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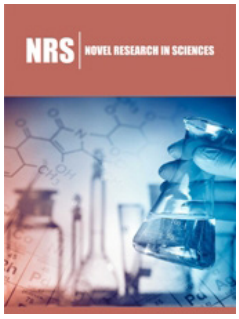
Review Article

Group A Streptococcus, the Story of the Perfect Warrior and the Lonely Defense

Sylvia Frisancho-Kiss*

Department of Anaesthesiology and Intensive Care, Hospital Komárno, Slovakia

ISSN: 2688-836X



***Corresponding author:** Sylvia Frisancho-Kiss, Department of Anaesthesiology and Intensive Care, Hospital Komárno, Slovakia

Submission: March 13, 2023

Published: March 27, 2023

Volume 14 - Issue 3

How to cite this article: Sylvia Frisancho-Kiss. Group a Streptococcus, the Story of the Perfect Warrior and the Lonely Defense. Nov Res Sci. 14(3). NRS.000837. 2023.
DOI: 10.31031/NRS.2023.14.000837

Abstract

The updated definition of sepsis encompasses the preeminence of the dysregulated immune response during disease pathogenesis. The emerging problem of unusually and disturbingly high lethality of group A Streptococcus (GAS) infection among children in the UK lately triggers one to rethink and personalize this definition. Group A Streptococci create an opportunity to demonstrate immune dysregulation in its abundance, when looking at the issue exclusively from the perspective of the pathogen, even though the story from the perspective of the diverse and often skewed immune system response of the host would be equally important. Due to the inherent nature of pathogen virulence, and susceptibility of hosts that are determined and dynamically shaped by ongoing genetic and environmental happenings, dysregulated immune response in a broader sense is contributing to infections on every degree of severity.

Abbreviations: GAS: Group A streptococcus; PANDAS: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; GBS: Group B streptococcus; Siglec:sialic acid-binding immunoglobulin-type lectins; HA: Hyaluronic acid; C3: Complement component 3; SIC: Streptococcal inhibitor of complement; MAC: Membrane attack complex; SPE: Streptococcal pyrogenic exotoxin; MHC II: Major histocompatibility complex II; IFN**γ**: Interferon gamma; TNFα: Tumor necrosis factor alpha; IL-1β: Interleukin one beta; MMPs: Matrix metalloproteinases; TSS: Toxic shock syndrome; PVL: Panton-Valentine Leukocidin; SLO: Streptolysin O; SLS: Streptolysin S; NF-κB: Nuclear factor kappa B; RBC: Red blood cells; ICU: Intensive care unit; ROS: Reactive oxygen species; NAD: Nicotinamide adenine dinucleotide; SIRS: Systemic inflammatory immune response

Keywords: Group A streptococcus; Immune evasion; Superantigen; Cytokine storm; Phagocytosis; Monoclonal antibodies

Introduction

GAS or Streptococcus Pyogenes(SP), is able to produce hundreds of millions of infections yearly, mostly self-limiting and local, but occasionally, with increasing prevalence, life threatening generalized septical conditions emerge with a mortality rate above half a million yearly [1]. After a previous viral exposure, in a chronically mentally and economically stressful environment, or a colonized background, there will be more ground for successful invasion. After infection, particularly acute sepsis, a period of immune silence and exhaustion with upregulated suppressive immune phenotype supervenes. Mechanisms of defense are impaired and local barriers of resistance are weakened. Bacteria gain survival advantage due to the ability to readily adapt to the changing environment. It is hard to find a similarly diverse pathogen in its ability to evade and hijack the immune response for its own invasive purpose, then it comes by surprise and appreciation, that the human immune system after all the obstacles is still able to implement a very efficient defense line to mitigate, localize and suffocate the symptomatic infection.

GAS produces an immensely wide array of derailing strategies to subdue the host and to shape the immune response to become dysfunctional and dysregulated. The optimal immune response is the one that efficiently and timely stops invasiveness, clears the

pathogen and prevents tissue and organ damage stemming from direct pathogen injury and collateral damage without extreme engagement, deterioration and exhaustion of the host; multiple evasion techniques however, lead to a skewed immune response. Based on existing research libraries, I will briefly describe the dominant, clinically alarming faces of equivocation used by GAS. Due to a large variety of virulence mechanisms, impaired opsonophagocytic, function direct osmotic cytolysis, macrophage apoptosis, superantigen mediated nonspecific deregulated T cell activation with cytokine storm, dismantling IgG molecules, impaired immune complex clearance, emergence of molecular mimicry and taking hostage of certain complement regulators and effectors, a sophisticated and complex frontline is triggered leading to considerable dissonance of the immune response, with defective phagocytosis and aberrant cytokine production. Reverberations of the immune response are complex, and they materialize on several levels.

Main Article

Group A Streptococci are gram positive cocci, present in carrier state on the pharyngeal mucosa of about 20% of the population, and human to human airborne transfer represents the main route of dissemination. If infection eventuates, there are a variety of possible clinical presentations. Pharyngitis, scarlet fever, impetigo, toxic shock syndrome, pneumonia, osteomyelitis, septic arthritis, necrotizing fasciitis, meningitis and late autoimmune consequences such as rheumatic fever, glomerulonephritis , pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, (PANDAS), Tourette syndrome may emanate. Large epidemics of high fever associated scarlet fever were prevailing during early 20th century, they subsided even before the introduction of antibiotics, but surges of the disease occur periodically, mostly in developing countries, with mortality rate of 16% to 25% and up to 50% in case of necrotizing fasciitis and toxic shock syndrome [2,3]. Of the predisposing factors, the most influential are extremes of age, male gender and non-white ethnicity, previous viral infections, intravenous drug users, diabetes, heart conditions and malignancy. The complex strategy of SP is embedded in deceiving the immune system and then forcefully attacking the body particularly by means of exotoxins. As per immune virulence mechanisms, the strength and type of receptor recognition are of significance. Bacterial adherence and cellular uptake are mediated by several host receptors. Group B pneumococcus (GBS) for example, the causative agent of neonatal sepsis and meningitis is recognized due to the composition of its polysaccharide capsule by lectin type, inhibitory Siglec receptors [4]. In case of encapsulated SP, the hyaluronic acid (HA) based capsule creates the first line of defense against immune mediated elimination. HA is a relatively structurally conserved entity of the extracellular matrix [5]. Anti-HA antibodies, due to the extent of homology with the host, may attack heart and joint tissue with autoimmune consequences. The value of the capsule for the pathogen is in prevention of C3 deposition and opsonization [6].

Adhesiveness is mediated by the interactions between HA capsule and CD44 molecule on the surface of epithelial cells [7]. Streptococcus pyogenes has more than 80 serotypes based on M protein structure. M protein is a major molecular mimicry antigen in late repercussions of GAS infections such as rheumatic fever, and an immunodominant antigen of the SP wall, resisting phagocytosis [8]. The M cell wall protein perpetrates multiple roles in SP virulence as adherence factor, invasion and antiphagocytic molecule [9]. Recent repeated surge of invasive infections was associated with certain more virulent serotypes, most frequently serotypes M1 and M3. M1 is distinctive due to the presence of extracellular SIC protein (streptococcal inhibitor of complement), that is capable of incorporating into the terminal membrane attack complex (MAC), and disables MAC associated cell lysis [10]. Streptococcal pyrogenic exotoxins (SPE) contribute to septic shock syndromes with multiorgan failure. They are mostly superantigens, which in diminutive amounts, bypassing the orderly route of antigen processing and presentation, that would lead to the emergence and expansion of specific T cell clones, directly bind to major histocompatibility complex II (MHCII) and cause massive polyclonal T cell activation, with cytokine storm, with excessive IFN-γ and TNF-α production [11,12]. Beyond that, pyrogenic exotoxin B is able to activate proIL-1β to its active form. SPE B is cleaved by cysteine protease to active form, and the enzyme can be inactivated by neutralizing antibodies. SPE is proficient at activating proIL-1β, cleaving fibronectin, activating MMPs, releasing biologically active kinines that cause overt vasodilation and increased permeability leading to the symptoms of capillary leak. The role of IL-1β is complex, while absolute deficiency is detrimental, proportionate increase is protective, overt presence drives pathology in toxic shock syndrome (TSS) [13,14].

Superantigens are typically ammunition to Staphylococcus aureus, Streptococcus pyogenes, equi, agalactiae, Yersinia pseudotuberculosis, Mycoplasma arthritis. Perhaps staphylococcal and streptococcal superantigens emerged from a common precursor. There are at least 12 known superantigens owned by GAS. Another hallmark superantigen is the bacteriophage encoded Panton-Valentine Leukocidin (PVL) of Staphylococcus aureus, capable of NF-kB activation [15]. One of the major determinants of GAS virulence is streptolysin O (SLO), a very potent antigenic, cholesterol dependent oxygen labile exotoxin, potentially leading to massive host cell apoptosis, including neutrophils and macrophages [16], epithelial cells, cardiomyocytes, hepatocytes, renal cells, synovial cells. Cytotoxicity requires direct cell to cell contact [17], attachment is possible due to the presence of cholesterol in the host cell membrane. Surface bound SLO oligomerizes and creates holes in the membrane [18,19] that ultimately leads to cell lysis. In several studies SLO levels correlated disease severity, and disease activity was successfully extenuated upon SLO removal or reduction under experimental conditions [20]. It is commendable to mention that SLO belongs to the wider group of cholesterol-dependent pore forming toxins, the family of 28, such as neurolysin, listeriolysin and perfringolysin. Curiously anti- perfringolysin monoclonal antibody was cross-reactive with SLO and was protective against streptococcal toxic shock syndrome [21]. Human albumin binds and neutralizes SLO [22]. Another important GAS toxin is NADase that

cleaves nicotinamide adenine dinucleotide (NAD) to nicotinamide and adenosine phosphoribosyl to cause energy depletion in the host cells. NADase is dependent on SLO for internalization, both are therefore synergistic in enhancing GAS virulence, and experimental deletion of NADase leads to SLO deficiency [23]. It has been shown that SLO is responsible for septic cardiomyopathy, when subtoxic doses of SLO cause calcium influx, reduced response to electrical stimulation and impaired contractility [24].

Streptolysin S (SLS) on other hand is an oxygen stable exotoxin, present in 99% of GAS isolates, lacking immunogenicity. Beyond its cytolytic effects, extinguishing neutrophils and macrophages, SLS modifies cytokine signaling [25]. SLS is known to cleave extracellular junctions to boost invasiveness, experimentally induces keratinocyte death and tissue injury [26,27].

GAS is not solely capable of escaping neutrophils, it also has a pronounced beta hemolytic activity (28), interacts with fibrinogen and produces streptokinase, a major thrombolytic enzyme [29]. Staphylococci and streptococci grow well on blood agar in laboratory and in patients. Streptococci in fact are categorized based on the extent of hemolysis to alpha, beta and gamma (no hemolysis) groups. The clinical importance of this categorization is valid, because beta hemolysis-mediated by oxygen stable S, and oxygen labile O streptolysin-is a complete breakdown of red blood cells (RBCs) , typical for group A-Streptococcus pyogenes and group B-Streptococcus agalactiae. During alpha hemolysis, induced by Streptococcus viridians, the bacterial hydrogen peroxide reduces hemoglobin to methemoglobin, by oxidizing iron (Fe2+ to Fe3+) , and the latter is not capable of binding and carrying oxygen. Newborns up to four months of age have heightened sensitivity towards methemoglobin production, hence they are more endangered by hypoxia [30]. Streptococci are catalase negative organisms, unable to reduce hydrogen peroxide to nontoxic breakdown products. The GAS interaction with the coagulation pathway is through streptokinase (SK) that binds to host plasminogen and induces fibrinolysis, to degrade the fibrin nets that were initiated to localize the infection. The SK-plasmin complex is irreversible and is resistant to intrinsic degradation by host a2- macroglobulin and a2- antiplasmin. Before the introduction of alteplase, which is manufactured using recombinant DNA technology in Chinese hamster ovary cells, streptokinase from group C streptococcus served as a thrombolytic agent [31]. Engagement of M1 protein on the arterial walls leads to a vasoplegic effect, and enhanced cytokine response mediated by Toll-like receptor 4 (TLR4) in the presence of fibrinogen [32].

Convalescent plasma and intravenous immunoglobulin have been used in invasive toxic infections and efficiently decreased mortality by decreasing superantigen induced polyclonal T cell activation. A combination of recombinant monoclonal neutralizing antibodies against major virulence toxins could be a further advancement in situations, when time is of essence and the effect of antibodies may be offset by pathogen speed. Certain streptococcus-related antibodies are equipped with cross-reactivity against host tissue in an inflammatory environment, hence monoclonal antibody choice should be carefully designed [33]. Unfortunately GAS is able to dismantle IgG molecules using at least two strategies, by secreting a IgG specific protease, separating Fab from Fc regions, or by endoglycosidase that separates the N-glycan region of Fc receptor responsible, if allowed, for the effector function of the antibody [34]. Self-reactivity is an emblematic late aftermath of GAS infection, the mechanism of emergence is molecular mimicry between pathogen and host tissue in an inflammatory environment, coming forth one to ten weeks after acute infection in forms of rheumatic fever or glomerulonephritis. The preeminent participating antigens of GAS are the M5 protein, the hyaluronic acid capsule, N-acetylglucosamine, 60kDa wall membrane antigen and a 67kDa antigen cross-reacting with myosin, tropomyosin, keratin, laminin, and vimentin od the host tissue [35]. Cross-reactivity is not unique to GAS, a similar association is attributed to Campylobacter jejuni and Guillain-Barre Syndrome , Borrelia burgdorferi and Lyme disease [36].

The complement evasive and antiphagocytic actions of PS are multifold. Beyond the above mentioned SIC protein, M protein binds to factor H, a negative regulator of the alternative complement pathway, protecting kidneys and RBC from complement mediated collateral damage. Under normal circumstances factor H is unable to bind to pathogen, but only to self, with the aim of enabling C3b mediated killing of pathogen and concurrent protection of self. Once factor H connects with GAS via M protein on one hand , and pathogen bound C3b on other hand, further complement activation and MAC formation will be disabled via decay accelerating activity, as if GAS was a self-molecule. Fibrinogen binding to protein M inhibits the activation of alternative complement pathway and deposition of C3b molecules on the surface of GAS. The outer hyaluronic acid capsid renders ultimate resistance towards phagocytosis due to its physical barrier function perhaps. Inhibition of phagocytosis is a survival mechanism to replicate and produce toxins. GAS carry C5a protease, early studies showing its function in cleaving the complement anaphylatoxin C5a, hence decreasing neutrophil mobilization and recruitment. In subsequent experiments C5a protease effect had been shown to be broader and C3a, C3 and C5 deficient mice had impaired bacterial clearance, under in vitro conditions due to C5a esterase mediated , C3 and C5 independent endothelial and epithelial GAS attachment [37]. In other aspects of ICU related sepsis, C5a may be detrimental [38], perhaps due to very high levels, when it becomes accessory to impaired phagocyte maturation and reactive oxygen species production, increased capillary permeability in animal models and critically ill patients .

Discussion

The discovery of penicillin, and antibiotics in general, was one of the most valuable revolutions in medicine. But even antibiotics have a scale of efficiency and specificity and lately their limits are more and more often reached. The emerging bacterial resistance is the consequence of constant upgrading and reciprocation of resistance mechanisms of these highly intelligent organisms, with the ultimate danger of creating “superbugs”, which raises the need to defend the host by additional means, to enhance potency

and to gain time. For the sake of success understanding the many faces of pathogen virulence, immune evasion and the degree and shape of individual immune response are desired. While basic science experiments create an unconditionally essential backbone of knowledge, they cannot be directly extrapolated to clinical conditions, hence comprehensive immune monitoring of individual patients in a clinical environment is vital. The emergence of lethal GAS cases is yet another example of broken tolerance in a broader sense. GAS is a capsulated aerotolerant coccus, equipped with several potent toxins. Due to its architecture it is able to resist phagocytosis, complement mediated killing, and the ongoing proinflammatory host response creates an environment of high energy consuming activation state that is derailed and neutralized in its executionary function. There is a hope that future immune support may come in the form of antidotes, monoclonal antibodies, even enhancers of phagocytosis and clearance to aid antibiotics in selected, severe life threatening conditions while reconciling the ongoing systemic inflammatory response syndrome (SIRS). In theory, similarly to development to antibiotic resistance, the decision on what treatment to apply when and for how long must be weighed, because countermeasures from pathogens, escape mechanisms to avoid recognition by neutralizing antibodies are likely to advance.

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