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# *Research Progress on Streptococcal Type VII Secretion System and Host Immune Response*

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***Abstract.*** Streptococci are important Gram-positive pathogenic bacteria, and their type VII secretion system (T7SS) plays a key role in host adaptation and pathogenicity. This paper reviews the structural characteristics, secretory functions, and regulatory effects on host innate immunity of streptococcal T7SS, focusing on the processes by which it mediates bacterial immune evasion and affects infection outcomes and disease severity through mechanisms such as interfering with immune recognition, regulating inflammatory cytokine secretion, and influencing immune cell functions. Meanwhile, the consensus and deficiencies of current research are analyzed, and the clinical application potential of T7SS in the development of novel antibacterial strategies is prospected, providing theoretical references for the prevention and control of streptococcal infections.

***Keywords:*** Streptococcus, type VII secretion system (T7SS), innate immune regulation

## 1. Introduction

### 1.1. Hazards and pathogenic mechanisms of streptococcal T7SS

Streptococci are important Gram-positive pathogenic bacteria that can cause a variety of infectious diseases such as pharyngitis, pneumonia, sepsis and meningitis, with high morbidity and potential lethality. Their pathogenicity mainly relies on a variety of virulence factors to achieve colonization and spread in vivo by interfering with host immune recognition, inducing imbalanced inflammatory responses and promoting immune evasion. The type VII secretion system (T7SS) is a unique secretion system of Gram-positive bacteria, first discovered in Mycobacterium, and plays an important role in bacterial adaptation, biological functions and virulence formation [1]. In recent years, T7SS has been identified in some streptococci, but its specific mechanism of action in the pathogenic process of streptococci remains unclear.

### 1.2. Research purpose and significance

Systematically clarifying the mechanism of action of T7SS in the interaction between streptococci and host innate immune responses helps to deeply analyze the molecular basis of the occurrence and development of streptococcal pathogenicity, and provides theoretical support for intervention strategies of related infectious diseases. Further analysis of the immune regulation process mediated

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by T7SS not only helps to reveal the potential mechanism of imbalanced inflammatory response and immune evasion during streptococcal infection, but also provides an important theoretical basis for optimizing prevention and control strategies and developing targeted intervention means for streptococcal infections [2].

### 1.3. Research status and content at home and abroad

Existing studies have shown that streptococcal T7SS is conserved in gene composition and overall structure, but there are still obvious differences among different streptococcal species, and the effector proteins secreted by it may be involved in the regulation of host immune processes. However, current relevant studies are mostly scattered reports, lacking systematic integration and summary of their mechanisms of action. At the same time, existing studies focus more on non-T7SS-related virulence factors, and the understanding of the overall role and network effect of T7SS in innate immune regulation is still limited. Therefore, this paper intends to systematically review the role and potential molecular mechanisms of streptococcal T7SS in host innate immune responses based on its structural characteristics and functional attributes.

## 2. Basic concepts of host innate immunity

### 2.1. Core components of innate immunity

Host innate immunity is the first line of defense against pathogen invasion. It limits pathogen spread through rapid recognition and response in the early stage of infection, and provides signal support for the initiation of adaptive immunity. Its function depends on the synergistic action of pattern recognition receptors (PRRs), immune effector cells and signaling pathways. PRRs are key molecules for recognizing pathogen-associated molecular patterns (PAMPs) [3]. Among them, Toll-like receptors (TLRs) are mainly distributed on the cell membrane or endosomal membrane, recognizing bacterial lipoproteins, lipoteichoic acid and nucleic acids; Nucleotide-binding Oligomerization Domain-like Receptors (NLRs) are located in the cytoplasm, participating in intracellular pathogen recognition and inflammasome activation [4]. In addition, RIG-I-like receptors (RLRs) mediate viral RNA recognition and induce type I interferon production, and C-type lectin receptors (CLRs) recognize fungal carbohydrate ligands, which together constitute the recognition basis of innate immunity.

At the cellular level, macrophages, neutrophils and dendritic cells are the main effector cells. Macrophages exert phagocytic bactericidal and inflammatory regulatory effects; Neutrophils achieve rapid sterilization through chemotactic migration and formation of neutrophil extracellular traps (NETs); Dendritic cells connect innate and adaptive immunity through antigen presentation and cytokine secretion, and jointly participate in inflammatory responses and pathogen clearance in the early stage of infection.

At the signal transduction level, PRR activation triggers the NF-κB and MAPK pathways. The NF-κB pathway promotes the entry of p65/p50 into the nucleus through IκBα degradation, inducing the expression of inflammatory cytokines such as IL-1β, IL-6 and TNF-α; The MAPK pathway activates the transcription factor AP-1 through cascaded phosphorylation of p38, JNK and ERK, regulating the production of inflammatory mediators [5]. In addition, the type I interferon pathway plays a key role in antiviral immunity, mediating viral effects by inducing IFN-α/β and interferon-stimulated genes (ISGs). The coordinated regulation of the above pathways is crucial for

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maintaining immune response and homeostasis, and may also become potential targets for streptococcal T7SS action.

### 2.2. Defensive role of innate immunity

Innate immunity is the first line of defense for the host against pathogen invasion, achieving pathogen clearance, inflammatory regulation and adaptive immune connection through a multi-level synergistic mechanism, and playing a key role in maintaining anti-infective capacity. In the early stage of infection, after pattern recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs), clearance reactions are rapidly initiated: macrophages and neutrophils kill pathogens through phagocytosis, lysosomal degradation and reactive oxygen species (ROS); The complement system is activated via the classical, alternative and lectin pathways, forming membrane attack complexes (MACs) and enhancing phagocytosis; Antimicrobial peptides such as defensins and Cathelicidin secreted by epithelial and immune cells inhibit pathogen growth and spread.

PRR activation further triggers the NF-κB and MAPK pathways, inducing the expression of inflammatory cytokines and chemokines such as IL-1β, IL-6 and TNF-α, and promoting the formation of inflammatory responses [6]. Inflammatory mediators enhance vascular permeability and promote the recruitment of immune cells to infection sites; Chemokines (such as CXCL8, CCL2) guide inflammatory cell migration and limit pathogen spread. Meanwhile, anti-inflammatory cytokines (such as IL-10, TGF-β) participate in negative regulation to avoid excessive inflammatory damage and maintain immune homeostasis [7].

In addition, innate immunity not only participates in the early clearance of pathogens, but also plays an important role in the activation of adaptive immune responses. After PRR recognition of pathogen-related signals, antigen-presenting cells such as dendritic cells gradually mature, present antigens to T cells, and provide necessary co-stimulatory signals, thereby promoting T cell activation. At the same time, cytokines such as IFN-γ and IL-4 can further affect the differentiation direction of T cells and participate in B cell activation and antibody response processes [8].

Overall, innate immunity jointly maintains the body's anti-infective defense function through pathogen clearance, inflammatory response regulation and coordination with adaptive immunity.

## 3. Streptococcus-induced inflammatory response

### 3.1. Immune recognition of streptococci

After streptococci invade the host, their cell wall-related components are first sensed by the host innate immune system. As Gram-positive bacteria, the surface peptidoglycan (PGN) and lipoteichoic acid (LTA) of streptococci can be recognized by a variety of pattern recognition receptors, thereby inducing inflammatory and immune responses [9]. Different from Gram-negative bacteria that mainly rely on lipopolysaccharide (LPS) to trigger immune responses, streptococcal-related immune activation is more related to surface components such as LTA, showing certain specificity. Meanwhile, virulence factors such as streptolysin O and capsular polysaccharide produced by streptococci can also affect the host immune response process through cell membrane damage and antigen exposure alteration [10].

The host's recognition of streptococcal-related components mainly relies on Toll-like receptor 2 (TLR2). TLR2 can form heterodimers with TLR1 or TLR6 respectively, thereby recognizing different types of lipid ligands and enhancing the ability to recognize pathogen components [11].

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After bacteria are phagocytosed, TLR9 can recognize unmethylated CpG sequences in bacterial DNA, further inducing immune responses. At the same time, after some bacterial components enter the cytoplasm, NOD1 and NOD2 can sense cell wall degradation products such as iE-DAP and MDP respectively, and activate downstream signaling pathways through RIPK2 to participate in immune regulation together with TLR-related signals [12]. This multi-level recognition mechanism composed of membrane surface, endosome and cytoplasm helps to enhance the host's perception and response to streptococcal infection.

In terms of signal transduction, TLR2 activation recruits IRAK and TRAF6 through the MyD88-dependent pathway, further activating the NF-κB and MAPK pathways. The NF-κB pathway releases p65/p50 into the nucleus through IκBα degradation, inducing the expression of inflammatory cytokines such as IL-1β and TNF-α [13]. The MAPK pathway activates AP-1 through p38, JNK and ERK, enhancing inflammatory responses. In addition, bacterial nucleic acids can activate receptors such as TLR9 and RIG-I, inducing type I interferon (IFN-α/β) production through IRF3/7, thereby enhancing antibacterial responses and promoting adaptive immune initiation [14].

### 3.2. Streptococcus-induced inflammatory response: Dual effects of host defense and tissue damage

As Gram-positive bacteria, streptococci need to break through the epithelial barrier and enter tissues to cause infection. After invasion, the innate immune system can be rapidly activated in a short time, whose main function is to clear pathogens, but excessive inflammatory responses often lead to tissue damage such as necrosis and pathological processes such as sepsis. Therefore, host defense and immunopathological damage often coexist. The host mainly recognizes streptococcal components through pattern recognition receptors, among which TLR2 recognizes cell wall components such as lipoteichoic acid, and NOD2 recognizes peptidoglycan degradation product MDP. After receptor activation, inflammatory cytokine expression is induced through the NF-κB and MAPK pathways, with IL-1β, IL-6 and TNF-α being key effector molecules.

IL-1β is mainly produced by macrophages, and its maturation and release depend on precursor synthesis induced by NF-κB and shear activation mediated by inflammasomes. IL-1β promotes the expression of E-selectin and ICAM-1 in vascular endothelial cells, thereby enhancing neutrophil recruitment and amplifying inflammatory responses through positive feedback. In a pneumococcal infection model, blocking IL-1β signaling can significantly reduce neutrophil infiltration, but simultaneously increase bacterial load [15].

IL-6 is mainly involved in the regulation of systemic inflammatory responses, promoting the liver to synthesize acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), and also has a certain impact on B cell differentiation and humoral immunity. Studies have found that IL-6 deficiency can instead reduce the host's mortality in some infection models, suggesting that in addition to its protective role, it may also participate in the excessive amplification of inflammatory responses during infection [16].

TNF-α is an important inflammatory mediator in the early stage of infection, which can increase vascular permeability and promote the recruitment of inflammatory cells to infection sites. However, its effect is closely related to the expression level. Moderate release of TNF-α is conducive to pathogen clearance, while sustained or excessive elevation may induce shock and multiple organ damage. Clinically, the effect of antagonistic therapy targeting TNF-α in sepsis is not as expected [17].

The above inflammatory cytokines influence and regulate each other. Studies have shown that TNF-α can induce the expression of IL-1β and IL-6, and IL-1β can further enhance the cell's

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response to TNF-α, thereby forming a continuously amplified inflammatory signal network. This process enhances anti-infective capacity, but may also promote the occurrence and progression of systemic inflammatory responses.

Chemokines play an important role in inflammatory cell recruitment. Among them, CXCL8 mainly promotes the aggregation of neutrophils to infection sites, while CCL2 is more involved in the recruitment of monocytes and macrophages. After arriving at the local site, neutrophils can clear pathogens through phagocytosis, reactive oxygen species (ROS) release and formation of neutrophil extracellular traps (NETs), but excessive NET formation may also cause vascular endothelial damage and increase the risk of thrombosis.

In the later stage of infection, in addition to continuing to participate in pathogen clearance, macrophages are also responsible for phagocytosing apoptotic neutrophils and secreting anti-inflammatory cytokines such as IL-10 to reduce excessive inflammatory responses; Meanwhile, they can participate in adaptive immune regulation through antigen presentation. Dendritic cells can uptake and process pathogen antigens, then migrate to lymph nodes, activate naive T cells through MHC molecules and co-stimulatory signals, and play a bridging role between innate and adaptive immunity.

In the long-term process of interaction with the host, streptococci have gradually formed a variety of immune evasion strategies. Among them, SpeB can degrade some chemokines and weaken inflammatory cell recruitment; M protein can bind complement regulatory-related molecules and inhibit complement-mediated clearance; In addition, DNase secreted by streptococci can destroy the NET structure, thereby reducing the host's efficiency of clearing bacteria and promoting persistent or recurrent infections [18].

### 3.3. Preliminary strategies for streptococcal immune evasion

In the process of long-term evolution, streptococci have gradually formed a variety of immune evasion methods to weaken the clearance effect of the host innate immune system, thereby facilitating the colonization, survival and spread of bacteria in the host. These mechanisms mainly involve multiple aspects such as surface structure masking, secretory enzyme degradation and host immune signal regulation, which are also important foundations for streptococcal pathogenicity and provide a reference background for the subsequent study of T7SS-related immune regulation.

Capsule plays an important role in surface structure-mediated immune evasion. Both group A streptococci and group B streptococci can form hyaluronic acid capsules, whose composition has certain similarity with the host extracellular matrix, so it can "disguise" the bacteria themselves to a certain extent, reduce the host's recognition of pathogen-associated molecular patterns (PAMPs) such as lipoteichoic acid and peptidoglycan, and further weaken the early immune activation mediated by PRRs [19]. Studies have found that capsule-deficient strains have significantly reduced virulence and are more easily phagocytosed by neutrophils, suggesting that capsule is of great significance in resisting host immune clearance.

In addition to physical masking, streptococci can also interfere with host immune responses by secreting a variety of enzymes. For example, cysteine protease SpeB can degrade some inflammation-related molecules and immune effector proteins, including IL-1β precursor, TNF-α, complement C3b and IgG, thereby weakening inflammatory signal transduction and opsonophagocytosis and helping bacteria evade immune attack. Some streptococci can also produce nucleases to degrade the DNA skeleton of neutrophil extracellular traps (NETs), further improving their survival ability in inflammatory environments [20].

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In addition, streptococci can enhance their own evasion ability by affecting the host immune regulation process. Some surface proteins can bind complement regulatory factors such as Factor H and C4b binding protein, thereby inhibiting continuous complement activation; At the same time, streptococci can induce the host to produce anti-inflammatory cytokines such as IL-10, reduce the activation level of macrophages and dendritic cells, and affect the antigen presentation process. The above multiple mechanisms together constitute a complex immune evasion network of streptococci, and also provide a theoretical basis for further exploring the specific immune regulation role of T7SS in streptococcal infection.

## 4. Structure and function of streptococcal type VII secretion system (T7SS)

### 4.1. Gene composition and structural characteristics of streptococcal T7SS

T7SS is considered an important molecular mechanism for streptococci to participate in immune evasion and host adaptation, and its functional exertion is closely related to the composition and structural characteristics of related gene clusters. Different from Gram-positive bacteria such as Mycobacterium tuberculosis that generally carry T7SS, T7SS in streptococci is not present in all strains, but mainly distributed in some highly pathogenic strains. Differences in T7SS gene composition and structure among different strains also suggest that it may have certain functional specificity in host colonization, immune regulation and pathogenic processes [21].

Streptococcal T7SS is mainly encoded by the conserved *ess* gene cluster, including core genes such as *essC*, *esxA* and *esxB* [2]. *essC* encodes a membrane-integrated ATPase, which is the energy-driven core of T7SS, and its ATP-binding domain is highly conserved in streptococci to maintain secretory function [22]. *esxA* and *esxB* encode core effector proteins secreted in the form of heterodimers, whose structural characteristics (WXG motif and related domains) mediate transmembrane transport and are important foundations for the immune regulatory function of T7SS [23]. In addition, *essA* and *essB* are involved in membrane structure stabilization and secretory channel assembly respectively. Genetic studies have shown that deletion of *essC* or *esxA* leads to complete loss of T7SS function, indicating that they are essential components of the secretion system [24].

In terms of distribution characteristics, T7SS is mainly present in GBS, some GAS and *Streptococcus suis*, while less or absent in oral commensal streptococci. GBS clinical isolates generally carry complete T7SS gene clusters, while commensal strains often have gene deletions [25]; T7SS in GAS is associated with invasive infection, suggesting that it may be involved in pathogenic transformation. This distribution characteristic reflects the adaptive evolution of T7SS and provides potential action sites for targeted intervention [26].

From the structural and mechanistic level, EssC forms an oligomeric ATPase complex and anchors to the inner membrane, driving substrate transport through ATP hydrolysis; EssB assembles a transmembrane channel to provide a transport path for effector proteins such as EsxA-EsxB [27]. Different from the signal peptide-dependent secretion mode of Gram-negative bacteria, streptococcal T7SS achieves substrate recognition and transport through the specific interaction between EsxA and EssC, thereby efficiently secreting effector proteins and regulating host immune responses [28].

In summary, streptococcal T7SS forms functional modules adapted to pathogenic needs through structural and distribution-specific evolution on the basis of retaining the conserved framework of Gram-positive bacterial secretion systems, providing a structural and genetic basis for its role in immune evasion [29].

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### 4.2. Secretory function of streptococcal T7SS

On the basis of gene composition and structural analysis, streptococcal T7SS achieves its biological functions through effector protein secretion, which is a key link in regulating host innate immunity and mediating immune evasion. Different from non-T7SS virulence factors such as capsules and proteases, T7SS effector proteins can directly enter the host cytoplasm, target immune signaling pathways and regulate cell functions [2].

T7SS secretion substrates are centered on EsxA and EsxB, and include a variety of auxiliary effector proteins. Studies have shown that EsxA secreted by GBS can target the macrophage NADPH oxidase complex, inhibit ROS production, thereby reducing bactericidal ability; EsxB inhibits the expression of inflammatory cytokines such as IL-1β and TNF-α by interfering with intracellular signal transduction [24]. This "dual inhibition mechanism" is a key feature that distinguishes T7SS from other virulence factors.

In addition, the T7SS secretion spectrum of different strains has functional diversity. Some strains can secrete EsxA/EsxB and nuclease effector proteins simultaneously to synergistically inhibit immune cell function and degrade NETs; Some *Streptococcus suis* secrete chemokine-degrading enzymes to block immune cell recruitment, reflecting significant functional differentiation [25].

The secretory function of T7SS is environmentally responsive and strain-specific. In the host infection microenvironment (such as low pH, oxidative stress), its expression level is significantly up-regulated, enhancing effector protein secretion [30]; Different strains can dynamically adjust the secretion spectrum according to the host environment, so as to adapt to different infection stages and tissue colonization needs.

In summary, streptococcal T7SS achieves fine regulation of innate immunity through the EsxA/EsxB-centered secretion system, and its functional diversity and environmental plasticity together constitute an important immune evasion mechanism and provide potential targets for targeted intervention.

### 4.3. Similarities and differences between streptococcal T7SS and T7SS of other Gram-positive bacteria

Based on the above analysis, comparison with the T7SS of *Mycobacterium tuberculosis* and *Staphylococcus aureus* shows that streptococcal T7SS presents significant specificity in gene structure and functional differentiation while retaining conserved mechanisms such as EssC-dependent ATP-driven secretion and Esx family core substrate secretion, which is closely related to its host adaptation [22].

At the gene cluster level, the three share core components such as EssC ATPase, EsxA/EsxB and EssA/EssB, but streptococcal T7SS shows obvious gene cluster simplification characteristics (about 5-8 genes), lacks complex regulatory factors, and is more of a "secretion-executive" structure compared with the ESX system of *Mycobacterium tuberculosis* [28]. Compared with *Staphylococcus aureus*, streptococcal T7SS lacks some Ecc-related auxiliary factors, but achieves substrate-specific recognition through EssC isoform differentiation, and some strains can encode 2-3 EssC subtypes to mediate the secretion of different effector proteins by division of labor. In addition, its gene cluster is often located on mobile genetic elements, resulting in significant heterogeneity in distribution among strains [31].

In terms of secretion substrates, both streptococci and *Mycobacterium tuberculosis* rely on EsxA/EsxB-like heterodimers, but functional outputs are differentiated. Streptococcal EsxA mainly inhibits NADPH oxidase activity and reduces ROS production, and EsxB interferes with

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inflammatory signaling pathways to inhibit pro-inflammatory factor expression [24]; The ESX-1 system of *Mycobacterium tuberculosis* mainly promotes intracellular survival and macrophage death-related processes, reflecting the functional difference between "immunosuppressive type" and "intracellular survival type".

In terms of functional lineage, in addition to immune regulation, *Staphylococcus aureus* T7SS is also involved in interbacterial competition, while streptococcal T7SS is more biased towards host immune regulation and colonization adaptation, and its interbacterial competition function is not yet clear. This difference may be related to the structure of effector proteins: streptococcal EsxA lacks a typical membrane destruction domain, but is rich in host protein interaction motifs, making it more inclined to regulate signal transduction processes [32].

In terms of immune interaction mode, *Mycobacterium tuberculosis* T7SS mainly achieves persistent intracellular infection by inducing macrophage death and inhibiting antigen presentation; Streptococcal T7SS achieves immune evasion through multi-dimensional mechanisms such as inhibiting immune cell recruitment, interfering with inflammatory signals and degrading NETs according to the characteristics of extracellular infection [28].

In terms of clinical correlation, streptococcal T7SS is closely related to invasive infections (such as sepsis, neonatal infections), showing strong tissue invasion ability; *Mycobacterium tuberculosis* T7SS is associated with chronic granulomatous diseases; *Staphylococcus aureus* T7SS is more associated with skin and soft tissue infections.

In terms of evolution, the T7SS of the three may originate from a common ancestral system, but form species-specific differentiation through horizontal gene transfer and gene loss/reconstruction. Streptococcal T7SS is only retained in some pathogenic strains and absent in commensal bacteria, suggesting that it is closely related to pathogenic evolution; In contrast, *Mycobacterium tuberculosis* T7SS is highly conserved and adapted to the obligate intracellular parasitic lifestyle [26].

In summary, streptococcal T7SS forms a specific secretion system adapted to extracellular pathogenic strategies through simplified gene structure, EssC isoform differentiation and effector protein functional remodeling on the basis of the conserved EssC-Esx framework, providing a molecular basis for its immune evasion and pathogenicity.

## 5. Regulatory effect of streptococcal T7SS on host immune response

### 5.1. Regulation of T7SS on innate immune recognition and inflammatory initiation

Innate immune recognition relies on the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) and activation of inflammatory signaling pathways. Streptococcal T7SS interferes with this process through multiple mechanisms, thereby inhibiting immune initiation and promoting immune evasion. On the one hand, T7SS can modify bacterial surface PAMPs through effector proteins to reduce their immunogenicity. For example, EsxA secreted by group B streptococci (GBS) can modify peptidoglycan structure, mask NOD2 recognition sites, thereby inhibiting related signal activation [24]. At the same time, T7SS can also regulate the expression and exposure of lipoteichoic acid (LTA), reduce TLR2/6 recognition and inhibit the MyD88-dependent signaling pathway [33]. On the other hand, T7SS can directly act on host PRRs, such as EspB secreted by GAS can degrade TLR4 and block NF-κB activation mediated by it [20]. Meanwhile, T7SS can also down-regulate the expression of TLR2, TLR4 and NOD2 and inhibit their activation, reducing the immune cell's ability to sense pathogens as a whole [34].

At the level of inflammatory initiation, T7SS achieves fine regulation of inflammatory responses by regulating key pathways such as NF-κB and MAPK. EsxA from GBS can inhibit IKK complex

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activation, block NF-κB signaling, thereby limiting excessive inflammation; Some GAS strains enhance NF-κB signaling by activating the TLR2-MyD88 axis to promote inflammatory responses [35].

In terms of the MAPK signaling pathway, effector proteins secreted by T7SS can regulate the phosphorylation levels of key molecules such as ERK, JNK and p38, thereby affecting the expression and release of downstream inflammatory cytokines [36]. In addition, T7SS may also participate in the activation of NLRP3 inflammasomes, promoting caspase-1 activation and the maturation and secretion of IL-1β, thereby further enhancing the inflammatory response process [37].

### 5.2. Effects of T7SS on inflammatory cytokines and immune cell functions

T7SS can further regulate the host immune response level by affecting inflammatory cytokine expression and immune cell functions, and plays an important role in the infection process. In terms of inflammatory cytokine regulation, T7SS mainly affects the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α by interfering with signaling pathways such as NF-κB and MAPK. Studies have shown that the role of T7SS is not completely consistent in different streptococci. During GBS infection, T7SS can inhibit the activation of related signaling pathways to a certain extent, thereby reducing pro-inflammatory cytokine expression and alleviating inflammatory responses; In GAS infection, T7SS may enhance the activity of the above pathways, promote inflammatory cytokine release and aggravate tissue damage [35]. In addition, T7SS can also affect the secretion of anti-inflammatory cytokines such as IL-10, and promote caspase-1-mediated IL-1β maturation by activating NLRP3 inflammasomes, thereby participating in the regulation of inflammatory response intensity and outcome [37]. In summary, T7SS achieves a dynamic balance between inhibiting immune clearance and regulating inflammatory damage through synergistic regulation of the inflammatory cytokine network and immune cell effector functions.

### 5.3. Effect of T7SS on infection outcome and disease severity

Streptococcal T7SS is considered an important virulence factor affecting the infection process and disease outcome. On the one hand, T7SS can interfere with host immune defense through secreting a variety of effector proteins, helping bacteria evade immune clearance, thereby enhancing their colonization and spread ability; On the other hand, it can also affect the balance of inflammatory responses, leading to abnormal release of inflammatory cytokines, aggravating tissue damage, and promoting the development of infection from local mild cases to severe stages such as sepsis and meningitis. Relevant animal experiment results show that compared with wild strains, T7SS-deficient strains have significantly weakened pathogenicity and significantly improved survival rate of infected hosts, suggesting that there is a close relationship between T7SS and the severity of streptococcal infection.

### 5.4. Clinical significance and application potential of T7SS

T7SS has certain transformation potential at the clinical application level. On the one hand, due to its close relationship with streptococcal virulence level, it can be used as a potential biomarker for screening highly pathogenic strains and assessing infection risk, assisting in judging the risk of disease progression. On the other hand, T7SS itself also provides a possible target for novel anti-

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infective strategies. Designing small molecule inhibitors or developing vaccines against its related effector proteins may reduce bacterial virulence while reducing dependence on traditional antibiotics, thereby coping with drug resistance to a certain extent. In addition, based on the characteristics of T7SS participating in inflammatory regulation, the research on its related mechanism provides a new idea for optimizing the combined strategy of anti-inflammatory therapy.

## 6. Summary and prospect of research progress

In recent years, research on streptococcal T7SS has made phased progress. At present, the academic community has initially formed a consensus on its basic structure and secretion mechanism, and its core role in streptococcal immune evasion and pathogenicity, confirming that T7SS can affect the infection process and disease outcome by regulating host innate immune responses; However, current research still has obvious deficiencies, mainly manifested in unclear interaction targets between effector proteins and host molecules, lack of systematic explanation of functional heterogeneity of T7SS in different strains, and most relevant studies stay at the basic experimental stage with slow progress in clinical transformation and application. Future research should focus on in-depth analysis of the molecular interaction mechanism between T7SS and the host, systematically clarify the structural and functional differences of T7SS in different streptococcal strains, develop small molecule inhibitors and candidate vaccines targeting T7SS on this basis, and explore their application value in clinical diagnosis, risk assessment and treatment, providing theoretical support and technical paths for precise prevention and control of streptococcal infections and research and development of novel antibacterial strategies.

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