

In Figure	Name	Gene	Ligands	Function	Effect on Complement	Refs
SURFACE BOUND VIRULENCE FACTORS						
1-1	ARP	<i>arp</i>	IgA	Antiphagocytic/ C evasion	Via C4BP/FH	(1)
1-1	Enn protein	<i>enn</i>	C4BP/ FH/ IgA or IgG3	Antiphagocytic/ C evasion	Via C4BP/FH	(2,3)
1-2	FbaA	<i>fbaA</i>	FH/ FHL-1	Adhesin/ increases invasion	Via FH	(4,5)
1-4	Fibronectin binding protein (PrtF1/Sfbl)	<i>prtF1/sfbl</i>	Epithelial cells/ fibronectin/ CD46 receptor on keratinocytes	Adhesin / invasin	Inhibition of C3b deposition	(6)
1-6	GAPDH	<i>plr</i>	Epithelium/ fibronectin/ plasmin(-ogen)/ C5a/ lysozyme/ myosin and actin	Adhesin/ increases invasion	Binding of C5a	(7)
1-5	Hyaluronic acid capsule	<i>hasABC</i>	Keratinocyte/CD44	Adhesin/ antiphagocytic	Reduces C3b deposition	(8)
1-1	M protein	<i>emm</i>	Keratinocyte/ CD46/ C4BP/ FH/ IgG/ FHL-1/ plasmin(-ogen)/ NCAM/ fibrin(-ogen), albumin	Adhesin/antiphagocytic/ invasion/ C evasion	Via C4BP/ FH/ FHL-1	(9-19)
1-1	Mrp	<i>mrp</i>	IgG / fibrinogen	Antiphagocytic/ C evasion	Via C4BP/FH	(20-22)
1-1	Protein H	<i>prh</i>	C4BP/ FH/ IgG/ albumin/ fibrinogen	Antiphagocytic/ IgG binding / C evasion	Via C4BP/FH and sterically hindrance by fibrinogen	(23-28)
1-1	Sir	<i>sir</i>	IgA / IgG	Antiphagocytic/ C evasion	Via C4BP/FH	(22)
1-7	Streptococcal C5a peptidase	<i>scpA</i>	C3, C3a, C5a	Cleavage of C3, C3a, C5a	Inactivates C3, C3a and C5a	(29,30)
1-3	Streptococcal collagen like protein 1 Scl1	<i>scl1</i>	FH/ FH related protein 1	C evasion	Via FH/ CFHR1	(31,32)
1-8	Vitronectin binding protein	unknown	vitronectin	Adhesin/ C evasion	Inhibiting MAC via C5b-7 and C9 binding	(33-35)
SECRETED VIRULENCE FACTORS						
2-D	EndoS/Mac-1	<i>ndoS</i>	IgG	Antiphagocytic/ C evasion	Degrades IgG/ Reduces C3b deposition	(36,37)

2-B	IdeS	<i>ideS</i>	IgG/ CD16b (FcγRIIIB)	Antiphagocytic/ C evasion	Degrades IgG/ Reduces C3b deposition	(38)
2-C	Mac-2	<i>mac</i>	IgG/ CD32 (FcγRII) / CD16b (FcγRIIIB)	Antiphagocytic/ C evasion	Degrades IgG/ Reduces C3b deposition	(39,40)
2-E	PepO	<i>pepO</i>	C1q	C evasion	Binds C1q inhibits C1q and IgG interaction/ suppression of C activation	(41)
2-A	SpeB	<i>speB</i>	Broad spectrum cysteine proteinase	Antiphagocytic/ C evasion/ invasion/ dissemination/ inhibits antimicrobial peptides	Degrades complement components properdin, C1-INH, C2, C3, C3b, C4, C5a, C6, C7, C8, C9	(42-45)
2-G	Streptococcal inhibitor of complement mediated lysis (SIC)	<i>sic</i>	C5b67 and C5b678 complexes	Inhibits antimicrobial peptides/ C evasion	Inhibits MAC formation	(46-48)
2-F	Streptokinase	<i>ska</i>	plasmin(-ogen)	Converts plasminogen to plasmin, increases invasion, tissue and extracellular matrix degradation/ C evasion	Reduces C3b deposition	(9)
NO COMPLEMENT INVOLVEMENT						
	Closely related to SIC (CRS)	<i>crs57</i>	C6, C7	Hypothesized to inhibit MAC formation		(65)
	DNase Sda1	<i>sda1</i>	Degrades DNA	Escape from Neutrophil extracellular traps (NETs)		(50)
	EndoS ₂	<i>ndoS2</i>	IgG and α ₁ -acid glycoprotein	Potentially antiphagocytic/ C evasion		(51)
	Fibronectin binding protein (29kDa)	<i>fbp</i>	fibronectin	Adhesin		(3)
	fibronectin-binding protein PrtF2/FbaB/PFBP	<i>pfbp</i>	Fibronectin	Adhesin		(52)
	Hemoprotein binding protein Shr	<i>shr</i>	Fibronectin, laminin	Adhesin		(53,54)
	Laminin binding protein Lbp	<i>lbp</i>	Laminin	Adhesin		(55)

	Lipoteichoic acid		Epithelial cells/fibronectin receptor	Adhesin		(3)
	NADase	<i>nga</i>	Catalyzes the hydrolysis of NAD ⁺ to nicotinamide and adenosine diphosphoribose	Induce apoptosis concert with SLO		(56)
	Serum opacity factor SOF/SfbII	several	fibronectin	Adhesin		(57)
	SfbX	<i>sfbX</i>	fibronectin	Adhesin		(58)
	SibA	<i>sibA</i>	IgG	Binding IgG, IgA and IgM, potential immune evasion		(59)
	SpnA	<i>spnA</i>	Degrades DNA	Escape from Neutrophil extracellular traps (NETs)		(60)
	SpyCEP/ScpC	<i>spyCEP</i>	Chemokine IL-8	Cleaves IL-8/inhibits neutrophil recruitment		(61,62)
	Streptolysin O	<i>slo</i>	Cholesterol and glycans	Lysis of a variety of host cells		(63) (64)
	Streptolysin S	<i>sag</i> locus	Unknown	Lysis of a variety of host cells		(63)
	α -enolase/SEN	<i>eno</i>	plasminogen	Increases invasion		(49)

Table 1: Virulence factors of *S. pyogenes*. Surface bound and secreted virulence factors are listed alphabetically. References refer to the supplemental reference list and comprise even references listed in the main text.

References for table 1

1. Akerstrom, B., Lindqvist, A., and Lindahl, G. (1991) Binding properties of protein Arp, a bacterial IgA-receptor. *Mol Immunol* **28**, 349-357
2. Perez-Caballero, D., Garcia-Laorden, I., Cortes, G., Wessels, M. R., de Cordoba, S. R., and Alberti, S. (2004) Interaction between complement regulators and Streptococcus pyogenes: binding of C4b-binding protein and factor H/factor H-like protein 1 to M18 strains involves two different cell surface molecules. *J Immunol* **173**, 6899-6904
3. Cunningham, M. W. (2000) Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* **13**, 470-511
4. Pandiripally, V., Gregory, E., and Cue, D. (2002) Acquisition of regulators of complement activation by Streptococcus pyogenes serotype M1. *Infect Immun* **70**, 6206-6214
5. Ma, C., Guo, Y., Gu, H., Zhang, L., Liu, H., Feng, H., and Wei, L. (2011) A novel monoclonal antibody against FbaA can inhibit the binding of the complement regulatory protein factor H to group A streptococcus. *Clin Vaccine Immunol* **18**, 552-558
6. Hyland, K. A., Wang, B., and Cleary, P. P. (2007) Protein F1 and Streptococcus pyogenes resistance to phagocytosis. *Infect Immun* **75**, 3188-3191
7. Terao, Y., Yamaguchi, M., Hamada, S., and Kawabata, S. (2006) Multifunctional glyceraldehyde-3-phosphate dehydrogenase of Streptococcus pyogenes is essential for evasion from neutrophils. *J Biol Chem* **281**, 14215-14223
8. Dale, J. B., Washburn, R. G., Marques, M. B., and Wessels, M. R. (1996) Hyaluronate capsule and surface M protein in resistance to opsonization of group A streptococci. *Infect Immun* **64**, 1495-1501
9. Ly, D., Taylor, J. M., Tsatsaronis, J. A., Monteleone, M. M., Skora, A. S., Donald, C. A., Maddocks, T., Nizet, V., West, N. P., Ranson, M., Walker, M. J., McArthur, J. D., and Sanderson-Smith, M. L. (2014) Plasmin(ogen) acquisition by group A Streptococcus protects against C3b-mediated neutrophil killing. *J Innate Immun* **6**, 240-250
10. Thern, A., Stenberg, L., Dahlback, B., and Lindahl, G. (1995) Ig-binding surface proteins of Streptococcus pyogenes also bind human C4b-binding protein (C4BP), a regulatory component of the complement system. *J Immunol* **154**, 375-386
11. Horstmann, R. D., Sievertsen, H. J., Knobloch, J., and Fischetti, V. A. (1988) Antiphagocytic activity of streptococcal M protein: selective binding of complement control protein factor H. *Proc Natl Acad Sci U S A* **85**, 1657-1661
12. Johnsson, E., Berggard, K., Kotarsky, H., Hellwage, J., Zipfel, P. F., Sjobring, U., and Lindahl, G. (1998) Role of the hypervariable region in streptococcal M proteins: binding of a human complement inhibitor. *J Immunol* **161**, 4894-4901
13. Courtney, H. S., Liu, S., Dale, J. B., and Hasty, D. L. (1997) Conversion of M serotype 24 of Streptococcus pyogenes to M serotypes 5 and 18: effect on resistance to phagocytosis and adhesion to host cells. *Infect Immun* **65**, 2472-2474
14. Whitnack, E., and Beachey, E. H. (1982) Antiopsonic activity of fibrinogen bound to M protein on the surface of group A streptococci. *J Clin Invest* **69**, 1042-1045

15. Whitnack, E., and Beachey, E. H. (1985) Inhibition of complement-mediated opsonization and phagocytosis of *Streptococcus pyogenes* by D fragments of fibrinogen and fibrin bound to cell surface M protein. *J Exp Med* **162**, 1983-1997
16. Frick, I. M., Crossin, K. L., Edelman, G. M., and Bjorck, L. (1995) Protein H--a bacterial surface protein with affinity for both immunoglobulin and fibronectin type III domains. *Embo J* **14**, 1674-1679
17. Kronvall, G. (1973) A surface component in group A, C, and G streptococci with non-immune reactivity for immunoglobulin G. *J Immunol* **111**, 1401-1406
18. Kronvall, G., Simmons, A., Myhre, E. B., and Jonsson, S. (1979) Specific absorption of human serum albumin, immunoglobulin A, and immunoglobulin G with selected strains of group A and G streptococci. *Infect Immun* **25**, 1-10
19. Ellen, R. P., and Gibbons, R. J. (1972) M protein-associated adherence of *Streptococcus pyogenes* to epithelial surfaces: prerequisite for virulence. *Infect Immun* **5**, 826-830
20. Courtney, H. S., Hasty, D. L., and Dale, J. B. (2006) Anti-phagocytic mechanisms of *Streptococcus pyogenes*: binding of fibrinogen to M-related protein. *Mol Microbiol* **59**, 936-947
21. Carlsson, F., Sandin, C., and Lindahl, G. (2005) Human fibrinogen bound to *Streptococcus pyogenes* M protein inhibits complement deposition via the classical pathway. *Mol Microbiol* **56**, 28-39
22. Stenberg, L., O'Toole, P., and Lindahl, G. (1992) Many group A streptococcal strains express two different immunoglobulin-binding proteins, encoded by closely linked genes: characterization of the proteins expressed by four strains of different M-type. *Mol Microbiol* **6**, 1185-1194
23. Blom, A. M., Magda, M., Kohl, L., Shaughnessy, J., Lambris, J. D., Ram, S., and Ermert, D. (2017) Factor H-IgG Chimeric Proteins as a Therapeutic Approach against the Gram-Positive Bacterial Pathogen *Streptococcus pyogenes*. *J Immunol* **199**, 3828-3839
24. Ermert, D., Shaughnessy, J., Joeris, T., Kaplan, J., Pang, C. J., Kurt-Jones, E. A., Rice, P. A., Ram, S., and Blom, A. M. (2015) Virulence of Group A Streptococci Is Enhanced by Human Complement Inhibitors. *PLoS Pathog* **11**, e1005043
25. Ermert, D., Weckel, A., Agarwal, V., Frick, I. M., Bjorck, L., and Blom, A. M. (2013) Binding of complement inhibitor C4b-binding protein to a highly virulent *Streptococcus pyogenes* M1 strain is mediated by protein H and enhances adhesion to and invasion of endothelial cells. *J Biol Chem* **288**, 32172-32183
26. Ermert, D., Weckel, A., Magda, M., Morgelin, M., Shaughnessy, J., Rice, P. A., Bjorck, L., Ram, S., and Blom, A. M. (2018) Human IgG Increases Virulence of *Streptococcus pyogenes* through Complement Evasion. *J Immunol*
27. Gomi, H., Hozumi, T., Hattori, S., Tagawa, C., Kishimoto, F., and Bjorck, L. (1990) The gene sequence and some properties of protein H. A novel IgG-binding protein. *J Immunol* **144**, 4046-4052
28. Frick, I. M., Akesson, P., Cooney, J., Sjobring, U., Schmidt, K. H., Gomi, H., Hattori, S., Tagawa, C., Kishimoto, F., and Bjorck, L. (1994) Protein H--a surface protein of *Streptococcus pyogenes* with separate binding sites for IgG and albumin. *Mol Microbiol* **12**, 143-151

29. Wexler, D. E., Nelson, R. D., and Cleary, P. P. (1983) Human neutrophil chemotactic response to group A streptococci: bacteria-mediated interference with complement-derived chemotactic factors. *Infect Immun* **39**, 239-246
30. Lynskey, N. N., Reglinski, M., Calay, D., Siggins, M. K., Mason, J. C., Botto, M., and Sriskandan, S. (2017) Multi-functional mechanisms of immune evasion by the streptococcal complement inhibitor C5a peptidase. *PLoS Pathog* **13**, e1006493
31. Caswell, C. C., Han, R., Hovis, K. M., Ciborowski, P., Keene, D. R., Marconi, R. T., and Lukomski, S. (2008) The Scl1 protein of M6-type group A Streptococcus binds the human complement regulatory protein, factor H, and inhibits the alternative pathway of complement. *Mol Microbiol* **67**, 584-596
32. Reuter, M., Caswell, C. C., Lukomski, S., and Zipfel, P. F. (2010) Binding of the human complement regulators CFHR1 and factor H by streptococcal collagen-like protein 1 (Scl1) via their conserved C termini allows control of the complement cascade at multiple levels. *J Biol Chem* **285**, 38473-38485
33. Podack, E. R., Kolb, W. P., and Muller-Eberhard, H. J. (1977) The SC5b-7 complex: formation, isolation, properties, and subunit composition. *J Immunol* **119**, 2024-2029
34. Podack, E. R., Preissner, K. T., and Muller-Eberhard, H. J. (1984) Inhibition of C9 polymerization within the SC5b-9 complex of complement by S-protein. *Acta Pathol Microbiol Immunol Scand Suppl* **284**, 89-96
35. Valentin-Weigand, P., Grulich-Henn, J., Chhatwal, G. S., Muller-Berghaus, G., Blobel, H., and Preissner, K. T. (1988) Mediation of adherence of streptococci to human endothelial cells by complement S protein (vitronectin). *Infect Immun* **56**, 2851-2855
36. Collin, M., and Olsen, A. (2001) EndoS, a novel secreted protein from Streptococcus pyogenes with endoglycosidase activity on human IgG. *EMBO J* **20**, 3046-3055
37. Lei, B., DeLeo, F. R., Hoe, N. P., Graham, M. R., Mackie, S. M., Cole, R. L., Liu, M., Hill, H. R., Low, D. E., Federle, M. J., Scott, J. R., and Musser, J. M. (2001) Evasion of human innate and acquired immunity by a bacterial homolog of CD11b that inhibits opsonophagocytosis. *Nat Med* **7**, 1298-1305
38. von Pawel-Rammingen, U., Johansson, B. P., and Bjorck, L. (2002) IdeS, a novel streptococcal cysteine proteinase with unique specificity for immunoglobulin G. *EMBO J* **21**, 1607-1615
39. Agniswamy, J., Lei, B., Musser, J. M., and Sun, P. D. (2004) Insight of host immune evasion mediated by two variants of group a Streptococcus Mac protein. *J Biol Chem* **279**, 52789-52796
40. Soderberg, J. J., Engstrom, P., and von Pawel-Rammingen, U. (2008) The intrinsic immunoglobulin g endopeptidase activity of streptococcal Mac-2 proteins implies a unique role for the enzymatically impaired Mac-2 protein of M28 serotype strains. *Infect Immun* **76**, 2183-2188
41. Honda-Ogawa, M., Sumitomo, T., Mori, Y., Hamd, D. T., Ogawa, T., Yamaguchi, M., Nakata, M., and Kawabata, S. (2017) Streptococcus pyogenes Endopeptidase O Contributes to Evasion from Complement-mediated Bacteriolysis via Binding to Human Complement Factor C1q. *J Biol Chem* **292**, 4244-4254

42. Honda-Ogawa, M., Ogawa, T., Terao, Y., Sumitomo, T., Nakata, M., Ikebe, K., Maeda, Y., and Kawabata, S. (2013) Cysteine proteinase from *Streptococcus pyogenes* enables evasion of innate immunity via degradation of complement factors. *J Biol Chem* **288**, 15854-15864
43. Kuo, C. F., Lin, Y. S., Chuang, W. J., Wu, J. J., and Tsao, N. (2008) Degradation of complement 3 by streptococcal pyrogenic exotoxin B inhibits complement activation and neutrophil opsonophagocytosis. *Infect Immun* **76**, 1163-1169
44. Tsao, N., Tsai, W. H., Lin, Y. S., Chuang, W. J., Wang, C. H., and Kuo, C. F. (2006) Streptococcal pyrogenic exotoxin B cleaves properdin and inhibits complement-mediated opsonophagocytosis. *Biochem Biophys Res Commun* **339**, 779-784
45. Terao, Y., Mori, Y., Yamaguchi, M., Shimizu, Y., Ooe, K., Hamada, S., and Kawabata, S. (2008) Group A streptococcal cysteine protease degrades C3 (C3b) and contributes to evasion of innate immunity. *J Biol Chem* **283**, 6253-6260
46. Fernie-King, B. A., Seilly, D. J., Davies, A., and Lachmann, P. J. (2002) Streptococcal inhibitor of complement inhibits two additional components of the mucosal innate immune system: secretory leukocyte proteinase inhibitor and lysozyme. *Infect Immun* **70**, 4908-4916
47. Fernie-King, B. A., Seilly, D. J., Willers, C., Wurzner, R., Davies, A., and Lachmann, P. J. (2001) Streptococcal inhibitor of complement (SIC) inhibits the membrane attack complex by preventing uptake of C5b-9 onto cell membranes. *Immunology* **103**, 390-398
48. Akesson, P., Sjolholm, A. G., and Bjorck, L. (1996) Protein SIC, a novel extracellular protein of *Streptococcus pyogenes* interfering with complement function. *J Biol Chem* **271**, 1081-1088
49. Pancholi, V., and Fischetti, V. A. (1997) A novel plasminogen/plasmin binding protein on the surface of group A streptococci. *Adv Exp Med Biol* **418**, 597-599
50. Buchanan, J. T., Simpson, A. J., Aziz, R. K., Liu, G. Y., Kristian, S. A., Kotb, M., Feramisco, J., and Nizet, V. (2006) DNase expression allows the pathogen group A *Streptococcus* to escape killing in neutrophil extracellular traps. *Curr Biol* **16**, 396-400
51. Sjogren, J., Struwe, W. B., Cosgrave, E. F., Rudd, P. M., Stervander, M., Allhorn, M., Hollands, A., Nizet, V., and Collin, M. (2013) EndoS2 is a unique and conserved enzyme of serotype M49 group A *Streptococcus* that hydrolyses N-linked glycans on IgG and alpha1-acid glycoprotein. *Biochem J* **455**, 107-118
52. Rocha, C. L., and Fischetti, V. A. (1999) Identification and characterization of a novel fibronectin-binding protein on the surface of group A streptococci. *Infect Immun* **67**, 2720-2728
53. Fisher, M., Huang, Y. S., Li, X., McIver, K. S., Toukoki, C., and Eichenbaum, Z. (2008) Shr is a broad-spectrum surface receptor that contributes to adherence and virulence in group A streptococcus. *Infect Immun* **76**, 5006-5015
54. Yamaguchi, M., Terao, Y., and Kawabata, S. (2013) Pleiotropic virulence factor - *Streptococcus pyogenes* fibronectin-binding proteins. *Cellular microbiology* **15**, 503-511
55. Terao, Y., Kawabata, S., Kunitomo, E., Nakagawa, I., and Hamada, S. (2002) Novel laminin-binding protein of *Streptococcus pyogenes*, Lbp, is involved in adhesion to epithelial cells. *Infect Immun* **70**, 993-997

56. Bricker, A. L., Carey, V. J., and Wessels, M. R. (2005) Role of NADase in virulence in experimental invasive group A streptococcal infection. *Infect Immun* **73**, 6562-6566
57. Kreikemeyer, B., Talay, S. R., and Chhatwal, G. S. (1995) Characterization of a novel fibronectin-binding surface protein in group A streptococci. *Mol Microbiol* **17**, 137-145
58. Courtney, H. S., Dale, J. B., and Hasty, D. I. (1996) Differential effects of the streptococcal fibronectin-binding protein, FBP54, on adhesion of group A streptococci to human buccal cells and HEp-2 tissue culture cells. *Infect Immun* **64**, 2415-2419
59. Fagan, P. K., Reinscheid, D., Gottschalk, B., and Chhatwal, G. S. (2001) Identification and characterization of a novel secreted immunoglobulin binding protein from group A streptococcus. *Infect Immun* **69**, 4851-4857
60. Hasegawa, T., Minami, M., Okamoto, A., Tatsuno, I., Isaka, M., and Ohta, M. (2010) Characterization of a virulence-associated and cell-wall-located DNase of *Streptococcus pyogenes*. *Microbiology* **156**, 184-190
61. Zinkernagel, A. S., Timmer, A. M., Pence, M. A., Locke, J. B., Buchanan, J. T., Turner, C. E., Mishalian, I., Sriskandan, S., Hanski, E., and Nizet, V. (2008) The IL-8 protease SpyCEP/ScpC of group A *Streptococcus* promotes resistance to neutrophil killing. *Cell Host Microbe* **4**, 170-178
62. Turner, C. E., Kurupati, P., Jones, M. D., Edwards, R. J., and Sriskandan, S. (2009) Emerging role of the interleukin-8 cleaving enzyme SpyCEP in clinical *Streptococcus pyogenes* infection. *J Infect Dis* **200**, 555-563
63. Alouf, J. E. (1980) Streptococcal toxins (streptolysin O, streptolysin S, erythrogenic toxin). *Pharmacol Ther* **11**, 661-717
64. Shewell, L. K., Harvey, R. M., Higgins, M. A., Day, C. J., Hartley-Tassell, L. E., Chen, A. Y., Gillen, C. M., James, D. B., Alonzo, F., 3rd, Torres, V. J., Walker, M. J., Paton, A. W., Paton, J. C., and Jennings, M. P. (2014) The cholesterol-dependent cytolysins pneumolysin and streptolysin O require binding to red blood cell glycans for hemolytic activity. *Proc Natl Acad Sci U S A* **111**, E5312-5320
65. Binks, M., McMillan, D., and Sriprakash, K. S. (2003) Genomic location and variation of the gene for CRS, a complement binding protein in the M57 strains of *Streptococcus pyogenes*. *Infect Immun* **71**, 6701-6706