited by the Crm-family decoy receptors.

MHC class I-like TNF decoy receptors

In 2003, Brunetti *et al.* (93) reported the discovery of a secreted TNF decoy receptor encoded by the 2L ORF of tanapox. This second class of TNF inhibitor is encoded in the genomes of a number of yatapoxviruses, including yaba monkey tumor virus, yaba-like disease virus, as well as the swinepox and deerpox viruses (94). The primary sequences of these proteins share no similarity with TNFRs or Crm family proteins but rather appear to be distantly related to MHC class I heavy chains. The binding of TNF by 2L proteins leads to the disruption of both TNFR1 and TNFR2 engagement by the cytokine and potentially blocks TNF-induced cytotoxicity. Akin to the previously described Crm decoys, most members of the 2L family of proteins display promiscuity in ligand binding with tight association reported for human, monkey, and even canine TNF α . The only exception is the 2L protein from swinepox, which seems to have strict species specificity for porcine TNF α . However, the 2L family as a whole is apparently specific for TNF α , with no reported activity against LT α or other TNF family ligands (94).

In 2009, Yang *et al.* (95) reported the structure of 2L encoded by yaba-like disease virus in complex with human TNF α , revealing that the decoy receptor does indeed adopt an MHC class-I like fold. 2L shares only 15% sequence conservation with the extracellular domains of MHC class I but exhibits remarkable structural similarity (Fig. 3). The α 1 and α 2 domains form the canonical platform domain flanked by two anti-parallel helices, with the helices packed closely together precluding a ligand binding groove as seen in antigen presenting MHC proteins. The disulfide bonds linking the α 2-domain helix with the beta-platform are conserved, as is linkage between the two sheets of the α 3 immunoglobulin-like constant domain. Unlike classical and many non-classical MHC class I proteins, 2L does not associate with β 2m. Instead, the α 3-domain is repositioned to make extensive contacts under the platform domain, many coming from a 32-residue insertion uniquely located in the CD-loop of the 2L α 3-domain. All three 2L domains contribute to TNF binding, which is associated with greater than 2000 Å² of buried surface area. The decoy receptor binds across the shallow groove between adjacent TNF subunits, burying the D-E and A-A' loops that are critical for the cytokine to engage TNFR1 and TNFR2 receptors, and also engages several residues located outside of the binding footprint of the signaling receptors. Although the 2L/TNF α complex crystallized with three decoy receptors associated around one TNF trimer, the physiologic stoichiometry necessary for functional inhibition is not currently known. Regardless, the positioning of 2L in the complex suggests that a single binding event would be sufficient to effectively disrupt the trimeric assembly of TNFRs necessary for signal transduction. This new spin on inhibiting TNF-induced inflammation holds interesting opportunities for decoy receptor-based therapeutics, as the similarity of 2L to host MHC proteins may provide an excellent platform to enable the engineering of agents with minimal immunogenicity.

Poxvirus-encoded decoy receptors for CD30L

CD30 is a member of the TNFR superfamily and is expressed primarily on activated T and B cells as well as resting CD8⁺ T cells (96). The ligand for CD30 is CD153 (CD30L), a member of the TNF ligand superfamily that is predominantly found as an uncleaved type-II

transmembrane protein (97). The interaction of CD30 with its ligand appears to induce TRAF-mediated signaling to induce T-cell proliferation and Th1-like responses, such as increased IFN γ production. Moreover, upon binding to its receptor, CD30L appears able to reverse signal to induce cell proliferation in neutrophils, B cells, and activated T cells and macrophages. In 2002, Panus *et al.* (98) reported that cowpox encodes an 89 residue secreted protein with greater than 50% sequence similarity to the ligand-binding CRDs of CD30, and that this viral CD30 (vCD30) specifically binds to the surface of cells expressing either mouse or human CD30L. Saraiva *et al.* (99) reported that ectromelia encodes a highly related decoy receptor that can block binding of CD30L to host cell surface receptors and can also induce reverse signaling through binding to cell surface CD30L, as assessed by IL-8 production levels. Further characterization of ectromelia vCD30 was investigated in a mouse pulmonary granuloma model, where addition of vCD30 decreased granuloma size by >80% and led to decreased levels of IFN γ production. Despite significant effects in this mouse model of inflammation, ectromelia virus lacking vCD30 showed no impairment in disease lethality or mortality (100). It remains to be seen whether CD30 or additional TNFR family decoys will be found in other viral genomes.

IL-1 family decoy receptors

The IL-1 superfamily of cytokines is an important mediator of inflammation in response to pathogens. Initially discovered in the early 1980s, this family is currently comprised of 11 members including IL-18 and IL-1 β (101). Both of these cytokines adopt a β -trefoil fold and are produced as pro-forms lacking any conventional secretion leader peptides. These cytokines are released in response to the activation of Toll-like and Nod-like receptors that drives the activation of caspase-1, the protease that cleaves the pro-forms of IL-18 and IL-1 β allowing for their secretion through poorly understood mechanisms. Binding of the mature forms of IL-18 and IL-1 β to their respective receptors leads to a multitude of pro-inflammatory effects, including the initiation of IFN γ production, and activation of B, T, and NK cells (102).

IL-1 cytokines are regulated at multiple levels including transcription, pro-form cleavage, and secretion. In addition, extracellular mechanisms of regulation exist for both IL-1 β and IL-18. For IL-1 β , secreted forms of an antagonist ligand (IL-1RA), as well as an inhibitory receptor that cannot signal (IL-1R2), are used to dampen inflammation. For IL-18 there is a secreted host decoy receptor (IL-18bp) that acts as a negative regulator, sequestering IL-18 and preventing recognition by the signaling receptor (103, 104). The numerous levels of regulation of these cytokines illustrate the potency they have in the initiation and maintenance of a pro-inflammatory state. Dysregulation or dysfunction within this system is associated with a number of diseases, including but not limited to multiple sclerosis, arthritis, psoriasis, gout, and inflammatory bowel disease (105–107).

IL-1 family cytokines play an important role in host defense against pathogens, and, not surprisingly, viruses have evolved strategies to inhibit their effects (5). For example, poxviruses encode CrmA, a serpin-like protease inhibitor that blocks the processing of IL-1 β and IL-18 by caspase-1, as well as plethora of proteins that are structurally related to bcl-2 that appear to modulate NF κ B signaling rather than apoptosis (108, 109). Again, the focus of this review is on secreted viral decoy receptors that sabotage IL-1 family cytokines (Fig. 4).

Poxvirus-encoded IL-18 decoy receptors

A protein exhibiting 20–30% sequence similarity to human IL-18bp has been identified in the genome of many different poxviruses ranging from molluscipox, to orthopox, to yatapoxviruses (5, 110). These viral IL-18 binding proteins (vIL-18bp) can effectively

inhibit both human and mouse IL-18 and lead to decreased levels of IFN γ produced in response to viral infection (111). The ectromelia virus-encoded decoy binds human and murine IL-18 with ~ 10 nM and ~ 1 nM affinity, respectively, parameters similar to those observed for the binding of these cytokines to human IL-18bp, and 5–10 fold higher than observed for host IL-18 signaling receptor binding (111–114). Consistent with these findings, murine infection with ectromelia virus containing a disrupted vIL-18bp led to increased IFN γ production and decreased viremia in the liver relative to wild-type virus (113). Future studies will no doubt continue to investigate whether these decoy receptors are useful in ameliorating IL-18 inflammatory disorders (115, 116).

In 2008, Krumm *et al.* (117) reported the crystal structure of human IL-18 in complex with the ectromelia decoy receptor. vIL-18bp is composed of a single h-type Ig-domain with two, four-stranded β sheets linked by two disulfide bonds and a network of hydrophobic interactions between the sheets. vIL-18bp binds the cytokine on one edge of its β -sandwich, engaging three surface cavities and burying ~ 1930 Å² of surface area. Analysis of the binding interface reveals that many of the key binding residues that vIL-18bp uses to engage its ligand are conserved among the viral and mammalian IL-18bps. Interestingly, the sequence of this single Ig domain does not bear significant similarity with any of the three Ig domains of the signaling IL-18 receptor encoded by mammals, which are thought to bind ligand in an analogous fashion as IL-1R binds IL-1 β (118) (Fig. 4). Comparison amongst the structures as well as mutational analysis indicate that a cluster of IL-18 residues engaged by the viral decoy receptor is also important for IL-18R binding, suggesting that the vIL-18bps operate through a mechanism of competitive inhibition.

Poxvirus-encoded IL-1 β decoy receptors

Most species of orthopoxviruses encode for a soluble IL-1 β receptor (IL-1 β R). Two proteins predicted to be structurally related to IL-1R based on sequence similarity were originally identified from the vaccinia virus genome in the early 1990s (119). Following that study, one of the proteins, B15R was shown to bind and inhibit IL-1 β , while the other was shown to have evolved into a Type I IFN binding protein. IL-1 β has a significant role in inducing inflammation and activating both the innate and adaptive immune responses following viral infection. IL-1 β has been shown to be the major endogenous pyrogen during the course of poxviral infection. Vaccinia virus with a vIL-1 β R (B15R) knockout demonstrated that B15R functions to suppress the febrile response (120). However, the B15R knockout virus shows an increased mortality and more rapid appearance of illness in mice when infected intranasally, suggesting that B15R may actually serve to attenuate disease symptoms (24). This may help increase the time this virus has in the host to replicate and spread.

Three crystal structures of host IL-1R1 complexes have been solved. Two of the complexes are with the naturally occurring ligands IL-1 β and the inhibitory ligand IL-1 receptor agonist (IL-1RA), while the third complex is that of IL-1R with a small antagonist peptide called AF10847 (121–123). Illustrated in Fig. 4, the structure of IL-1R, published in 1997 by Vigers *et al.* (121), confirmed the three-Ig domain topology of this receptor that wraps around its β -trefoil folded ligand resembling a horseshoe around a stake. Comparison of all three structures pointed to a functional hinge between the second and third Ig domain allowing for a 20 degree rotation inwards from the IL-1RA-bound structure to the IL-1 β -bound structure, and another 70 degree rotation inwards, as well as a 170 degree twisting motion between the IL-1 β -bound structure and the IL-1R/AF10847 complex (121–123). The viral IL-1 β decoy receptors share approximately 23% sequence identity and 59% sequence similarity with human IL-1R1 and are predicted to be very structurally similar (124) (Fig. 4). In contrast to host IL-1R1 that effectively binds IL-1 α , IL-1 β , and IL-1RA, the viral decoys have only been shown to engage IL-1 β with high affinity (24, 125). No structure of a viral IL-1 β decoy has yet been published and it will be interesting to see any structural

differences between the viral decoys and the host receptors and how that may relate to the ligand specificity.

Interference of interferons

Interferons (IFNs) were first identified in 1957 by Isaacs and Lindenmann (126) as potent antiviral agents. They are now known to play a crucial role in linking the innate and adaptive arms of immunity (127–129). Since their discovery, the biological functions ascribed to IFNs have expanded to include the modulation of inflammatory processes to anticancer activities, among other processes. There are three types of IFNs. Type I IFNs include IFN α , IFN β , IFN δ , IFN ϵ , IFN κ , IFN τ , and IFN ω , with IFN α having multiple subtypes in humans. Type-I IFNs are expressed by most cell types and upon secretion, can act in both autocrine and paracrine fashions. Upon viral infection, the first two Type-I IFNs to be produced are IFN β and IFN α , which are able to induce the further production of type-I IFNs in a positive feedback fashion (130). All Type I IFNs signal through the heterodimeric receptor composed of IFNAR1 and IFNAR2, which are expressed ubiquitously on cells and are comprised of four and two fibronectin-III domains, respectively, in their extracellular regions (131, 132). Signaling through IFNAR1/2 activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and results in the upregulation of hundreds of IFN-stimulated genes to evoke a potent antiviral state. Some of the many effects of IFN signaling include upregulation of dsRNA-activated protein kinase (PKR), and increased MHC class I and Fc γ receptor expression (133, 134).

IFN γ is the sole member of the Type II IFN family and signals through a heterodimeric receptor composed of IFNGR1 and IFNGR2 expressed on most cell types. This signal transduction pathway activates the JAK/STAT pathway, followed by activation of γ -activating factor (GAF), which acts as a transcription factor for the γ -activation site (GAS) (135, 136). IFN γ also serves to increase MHC class I expression, but unlike Type I IFNs, IFN γ increases expression of MHC class II molecules as well, leading to activation of T-helper 1 (Th1) response targeting intracellular pathogens such as viruses (137).

Initially described in 2003, Type III IFNs are structurally distinct from Type I IFNs and signal via a different receptor pair composed of IL10R2 and IFN λ R1. While IL10R2 is shared among IL-10, IL-22, and IL-26, IFN λ R1 is unique to Type III IFNs. Both IL-10R2 and IFN λ R1 are comprised of two fibronectin domains (138–140). Despite sharing limited sequence identity, and utilizing a completely different heterodimeric receptor, the signaling outcomes of both Type I and Type III IFNs appear nearly identical (141). One of the main differences between Type I and Type III IFNs appears to be in regards to tissue specificity. The Type III IFN system seems to function mainly in epithelial cells and may contribute to viral immunity by protecting skin and mucosal surfaces (142, 143).

Poxvirus-encoded Type I IFN decoy receptors

Viruses, both large and small, target signaling pathways and effectors of Type-I IFNs within infected cells. Poxviruses, with their comparatively large genomes, can accommodate an arsenal of intracellular inhibitors, as well as decoy receptors specific for Type-I IFNs (IFN1bps) that are secreted by infected cells and can also bind back to the surface of cells (5, 144, 145). IFN1bps have been identified in many orthopoxviruses including vaccinia, ectromelia, variola, buffalopox, camelpox, and cowpox, as well as in yaba-like disease virus, a member of the yatapox family (5). Amongst the orthopoxviruses, IFN1bps share upwards of 90% sequence identity. Based on their sequences, it is predicted that the IFN1bps contain three Ig domains (Fig. 5).

Several studies have demonstrated the ability of both the vaccinia decoy (B18R) and the ectromelia decoy (EVM166) to functionally inhibit the antiviral effects of Type-I IFNs. These proteins are capable of blocking diverse Type-I IFNs from several species including human, mouse, rat, cow, and rabbit (27, 146). Interestingly, while both proteins can block human and murine IFN α as well as a human IFN β , neither can efficiently inhibit murine IFN β (143). Regardless, the ability of these decoys to inhibit IFNs across a relatively wide species range is impressive, as host Type-I IFN receptors bind their ligands in a species-restricted manner. Functional studies of Colamonici *et al.* (147) showed that B18R prevents the Type-I IFN dependent activation of IFN-stimulated genes. Alcamí *et al.* further demonstrated that addition of B18R to HeLa cells blocked IFN-dependent JAK1 phosphorylation. Consistently, deletion of IFN1bps from either the vaccinia or ectromelia genome resulted in decreased virulence in mouse models of infection (148). These IFN1bps have also been reported to be a significant target of the humoral immune response during ectromelia infection. Indeed, EVM166 immunization was protective against a lethal challenge of wild-type EV.

Yatapoxvirus-encoded IFN λ decoy receptor

While the roles of Type I and Type II IFNs in the context of viral infection are very clear, Type III IFNs are somewhat new on the antiviral scene. While it appears that the signaling events following engagement of the receptors to IFN λ are very similar to those of Type I IFNs, there are a few main differences to note. While most cells can produce both Type I and Type III IFNs, only certain cell types can respond to Type III IFNs. Epithelial cells and plasmacytoid dendritic cells appear to exclusively express the IL10R2 and IL28R1 heterodimeric receptors, and thus it appears that IFN λ function is more directed toward protecting the body's first line of defense, the epithelia. One other difference is that Type III IFNs appear to be much less potent than Type I IFNs in assays testing the antiviral and anti-proliferative potency of these cytokines (149).

Type III IFNs can contribute significant antiviral effects in epithelial cells and may also be important antiviral mediators in the context of poxvirus infections (150, 151). In 2007, Huang *et al.* (152) showed that a yaba-like disease virus decoy (Y136) can inhibit human Type III IFNs in addition to Type I IFNs. Illustrated in Fig. 5, Y136 is likely to be comprised of three Ig domains, similar to the orthopox IFN1bps that are incapable of disrupting IFN λ -mediated signals. The difference in cytokine targeting between these two proteins may point to differences between orthopoxviruses and yatapoxviruses as far as cell types that are affected. Orthopoxviruses are spread via inhaled respiratory secretions into the upper respiratory tract where the virus infects the mucous membranes, then spreads to the regional lymph nodes, liver, and spleen. After a period of latency the infection then spreads to the dermal layer of the skin. Yatapoxviruses, however, are transmitted by arthropod vectors, and infection stays in the epithelium for the duration of the disease (22, 153). The IFN binding proteins from yatapox may have been under more environmental pressure in the epithelium to develop a method for inhibiting Type III IFNs.

Poxvirus-encoded IFN γ decoy receptors

While many viruses target intracellular signaling components related to IFN γ signaling, such as the inhibition of the JAK/STAT pathway, poxviruses alone are known to encode for secreted IFN γ decoy receptors (5) (Fig. 5). These secreted proteins display anywhere from 20–25% sequence similarity with the extracellular region of host IFN γ Rs. They are comprised of two fibronectin type III domains and include a novel C-terminal 60 amino acids (155, 156). Orthopoxviral IFN γ decoys display broad species recognition and inhibition for IFN γ (25, 160, 161). In contrast, the decoy encoded by myxoma virus (M-T7) exhibits a strict species specificity for rabbit IFN γ (157). This is similar to mammalian IFN γ receptors which display a high degree of species specificity when engaging their

ligand (158, 159). The importance of the ectromelia IFN γ decoy receptor in immune evasion is supported by experiments with the knockout virus, where mice that normally succumb to viral infection have much higher survival rates (154).

In 2008, Nuara *et al.* (155) reported the structure of ectromelia IFN γ bp in complex with human IFN γ at 2.2 Å resolution. As can be seen in Fig. 5, the crystal structure reveals four IFN γ bps chains bound to two IFN γ dimers. The novel C-terminal region, which turned out to be critical for tetramerization of the decoy, forms a helix-turn-helix (HTH) motif that is structurally related to the TFII transcription factor from yeast. Mutational and functional studies support that IFN γ BP tetramers are required for efficient IFN γ inhibition (155). The binding interface between IFN γ and the viral decoy receptor shares a number of features with the complex formed with human IFN γ 1, but also reveals a number of novel contacts (162) (Fig. 5). The vIFN γ bp made extensive contacts using six different receptor loops that bound to IFN γ on the A, B, and F helices as well as on the AB loop. However, in contrast to data that indicates the host receptors do not make significant and high affinity contacts with the unstructured C-terminal tail of IFN γ , the vIFN γ bp made extensive contacts with this region (162–165). The decoy receptor engagement of the IFN γ C-terminal region accounts for almost half of the buried surface area in the complex. One other significant difference to note is that the vIFN γ bp makes less contacts on the IFN γ helices and more importantly less on the AB loop. The AB loop has been shown by mutagenesis to be very important in regards to species specificity of receptors to the IFN γ cytokine (166). It appears from this crystal structure that the species promiscuity of these viral decoys may be related to the sacrifice of contacts in the AB loop region, and potentially the gain of contacts in the C-terminal region of IFN γ .

Concluding remarks and perspective

As we continue to learn more about the immune evasion tactics of viruses, particularly in regards to secreted viral decoys, doors are being opened to the vast possibilities of creating safer vaccines, as well as to the potential for virally derived therapeutics for the treatment of inflammatory disorders. Many of the hurdles in engineering an efficient drug-affinity maturation, specificity, and competition with endogenous receptors have already been overcome by these secreted viral proteins. More and more viral immunomodulatory decoys are being tested for their pharmacological potential, ranging from immune disorders such as arthritis, to the treatment of allergies. Viral CKBPs have been investigated in the treatment of allergic airway hyperreactivity, inflammatory responses in allograft and xenograft transplantation, and intimal hyperplasia, which is a serious consequence of vascular injury and a primary reason for late bypass graft failure (42–44, 167). The viral TNFR/chemokine binding protein from ectromelia virus, CrmD, has been found to be effective in the abatement of inflammation in a murine model of Crohn's disease (168). Exploitation of viruses for uses in human therapy is an emerging trend in this field.

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Fig. 1. Viral decoy receptor inhibition of chemokines

Herpesviruses and poxviruses encode chemokine binding proteins (vCKBPs) that sequester chemokines and block their biological function. vCCI and Evm1 block chemokine-receptor interactions. A41, E163, and the SECRET domain inhibit the ability of chemokines to interact with cell surface GAGs. M3 blocks both. EHV/BHV gG blocks both receptor and GAG interactions. HSV gG blocks GAG interactions. pUL21.5 blocks hCCL5 receptor interaction. The structures of viral CKBPs are shown in ribbon, while the chemokines structures are represented by molecular surface. The proteins whose structures are not known are shown as cartoons. Molecular surface of chemokines colored in shades of red have been solved in complex with the viral protein while chemokines in neutral shade have been modeled in for illustration purposes. PDB codes for the structures are as follows: M3-hCCL2 complex (2NZI), GAG (1HPN), vCCI-hCCL4 (2FFK), SECRET-hCX3CL1 (3ONA), Evm1 (2GRK), and A41 (2VGA).

Fig. 2. Structural mimicry of chemokine receptor and GAG interactions by viral decoys
 (A) Herpesvirus M3 engages both receptor binding and GAG binding epitopes on hCCL2 or hXCL1 chemokines. (B) The NMR solution structure of vCCI in complex with hCCL4 outlines the overlap between the vCCI chemokine binding site and the receptor interaction region. (C) The footprint of the SECRET domain of poxviral protein CrmD on hCX3CL1 points to inhibition of chemokine-GAG interactions as the likely mechanism for chemokine inhibition. The SECRET domain contacts this chemokine using the opposite face, or β sheet I instead of β sheet II, which is utilized by all other characterized vCKBPs. PDB codes for the structures are as follows: M3-hCCL2 (2NZI), M-hXCL1 (2NYZ), vC-hCCL4 (2FFK), SECRET-hCX3CL1 (3ONA).

Fig. 3. Viral decoy receptor inhibition of TNF

Poxviruses encode multiple proteins that inhibit TNF. Orthopoxviruses and leporipoxviruses encode for vTNFRs that resemble the extracellular domain of host TNFRs. Yatapoxviruses encode for a TNFbp that resembles MHC class I heavy chain. The 2L, CrmC, and CrmE decoys are specific TNF α inhibitors, while CrmB and CrmD are able to inhibit both TNF α as well as LT α . vCD30 inhibits receptor binding to CD30L and signals through CD30L. Inhibition of TNF cytokines blocks downstream signaling cascades. For each component of this figure, structures that are known are represented by a ribbon (receptors), or surface representation (cytokines) of the solved structure, while molecules whose structures are still unknown are represented by a cartoon illustration. PDB codes for the structures are as follows: TNFR2-TNF α , TNFR1-LT α (1TNR), TNF α (2TNF), 2L-TNF α (3IT8), CrmE (2UWI), CrmD SECRET (3ON9).

Fig. 4. Viral decoy receptor inhibition of the IL-1 family

Poxviruses encode many proteins to inhibit members of the IL-1 family of cytokines, specifically IL-1 β and IL-18. In the extracellular milieu, viral IL-1 β R and viral IL-18bp prevent cytokine recognition by their respective host receptors. Inhibition of the IL-1 family interferes with IFN γ secretion and thus activation of NK, T, and B cells. For each component of this figure, structures that are known are represented by a ribbon (receptors), or surface representation of the solved structure (cytokines), while molecules whose structures are still unknown are represented by a cartoon illustration. IL-1RacP has been separately modeled in next to IL-1R1 and IL-1R2 for better viewing. PDB codes for the structures are as follows: IL-1 β (1ITB), IL-1R2-IL-1 β (3O4O), IL-1R1 signaling complex (4DEP), IL-1RA (1ILR), and vIL-18bp-IL-18 (3F62).

Fig. 5. Viral decoy receptor inhibition of IFNs

Poxviruses encode for secreted IFNbps that bind to Type I, II, or III IFNs and prevent recognition by host receptors. Inhibition of IFNs prevents activation of the JAK/STAT pathway and thus the establishment of an antiviral state. Yaba136 has been shown to inhibit both Type I and Type III IFNs, while vIFNα/βbps such as B18R or EVM166 have been shown to inhibit only Type I IFNs. Additionally, the vIFNα/βbp is positioned near the cell surface, as these proteins have been shown to bind to the surface of cells. For each component of this figure, structures that are known are represented by a ribbon (receptors), or surface representation of the solved structure (cytokines), while molecules whose structures are still unknown are represented by a cartoon illustration. PDB codes for the structures are as follows: IFNλR1-IFNλ (3OG6), IL-10R2 (3O4O), IFNAR1/2-IFNα2 (3SE3), IFNγR1-IFNγ (1FG9), and vIFNγbp:IFNγ complex.