Bacteriophage Resistance Mechanisms in the Fish Pathogen Flavobacterium psychrophilum: Linking Genomic Mutations to Changes in Bacterial Virulence Factors

Flavobacterium psychrophilum is an important fish pathogen in salmonid aquaculture worldwide. Due to increased antibiotic resistance, pathogen control using bacteriophages has been explored as a possible alternative treatment. However, the effective use of bacteriophages in pathogen control requires overcoming the selection for phage resistance in the bacterial populations. Here, we analyzed resistance mechanisms in F. psychrophilum after phage exposure using whole-genome sequencing of the ancestral phage-sensitive strain 950106-1/1 and six phage-resistant isolates. The phage-resistant strains had all obtained unique insertions and/or deletions and point mutations distributed among intergenic and genic regions. Mutations in genes related to cell surface properties, gliding motility, and biosynthesis of lipopolysaccharides and cell wall were found. The observed links between phage resistance and the genetic modifications were supported by direct measurements of bacteriophage adsorption rates, biofilm formation, and secretion of extracellular enzymes, which were all impaired in the resistant strains, probably due to superficial structural changes. The clustered regularly interspaced short palindromic repeat (CRISPR) region was unaffected in the resistant isolates and thus did not play a role as a resistance mechanism for F. psychrophilum under the current conditions. All together, the results suggest that resistance in F. psychrophilum was driven by spontaneous mutations, which were associated with a number of derived effects on the physiological properties of the pathogen, including reduced virulence under in vitro conditions. Consequently, phage-driven physiological changes associated with resistance may have implications for the impact of the pathogen in aquaculture, and these effects of phage resistance on host properties are therefore important for the ongoing exploration of phage-based control of F. psychrophilum.

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