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Staphylococcus Aureus Plygrcs Endolysin, along with the Unexpected Discovery of Its Interaction with Cold Shock Protein C (cspc): A Potential Biotherapeutic Target for Treating Mrsa Infections

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Staphylococcus aureus is a major pathogen responsible for hospital and community-associated infections. Methicillin-resistant S. aureus (MRSA) is one of the clinical challenges worldwide. Hence, novel alternative antibacterial strategies are urgently required. The phage-encoded/recombinant endolysins, which degrade the bacterial cell wall by hydrolyzing peptidoglycans, are potential biotherapeutics for treating bacterial infections. PlyGRCS, a bacteriophage endolysin, consists of a catalytic CHAP domain and a cell-wall binding domain SH3_5 linked by a flexible region. It exhibits both amidase and endopeptidase activities. We determined the crystal structure of full-length PlyGRCS for the first time, refined to 2.1 Å resolution. An unexpected discovery revealed that it binds to cold-shock protein C (CspC). The lytic activity of PlyGRCS is diminished in the presence of CspC. Moreover, PlyGRCS deficient in Ca2+ and mutants in the catalytic and Ca2+ binding regions highlighted key functional residues crucial for its lytic activity against MRSA. Microbial assays demonstrated substantial lytic activity of PlyGRCS against various S. aureus strains and clinical isolates (MRSA, CA-MRSA, HA-MRSA, and LA-MRSA). The in-depth studies provide insights into the molecular mechanisms underlying the bacteriolytic activity of PlyGRCS against S. aureus.