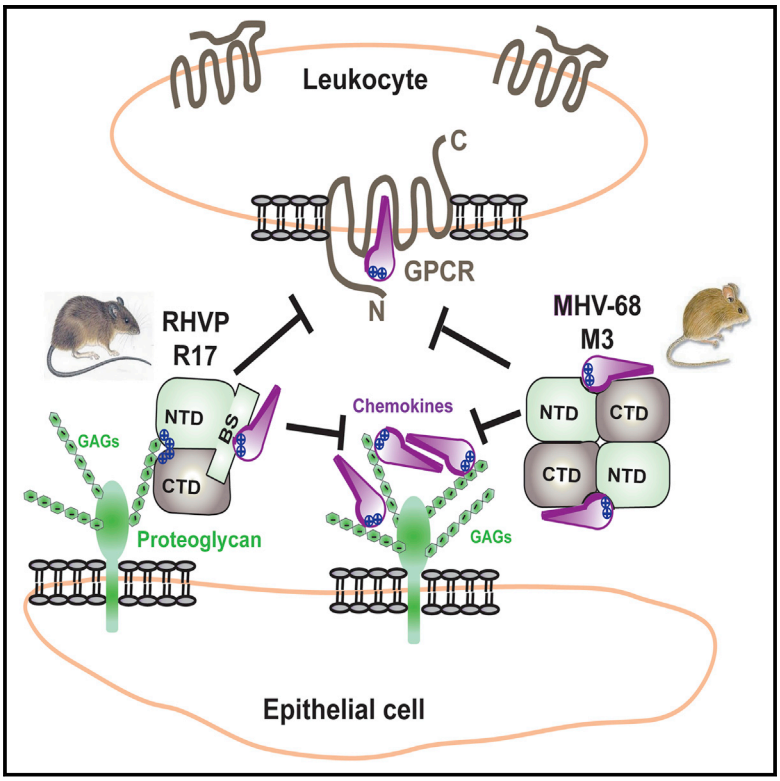
Article

Structure

Parallel Evolution of Chemokine Binding by Structurally Related Herpesvirus Decoy Receptors

Graphical Abstract



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In Brief

Lubman and Fremont describe the atomic structure of the herpesvirus-encoded chemokine binding protein R17 alone and in complex with a high-affinity ligand, CCL3. The study offers novel insights into the conserved and unique mechanisms that different pathogens use to undermine host chemokine signaling networks.

Highlights

- Crystal structures of RHVP R17 alone and in complex with CCL3 have been determined
- R17 is similar to MHV-68 M3 although the location of chemokine binding is distinct
- Chemokine residues that stabilize R17 complexes have been mapped by mutagenesis
- Pathogen decoys mimic GPCRs in engagement of invariant chemokine determinants

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Parallel Evolution of Chemokine Binding by Structurally Related Herpesvirus Decoy Receptors

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SUMMARY

A wide variety of pathogens targets chemokine signaling networks in order to disrupt host immune surveillance and defense. Here, we report a structural and mutational analysis of rodent herpesvirus Peru encoded R17, a potent chemokine inhibitor that sequesters CC and C chemokines with high affinity. R17 consists of a pair of β-sandwich domains linked together by a bridging sheet, which form an acidic binding cleft for the chemokine CCL3 on the opposite face of a basic surface cluster that binds glycosaminoglycans. R17 promiscuously engages chemokines primarily through the same N-loop determinants used for host receptor recognition while residues located in the chemokine 40s loop drive kinetically stable complex formation. The core fold adopted by R17 is unexpectedly similar to that of the M3 chemokine decoy receptor encoded by MHV-68, although, strikingly, neither the location of ligand engagement nor the stoichiometry of binding is conserved, suggesting that their functions evolved independently.

INTRODUCTION

Chemokines are a group of small cytokines that orchestrate host defense against microorganisms in vertebrates (Esche et al., 2005; Gerard and Rollins, 2001). Pro-inflammatory chemokines play an essential role in the clearance of a broad array of pathogens through the recruitment of effector leukocytes (Luster, 1998). Chemokines establish gradients through specific interactions with glycosaminoglycans (GAGs), and direct target cell migration and activation by binding to G-protein-coupled chemokine receptors (Allen et al., 2007; Handel et al., 2005). Chemokine networks are characterized by ligand-receptor promiscuity, antagonistically acting ligands, and non-signaling decoy receptors (Allen et al., 2007; Fernandez and Lolis, 2002; Handel and Lau, 2004). All chemokines adopt a similar fold consisting of an extended N terminus followed by a long flexible loop (N loop), a three-stranded β sheet, and a C-terminal α helix (Fernandez and Lolis, 2002). The structural determinants of chemokine G-protein-coupled receptor (GPCR) recognition have recently been illuminated by studies of CXCR4 in complex with a herpesvirus-encoded chemokine and CX3CL1 in complex with a herpesvirus-encoded chemokine receptor (Burg et al., 2015; Qin et al., 2015). Receptor activation is thought to occur in several steps whereby initial binding of the chemokine N loop causes conformational changes in the receptor, allowing the N-terminal residues of the chemokine to insert between transmembrane helices of the GPCR (Kufareva et al., 2015).

Pathogens undermine host chemokine signaling networks using a number of different strategies. Large DNA viruses, such as herpes- and poxviruses, encode versions of chemokines, chemokine receptors, and unique soluble chemokine binding proteins capable of sequestering host chemokines with distinct specificity (Alcami, 2003; Alcami and Lira, 2010; Epperson et al., 2012). The first secreted chemokine decoy receptor was discovered in orthopoxviruses, and it is now established that a wide array of chemokine binding proteins are encoded by poxviruses (Patel et al., 1990; Smith et al., 1997). Unique chemokine binding proteins had been identified in all three subfamilies of herpesviruses, with perhaps the best characterized being M3 encoded by mouse gammaherpesvirus 68 (MHV-68) (Heidarieh et al., 2015). Bloodsucking ticks and the helminth parasite *Schistosoma mansoni* have also been shown to produce chemokine binding proteins (Deruaz et al., 2008; Smith et al., 2005).

We recently discovered a novel chemokine decoy receptor encoded by rodent herpesvirus Peru (RHVP) (Lubman et al., 2014). RHVP is a gammaherpesvirus (rhadinovirus)-related to MHV-68 (Stevenson and Efstathiou, 2005) and Kaposi's sarcoma-associated herpesvirus (Lee et al., 2015) that establishes acute and latent infection in laboratory mice with overt pathology evident only in immunocompromised animals (Loh et al., 2011). We demonstrated that R17 binds all human and murine CC and C chemokines tested (mCCL2 and hCCL2; mCCL3 and hCCL3; mCCL4, mCCL5, and hCCL5; mCCL8, mCCL11, mCCL20, mCCL24, mCCL19, mCCL12, and mXCL1) but not any of the CXC or CX3C chemokines (mCXCL8, mCXCL10, mCXCL9, mCXCL2, mCXCL12, mCXCL1, and CX3C). Functionally, recombinant R17 potently inhibits CCL3-driven chemotaxis of human peripheral blood mononuclear cells (PBMCs) and CCL2-driven transmigration of human THP-1 monocytes