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New Member of the Multigene Family of Complement Control Proteins in Herpesvirus Saimiri

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A number of glycoproteins are regulators of the complement cascade and prevent damage to cells by inappropriate activation of complement. In humans, all of them are encoded by a multigene family on chromosome I and share a characteristic structural feature, the short consensus repeats of about 61 amino acids with a constant framework of cysteine, proline, and tryptophan. We found the gene for glycoproteins of analogous structure in herpesvirus saimiri, a T-lymphotropic tumor virus of New World primates. Unspliced transcripts code for a membrane-bound 65- to 75-kDa virion surface component, while spliced mRNA instructs a secreted glycoprotein of 47 to 53 kDa. Expression of complement control proteins suggests a novel mechanism of counteracting host immune defense to prevent elimination of a virus that is capable of persisting in circulating lymphocytes.

A group of lymphotropic herpesviruses, such as the human Epstein-Barr virus and the simian herpesvirus saimiri, form the distinct subfamily *Gammaherpesvirinae* (33). Some of these exhibit an oncogenic phenotype because they possess genes whose expressions are associated with lymphocyte transformation in vitro and induction of fulminant lymphomas in various nonhuman primates (14). Transforming activity of herpesvirus saimiri is correlated with genes termed STP-A or STP-C (saimiri transformation-associated protein of subgroup A or C) (19) that are located next to the left end of the genomic low G+C coding DNA (5, 10, 28). Neighboring sequences include a new type of U-like RNA gene (2, 23, 27, 37) and the intronless gene for dihydrofolate reductase (35) (Fig. 1A), which appears to be unique among animal viruses up to now. In the course of determining the nucleotide sequence of this genomic section by the chain termination method (34), we detected the gene for a polypeptide with striking similarity to members of the complement control protein family (7, 13, 26, 30, 31). The open reading frame has the coding capacity for a polypeptide of 360 amino acids with seven potential N-linked glycosylation sites (NxT/S), a predicted signal peptide of 20 amino acids (36), and a transmembrane domain of 23 residues (positions 328 to 350) near the carboxyl terminus (Fig. 1B and 2A). The body of the polypeptide between amino acids 21 and 265 consists of four repeat units (33 to 37% amino acid identity) that share a typical pattern of cysteine, proline, and tryptophan and several hydrophobic residues (Fig. 2). A search in protein data bases indicated that the herpesvirus saimiri polypeptide has significant similarity to the known members of the complement protein family that interact with C3b and C4b, including C4b-binding protein (9), membrane cofactor protein (CD46) (24), decay-accelerating factor (DAF) (CD55) (8, 25), complement receptor type I (CD35) (20), complement receptor type II (CD21) (38), and factor H (32). The global structural layout of the herpesvirus saimiri protein, termed CCPH (complement control protein homolog), is most similar to those of the cell membrane-associated complement regulators DAF and membrane cofactor protein (Fig. 2A). By using the FASTA option of the Genetics Computer Group (University of Wisconsin) software package (11), the herpesvirus saimiri CCPH had a high score for similarity to the 35-kDa secretory protein of vaccinia virus that was shown to bind C4b and to down-regulate both classical and alternative pathways of complement activation (18, 21, 22). Northern (RNA) blot hybridization detected transcripts of about 1.5 and 1.7 kbp in owl monkey kidney cells that were lytically infected with herpesvirus saimiri (Fig. 3A) (15). [^{32}P]dATP-labeled second-strand synthesis of cDNA with a transcript-specific oligonucleotide as a primer gave identical results (Fig. 3B). To address the question of mRNA processing, cDNAs were amplified by the polymerase chain reaction, cloned into the phagemid pBluescript KS− (Stratagene, La Jolla, Calif.), and sequenced. The nucleotide sequence of cDNAs showed that CCPH transcripts occur as unspliced or single-spliced mRNA (Fig. 1). The unspliced mRNA has the capacity to code for a membrane-bound glycoprotein (mCCPH); splicing removes a 193-bp intron which encodes the transmembrane domain and results in a possible secretory protein (sCCPH) with a different carboxyl terminus (Fig. 1B). A similar splicing mechanism is known to exist in the human DAF gene, in which the majority of transcripts specifying the membrane-bound form of DAF is spliced and in which unspliced transcripts containing an intron encoding contiguous protein sequence resulted in a secreted form of DAF (8). Randall and colleagues (29) have described neutralizing mouse monoclonal antibodies (SD and SE) that precipitated 45- to 52-kDa and 65- to 75-kDa glycoproteins from extracts of infected cells (Fig. 4B), and the latter ones were also precipitated from detergent extracts of purified virions (Fig. 4A, lane 3). We found that the smaller glycoprotein is secreted into the fluids of herpesvirus saimiri-infected cell cultures (Fig. 4A, lane 2). To express the CCPH gene, cDNAs were cloned into the eukaryotic expression vector pCMV4 (3), which contains the simian virus 40 replicon and promotes expression via the major immediate-early enhancer-promoter of human cytomegalovirus (6). COS-7 cells were transfected by the $CaPO_4$

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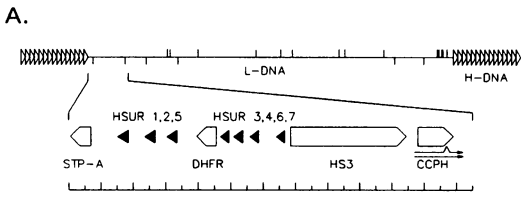


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     <<<          predicted signal peptide
     M  Y  T  L  H  Y  I  C  L  V  L  S  C  V  I  Y  F  V
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  >>>
W  T><L  S  C  P  T  R  N  Q  Y  V  S  V  K  Y  V  N  L  T
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N  Y  S  G  P  Y  P  N  G  T  T  L  H  V  T  C  R  E  G  Y
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C  Q><K  K  K  C  S  T  P  Q  D  L  L  N  G  R  Y  T  V  T
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G  S  T  T  S  A  C  L  L  K  R  G  G  R  V  D  W  T  P  R
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P  P  I  C  D><I  K  K  C  K  P  P  P  Q  I  A  N  G  T  H
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P  A  I  P  E  C  M><K  I  S  S  P  K  G  D  M  P  G  I  N
CCAGCTATTCCTGAATGTATGAAGATATCTTCTCCAAAAGGAGACATGCCTGGCATAAAC  1200
          splice donor >
S  N  E  D  N  S  T  P  S  G  R  I  C  N  G  N  C  T  T  S
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                                    < splice acceptor
domain                        >>>    G  A  E  C  A  C  P
I  I  I  G  I  I  L  T  G  V  C  L><H  R  C  R  V  C  M  S
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 G  S  N  Y  P  I  S  S  > carboxyl terminus of secreted ccph
G  Q
GGGCAGTAACTACCCAATTTCTTCATAAATATGAGAATCTCCGTTACAAGTTCTTAACTG  1500
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TATTAGTCTTGGTAGCAGCTAGAATAAATCACTTTAAGTTTAAAAGTTTAAAAATTTCCT  1860
GTCAATGTGGTTTGCTTGGAACAAGGTGTCTACTTAGGATGTGAGTCATTTACTCTTTGA  1920
AGTTCAAAAAAAATAACATAGTTAAAAGCTAAGCCCATTTTCAGTGATATTTAAAAGCTT  1980
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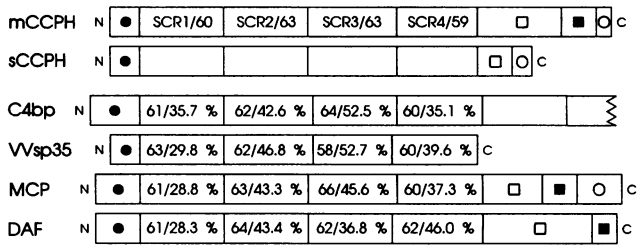
FIG. 1. Genomic localization and nucleotide sequence of the gene encoding the CCPH of herpesvirus saimiri. (A) Representation of the herpesvirus saimiri genome, which consists of 113-kbp low G+C coding DNA (L-DNA) that is flanked by 1.44-kbp high G+C noncoding tandem repetitions (H-DNA). Vertical bars indicate the restriction maps for *Eco*RI (above horizontal line) and *Kpn*I (below horizontal line). The leftmost 12.5 kbp are enlarged, showing the genes for seven U-like RNAs (HSUR 1 to 7) as solid triangles and the protein coding reading frames for the STP-A and dihydrofolate reductase (DHFR), the third open reading frame of herpesvirus saimiri (HS3) (1), and the CCPH as directed open boxes; transcripts of the CCPH gene are shown by arrows. (B) The sequence of three *Hin*dIII fragments of 70, 1303, and 601 bp is shown. The stop codon of HS3, poly(dA) signals, and synthetic oligonucleotides used for cDNA amplification and expression cloning are underlined; splice donor and splice acceptor sites are marked by angle brackets. The order of amino acids, in one-letter code, was deduced from the nucleotide sequence; the short consensus repeats are flanked by single angle brackets; potential N-linked glycosylation sites (NxT/S) and conserved cysteine residues within the repeating units are underlined; the signal peptide and transmembrane domain are predicted as indicated, and the carboxyl terminus of secreted CCPH is marked.

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CCPH-SCR2   kkkCstPqDllNGrytvtgnly.YGsvItYtCNsGYsLIGsttSaCllkrggrvdWtprpPiCD
C4bp-SCR2   ykrCrhPgElrNGQveiktdl.sFGsqIeFsCseGFfLIGsttSrCevqdrg.vgWshplPqCE
VVsp35-SCR2 krrCpsPrDidNGQldi.ggv.dFGssItYsCNsGYhLIGeskSyCelgstgsmvWnpeaPiCE
DAF-SCR3    kksCpnPgEirNGQidvpggil.FGatIsFsCNtGYkLfGstsSfClis.gssvqWsdplPeCr
MCP-SCR2    retCpyirDplNGQavpangtyeFGyqmhFiCNeGYyLIGeeilyCelk.gsvafWsgkpPiCE

consensus   ---C--P-D--NGQ---------FG--I-F-CN-GY-LIG---S-C---------W----P-CE
```

FIG. 2. Comparison of complement regulatory proteins. (A) The membrane-associated and secreted forms of the herpesvirus saimiri CCPH (mCCPH and sCCPH, respectively) are divided in their structural domains (signal peptide [●], short consensus repeats (SCRs), Ser/Thr-rich region [□], transmembrane domain [■], carboxyl-terminal tail [○]), as are the human C4b-binding protein (C4bp), membrane cofactor protein (MCP), DAF, and the major secretory protein of vaccinia virus (VVsp35). The SCRs of the CCPH were compared with the positionally corresponding SCRs and the results are given (length in amino acids/percent identity). (B) The best-matching SCRs were aligned, and their common consensus was determined when four of five sequences matched. Gaps imposed to maximize alignment are indicated by periods, and consensus residues are indicated by capital letters.

precipitation method with either mCCPH or sCCPH cDNA expression clone and analyzed by indirect immunofluorescence assay with monoclonal antibody SE and anti-mouse immunoglobulin G conjugated to fluorescein isothiocyanate as the second antibody. Cells fixed and penetrated as described previously (29) showed a broad cytoplasmic fluorescence. When COS-7 cells were first exposed to monoclonal

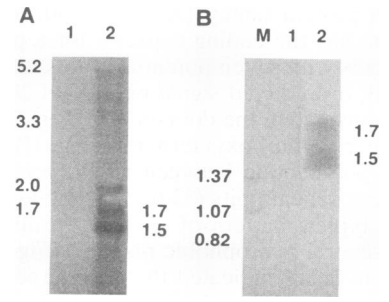

FIG. 3. Transcription of the CCPH gene. (A) A Northern blot was hybridized with a randomly labeled cDNA probe. Lane 1 represents the negative control with RNA from mock-infected cells loaded, and lane 2 corresponds to RNA from herpesvirus saimiri-infected owl monkey kidney cells. Two bands were detected at 1.5 and 1.7 kbp; the additional signals at 2.0 and 5.2 kbp are probably artificial since they coincide with rRNA. (B) Total RNA from mock-infected (lane 1) and infected (lane 2) owl monkey kidney cells was reverse transcribed by using oligo(dT) as a primer. Second-strand synthesis was done with a synthetic oligonucleotide (positions 362 to 386 in Fig. 1), [α-^{32}P]dATP, and T7 DNA polymerase. Two mRNAs of about 1.5 and 1.7 kbp were detected.

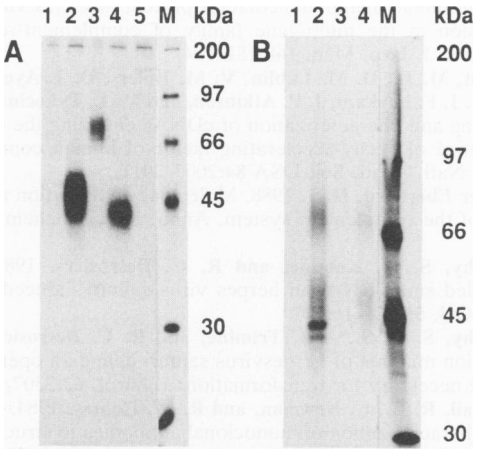

FIG. 4. Detection of the herpesvirus saimiri CCPH by radioimmunoprecipitation with monoclonal antibody SE. Cells were labeled for 15 h with [^{35}S]cysteine, infected cells at 48 to 60 h postinfection, COS-7 cells at 48 h posttransfection. Virion particles were purified by centrifugation through sucrose gradients. Glycoproteins were prepurified by running the cell extracts or cell culture supernatants through phosphate buffer-equilibrated concanavalin A–Sepharose columns to bind glycosylated proteins which were cleared with elution buffer (50 mM Tris [pH 8], 1 mM $MgCl_2$, 1 mM $CaCl_2$, 150 mM methyl-α-D-mannopyranoside, 250 mM methyl-α-D-glucopyranoside, 1% Triton X-100, 1% sodium deoxycholate, 0.1% sodium dodecyl sulfate [SDS], 2 mM phenylmethylsulfonyl fluoride, 5 mM EDTA) for 2 h. Proteins were precipitated with mouse monoclonal antibody SE, and complexes were bound to protein A-Sepharose, extensively washed with cell lysis buffer (50 mM Tris [pH 8], 150 mM NaCl, 0.1% SDS, 100 μg of phenylmethylsulfonyl fluoride per ml, 1% Triton X-100, 0.5% sodium deoxycholate), boiled, and electrophoresed on 10 to 12% polyacrylamide gels. In panel A, lanes contain glycoproteins precipitated from cell culture supernatants of uninfected owl monkey kidney cells (lane 1) and herpesvirus saimiri strain 11-infected owl monkey kidney cells (lane 2), purified virion particles (lane 3), and supernatants of COS-7 cells transfected with an sCCPH expression clone (lane 4) and COS-7 cells transfected with the expression vector only (lane 5). Lane M shows relative molecular mass marker proteins. In panel B, the lanes contain proteins precipitated from total cell extract of mock-infected (lane 1) and infected (lane 2) cells and glycoproteins precipitated from prepurified cell extracts of mock-infected (lane 3) and infected cells (lane 4).

antibody SE at 0°C for 15 min, fixed but not permeabilized, and reacted with anti-mouse immunoglobulin G, only cells transfected with the unprocessed cDNA were stained, thus confirming surface expression of mCCPH (data not shown). Neither protein was detectable by immunoprecipitation of COS-7 cell extracts; however, the sCCPH protein secreted from COS-7 cells was precipitated by monoclonal antibody SE (Fig. 4A, lane 4). The different gel mobility of sCCPH proteins may be the result of variable glycosylation patterns in different cells. In summary, it demonstrates that the mCCPH is a viral structural component, while the truncated form sCCPH is secreted by productively infected cells.

Both classical and alternative activations of the complement cascade are important pathways in induction of the inflammatory response. This mechanism of host immune defense is regulated by several membrane-bound and soluble glycoproteins to limit the reaction to local requirements. Herpesvirus saimiri is the first known example of an animal virus expressing a membrane glycoprotein and a secreted derivative with the characteristic structure of an inhibitor of complement activation. Multiple mechanisms by which an animal virus could counteract host immune defense mechanisms by expressing complement binding proteins could be envisaged. Suppression of the classical pathway of complement activation could be relevant if antibodies directed against viral surface glycoproteins react with membrane-bound structures of persistently infected blood cells. Vaccinia virus produces a secreted complement regulator of a related structure that is not glycosylated. In contrast, glycoprotein C of herpes simplex virus, a membrane component that is dispensable for replication in culture, binds C3b and has decay-accelerating activity (16, 17). This protein, however, does not reveal significant sequence homologies to the known cellular complement regulators. Perhaps complement down-regulation can be relevant for the herpesvirus cell cycle or persistence, and different herpesviruses may have acquired this function independently. The mCCPH gene of herpesvirus saimiri is free of introns, which suggests that the gene was captured from the cell by a mechanism involving reverse transcription. Herpesvirus saimiri is capable of persisting in lymphocytes of the blood stream and can be isolated continuously from such cells (12). Inhibition of the alternative complement activation pathway by a virion surface molecule could protect cell-free particles from lysis, as membrane structures are continuously coated with C3b and can be subject to elimination by the complement system (4).

Nucleotide sequence accession number. The nucleotide sequence data will appear in the EMBL, GenBank, and DDBJ nucleotide sequence data bases under accession number X60283.

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