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REVIEW

Pathogenesis of Streptococcus pyogenes and immune response

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Abstract:

Streptococcus pyogenes is a Gram-positive beta-hemolytic bacteria, also known as group A streptococci, that causes a range of infections. The most common presentation is acute pharyngitis. GAS can be subdivided into >100 serotypes by the M-protein antigen that is located on the cell surface and by fimbriae (hairlike fuzz) that project from the outer edge of the cell. Classically, typing of the surface M protein relied upon available polyclonal antisera. GAS produce and release into the surrounding medium a large number of biologically active extracellular products. Some of these are toxic for human and other mammalian cells. Streptolysin S (SLS) is a small oxygen-stabile toxin responsible for β-hemolysis of GAS on blood agar, while streptolysin O (SLO) is an oxygen-labile, cholesterol-dependent toxin .Both SLS and SLO injure cell membranes, not only lysing red blood cells, but also damaging other eukaryotic cells and membranous subcellular organelles.15 Streptolysin O is antigenic; streptolysin S is not. Streptococcal pyrogenic exotoxins (SPEs) are secreted factors with the capacity to act as superantigens and trigger T-cell proliferation and cytokine release.

Introduction

Streptococcus pyogenes, commonly known as group A streptococcus (GAS) is a fermentative, facultative anaerobe, nonmotile, nonspore-forming gram-positive coccus, which occurs in chains or pairs, having a diameter of 0.5-1.0 μm (1). *Streptococcus pyogenes* （group A streptococcus） is a gram positive bacteria that associated with a variety of mucosal and invasive human infections . group A Streptococci are important cause of sever life threatening life illness among the elderly and immuncompromised individuals . although A group Streptococcus considered an extracellular pathogen , recent studies have demonstrated that strains of these bacterium can internalize into epithelial cells both in vitro and in vivo (2).

Streptococcus pyogenes is differentiated as group A streptococcus (GAS) as it contains N- acetyl glucosamine linked to rhamnose polymer (3). The group A streptococci are fastidious organisms that have complex growth requirements. A highly nutritious growth medium that provides optimal growth GAS are generally grown on agar media supplemented with blood. This technique allows the detection of β-hemolysis, which is important for subsequent identification steps special procedures have been developed to optimize the identification of *S. pyogenes* in throat cultures when properly performed and interpreted, culturing throat swabs on a 5% sheep blood agar with trypticase soy base (4).

S. pyogenes is capable of infecting humans, mainly through adhesion and colonization of the host mucosal surface epithelial cells of the upper respiratory tract has also been associated with inflammatory complications such as scarlet fever

chronic diseases including tonsillar hypertrophy and sleep apnea and the post-infectious sequelae including acute rheumatic fever (5).

A variety of virulence factors are associated with the severity of GAS infection including streptolysin O and S (hemolysin), streptokinase, streptodornase, M protein and its related protein, hyaluronic acid capsule, hyaluronidase, the cysteine protease SpeB, superantigen proteins (SAgs), and several phage-encoded exotoxins, SAgs contribute to GAS pathogenicity based on their immune stimulatory activity. *sag* genes distribution has been used as a method for the detection of genomic heterogeneity, the correlation between gene contents, and the determination of clinical manifestation (6)

Protein M is considered as the main virulence factor, limiting phagocytosis, disturbing the function of complement, and being responsible for adhesion M protein is the most analyzed virulence factor which can be used in the serotype classification of S.pyogenes . Virulence factors are equally distributed within S. pyogenes; some are encoded by chromosomes, while others depend on the presence of mobile genetic elements. Confirmation of their presence or absence is considered as a simple clinical diagnosis method (7).

Moreover, invasive S. pyogenes strains, which cause deep soft-tissue infections and fasciitis as well as streptococcal toxic shock syndrome (STSS) and sepsis, also produce highly specific toxins with special pro-inflammatory properties. Streptococcal pyrogenic Exotoxins (SPE) possess superantigen properties and bridge antigen-presenting cells with immune

system effector cells, leading to their polyclonal activation This activation leads to accelerated T lymphocyte proliferation and liberation of significant quantities of proinflammatory cytokines, leading to toxic shock (8).

Group A streptococci bacteria express extracellular toxins to directly attack immune cells or induce harmful by-products. Streptolysin O (SLO) is a 69-kDa cholesterol-dependent and oxygen-labile cytolysin that contributes to beta-hemolysis in blood agar medium . SLO oligomerizes to form large pores 25 to 30 nm in host cell membranes ,SLO promotes resistance to phagocytic killing by disrupting the integrity of host cell membranes (9).

Pathogenesis of *S. pyogenes*

Group A streptococci are transmitted through a number of modalities. Direct person-to-person transmission occurs through the inhalation of respiratory droplets or through skin contact. Transmission through environmental reservoirs has been strongly implicated in experimental or outbreak investigations, either through direct contact with contaminated objects and surfaces or through dust particles. transmission through consumption of food inoculated by food handlers colonized with *S. pyogenes* has become less common, it still occasionally occurs and does result in outbreaks (10).

The first step in GAS disease pathogenesis involves successful colonization of the upper respiratory mucosa to cause pharyngitis or skin to cause impetigo, cellulitis of human host. A large number of adherence factors for epithelial cells and extracellular GAS have been described, including lipoteichoic acid (LTA) , M protein, pili, and fibronectin-binding proteins including Sfb1 and SOF, the first receptor for LTA was fibronectine (fn), (2 ,11). GAS biofilm formation facilitates persistence within the human host. Both M protein and fibronectin-binding proteins are important for

subsequent endocytotic uptake of GAS into respiratory epithelial cells. This process of intracellular invasion allows GAS access to a privileged intracellular niche, and represents a proximal step in the pathogenesis of systemic infection.(12).

S. pyogenes produce of streptolysin O (SLO),and streptolysin S (SLS) a pore-forming toxins are toxic to multiple host cell types including macrophages and neutrophils, and thus promote GAS tissue damage and resistance to phagocytic clearance. SLO in particular can induce the accelerated apoptosis of immune cells. The GAS hyaluronic acid capsule is nonimmunogenic, mimicking a common human matrix component, and cloaks opsonic targets on the bacterial surface from phagocyte recognition. The GAS hyaluronic acid capsule is nonimmunogenic, mimicking a common human matrix component, and cloaks opsonic targets on the bacterial surface from phagocyte recognition. (9)

Many *S. pyogenes* strains also produce NAD-glycohydrolase (NADase), an enzyme that is translocated into the cytosol of epithelial cells in an SLO-dependent fashion. NADase inhibits the fusion of lysosomes with *S. pyogenes*-containing autophagosomes, preventing their maturation into degradative autolysosomes and prolonging intracellular survival. In this way, SLO and NADase enhance the survival of *S. pyogenes* within epithelial cells and may contribute to its overall persistence in the pharynx (7)

In the case of GAS, factors which avoid entrapment by phagocytes include peptidase ScpA, serine protease ScpC, DNAses. Capsule, M protein, (SpeB) cysteine protease and (SIC) streptococcal inhibitor of complement-mediated lysis inhibit complement and antibody functions (13).

Group A streptococci also impairs phagocytic mechanisms with the help of the factors, Mac (1 and 2) and SIC. Cytolysins which promote phagocytic lysis and apoptosis are also used by GAS. Finally, GAS resist effectors of phagocytic killing by D- anylation of (LTA) lipoteichoic acid, SpeB, SIC, M protein and GpoA (glutathione peroxidase) (14).

Immunologic response

Although many GAS constituents and extracellular products are antigenic, protective immunity is type-specific, mediated by opsonic anti-M-protein antibodies. These antibodies protect against infection with a homologous M type but confer no immunity against other M types.

Therefore, multiple GAS infections attributable to different M types are common during childhood and adolescence. Anti-M antibodies persist for years, perhaps for life, protecting against invasive infection but not against pharyngeal carriage.Type-specific antibody against M protein is not usually detectable until 6 to 8 weeks after infection. Therefore, its primary role may not be in the limitation or termination of active infection, but rather in the prevention of reinfection by the same serologic type. (15)

In humans, very little is known about the cellular component of an anti-GAS immune response. A previous study indicated the presence of anti-GAS Th1 T cells, but, as whole bacteria were used in their stimulation assays, it cannot be excluded that the observed responses in part derived from innate cells Regarding responses against single proteins, CD4 T cells (directed against GAS M protein) are found in tonsils of patients with recurrent tonsillitis and tonsillar hypertrophy, and these CD4 T cells proliferate and produce cytokines (IFN-g, IL-2, IL-4, IL-5, and IL-6) . It has also been suggested that the M protein induces human regulatory T cells to suppress adaptive

responses as a defense mechanism of GAS . Hence, it is clear that exposure to GAS bacteria in fact induces cellular immune responses in humans against the M protein, but the details of this response are still obscure. More importantly, nothing is known about the cellular immunity against protein targets other than the M protein. Because the M protein is highly vAariable, and immune responses to the M protein may be harmful to the host, studies with non-M protein Ags are important regarding the development of future GAS vaccine (16)

References:

1-Amano,A.; Ichiro Nakagawa,I. and Yoshimori,T.(2006).Autophagy in Innate Immunity against Intracellular Bacteria, *The Journal of Biochemistry*. 161–166

2-Ghasemi A., Namaki S , Abbas Mirshafiey, PhD Streptococcus pyogene journal of clinical chines medicine volume 4 ; supplement:9-18

3-Slotved H.C., Elliott J., , ompson T., and Konradsen H. B. (2003).“Latex assay for serotyping of group B Streptococcus isolates,” Journal of Clinical Microbiology, vol. 41, no. 9, pp. 4445–4447,

4-Shulman ,S.T.; Bisno, A.L. and Clegg ,H.W.(2012). Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis:2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 55(10):e86–e102.

5-Wessels ,M.R. (2016).Streptococcal Pharyngitis N Engl J Med .364:648-55

6-Helal Z.M., Rizk DE.E., Adel El-Sokkary M.M. , and Hassan R.(2020) Prevalence and Characterization of Streptococcus pyogenes Clinical Isolates from Different Hospitals and Clinics in Mansoura. Hindawi International Journal of Microbiology Volume Article ID 5814945, 11 pages https://doi.org/10.1155/2020/5814945

7-Walker ,M. J.; Barnett ,T. C.; McArthur ,J. D.; Cole ,J. N. and Gillen C. M.(2014). Disease manifestations and pathogenic mechanisms of group A streptococcus. Clinical Microbiology Reviews. 27(2):264–301

8-Golińska ,E.; Linden ,M.; Więcek ,G.; D. Mikołajczyk ,D.; Machul ,A.;Samet ,A.; Piórkowska ,A.; Dorycka, M.; Heczko , P.B.and Strus,M.(2016). Virulence factors of Streptococcus pyogenes strains from women in peri-labor with invasive infections. Eur J Clin Microbiol Infect Dis . 35:747–754

9-Timmer, A.M.; Timmer,J.C.; Pence, M.A.; Hsu, L.C.; Ghochani,M.;. Frey, T.G.; Karin, M.; Salvesen, G.S. and Nizet,V. (2009). Streptolysin O Promotes Group A *Streptococcus* Immune Evasion by Accelerated Macrophage Apoptosis THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 284, NO. 2, pp. 862–871

10-Kemble , S. K.; Westbrook , A.; Lynfield , R.; Bogard, A.; Koktavy ,N. and Lappi V.(2013). Foodborne outbreak of group a streptococcus pharyngitis associated with a high school dance team banquet--Minnesota, 2012. Clinical Infectious Diseases. 57(5):648–654

11-Bisno AL, Brito MO, Collins CM. Molecular basis of group A streptococcal virulence (2003). Lancet Infect Dis;3:191–200.

12-Doern CD, Roberts AL, Hong W, et al. (2009). Biofilm formation by group A Streptococcus: a role for the streptococcal regulator of virulence (srv) and streptococcal cysteine protease (SpeB). Microbiology;155:46–52

13-Ogawa, H.; Ogawa, M.; Terao, T.; Sumitomo,Y.; Nakata, T.; Ikebe,M.; Maeda,K.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

14-Kwinn ,L.A. and Nizet,V. (2007).How group A *Streptococcus* circumvents host phagocyte defenses

15-Mortensen R., Nissen T.N.,, Thoma Blauenfeldt T., Christensen J.P., Andersen P. and Dietrich J.(2015).Adaptive Immunity against Streptococcus pyogenes in Adults Involves Increased IFN-g and IgG3 Responses Compared with Children
The Journal of Immunology, Print ISSN: 0022-1767 Online ISSN: 1550-6606.2015

16-Price J. D., J. Schaumburg C. Sandin, J. P. Atkinson, G. Lindahl, and C. Kemper. (2005). Induction of a regulatory phenotype in human CD4+ T cells by streptococcal M protein. J. Immunol. 175: 677–684