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Immune modulation by virus-encoded chemokine binding proteins

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ABSTRACT

Chemokines are chemoattractant cytokines that mediate the migration of immune cells to sites of infection playing an important role in innate and adaptive immunity. As an immune evasion strategy, large DNA viruses (herpesviruses and poxviruses) encode soluble chemokine binding proteins that bind chemokines with high affinity, even though they do not show sequence similarity to cellular chemokine receptors. This review summarizes the different secreted viral chemokine binding proteins described to date, with special emphasis on the diverse mechanisms of action they exhibit to interfere with chemokine function and their specific contribution to virus pathogenesis.

1. Introduction

Q2 Viral infection stimulates the production of cytokines and chemokines that trigger an immune response that can eliminate the invading virus. Interferons (IFNs) and tumor necrosis factor (TNF) are cytokines that induce anti-viral states or apoptosis within the innate immune response (Biron, 2001; Guidotti and Chisari, 2000). Chemokines are chemotactic cytokines that play a crucial role in inducing the migration of immune cells to areas of infection (Baggiolini, 1998). They are classified into four classes: C, CC, CXC and CX3C chemokines according to the position of the N-terminal cysteine residue(s) (Zlotnik and Yoshie, 2000). Chemokines are secreted from the cell and immobilized on the cell surface through their interaction with glycosaminoglycans (GAGs) and establish a concentration gradient that is important to direct leukocytes to sites of infection (Handel et al., 2005; Johnson et al., 2005). Immune cells are activated through specific high affinity interactions between chemokines and the G-protein coupled receptors (GPCRs) (Blanpain et al., 2003; Proudfoot, 2002; Zlotnik et al., 2006) (Fig. 1A). The three-dimensional fold of all monomeric chemokines is conserved. The N-loop is followed by a 3_{10} helix, the three β-strands form a β-pleated sheet and these are connected by the 30's and 40's loops. The 50's loop connects the last secondary structural, a C-terminal α-helix (Fernandez and Lolis, 2002) (Fig. 2A). Chemokines interact with GPCRs and GAGs through distinct binding sites that may overlap.

Poxviruses and herpesviruses are large DNA viruses that dedicate a great part of their genetic information to escape and modulate the host immune response (Finlay and McFadden, 2006; Seet et al., 2003a). Variola virus (VARV), a member of the poxvirus family, was the causative agent of smallpox, one of the most virulent human diseases (Smith and McFadden, 2002), and vaccinia virus (VACV) is the vaccine used to eradicate smallpox by 1980. Ectromelia virus (ECTV) causes a smallpox-like disease in mice, cowpox virus (CPXV) is a rodent virus of broad host range that causes sporadic infections in other mammals, and myxoma virus (MYXV) causes myxomatosis in rabbits. Animal infections with VACV, ECTV, CPXV and MYXV are used as models to study poxvirus pathogenesis and their interaction with the immune system. The herpesvirus family includes important human pathogens such as herpes simplex virus (HSV), varicella zoster virus or cytomegalovirus.

Poxviruses and herpesviruses have evolved a variety of mechanisms to evade their destruction by the host immune system. One of

Abbreviations: CKBP, chemokine binding protein; CPXV, cowpox virus; Crm, cytokine response modifier; ECTV, ectromelia virus; GAGs, glycosaminoglycans; GPCR, G-protein coupled receptor; HSV, herpes simplex virus; IFN, interferon; IFNγ-R, interferon gamma receptor; MHV-68, murine gammaherpesvirus 68; MYXV, myxoma virus; ORFV, orf virus; SCP, secret domain containing protein; gG, glycoprotein G; SgG, secreted portion of gG protein; SECRET, smallpox virus encoded chemokine receptor; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; VACV, vaccinia virus; VARV, variola virus; WR, strain western reserve.

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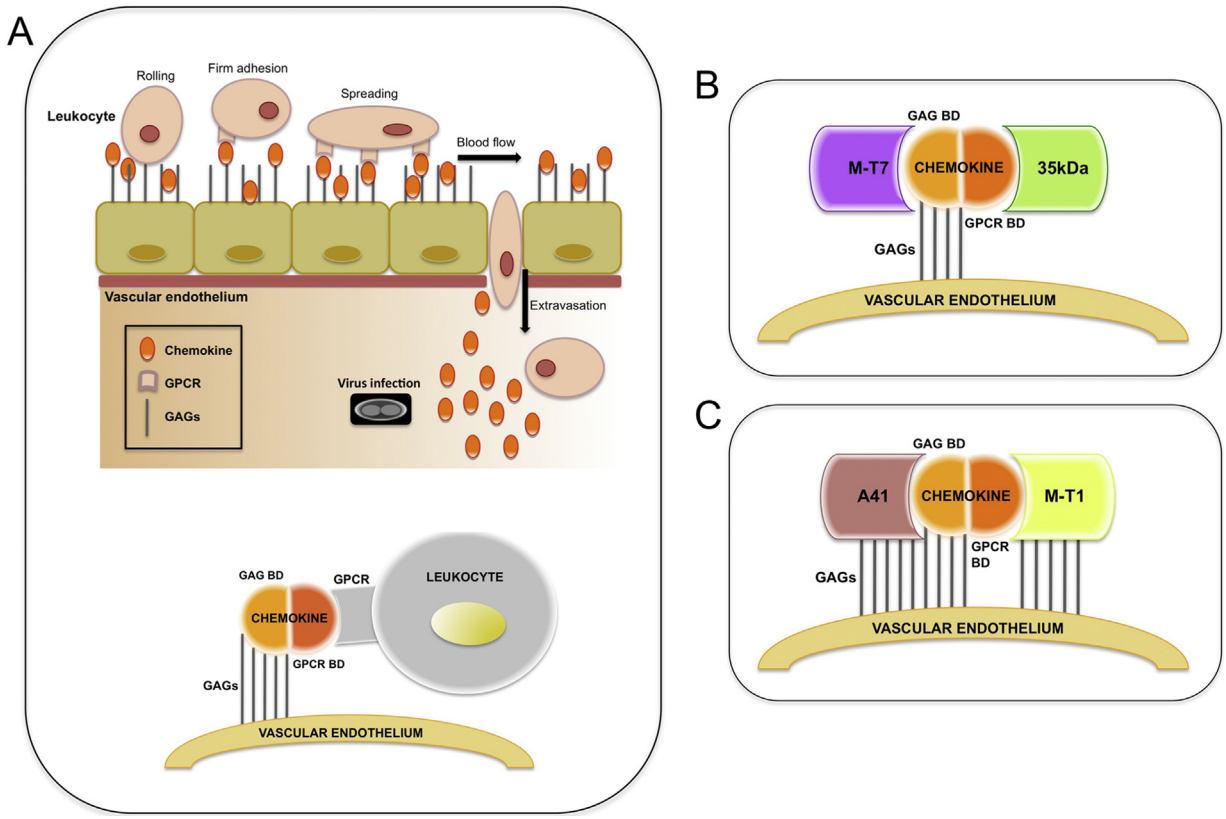

Fig. 1. Different mechanisms of interaction between viral CKBPs and chemokines. (A) Leukocytes are recruited into the inflamed tissue through the interaction of chemokines presented on the surface of GAGs. First, leukocytes roll on the endothelial surface trough low affinity interactions. The high affinity interaction between chemokines and GPCRs on leukocyte triggers the extravasation of the cell to sites of infection. (B) Virus-encoded CKBPs may bind the chemokines through their GAG binding domain (GAG BD) or their GPCR binding domain (GPCR BD), (C) viral CKBPs may simultaneously interact with GAGs to anchor the CKBP to the cell surface.

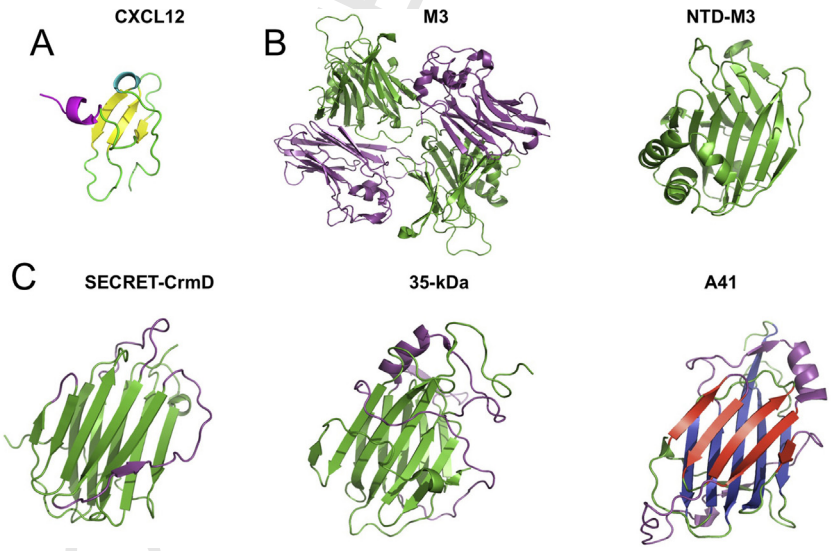

Fig. 2. Structure of CKBPs. (A) Structure of the CXCL12 chemokine (PDB: 1A15) (Dealwis et al., 1998). The three antiparallel β-strands are diagrammed in yellow, the single turn of a 3_{10} helix is represented in blue and the C-terminal α-helix is represented in magenta. (B) Structure of the M3 protein (PDB: 1MKF). The C-terminal domain is represented in magenta and the N-terminal domain (NTD) is represented in green. (C) Structure of the SECRET domain of CrmD (PDB: 3ON9), the 35-kDa (PDB: 1CQ3) and A41 (PDB: 2VGA) CKBPs. The three proteins share the same β-sandwich structure topology but have different connecting loops that are represented in magenta. The β-sheet II and the β-sheet I are represented in red and in blue, respectively, in the A41 protein. All the structures were created using Open-Source PyMOL (http://pymol.org/).

these strategies is the expression of proteins that interfere and modulate the chemokine system, including viral chemokine homologues, viral chemokine receptor homologues and viral chemokine binding proteins (CKBPs) (Alcami, 2003; Alcami and Koszinowski, 2000). CKBPs are secreted proteins with no sequence similarity to their cellular counterparts and can interrupt the chemokine function *via* distinct mechanism of action, abrogating the formation of the chemokine gradient or the interaction between chemokines and their specific cellular receptor (Fig. 1B and C). CKBPs have been found in non-viral pathogens such as the trematode

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