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Outline of Doctoral Thesis

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Staphylococcus aureus is one of the most frequent causative agents of bovine mastitis. The use of antibiotic as a standard treatment has led to the emergence of antibiotic-resistant strains. One alternative strategy to control *S. aureus* is to exploit lytic phages as an agent to kill the bacteria. Wall teichoic acid (WTA) is famous as a phage receptor in *S. aureus.* Staphylococcal phages utilize the backbone of WTA and/or *N*-acetyl glucosamine (GlcNAc) residues consist of α-GlcNac and β-GlcNac which transfer by TarM and TarS, respectively. In the evolution of WTA, the backbone is preserved in all *S. aureus* strains while one of the GlcNac residues is often missing (e.g. RN4220 has both GlcNAc residues but SA003 naturally lacks of α-GlcNAc). Staphylococcal Twort-like phages (including ϕSA012 and ϕSA039) are well known to utilize the backbone of WTA hence expected to have wide host range. ϕSA012 and ϕSA039 is similar in genomic level yet showing different host preference. The detail host recognition mechanism of those phages is unknown to date.

In Chapter 2, whole genome of phage resistance SA003 co-cultured with ϕSA012 was analyzed. The study showed that most of mutated genes product were linked to the cell wall synthesis including WTA. One mutated gene encodes RNA polymerase alpha subunit which may contribute in the inhibition of post-adsorption of the phage.

In Chapter 3, complementation study was conducted to confirm the role of mutated genes in phage resistance. The products of six genes were linked to phage adsorption efficiency while two genes were linked to post-adsorption. Mutation in two WTA-related gene products (TagO which transfers WTA linker and TarS which transfers β-GlcNAc residue into WTA) were manifested by the decrease of WTA production. While

mutation in other cell wall-related genes were manifested by sliminess suggestive capsular polysaccharide and total sugar of whole cell.

In Chapter 4, phage-resistant SA003 and various deletion mutants of *S. aureus* were used to compare the host recognition mechanism of ϕSA012 and ϕSA039. Even though the phages belong to Twort-like group, ϕSA039 exhibited different host recognition mechanism compare to current well known phages. ϕSA039 utilized β-GlcNAc residue and the backbone of WTA in which β-GlcNAc residue was used as the main receptor.

In summary, this study revealed that *S. aureus* SA003 developed phage resistance mechanism through inhibition of phage adsorption and post-adsorption. By utilizing phage-resistant strains and generating various deletion mutants of *S. aureus*, it was confirmed that even though ϕSA012 and ϕSA039 were closely related on the genomic level, the host recognition mechanism of these phages was different. ϕSA039 utilizes not only the backbone but also β-GlcNAc residue as its receptors, therefore, generalizing the Twort-like phages by observing certain representative species may lead to misunderstanding.