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Research Progress on Bacteriophages and Endolysins Against *Streptococcus suis*

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Abstract: *Streptococcus suis* is a well-known zoonotic pathogen. The rise of multidrug-resistant strains has made traditional antibiotic treatments largely unreliable, pushing us to look for alternative antimicrobial strategies. Bacteriophages and their endolysins are now drawing serious attention. They are highly specific and rarely trigger new resistance. In this review, we summarize the taxonomy and life cycle of *S. suis* phages. We then focus on the structural domains of endolysins and how they physically break down bacterial cells. Practical uses of these agents in veterinary medicine, food safety, and environmental control are also discussed. We also point out several bottlenecks restricting their commercial use—namely, the narrow host range and poor stability *in vivo*. Addressing these issues is essential for future product development.

Keywords: *Streptococcus suis*; Bacteriophage; Endolysin; Antimicrobial resistance; Alternative therapy

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1. Introduction

Swine streptococcosis is primarily known for triggering meningitis and septicemia in pigs, which drags down the swine industry economically. The real threat, however, is its zoonotic potential. *S. suis* can jump to humans, occasionally causing severe public health outbreaks [1]. Over the last few decades, farmers relied heavily on antibiotics to control this disease. It worked to some extent, but the downside was inevitable: a rapid enrichment of resistance genes. If you look at clinical *S. suis* isolates today, the resistance rates to penicillin, tetracyclines, and macrolides are stubbornly high. Conventional treatments are basically failing when dealing with multidrug-resistant (MDR) or even pan-resistant strains [2]. We urgently need new antimicrobial agents that work differently and do not easily trigger cross-resistance. This is exactly why bacteriophages—viruses that strictly parasitize bacteria—are making a comeback. During the infection cycle, phages release endolysins to break open the host cell. Unlike broad-spectrum antibiotics, these biological agents directly destroy the physical structure of the bacterial cell wall. They kill fast and leave the host's normal microbiota mostly undisturbed, offering a practical new way to handle swine streptococcosis [3].

2. Biological characteristics of *Streptococcus suis* bacteriophages

2.1. Morphological classification and genomic characteristics

Based on the International Committee on Taxonomy of Viruses (ICTV) rules, most natural bacteriophages fall under the order *Caudovirales*. They are grouped into *Myoviridae, Siphoviridae*, and *Podoviridae* depending on their tail structures [4]. The *S. suis* phages we have isolated so far fit right into these three families. Take the phage Liu et al. [5] found in diseased pig samples as an example. Transmission electron microscopy (TEM) showed it had an icosahedral head and a long, contractile tail, putting it squarely in the *Myoviridae* family. Zhao et al. [6] reported another one, vB_SsuM-SS201, which looks similar under TEM. This variation in shape usually hints at different evolutionary paths. Genomically speaking, sequencing tells us these phages carry double-stranded DNA (dsDNA). More importantly, their genomes almost always contain complete lysis modules, including *holin* and *endolysin* genes [7]. This makes them a natural genetic reservoir for finding new antimicrobial enzymes.

2.2. Lytic cycle and lysogenic risk

When we study the life cycle of *S. suis* phages, the focus is heavily on virulent strains. A virulent phage uses its tail fibers to latch onto specific host receptors, injects its nucleic acid, takes over the host's metabolism to copy itself, and finally uses endolysins to break out [8]. Temperate phages, on the other hand, behave very differently and deserve more scrutiny. Instead of lysing the cell right away, they slip their genome into the host chromosome as a prophage [9]. This carries a serious risk. Huang et al. [10] pointed out that this integration can pass new virulence factors to *S. suis* through horizontal gene transfer, essentially making the bacteria more dangerous. We also know, thanks to Zhang et al. [11], that things like mitomycin C can force these prophages into the lytic cycle. Because of this, anyone trying to develop phage therapies must run whole-genome sequencing first. You have to screen out any lysogeny-related or virulence genes to avoid the nightmare of "treatment-induced pathogenesis" in a clinical setting.

2.3. Isolation, identification, and potency evaluation

Finding a highly efficient phage comes down to where you look. Phage numbers go up when host bacteria are plentiful. Therefore, sampling places like slaughterhouse wastewater or the tonsils of sick pigs gives you a much better hit rate with the double-layer agar plate method [12]. Once you purify a phage, TEM is the standard first step to classify it. But to know if it is actually useful, you need a one-step growth curve. By measuring the latent period, rise period, and burst size, you get a clear picture of whether the phage can replicate fast enough to suppress an infection in a living animal [13].

3. *Streptococcus suis* bacteriophage endolysins

3.1. Modular structure and catalytic specificity

Endolysins are peptidoglycan hydrolases. Phages code for them late in the infection cycle. The endolysins from *S. suis* phages usually have a classic modular setup: an N-terminal catalytic domain (CD) and a C-terminal cell wall-binding domain (CBD) [14]. The CD decides how the lysis happens chemically. For instance, amidases cut the amide bond between N-acetylmuramic acid and L-alanine, while glycosidases break glycosidic bonds [15]. When Wang et al. [16] cloned an early anti-*S. suis* endolysin, it turned out to be an amidase. The CBD, on the other hand, works almost like a targeting system. It recognizes specific teichoic

acids or polysaccharides on the *S. suis* cell wall, locking the CD exactly where it needs to be. This split in function makes the whole lysis process much more efficient [17].

3.2. Unique advantages and mechanism of action

How endolysins kill bacteria is basically pure physical destruction. The moment the enzyme touches the cell, it cuts the peptidoglycan backbone. The internal osmotic pressure does the rest; the wall disintegrates instantly, and the cell dies [18]. Think about β-lactam antibiotics. They passively block cell wall synthesis. Endolysins are much more aggressive—they actively degrade the wall that is already there. Because the target is on the outside of the cell and highly conserved, bacteria struggle to mutate their way out of it. This explains why endolysins still pack a punch against MDR strains [19]. Liu et al. [20] showed this clearly in vitro: recombinant endolysins caused the turbidity of dense, drug-resistant *S. suis* cultures to drop within minutes.

3.3. Heterologous expression strategies

You cannot practically harvest endolysins by just growing huge batches of phages. We have to rely on prokaryotic expression systems to get them. The *Escherichia coli* pET system is the go-to choice simply because the protocols are so well-established [21]. The main headache in the lab, though, is stopping the proteins from forming inclusion bodies. To get soluble, active endolysins, researchers usually have to slow down protein folding. This means using less inducer and dropping the temperature—say, inducing overnight at 16°C. When it comes to purification, adding a polyhistidine (His) tag makes life easy. You can pull the protein out quickly using nickel affinity chromatography [22].

4. Application potential and challenges

4.1. Therapeutic efficacy in animal infection models

You can only push a formulation so far without *in vivo* data. Loc Carrillo et al. [23] were among the first to test this, using a mouse model infected with *S. suis*. Injecting phages into the abdominal cavity dropped the bacterial load in the blood significantly. Later, Jiang et al. [24] took it a step further by using piglets, proving that phages actually work in the natural host. Endolysins show similar promise. Li et al. [25] used a mouse meningitis model and found that recombinant endolysins not only cleared pathogens from the blood but also reduced inflammation in the central nervous system. The catch, however, is the extremely narrow host range. A single phage usually only hits specific serotypes. People have tried mixing phages into "cocktails," but this brings its own problems—phages end up competing for the same receptors or interfering with each other's replication, making the formulation incredibly hard to optimize [26].

4.2. Food preservation and environmental biocontrol

The usefulness of these agents goes beyond the clinic; they fit right into the "farm-to-table" pipeline. Oliveira et al. [27] tried spraying lytic phages directly onto fresh pork. The phages stopped *S. suis* from growing and left no toxic residues behind, which is a huge plus compared to chemical preservatives. On the farm, there is theoretical potential in adding phages to pig barns or wastewater systems. Because phages self-replicate, they could keep pathogenic bacterial levels down over time, which would also mean fewer resistance genes leaking into the wider environment [28].

5. Prospects

If we look at the big picture, we have made solid progress in understanding how these phages and endolysins work. But we are still a long way from actually producing and using them on a commercial scale. Three major problems are holding us back: formulation stability, host adaptability, and the challenges of protein engineering.

Poor stability is arguably the biggest roadblock. Both phages and endolysins are sensitive to temperature and pH shifts, which easily ruin their structure. If you give them to an animal orally, stomach acid and digestive enzymes tear them apart quickly. Add the host's immune system clearing them out [29], and you end up with a very short half-life. It is incredibly hard to keep an effective dose at the actual infection site. The narrow host range is just as frustrating. A single phage might only lyse one serotype. Even cocktail mixes often fail in real-world farm conditions due to the interference mentioned earlier [30]. Then there is the gap between lab research and factory production. Scaling up phage cultivation is risky because host bacteria can mutate. Producing endolysins often results in massive amounts of inclusion bodies. Right now, the industry simply does not have cheap, scalable fermentation and purification methods. Without unified quality control standards—and with a serious lack of field trials in large animals—commercialization is stalled.

How do we get past this? We need to stop relying on blind screening and start using rational design. Protein engineering could let us swap or modify the binding and catalytic domains of endolysins. This might finally solve the host range issue and make them kill faster. We should also look outside biology. Using nanomaterials to build delivery systems—like liposomes or microcapsules—could protect these proteins from degrading in the stomach and allow for slow, targeted release. But the most urgent task right now is the "last mile." We need to push forward with large animal trials and field tests. Accumulating real pharmacokinetic and safety data, while setting up standardized manufacturing rules, is the only way this green antimicrobial strategy will ever make it to the livestock market.

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