How group A *Streptococcus* circumvents host phagocyte defenses

Laura A Kwinn & Victor Nizet†

†Author for correspondence Division of Pediatric Pharmacology & Drug Discovery, University of California, San Diego School of Medicine, Skaggs School of Pharmacy & Pharmaceutical Sciences, 9500 Gilman Drive, Mail Code 0687, La Jolla, CA 92093-0687, USA
Tel.: +1 858 534 7408; Fax: +1 858 534 5611; vnizet@ucsd.edu

Group A *Streptococcus* (GAS) is a Gram-positive bacterium associated with a variety of mucosal and invasive human infections. GAS systemic disease reflects the diverse abilities of this pathogen to avoid eradication by phagocytic defenses of the innate immune system. Here we review how GAS can avoid phagocyte engagement, inhibit complement and antibody functions required for opsonization, impair phagocytotic uptake mechanisms, promote phagocyte lysis or apoptosis, and resist specific effectors of phagocyte killing such as antimicrobial peptides and reactive oxygen species. Understanding the molecular basis of GAS phagocyte resistance may reveal novel therapeutic targets for treatment and prevention of invasive human infections.

Keywords: complement, group A *Streptococcus*, innate immunity, macrophage, neutrophil, phagocytosis, *Streptococcus pyogenes*, virulence factor

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Group A *Streptococcus* (GAS; *Streptococcus pyogenes*) is a Gram-positive bacterium associated with a wide spectrum of disease conditions in the human host. While the majority of GAS disease is limited to superficial sites such as the pharyngeal mucosa ('strep throat') or skin (impetigo), the organism is also a leading agent of invasive infections, including the life-threatening conditions of necrotizing fasciitis and toxic shock syndrome. The annual burden of invasive GAS infection is estimated at over 650,000 cases and 150,000 deaths worldwide [1], reflecting the global dissemination of strains of enhanced virulence potential, including a highly prevalent clone of the M1T1 serotype [2]. The propensity of GAS to produce systemic infection in otherwise healthy children and adults defines a capacity of the pathogen to resist host innate immune clearance mechanisms that normally function to prevent microbial dissemination beyond epithelial surfaces.

Phagocytic cells such as neutrophils and macrophages represent a critical element of innate immunity against invasive bacterial infection. The general effectiveness of these cells in host defense bespeaks specialized functions in directed migration, microbial uptake and production of a variety of bactericidal effector molecules. In this review, we examine the multiple virulence factors of GAS capable of interfering with the host phagocyte defense system, placing a particular emphasis on recent discoveries established through molecular genetic analysis of the pathogen.

Impairment of phagocyte recruitment

Circulating leukocytes respond to chemotactic signals to leave the vasculature and migrate to the site of infection. While chemoattractants include products from the bacteria cell wall (e.g., *N*-formyl peptides), the strongest and most specific stimuli are host-derived. GAS has evolved mechanisms to interfere with two of the most potent molecules promoting neutrophil recruitment, the CXC chemokine interleukin (IL)-8 and the complement-derived anaphylotoxin C5a. In this way the kinetics of the innate immune response to GAS infection are delayed, favoring bacterial survival.

IL-8 is a multifunctional protein involved in the migration of neutrophils out of the bloodstream and towards the site of infection. Not only does IL-8 act a potent chemoattractant [3], it can also be found tethered to the luminal surface of the microvasculature where it provides a stop signal to rolling neutrophils [4,5]. GAS produce a protease (ScpC, also known as SpyCEP) that specifically cleaves the C terminus of IL-8, leading to functional inactivation of the chemokine [6]. ScpC also cleaves the murine CXC chemokines KC and MIP-2 [7]. Loss of ScpC expression dramatically reduces GAS virulence in the mouse necrotizing fasciitis model, reflecting increased neutrophil influx to the site of infection [7].

C5a is an 11-kD fragment of the complement cascade with multiple inflammatory properties, including the recruitment of neutrophils and stimulation of their bactericidal capacity against GAS [8]. However, GAS express an endopeptidase, ScpA, which cleaves human C5a between His-67 and Lys-68, residues within the critical recognition site for leukocyte surface receptors [9]. The anchorless surface dehydrogenase (SDH) is also shed from the GAS surface whereupon it binds and inactivates human C5a [10], providing another impediment to host neutrophil chemotaxis.

Escape from neutrophil extracellular traps

It has recently been appreciated that, apart from their phagocytic function, neutrophils can efficiently capture and kill microbes in the extracellular space. This process involves neutrophil extrusion of a matrix of DNA and histones known as neutrophil extracellular traps (NETs), which ensnare bacteria and subject them to microbicidal effectors including the granule proteases elastase and myeloperoxidase [11]. With chromatin representing the principal scaffold of NETs, the contribution of several GAS DNAse enzymes to pathogenesis has come under examination. A GAS strain with mutations in three encoded DNAses is significantly attenuated in murine skin and systemic infection models as well as pharyngeal infection of cynomolgus macaques [12]. Among these was the highly active bacteriophage-encoded DNAse Sda1, present in the secreted proteome of the virulent M1T1 GAS clone associated with severe, invasive infections [13]. Sumby and collegues demonstrated significantly increased extracellular killing of isogenic DNAse mutant GAS by human neutrophils using conditions known to promote NETs [12], and subsequent targeted mutagenesis and heterologous expression of Sda1 revealed that the enzyme is necessary and sufficient for promoting GAS NET degradation and resistance to neutrophil killing *in vitro* and *in vivo* [14]. Moreover, pharmacological inhibition of Sda1 DNAse activity preserved host NET function and reduced the severity of GAS skin infection [14].

Interference with complement function

Following activation of the classical or alternative complement pathways, opsonization of foreign microbes occurs through deposition of C3b and its cleavage fragment iC3b on their surface. Complement receptors (CR) on neutrophils and macrophages engage the bound C3b (CR1) or iC3b (CR3 and CR4) to facilitate phagocytosis. Since the complement system is capable of efficient self-amplification, potential host cell damage is mitigated by the counter-regulatory proteins C4b-binding protein (C4BP) and factor H (FH) that dampen the activity level of the classical and alternative pathways, respectively. GAS exhibits the capacity to acquire C4BP and FH, and these phenotypes have been explored for potential roles in impeding host complement activation or preventing efficient opsonophagocytosis.

C4BP interferes with the assembly of the membrane-bound C3 convertase of the classical pathway [15]. GAS is able to selectively acquire host C4BP from human serum through the action of the hypervariable regions of several M-protein family members, thereby inhibiting classical pathway activation [16,17]. Monoclonal antibody mapping studies reveal the point of interaction of GAS M proteins with C4BP overlaps with potential C4b binding sites [18]; however, the multi-armed structure of C4BP allows it to retains its ability to act as a cofactor for C4b degradation even when bound to M protein. A strong correlation can be established between C4BP acquisition on the GAS surface and evasion of phagocytosis, highlighting the importance of this innate immune resistance mechanism [19]. The lack of consensus sequence motifs among C4BP binding M-protein hypervariable regions reflects an interesting capacity for sequence divergence across M types while maintaining highly specific ligand-binding functions [20].

FH and the variant splice form of its coding gene, FH-like protein (FHL)-1, are central fluid-phase regulators of the alternative complement pathway, functioning to accelerate the decay of the C3 convertase (C3bBb) and acting as cofactors for factor I-mediated degradation of C3b [21]. M protein has long been known to restrict deposition of C3b on the GAS surface, a function that can be correlated to resistance to phagocytosis [22]. Many GAS M proteins were found capable of binding FH and FHL-1 proteins through their conserved C-repeat region and/or hypervariable N-terminal regions [23,24]. However, the overall significance of M protein binding to FH and FHL-1 to complement resistance remains a matter of debate. Affinities for FH and FHL-1 vary widely by M-type – M18 possesses the highest affinity, while M1 and M3 proteins, representing strains commonly associated with invasive disease, show little if any binding [25]. Recently, the M5 protein was shown to bind FH and FHL-1 at its N terminus, but the bacteria resisted phagocytosis equally well regardless of the inclusion or exclusion of this N-terminal binding domain [26], corroborating similar observations using an M6 serotype strain [27]. In M1 strains, the M protein is dispensible for FH/FHL-1 binding; instead, the surface-anchored protein Fba mediates binding to these complement regulatory factors. Fba promotes M1 GAS survival in human whole blood and prevents deposition of C3b on the bacterial cell surface [28].

Deposition of complement on GAS occurs via the classical pathway even under nonimmune conditions, but can be blocked by the ability of M proteins of certain GAS serotypes to bind fibrinogen, which reduces the amount of classical pathway C3 convertase on the bacterial surface. The M-related protein Mrp, expressed by more than half of GAS strains, also recruits fibrinogen to the bacterial surface in a fashion that impairs complement deposition [29]. Binding of fibrinogen and fellow plasma protein albumin to the B- and C-repeats of GAS M protein plays an important role in determining the location of opsonic and nonopsonic epitopes [30].

The terminal complement pathway generates the membrane attack complex C5–9, which can disrupt bacterial cell membranes leading to hypoosmotic lysis; although this may not be the case in Gram-positive bacteria due to the thickness of the peptidoglycan layer in the cell wall. M1 and M57 serotypes of GAS release the protein serum inhibitor of complement (SIC) that couples with clusterin and histidine-rich glycoprotein, two serum regulators of membrane-attack complex activity, consequently inhibiting complement-mediated cell lysis in an erythrocyte model [31]. While preventing uptake of C567 onto the cell surface is a measurable property of SIC [32], the protein has several additional activities that are likely more important contributors to GAS phagocyte resistance (see below).

Interference with antibody-mediated opsonization

Immunoglobulins (Igs) generated against specific bacterial epitopes provide a second effective form of opsonization, promoting engagement and uptake by host phagocytes expressing surface receptors for the Ig Fc domain. GAS confounds this branch of host innate defense by a variety of means, including molecular mimicry, antigenic diversity, and specific proteins that degrade Ig molecules, bind them in a nonopsonic fashion, or interfere with their recognition by phagocyte Fc receptors. In contrast to the serotype-specific polysaccharide capsules of group B *Streptococcus* and *Streptococcus pneumoniae*, which represent primary targets of protective immunity, the invariant GAS capsule consists of a homopolymer of hyaluronic acid, identical to a major constituent of the mammalian extracellular matrix. This effective mimicry provides the bacterium a protective cloak not recognizable as a foreign antigen. And while the M protein on the GAS cell surface can serve as a target of protective immunity, hypervariability of its N-terminal domain has generated more than 100 known serovariants among which lack of cross-protection is commonplace.

The effector function of Ig may be thwarted when the pathogen binds its Fc region, effectively decorating the bacterial surface with the host molecule in a 'backwards', nonopsonic orientation. The surface-expressed GAS fibronectin-binding protein (Sfb)I binds the Fc region of the Fc region of IgG, preventing phagocytosis of IgG-coated red-blood cells (RBCs) and Ab-dependent cell cytotoxicity by macrophages [33]. Several M protein types and related family members also show capacity for binding the Fc domains of IgG and/or IgA [34–36]. Protein H, a GAS surface protein structurally related to M protein, interacts with the Fc region of IgG and inhibits IgG-dependent complement activation on the bacterial cell surface [37]. However, it should be noted that there is scant evidence that Fc binding proteins of GAS or other bacteria can specifically bind antibacterial IgG, without first becoming saturated with abundant nonimmune IgG.

The broad spectrum GAS cysteine protease SpeB has been shown to cleave IgG, -A, -M, -D and -E antibodies *in vitro* [38]. This degradation occurs even when IgG is specifically bound to a bacterial antigen via its Fab regions; yet when the IgG Fc region is bound to GAS surface proteins in a nonopsonic fashion, it is then spared from SpeB proteolysis [39]. Mac-1/IdeS, a second GAS cysteine protease [40], cleaves IgG *in vitro* and *in vivo*, targeting the lower Fc region [41,42]. Mac-1/IdeS further exhibits homology to the alpha-subunit of a leukocyte B2-integrin, CD11b, which binds to FcγRIIIB (CD16) on the surface of neutrophils inhibiting phagocytosis and activation of the oxidative burst [43]. Subsequently, the closely related Mac-2 protein was found to bind both Fcγ RII and III receptors, likewise serving to competitively inhibit host phagocyte recognition of IgG on the bacterial surface [41]. Like Mac-1/IdeS, Mac-2 exhibits IgG endopeptidase activity [44]. Finally, the secreted GAS protein EndoS hydrolyzes the chitobiose core of the asparagine-linked glycan on IgG, preventing recognition of IgG by phagocyte Fc receptors, blocking complement activation through the classical pathway and impairing opsonophagocytosis [38,45].

Avoidance of phagocytic uptake

Beyond interference with complement and antibody-mediated opsonization, GAS employs several strategies to resist its uptake into phagocytes.

Although the GAS hyaluronic acid capsule does not block C3 deposition on the bacterial surface, its antiphagocytic function is supported by several lines of evidence. Capsule-deficient GAS generated by targeted mutagenesis of the *has* biosynthetic operon or through hyaluronidase treatment become susceptible to phagocytic clearance and less virulent in animal challenge models [46]. Conversely, GAS variants with increased encapsulation are generated by animal passage and mucoid strains are linked epidemiologically to greater invasive disease potential [47]. The hyaluronic acid capsule appears to restrict access of phagocytes to a variety of opsonins on the bacterial surface [48].

GAS also possess the capacity to utilize various host matrix proteins to shield their surface and/or promote formation of bacterial aggregates whose particle size may exceed the uptake capacity of host phagocytes. For example, the SfbI protein can bind fibronectin that can in turn recruit collagen, leading to matrix deposition on and between bacteria and the development of large aggregates [49]. Under physiological conditions, the B- and C-repeat regions of GAS M protein can bind fibrinogen and albumin, thus masking them from antibody binding [30]. GAS have been shown to aggregate and form intratissue microcolonies or biofilms on uncoated polystyrene surfaces or those coated with fibronectin or collagen [50], likely restricting phagocyte access. Finally, the multifunction secreted SIC protein can colocalize with the F-actin binding domain of ezrin that links the phagocyte cytoskeleton to the plasma membrane. This interference can be viewed as a mechanism to impair the biophysical events required or phagocytic uptake, as evidenced by the enhanced internalization of SIC-deficient mutants by human neutrophils [51].

Cytotoxicity & phagocyte apoptosis

GAS elaborate a variety of potent cytotoxins, and another important mechanism for innate immune resistance appears to involve triggering the death of the phagocytic cell types before bacterial killing can be accomplished. The pore-forming GAS β-hemolysin streptolysin S (SLS) exerts cytocidal activity on host neutrophils and thereby promotes GAS resistance to phagocytic killing [52,53]. The structurally unrelated cholesterol-binding cytolysin streptolysin O (SLO) is also toxic to human neutrophils and impairs their phagocytic capacity [54,55]. Consequently, both the SLS and SLO toxins are key virulence factors in the pathogenesis of invasive GAS infection [52,56,57]. The antiphagocytic functions of SLO may be more complex than direct cytolysis, as in an epithelial cell model SLO is seen to allow GAS to avoid lysosomal localization [58]. SLO also serves to deliver an NADase toxin to the host cell cytoplasm in a process known as cytolysin-mediated translocation [59]; the NADase activity depletes the host cell energy stores [60]. Finally, M protein released from the GAS surface can also be conceptualized as a toxin, forming complexes with fibrinogen that bind to β-integrins on host neutrophils, provoking the release of heparin binding protein and inflammatory changes leading to vascular leakage and severe disease [61].

Upon phagocytosis, GAS mediate a program of accelerated neutrophil apoptosis that can be correlated to enhanced phagocyte resistance relative to a variety of other common human pathogens [62]. Although the GAS virulence factors involved in the neutrophil apoptosis differentiation program and their cellular targets remain to be elucidated, epithelial cell models suggest GAS can induce a unique apoptosis pathway based on caspase-9 release, mitochondrial dysfunction and calcium regulation [63,64]. Additional evidence links GAS-induced macrophage apoptosis to activation of matrix metalloproteases by the cysteine protease SpeB [65].

Resistance to effectors of phagocyte killing

After phagocytic uptake of the target bacteria, neutrophils and macrophages deploy an array of bactericidal mechanisms including vacuole acidification, generation of reactive oxygen and nitrogen species, and production of cationic molecules including antimicrobial peptides (cathelicidins and defensins), myeloperoxidase and lysozyme [66]. Recently it has been shown that GAS can escape from the phagosome into the cytoplasm of neutrophils [67]. Since viable GAS can be isolated from inside host phagocytic cells both *in vitro* and *in vivo* [68], the traditional interpretation of GAS as an 'extracellular' bacterial pathogen is undergoing re-evaluation. Consequently, increased attention has been focused on the molecular basis of GAS survival within phagocytes. M protein was found to inhibit the fusion of azurophilic granules with the phagosome and other membrane trafficking events required for phagosome maturation [69,70].

Lacking catalase or carotenoid pigment such as those expressed by *Staphylococcus aureus*, GAS has generally been considered susceptible to host

oxidative burst killing. However, a recent study revealed that GAS expression of GpoA glutathione peroxidase allows the organism to adapt to oxidative stress and contributes to virulence in several animal models of pyogenic GAS infection [71]. Another mechanism of neutrophil intracellular killing involves the action of cathelicidin antimicrobial peptides, as demonstrated by the increased susceptibility of cathelicidin-deficient mice to invasive GAS infection [72]. One mechanism by which GAS resists cathelicidin killing is through incorporating positively charged residues into its cell wall lipoteichoic acid, leading to electrostatic repulsion of the cationic antimicrobial peptide. In this fashion, D-alanylation of teichoic acids mediated by the *dlt* operon promotes GAS resistance to cathelicidins and to neutrophil killing [73]. The human cathelicidin LL-37 and neutrophil α-defensins can be bound and inactivated by GAS protein SIC [74]. Finally, the secreted cysteine protease SpeB is trapped on the GAS surface by a2-macroglobulin bound to the bacterial surface protein GRAB; the retained SpeB is capable of degrading LL-37 and protecting the bacteria against its antimicrobial action [75].

Regulation of GAS virulence phenotypes

Expression of GAS virulence phenotypes is under the control of a complex set of global transcriptional regulators. These comprise two-component sensor kinase/response regulators, standalone response regulators and alternative sigma factors. Together, these frameworks coordinate GAS response pathways, including those functions to subvert host phagocyte clearance. For example, genes positively regulated by Mga (mutli-gene regulator) include those encoding M and M-like proteins responsible for impairing opsonization and promoting GAS neutrophil survival, the C5a peptidase (ScpA) targeting neutrophil chemokines, and the multifunctional antiphagocytic SIC protein [76]. Gene expression analysis of phagocytosed GAS uncovered a two-component response regulator Ihk/Irr critical for pathogen survival [77]. Ihk/Irr influences expression of 20% of the GAS genome, notably including genes involved in cell wall formation and peptidoglycan synthesis. Elimination of the response regulator gene (*irr*) yielded a GAS mutant that was unable to resist killing by cationic antimicrobial peptides and reactive oxygen species, and that was severely attenuated for virulence in the mouse necrotizing skin infection model [78].

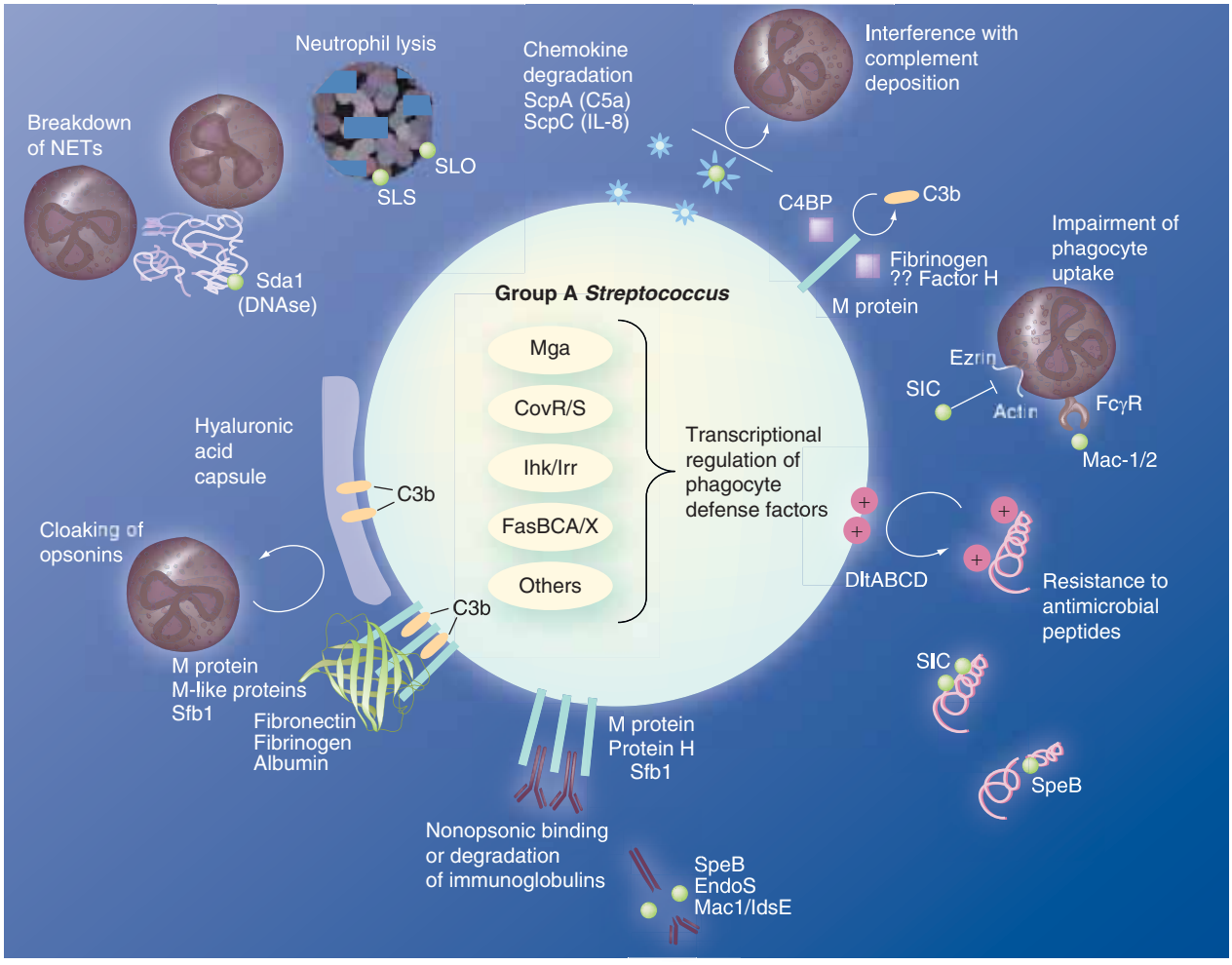
The two-component GAS global regulator CovR/S (for control of virulence) modulates the expression of several GAS virulence factors including the hyaluronic acid capsule, cysteine protease SpeB and the cytotoxin SLS [79]. CovR/S is thought to play a role in GAS adaptation to multiple stresses, including heat, acid and hyperosomolarity stress [80]. Recent data indicate that genetic mutations in the *covR/S* locus can be correlated with a phenotypic switch from mucosal to invasive forms of GAS infection. In comparing the transcriptional profile of GAS isolates from pharyngeal versus systemic infection, two distinct patterns emerged [81]. The switch from the pharyngeal to the invasive pattern could be recapitulated by mouse passage, and was traced to mutations in either CovR or CovS that lead to increased expression of hyaluronic acid capsule, IL-8 protease ScpC, protein SIC, DNAse Sda1, together with decreased expression of the cysteine protease, SpeB [81]. Loss of SpeB preserved M protein and streptokinase on the GAS surface, which allows accumulation and activation of the host protease plasmin, facilitating spread of the organism to the deep tissues [82].

A fascinating recent study by Graham and collegues has examined the transcriptional profile of GAS during the course of necrotizing soft-tissue infection and revealed a coordinated pattern of regulatory changes promoting increased expression of virulence factors involved in innate immune resistance and host tissue damage [83]. Upregulation of the Mga, IhK/Irr and FasBCA/X [84] regulators together with downregulation of negative transcription control factors such as CovR/S and PerR [71] in sum result in the robust *in vivo* expression of SIC, SLS, DNAse, IL-8 protease, M protein, SodA, hyaluronic acid capsule and other factors that can block phagocytic uptake, promote GAS resistance to phagocyte intracellular killing mechanisms or prove lethally toxic to the phagocytes.

Conclusions

GAS derives its scientific name *S. pyogenes* from the Latin for 'pus-generating', consistent with neutrophilic infiltrates observed at the site of acute GAS infection. The rising prevalence of deep-seated, invasive GAS infections corroborates the sophisticated suite of defense mechanisms the pathogen has evolved to avoid clearance by the host phagocyte response. As summarized in (Figure 1), these GAS virulence traits interfere at multiple points, from initial

Figure 1. Several virulence mechanisms by which the pathogen Group A *Streptococcus* resists host phagocyte defenses.



C4BP: C4b-binding protein; NET: Neutrophil extracellular trap; SIC: Serum inhibitor of complement; SLS: *Streptolysin* S; SLO: *Streptolysin* O.

neutrophil recruitment, to the processes of opsonization, to bacterial entrapment and uptake, and to intracellular effectors of bacterial killing; in several cases a single GAS molecule impairs multiple host defense mechanisms (e.g., the M protein). In certain strains of GAS, for example the globally disseminated M1T1 clone, accumulation of a larger repertoire of virulence factors (e.g., SIC and DNAse Sda1) poses a particular challenge to innate host defenses, and finds corroboration in epidemiological associations to severe disease, including necrotizing fasciitis and toxic shock syndrome. Moreover, mutations in the global transcriptional regulatory networks governing expression of GAS virulence genes may suddenly alter the pathogen-phagocyte equation, resulting in quantum shift toward enhanced invasive disease potential.

Future perspective

Most bacterial pathogens associated with significant human infection also typically exist in the transient microflora of healthy individuals in the context of asymptomatic colonization. Experimental analysis of GAS interaction with phagocytic cells of the innate immune system represents a useful paradigm for discovery and understanding of the underlying mechanisms dictating the development or prevention of serious bacterial infection. Much work remains to be done – of the many GAS factors reviewed in this paper, only a subset have been definitely proven to contribute to innate immune subversion *in vivo*, while others have been shown to promote GAS phagocyte resistance in *ex vivo* systems, and still others have simply been shown to interact *in vitro* with host effector molecules in a

fashion that could be predicted to promote the pathogen's survival. Future investigations will begin to define variations in host phagocyte defense dictated by genetic polymorphism or other factors such as concomitant viral infection that may render individual patients particularly vulnerable. Although GAS remain universally susceptible to β-lactam antibiotics including penicillin, considerable morbidity and mortality associated with invasive GAS disease reflects the pathogen's potential for rapid tissue spread and triggering organ system dysfunction. GAS vaccine development has progressed slowly, complicated by the lack of an immunogenic capsular polysaccharide, great antigenic diversity of the surface M protein and caution regarding the association of immunological cross-reactivity with the post-infectious complication of rheumatic heart disease. Improved understanding of the molecular basis of GAS phagocyte resistance may provide opportunities for therapeutic intervention, wherein novel pharmacologic agents act not to kill the bacterium directly, but rather to render it susceptible to our normal innate defenses.

Executive summary

Human infections caused by Group A Streptococcus

- Group A *Streptococcus* (GAS) is a major pathogen producing a wide spectrum of superficial and invasive human infections.
- Invasive GAS infections, including necrotizing fasciitis and toxic shock syndrome, strike up to 650,000 people annually with a mortality of 10–30%.
- The propensity of GAS to produce invasive infection in previously healthy individuals reflects several virulence determinants capable of interfering with innate phagocytic defense mechanisms.

GAS factors help the pathogen avoid engagement by phagocytes

- The complement-derived chemoattractant peptide C5a is cleaved by the GAS peptidase ScpA.
- The CXC chemokine interleukin-8 is degraded by the GAS serine protease ScpC.
- GAS DNAses prevent capture in DNA-based neutrophil extracellular traps.

GAS molecules inhibit complement & antibody function

- The GAS hyaluronic acid capsule is nonimmunogenic, mimicking a common human matrix component, and cloaks opsonins deposited on the bacterial surface from phagocyte recognition.
- M and M-like proteins and Sfb1 recruit host matrix proteins (fibronectin, fibrinogen and collagen) to form a protective coating against opsonin recognition.
- M protein binds complement regulator C4b-binding protein to limit C3b deposition.
- The protein streptococcal inhibitor of complement (SIC) interferes with formation of the C5–9 terminal complement membrane attack complex.
- M protein and Sfb1 nonopsonically bind immunoglobulin via the Fc domain.
- Cysteine protease SpeB degrades immunoglobulins.

GAS impairs phagocytotic uptake mechanisms

- EndoS hydrolyses the IgG glycans involved in Fcγ receptor recognition.
- Mac-1 and -2 bind to neutrophil Fc receptors, inhibiting recognition of IgG on bacterial surface.
- Protein SIC impairs actin cytoskeletal arrangements required for bacterial uptake.

GAS promote phagocyte lysis and apoptosis

- The pore-forming streptolysin S and streptolysin O are cytotoxic to neutrophils and macrophages.
- GAS induces an accelerated apoptosis program in human neutrophils.

GAS resists specific effectors of phagocyte killing

- D-alanylation of lipoteichoic acid, SpeB proteolysis and SIC binding interfere with host cationic antimicrobial peptide function.
- GAS escape the phagosome, and M protein can block azurophilic granule:phagosome fusion.
- GpoA glutathione peroxidase allows GAS to adapt to oxidative stress.

Transcriptional control of GAS phagocyte resistance phenotypes

- GAS tightly regulates the expression of these phagocyte resistance factors through an interacting web of transcriptional regulators including CovR/S, Mga and Ihk/Irr.

Future perspective

- Understanding the molecular basis of GAS phagocyte resistance may reveal novel therapeutic targets for treatment and prevention of invasive human infections.

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Affiliations

- *Laura A Kwinn*
Division of Pediatric Pharmacology & Drug Discovery, University of California, San Diego School of Medicine, La Jolla, CA 92093, USA
Tel.: +1 858 534 9760;
Fax: +1 858 534 5611;
lkwinn@ucsd.edu
- *Victor Nizet*
Division of Pediatric Pharmacology & Drug Discovery, University of California, San Diego School of Medicine and Skaggs School of Pharmacy & Pharmaceutical Sciences, 9500 Gilman Drive, Mail Code 0687, La Jolla, CA 92093-0687, USA
Tel.: +1 858 534 7408;
Fax: +1 858 534 5611;
vnizet@ucsd.edu