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Broad Host Range Bacteriophage Cocktail for Reduction of Staphylococcus aureus as Potential Therapy for Atopic Dermatitis

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Abstract : Background: Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that is characterized by dry skin and flares of eczematous lesions and intense pruritus. Multiple lines of evidence suggest that AD is associated with increased colonization by Staphylococcus aureus, which contributes to disease pathogenesis through the release of virulence factors that affect both keratinocytes and immune cells, leading to disruption of the skin barrier and immune cell dysfunction. The aim of the current study is to develop a bacteriophage-based product that specifically targets S. aureus. Methods: For the discovery of phage, environmental samples were screened on 118 S. aureus strains isolated from skin samples, followed by multiple enrichment steps. Natural phages were isolated, subjected to Next-generation Sequencing (NGS), and analyzed using proprietary bioinformatics tools for undesirable genes (toxins, antibiotic resistance genes, lysogeny potential), taxonomic classification, and purity. Phage host range was determined by an efficiency of plating (EOP) value above 0.1 and the ability of the cocktail to completely lyse liquid bacterial culture under different growth conditions (e.g., temperature, bacterial stage). Results: Sequencing analysis demonstrated that the 118 S. aureus clinical strains were distributed across the phylogenetic tree of all available Refseq S. aureus (~10,750 strains). Screening environmental samples on the S. aureus isolates resulted in the isolation of 50 lytic phages from different genera, including Silviavirus, Kayvirus, Podoviridae, and a novel unidentified phage. NGS sequencing confirmed the absence of toxic elements in the phages' genomes. The host range of the individual phages, as measured by the efficiency of plating (EOP), ranged between 41% (48/118) to 79% (93/118). Host range studies in liquid culture revealed that a subset of the phages can infect a broad range of S. aureus strains in different metabolic states, including stationary state. Combining the single-phage EOP results of selected phages resulted in a broad host range cocktail which infected 92% (109/118) of the strains. When tested in vitro in a liquid infection assay, clearance was achieved in 87% (103/118) of the strains, with no evidence of phage resistance throughout the study (24 hours). A S. aureus host was identified that can be used for the production of all the phages in the cocktail at high titers suitable for large-scale manufacturing. This host was validated for the absence of contaminating prophages using advanced NGS methods combined with multiple production cycles. The phages are produced under optimized scale-up conditions and are being used for the development of a topical formulation (BX005) that may be administered to subjects with atopic dermatitis. Conclusions: A cocktail of natural phages targeting S. aureus was effective in reducing bacterial burden across multiple assays. Phage products may offer safe and effective steroid-sparing options for atopic dermatitis.

Keywords : atopic dermatitis, bacteriophage cocktail, host range, Staphylococcus aureus
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