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Review

Viral regulators of complement activation: Structure, function and evolution☆

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ABSTRACT

The complement system surveillance in the host is effective in controlling viral propagation. Consequently, to subvert this effector mechanism, viruses have developed a series of adaptations. One among these is encoding mimics of host regulators of complement activation (RCA) which help viruses to avoid being labeled as 'foreign' and protect them from complement-mediated neutralization and complement-enhanced antiviral adaptive immunity. In this review, we provide an overview on the structure, function and evolution of viral RCA proteins.

1. Introduction

Given that viruses are obligate intracellular parasites they are exposed to constant host-induced pressures, which drive adaptations (Paterson et al., 2010). On that account, viruses have developed mechanisms to subvert various key host immune barriers including the humoral and cellular responses (Alcami and Koszinowski, 2000) as well as the effector functions including the complement system (Pyaram et al., 2010b; Lambris et al., 2008; Rattan et al., 2013) and thus, are dubbed as "masterpieces of evolution" (Vossen et al., 2002).

It is often argued by immunologists that if viruses subvert a particular immune response, then that provides a stronger evidence of participation of that component in controlling these entities (Vance, 2010). This is clearly true for the complement system as studies performed for over three decades decisively demonstrated that complement annuls viruses by direct as well as indirect mechanisms. The direct mechanisms include neutralization by aggregation, opsonisation, lysis, and promotion of phagocytosis through complement receptors (Pyaram et al., 2010b), while the indirect mechanisms include boosting of the protective acquired immune responses. It is now also unambiguous that cross talks between the complement system and the acquired immunity result in boosting of the virus specific B cell (Carroll and Isenman, 2012) and T cell responses (Heeger and Kemper, 2012; Dunkelberger and Song, 2010).

Concerning counteradaptations for evading the host complement system, both DNA as well as RNA viruses have devised a series of strategies which include encoding structural and/or functional mimics of host complement regulatory proteins (Kotwal et al., 1990; Rosengard et al., 2002; Mullick et al., 2003a; Albrecht and Fleckenstein, 1992; Spiller et al., 2003a), acquisition of host complement regulatory proteins (Vanderplasschen et al., 1998; Amet et al., 2012; Saifuddin et al., 1995; Johnson et al., 2009),

Abbreviations: C4BPA, C4 binding protein-α chain; CCP, complement control protein; CFA, cofactor activity; CP, classical pathway; CPV IMP, cowpox inflammation modulatory protein; CR1, complement receptor 1; DAA, decay-acceleration activity; DAF, decay-acceleration factor; FH, factor H; FI, factor I; hRCA, human RCA; HSV gC, herpes simplex virus glycoprotein C; HVA, herpesvirus aeteles; HVS CCPH, herpesvirus saimiri complement control protein homolog; KAPOSICA, Kaposi's sarcoma-associated herpesvirus inhibitor of complement activation; KSHV, Kaposi's sarcoma-associated herpesvirus; LP, lectin pathway; MCP, membrane cofactor protein; MD, molecular dynamics; MOPICE, monkeypox inhibitor of complement enzymes; RCA, regulators of complement activation; RCP-1, rhesus rhadinovirus complement control protein-1; RRV, rhesus rhadinovirus; SPICE, smallpox inhibitor of complement enzymes; SPR, surface plasmon resonance; VCP, vaccinia virus complement control protein; γ-HV68, murine γ-herpesvirus 68.

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inhibition of complement synthesis (Mazumdar et al., 2012), upregulation of host complement regulatory proteins on the infected cells (Takemoto et al., 2007; Spiller et al., 1996) and use of complement receptors for cellular entry (Cattaneo, 2004). As expected, the mimics of complement regulatory proteins are found only in viruses with a larger coding capacity like poxviruses and herpesviruses. These viruses have been found to express homologs of the regulators of complement activation (RCA) (Mullick et al., 2003b) as well as non-RCA (CD59 (Albrecht et al., 1992; Bramley et al., 1997) and HSV gC (Friedman et al., 1984)) proteins. In the present review, we provide an overview on the structure, function and evolution of the virus-encoded RCA (vRCA) proteins.

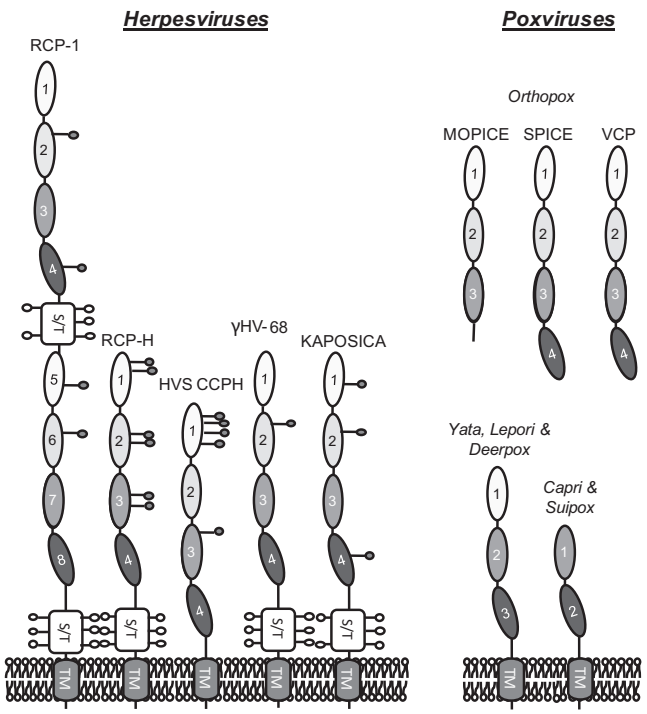
2. Structure of viral RCA (vRCA) proteins

2.1. Domain organization in vRCA proteins

Viral RCAs are the mimics of human RCA (hRCA) proteins and have essentially similar structure. Thus, like hRCAs, the viral regulators are solely composed of a single type of domains known as complement control protein (CCP) domains or sushi domains, which are linked together by short linkers of four amino acids. These CCP modules are composed of about 60 amino acids (Table 1) and are characterized by one invariant tryptophan and four invariant cysteines with the presence of some highly conserved glycines, prolines and hydrophobic residues (Supplementary Fig. 1). The NMR studies on vaccinia virus regulator VCP showed that like human CCP modules, the virus encoded CCP modules also contain 6–8 β-strands which are arranged in an antiparallel manner (Wiles et al., 1997). The general structure of the CCP domain consists of a central 4-stranded β-sheet, surrounded by two smaller 2-stranded β-sheets, but variations with missing strands are frequently observed. Further, the entire structure is stabilized by two disulphide bonds – Cys_I to Cys_{III} and Cys_{II} to Cys_{IV} – giving the domain β-barrel shape (Herbert et al., 2002). An appealing feature of the CCP domain is that the fold exposes most of its side chains to the solvent providing a relatively larger surface area compared to the proteins of the similar molecular weight.

The biochemical characterization of hRCA proteins has revealed that all the CCP modules do not impart complement regulatory activities to the RCA proteins and rather, a definite number, order and organization of CCP modules dictate the complement regulatory activities. Because viruses have limited genome size, it is anticipated that they encode only a small string of CCPs which are enough to impart regulatory properties. Consistent with this premise, and unlike hRCA proteins which are formed by 4–59 CCPs, virus-encoded RCA proteins are formed only by 2–8 CCPs (Fig. 1). In poxviruses, the RCA proteins are made of 2–4 CCPs. Viruses like vaccinia, variola and cowpox encode for 4 CCP-containing RCAs, while monkeypox encodes for a 3 CCP-containing RCA due to the presence of a premature stop codon in the fourth domain. The other poxviruses that encode for 3 CCP-containing regulators include yatapox, leporipox, and deerpox. Interestingly, some viruses like capripox and suipox encode for 2 CCP domain regulators. In herpesviruses, the RCAs show the presence of 4 or 8 CCP modules: viruses such as Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8), Herpesvirus saimiri (HVS), Herpesvirus aeteles (HVA), murine γ-herpesvirus 68 (γ-HV68), Rhesus rhadinovirus (RRV) isolate H26–95 and woodmouse herpes viruses (WoHV) encode 4 CCP containing RCA, while RRV isolate 17577 encodes an 8 CCP-containing RCA.

In vRCAs, the domain organization also varies owing to splicing of the gene; this however has been reported only for the herpesviral RCA genes. Studies on the RRV isolate 17577 transcripts show that it has two alternatively spliced transcripts in addition to the full-length mRNA, which encodes a protein with two sets of 4 CCP modules followed by a serine/threonine rich (S/T) region and a transmembrane (TM) region at the C-terminus. The larger spliced variant is composed of a truncated CCP1 followed by CCP modules 5–8 and S/T and TM regions, whereas the smaller variant encodes only for a truncated CCP1 along with a few residues of the C-terminus (Mark et al., 2007). Splicing of RCA gene has also been reported in case of KSHV and HVS but in these viruses, it does not result in variation in the number of CCP modules rather, it results in absence of S/T or TM regions (Albrecht and Fleckenstein, 1992; Spiller et al., 2003b).



vRCA	Decay-acceleration activity (DAA)		Cofactor activity (CFA)	
	AP DAA	CP DAA	C3b	C4b
RCP-1	+	+	+	+
RCP - H	+*	+	+	+
HVS-CCPH	+*	+	+	+
γ HV - 68	ND	ND	ND	ND
KAPOSICA	+*	+	+	+
MOPICE	-	-	+	+
SPICE	+*	+	+	+
VCP	+*	+	+	+
Yata, Lepori, Deerpox RCA	ND	ND	ND	ND
Capri,Suipox RCA	ND	ND	ND	ND

Fig. 1. Schematic representation of pox and herpes viral RCAs. The CCP domains of each regulator are numbered from N- to C-terminus, and serine/threonine rich region (S/T), trans-membrane (TM) region and glycosylation sites are marked. Black and white balloons represent N- and O-glycosylation sites, respectively. Homologous CCP domains are represented by the same shade. The table depicts the regulatory profile of the vRCAs. Abbreviations: RCP-1, rhesus rhadinovirus complement control protein-1; RCP-H, rhesus rhadinovirus complement control protein-H; HVS CCPH, herpesvirus saimiri complement control protein homolog; γ-HV68 RCA, murine γ-herpesvirus 68 regulator of complement activation; KAPOSICA, Kaposi's sarcoma-associated herpesvirus inhibitor of complement activation (also termed as KCP); MOPICE, monkeypox inhibitor of complement enzymes; SPICE, smallpox inhibitor of complement enzymes; VCP, vaccinia virus complement control protein; RCA, regulator of complement activation; AP-DAA, alternative pathway C3-convertase decay-acceleration activity; CP-DAA, classical pathway C3-convertase decay-acceleration activity; CFA, cofactor activity; *, weak activity; ND, not determined.