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Review Article

The Conjugation of Pathogenicity Factors and Metabolic Adaptation in Streptococcus Pyogenes

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Abstract

Streptococcus pyogenes belongs to the long-known and most relevant conditional human pathogens. Due to the production of various pathogenicity factors, *S. pyogenes* is adapted to colonize mucosal and cutaneous surfaces and to evade immune defense. These are surface structural components (M-proteins, factors binding blood proteins, lipoteichoic acids) and secreted proteins (pathogenicity enzymes - serine and cysteine proteinases, including C5a-peptidase; glycolytic enzymes - glyceraldehyde-3-phosphate dehydrogenase and α-enolase; streptolysin O, etc.). The same pathogenicity factor is involved in different stages of the infectious process, from adhesion, biofilm formation and invasion, to inhibition of complement components, immunoglobulins, disruption of opsonization and phagocytosis. *S. pyogenes* is capable of persistence within phagocytes. Under conditions of deficiency of glucose, the main source of energy production, the pathogen is capable of synthesizing ATP by catabolizing arginine. The conjugation of metabolic changes and virulent activity is controlled by bipartite and individual gene transcription regulators. Strategies to develop combined, recombinant vaccines based on pyogenic *Streptococcus* proteins are promising. Significant immunogenicity along with M-proteins, C5a peptidase and CspA protease was revealed in the regulatory proteins Rgg and MutR.

Keywords: *Pathogenicity Factors; Metabolic Adaptation; Regulatory Proteins*

Introduction

The dominance of *S. pyogenes* in the epidemiology of streptococcal infections is conditioned by the pathogen capacity to produce a wide spectrum of pathogenicity factors, high genome plasticity and metabolic adaptation, which allow to colonize the tissue surface and evade immune protection. The material of the article is based on a literature review of studies on pathogenicity factors, molecular mechanisms of adaptation and the role of transcriptional regulatory systems in pyogenic *Streptococcus*. Studies concerning the mechanisms of metabolic adaptation of the pathogen, analysis of the role of bicomponent and individual regulatory proteins, including Rgg and MutR, aimed at the development of recombinant vaccines based on M-proteins, anticomplementary streptococcal proteinases, Streptolysin O.

S. pyogenes pathogenicity factors

The following biomolecules belong to the pathogenicity factors of *S. pyogenes*, providing adhesion, colonization, biofilm formation, invasion, resistance and evasion of immune protection:

- Surface structural components (M-protein family; fibronectin-binding proteins-F1 and F2, SfbI, SfbII, SOF, PFBP, FbaA and FbaB; streptococcal collagen-like protein 1 - Scl1; filamentous protein structures - fibrils and fimbria; lipoteichoic acids).

- Secreted proteins, including pathogenicity enzymes (proteinases, streptokinase, hyaluronidase, DNAases, etc.) and toxins (streptolysins S and O).

Among the pathogenicity factors belonging to the surface structural components of *S. pyogenes*, M-proteins are particularly significant. The M-protein family includes M-proteins proper and M-like proteins (H, Enn, Arp, Sir). They are characterized by a variable N-terminus, which is typospecific and a conservative C-terminus, responsible for antiphagocytic activity. M proteins joining with Fc-fragment of IgA and IgG, with complement components C3b, C4br, with plasminogen, fibronectin and other blood proteins inhibit complement system activation, opsonization and phagocytosis [1,2].

Fibronectin-binding proteins of *Streptococcus*, binding to fibronectin on the surface of tissue cells, inhibit C3b attachment.

Collagen-like protein-1 is involved in the processes of adhesion and biofilm formation, and contributes to pathogen evasion from neutrophil extracellular traps.

Filamentous structures (fibrils and fimbriae) are found on the surface of *Streptococcus* cells. They mediate adhesion to host cells and components of the extracellular matrix and promote bacterial aggregation [3]. Lipids of the bacterial membrane, lipoteichoic acids, contribute to overcoming the repulsive electrostatic forces between microorganisms and the surface of tissue cells and facilitate adhesion of microbial cells.

Many proteolytic enzymes of pyogenic *Streptococcus* are able to cleave proteins and nucleic acids, damage structural components of tissue cells, promote pathogen evasion of immune protection factors [4,5].

Cysteine and serine proteinases can inactivate cytokines, complement components, and immunoglobulins. *Streptococcus* cysteine proteinase, IdeS, is capable of cleaving the hinge region of IgG. Serine proteinase (SpyCEP) activates the cleavage and inactivation of IL-8 chemokines that recreate neutrophils into the zone of microbial invasion [6]. SpyCEP and C5a-peptidase inactivate the C5a component of the complement that activates neutrophil chemotaxis [6,7].

S. pyogenes also secrets endopeptidases (IdeS/Mac-1, Mac-2, and EndoS) that degrade immunoglobulins. IdeS/Mac-1, Mac-2 bind to the Fc-fragment of Ig, and EndoS cleaves the glycan in the immunoglobulin molecule. Streptococcal esterase (SsE) promotes colonization and spread of the pathogen by hydrolyzing the platelet-activating factor phospholipid mediator (PAF, platelet-activating factor). Produced by endothelial cells, neutrophils, macrophages and eosinophils, PAF mediates IL-12-induced chemotaxis of natural killer cells and neutrophils. Inactivation by PAF esterase attenuates neutrophil migration and recruitment to the affected area [8].

Streptokinase (Ska) catalyzes the conversion reaction of plasminogen to plasmin that can activate metalloproteinases. Subsequent fibrinolysis and degradation of components of the extracellular matrix and basal membrane of tissue cells facilitate pathogen invasion. The enzyme promotes the binding of plasminogen and plasmin to proteins screened on the surface of the microbial cell (M-proteins, glyceraldehyde-3-phosphate dehydrogenase and α-enolase).

Streptococcal complement inhibitor (SIC) prevents the lytic action of complement by inhibiting the activation of the attack complex [9]. SIC combining with complement proteins C4BP and FH, which are cofactors of serum proteinase (CFI) activates cleavage of C4b and C3b fractions; binding plasminogen with surface of *S. pyogenes* inhibits opsonization; promotes adhesion of pathogen to tissue cells. In essence, *S. pyogenes* inhibits a variety of pathways for complement activation, using both surface-expressed and secreted complement inhibitors [10,11].

S. pyogenes secretes deoxyribonucleases - SdaD2, SpdI1, SpnA and SdaB - that cleave phosphodiester bonds in nucleic acid molecules, including those that destroy neutrophil DNA-based extracellular traps.

Streptococcal hyaluronate lyase and hyaluronidase, by cleaving hyaluronic acid in the membranes of tissue cells, promote the spread of the pathogen in the infected tissue.

Streptolysins O and S (pore-forming toxins or hemolysins) can damage phagocytic cells [12,13]. Streptolysin S has hemolytic activity and damages erythrocyte membranes. Streptolysin O is characterized by broader cytolytic activity. By damaging the membranes of phagolysosomes, it promotes the entry of streptococcal NAD+glycohydrolase from the phagosome into the cytosol of the phagocyte, which cleaves intracellular NAD. As a result, the phagocytosis process is not completed and the pathogen persists in the phagocytic cell.

Superoxide dismutase (SodA) and glutathione peroxidase (GpoA) contribute to the viability of *Streptococcus* under phagocytic oxidative stress [6]. They catalyze the conversion of superoxide anions into oxygen and hydrogen peroxide, thereby reducing the bactericidal action of phagocytes.

Analysis of the action of *S. pyogenes* pathogenicity factors produced in the exponential or stationary phase of development shows the involvement of the same factor at different stages of the development of the infection process - from adhesion, colonization and invasion to inhibition of the activity of complement components, immunoglobulins, phagocytes. Connecting with IgA, IgG, plasminogen and other blood proteins, binding with some complement fractions, they inhibit the processes of opsonization and phagocytosis carried out by neutrophils and macrophages, reduce the activity of cyto- and chemokines [10,11,14].

There is also synergism, conjugation of pathogenicity factors in colonization and inhibition of the activity of the main immune defense effectors - antibodies, complement and phagocytes. About ten microbial components, including fibrils and fimbriae, lipoteichoic acid, M protein, fibronectin- and collagen-binding proteins, the cytosolic glycolysis enzyme, glyceraldehyde Z-phosphate dehydrogenase, screened on the bacterial cell surface, are involved in the pathogen adhesion process alone [3].

Bioinformatic analysis of the full genome in pathogenic strains of *S. pyogenes* was used to study the mechanisms of counteracting the protective functions of macrophages and the persistence of the pathogen in the cytosol of phagocytes [15,16].

In addition to the production of pathogenicity factors, the adaptability of pyogenic *Streptococcus* is associated with biofilm formation [17]. Streptococcal glycolysis enzymes activate the synthesis of exopolysaccharides necessary for the formation of the intercellular matrix, the formation of microcolonies and further the biofilm of the pathogen. Biofilm creates conditions that weaken the effects of innate immunity factors. It is important that within the biofilm, pathogen populations being in different growth and development phases, with different energy requirements and metabolic activity against the background of fairly stable physical and chemical microenvironment conditions and provision with nutrient substrates are more adapted to adverse influences. The diversity of gene and phenotypic characteristics of pathogen populations in biofilms, perhaps, to a certain extent explains the high adaptability and invasiveness of the pathogen. It is within biofilms that the processes of horizontal transfer of pathogenicity genes are particularly intensive.

The role of non-chromosomal genetic factors and regulatory systems of the pathogen, providing colonization and overcoming the immune forces of the microorganism, is important in this exchange of genetic material. In *S. pyogenes*, the exchange of genetic material is performed through moderate phages, plasmids, and transposons [18].

In addition, the synthesis of a number of pathogenicity factors of pyogenic *Streptococcus* is often determined by these mobile genetic elements. For example, the hyaluronidase and DnAase (Sdn) genes are localized in moderate phages. In addition to mobile genetic elements, antigenic drift under the influence of immune protection factors and the response of gene transcription regulators to changing microenvironment conditions are significant in the high adaptability of pyogenic *Streptococcus*.

Adaptation characteristics of *S. pyogenes*

Early studies of metabolism aimed at satisfying the needs of *S. pyogenes* for certain nutrients were associated with the development of the composition of nutrient media for their cultivation. Subsequent molecular biological studies made it possible to reveal the dependence of pathogen virulence on substrate supply, on metabolic changes, and on the activity of microbial proteo- and glycolytic enzymes. The role of metabolic adaptation in colonization by *Streptococcus* of mucosal or skin surface, in persistence inside phagocyte, in certain resistance to changes of pH and osmotic gradient of microenvironment was determined.

The efficiency of adaptation mechanisms, the transcription of virulence factors in streptococci is controlled by three groups of regulators: two-component systems (TCS), individual or autonomous regulators, and non-coding RNA. In *S. pyogenes*, 40 individual and 13 two-component gene transcription regulators are known. In all TCSs, the first component consists of a transmembrane sensory histidine kinase and the second is represented by an associated cytoplasmic response regulator. The regulatory activity of the genes encoding the Ihk/Irr TCS is activated during pathogen persistence in the phagocyte. Apparently, the increased expression of these genes contributes to the survival of *Streptococcus* in the phagocyte [19].

Among the regulatory proteins in pyogenic *Streptococcus*, Rgg and MutR, responsible for the regulation of virulence gene transcription and genes controlling the activity of enzymes of metabolic pathways of carbohydrate and amino acid metabolism, have been well studied [20-22]. The regulatory protein MutR has been shown to control *S. pyogenes* adhesiveness and biofilm formation [21].

For *S. pyogenes*, glucose is the main source of energy supply. Anaerobic glycolysis in the cytosol via the Embden-Meyerhoff-Parnassus pathway produces two molecules of ATP and two molecules of NADH2. One of the functions of NADH2, a coenzyme of pyridine dehydrogenase, is to accept the hydrogen atoms generated during anaerobic glycolysis, thus reducing the acidification of the microenvironment.

Some streptococcal cytosolic glycolysis enzymes (glyceraldehyde-3-phosphate dehydrogenase, α-enolase, phosphoglycerate kinase, phosphoglycerate mutase and triosophosphatisomerase) can screen to the surface of the pathogen cell membrane and promote the adhesion process [23]. They catalyze the synthesis of exopoly-saccharides required for the intercellular matrix, microcolony formation, and pathogen biofilm formation. The main enzyme of glycolysis glyceraldehyde-3-phosphate dehydrogenase (GAPDH) screening on the surface of the microbial cell is also capable of binding to the C5a complement fraction, thereby inhibiting neutrophil chemotaxis. And EndoS (endo-β- N- acetylglucosaminidase) enzyme cleaves the carbohydrate component in the IgG molecule.

The pathogen under conditions of deficiency of carbohydrate sources of energy generation, for example during colonization of the skin surface poor in nutrient substrate, is able to synthesize ATP in the reaction of arginine hydrolysis. Streptococcal arginine deaminase converts arginine to ornithine, ammonia, and CO_2, and ATP is produced. Arginine catabolism not only supplements the energy resources of the microbial cell but also reduces environmental acidification [24,25].

Conclusion

The analysis of publications on molecular biological studies of pyogenic *Streptococcus* allows us to distinguish two main directions. The first is the study of the molecular mechanisms of pathogenicity factors, their involvement in colonization and evasion of immune defense. The second is related to the study of pathogen metabolism, mainly carbohydrate and amino acid metabolism. The second direction has fundamental aspects concerning the peculiarities of the metabolic pathways of carbohydrate, amino acid, lipid and other types of metabolism in *S. pyogenes*. Applied aspects are related to the analysis of metabolic adaptation pathways of *Streptococcus* to adverse microenvironment conditions (glucose deficiency, environmental acidification, etc.) and connection of the pathogen virulent activity with metabolic changes, in particular replenishment of energy deficiency due to arginine catabolism. The mechanisms of conjugation of changes in metabolism and virulence controlled by regulators of virulence factor gene transcription and metabolic adaptation, including autonomous regulators - Rgg and MutR proteins - are relevant.

Studies of transcriptomics and proteomics of carbohydrate and amino acid metabolism, pathogenicity factors, and regulatory systems of *S. pyogenes* specified the molecular mechanisms of adhesion, invasion, and evasion of the pathogen from immune protection. The results of molecular biological studies have actualized the development of anti-streptococcal vaccines based on the variable and conserved regions of M proteins, especially serotype M1-based esterase (Sse) M1, which exhibits immunogenicity by increasing IgG titer [26]. Fibronectin-binding proteins, pili components, C5a peptidase, and CspA protease are being investigated as immunogenic and protective recombinant polypeptide components in anti-streptococcal vaccine development. TCS and autonomous regulators of virulence factor gene transcription and metabolic adaptation are also considered as potential components of prophylactic drugs. Given the conjugation of pathogenicity factors, the development of vaccines combining several regulators, including Rgg and MutR, is desirable [27].

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