Resistance to an RNA Phage Revealed Through Bulk and Single-cell RNA Sequencing

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Bacterial defenses against DNA phages are well-documented, yet mechanisms of resistance against RNA phages remain largely unexplored. In this study, we investigate the transcriptional response of *Escherichia coli* to infection by MS2, a single-stranded RNA phage that predates and kills cells within less than an hour. Bulk RNA sequencing revealed a rapid takeover by MS2, but a substantial part of the population remained viable post infection. Host transcriptional changes during early infection were limited, but a notable response was a transient and sharp increase in nhaR expression, a regulator of biofilm formation. Later, surviving cells exhibited partial downregulation of the virus receptor as well as upregulation of biofilm-associated genes. This implicated that biofilm pathways play a key role in resistance, which was confirmed using knockout and overexpression experiments. Single-cell transcriptomics revealed that infected cells and those that were exposed to virus and uninfected, both initiated this resistance pathway. We propose that the upregulation of resistance genes during initial stages of phage infection, specifically in cells that survive failed infection attempts, confers protection against subsequent infections. These findings provide fresh insights into RNA phage-host interactions and the adaptive strategies of bacterial populations.