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Review

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Complement evasion by human pathogens

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Summary

The human complement system has a pivotal role in the recognition, opsonization and elimination of microbial intruders. This functionality is maintained by a well-balanced interaction network of serum proteins and cell-surface receptors.

Over thousands of years of co-evolution, many microorganisms have developed specific complement-evasion strategies to escape the attack of the immune system. Although some of these strategies are highly specific for a single species, others are shared more broadly among bacteria, viruses, fungi and parasites.

The most prevalent complement-evasion mechanism seems to be the capture of soluble host complement regulators on the microbial surface or the expression of their structural mimics. However, the inactivation of complement components by proteolytic degradation or specific inhibition of essential functional sites is also frequently observed.

Staphylococcus aureus has a particularly wide and diverse arsenal of complement-evasion proteins, many of which have been discovered only recently. These numerous evasion strategies could contribute to the high virulence of this bacterium.

Structural biology is an indispensable tool for characterizing the structure and function of complement-evasion proteins. Recent publications of the co-crystal structures of evasion proteins with their human targets have allowed an even deeper insight into the molecular basis of these escape mechanisms.

The rapid increase in the structural and functional understanding of complement evasion could serve as an important starting point for the development of antimicrobial or complement-targeting therapeutics.

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John D. Lambris is the Dr Ralph and Sallie Weaver Professor of Research Medicine at the department of Pathology and Laboratory Medicine of the University of Pennsylvania, Philadelphia, USA. After earning his Ph.D. in biochemistry from the University of Patras, Greece, he dedicated his research to various aspects of the complement system. In his laboratory at the University of Pennsylvania, he applies ideas and methods that are embodied in engineering, computer science, physics, chemistry and other fields to address today's challenges in complement research. His current research efforts include the development of small-size complement inhibitors, the crosstalk of complement with other pathways and complement evasion by bacteria and viruses. He has been the president of the International Complement Society and is the founder and executive director of the Aegean Conferences.

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Brian V. Geisbrecht is an assistant professor of cell biology and biophysics at the University of Missouri–Kansas City (UMKC), Missouri, USA. He earned a Ph.D. in biological chemistry from The Johns Hopkins University School of Medicine, Maryland, USA, which was followed by a postdoctoral appointment in biophysics and biophysical chemistry at the same institution. Since joining UMKC in 2004, his laboratory has focused on understanding the molecular basis of host–pathogen interactions in infectious diseases by using various complementary approaches from structural biology (X-ray crystallography, nuclear magnetic resonance and X-ray scattering), biophysics and biochemistry.

Supplementary information S1 (table): Microbial complement-targeting proteins

	Pathogen Protein	Target	Action	Ref
Bacteria				
***Actinobacillus* spp.**				
Omp100	Outer membrane protein 100	fH	Recruitment of regulators	1
***Bordetella* spp.**				
FHA	Filamentous hemagglutinin	C4BP, (fH, FHL-1)	Recruitment of regulators	2
***Borrelia* spp.**				
CRASP	Complement regulator-acquiring surface proteins	fH, FHL-1	Recruitment of regulators	3
Erp	OspE/F-related proteins	fH	Recruitment of regulators	4, 5
n/a	CD59-like protein	C8, C9	Prevents MAC formation	6
***Escherichia* spp.**				
OmpA	Outer membrane protein A	C4BP	Recruitment of regulators	7
StcE	Secreted protease of C1 esterase inhibitor	C1-INH	Recruitment of C1-INH	8
TraT	TraT outer membrane protein	C5b6	Prevents MAC formation	9
***Fusobacterium* spp.**				
n/a	Unknown factor	fH	Recruitment of regulators	10
***Haemophilus* spp.**				
n/a	Unknown factor	C4BP, fH	Recruitment of regulators	11, 12
***Moraxella* spp.**				
UspA1/2	Ubiquitous surface protein A1 / A2	C4BP	Recruitment of regulators	13
***Neisseria* spp.**				
LOS	Lipooligosaccharide	fH, FHL-1	Recruitment of regulators	
GNA1870	Genome-derived neisserial antigen 1870	fH, FHL-1	Recruitment of regulators	14
Por	Outer membrane porins	C4BP, fH, FHL-1	Recruitment of regulators	15, 16
n/a	Type IV pili	MCP	Attachment to epithelial cells	17
***Porphyromonas* spp.**				
prtH	prtH protease	C3, IgG	Degrades C3 and IgG	18

***Pseudomonas* spp.**				
PaE	Pseudomonas elastase	C1q, C3	Degrades C1q and C3	19
PaAP	Pseudomonas alkaline protease	C1q, C3	Degrades C1q and C3	19
Tuf	Elongation factor	fH, FHL-1	Recruitment of regulators	20
***Serratia* spp.**				
n/a	56 kDa protease	C5a, C1-INH	Degrades C5a, degrades C1-INH	21, 22
***Staphylococcus* spp.**				
CHIPS	Chemotaxis inhibitory protein of S. aureus	C5aR	Antagonizes C5a	23
Efb	Extracellular fibrinogen-binding protein	C3/C3b/C3d	Inhibition of C3 and C3b-containing convertases	24-26
Ehp [a]	Efb-homologous protein	C3/C3b/C3d	Inhibition of C3 and C3b-containing convertases	26, 27
SAK	Staphylokinase	C3b, IgG (via Plasmin)	Cleaves complement proteins, removes C3b from surface	28
Sbi	S. aureus IgG-binding protein	IgG	Inhibits Ig interaction with C1q	29
SCIN	Staphylococcal complement inhibitor	C3 Convertases	Inhibits C3 activation to C3a/C3b	26, 30
SpA	S. aureus protein A	Ig's, gC1q-R	Inhibits Ig interaction with C1q	31
SSL-7	Staphylococcal superantigen-like protein 7	C5	Prevents C5 cleavage	32
***Streptococcus* spp.**				
Bac	-Protein	IgA, fH	Recruitment of regulators	33
Fba	Fibronectin-binding protein	fH, FHL-1	Recruitment of regulators	34
Hic [b]	Factor H-binding inhibitor of complement	fH	Recruitment of regulators	35
IdeS	IgG-degrading Enzyme of S. pyrogenes	IgG	Cleaves IgG, no interaction with C1q	36
M [b]	Surface proteins M family (Arp, Sir, etc.)	fH, C4BP, FHL, FHR, MCP	Recruitment of regulators	37
PLY	Pneumolysin	IgG, C1q	Complement activation / depletion	38, 39
PspA	Pneumococcal surface protein A	unknown	Potential impairing of AP and complement receptors	40
PspC [c]	Pneumococcal surface protein C	fH (C3, IgA)	Recruitment of regulators, Potential degradation of C3/C3b	41-44
scpA/B	Streptococcal C5a peptidase	C5a	Degrades C5a, Disrupts signaling	45-47
SIC	Streptococcal inhibitor of complement	C5b-7, C5b-8	Prevention of MAC formation	48, 49
SPE B	Streptococcal pyrogenic exotoxin B	Properdin, Ig's	Degrades Properdin, Ig's	36, 50
SpG	Streptococcus protein G	Ig's	Inhibits Ig interaction with C1q	51

***Yersinia* spp.**				
YadA	Yersinia adhesin A	fH	Recruitment of regulators	52
Viruses				
Herpes viruses				
gC1/2	Transmembrane glycoproteins C1,C2 (HSV)	C3b	Binds to C3b, decay acceleration (only AP), inhibits binding of properdin & C5	53
gE+gI	Glycoproteins E+I (HSV)	IgG	Fc-receptor, less activation	54, 55
gp34,68	Glycoproteins 34, 68 (HCMV)	IgG	Fc-receptors, less activation	56, 57
gpI+gpIV	Glycoproteins I+IV (VZV)	IgG	Fc-receptor, less activation	58
KCP [d]	Kaposi's sarkoma-associated complement control protein (KSHV)	C3b	Mimics regulators (cofactor/decay acceleration	59
Retroviruses				
gp41	Envelope glycoprotein 41 (HIV)	C1q, fH, CD59	Direct CP activation, Recruitment of regulators, decrease CD59 expression	60-62
gp120	Envelope glycoprotein 120 (HIV)	MBL, fH	Direct LP activation, Recruitment of regulators	62, 63
Tat	Transactivator of transcription (HIV)	C1-INH	Induces C1-INH expression	64
Poxviruses				
IMP	Cowpox control inflammation modulatory protein (Cowpox Virus)	C3b, Convertases	Mimics regulators (cofactor/decay acceleration)	65
MOPICE	Monkeypox inhibitor of complement enzymes (monkeypox virus)	C3b	Mimics regulators (only cofactor activity)	66
SPICE	Smallpox inhibitor of complement enzymes (variola virus)	C3b, Convertases	Mimics regulators (cofactor/decay acceleration)	67
VCP	Vaccinia virus complement control protein (vaccinia virus)	C3b, Convertases	Mimics regulators (cofactor/decay acceleration)	68
Filoviruses				
NS1	Non-structural protein 1 (West Nile virus)	fH	Recruitment of regulators	69
Fungi				
Aspergillus fumigatus				
n/a	Unknown factor	fH, FHL-1, C4BP	RCA recruitment	83

Candida albicans				
CRASP-1	Complement regulator-acquiring surface protein 1	fH, FHL-1, C4BP	Recruitment of regulators	84, 85
Gpm1p	Phosphoglycerate mutase	fH, FHL-1	Recruitment of regulators	86
Parasites				
***Echinococcus* spp.**				
n/a	Hydatid cyst wall	fH	Recruitment of regulators	70
***Ixodes* spp.**				
IRAC	Ixodes ricinus anti-complement protein	AP convertase	Decay acceleration	71
ISAC	Ixodes scapularis anti-complement protein	AP convertase	Decay acceleration	72
***Onchocerca* spp.**				
mf	Microfilariae	fH	Recruitment of regulators	73
***Ornithodoros* spp.**				
OmCI	Ornithodoros moubata complement inhibitor	C5	Binds to C5 (potentially blocks binding to C5 convertase)	74
***Schistosoma* spp.**				
CRIT	Complement C2 receptor trispanning	C2	Inhibits CP convertase formation	75
m28	28kDa membrane serine protease	iC3b	Cleaves iC3b, restricts CR3 binding	76, 77
Pmy [e]	Paramyosin	C8, C9, C1q, IgG	Prevents MAC formation Decreases AP activation	78-81
***Trypanosoma* spp.**				
CRIT	Complement C2 receptor trispanning	C2	Inhibits CP convertase formation	75
T-DAF	Trypanosoma decay-accelerating factor	Convertase	Destabilizes convertase	82

[a]Ehp has also been termed extracellular complement-binding protein (Ecb). [b]As Hic is not a member of the classical PspC familiy but a PspC-like protein, it is listed as separate protein. [c]Former names: cholin-binding protein (CbpA), *Streptococcus pneumoniae* secretory IgA-binding protein (SpsA) and pneumococcal C3-binding protein A (PbcA). [d]KPC has also been termed kaposica. [e]Paramyosin has previously been described as Schistosome complement inhibitor protein 1 (SCIP-1). AP, alternative pathway; C1-INH, C1 esterase inhibitor; C4BP, C4-binding protein; C5aR, C5a receptor; CP, classical pathway; DAF, decay accelerating factor; fH, factor H; FHL, factor H-like protein; Ig, immunoglobulin; MBL, mannose-binding lectin; MCP, membrane cofactor protein.

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