Multum in parvo: The mechanism of a phage derived peptide antibiotic

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A key step in the bacteriophage life cycle is the requirement to breach the peptidoglycan layer of the bacterial cell wall. While a variety of lysis mechanisms have evolved, the simplest are found in single stranded DNA or RNA bacteriophages that, constrained by the small size of their genomes, encode a single gene lysis (SGL) protein. The first discovered and most studied example is Protein E from ΦX174 in the Microviridae family; a 91 amino acid peptide with a single transmembrane domain at its N-terminus. Protein E expression, dependent on the host chaperone SlyD, is sufficient for lysis of bacteria via inhibition of the phospho-MurNAc-pentapeptide translocase MraY, an essential enzyme in the biosynthesis of peptidoglycan. Despite the historic importance of ΦX174, the lysis mechanism remains poorly defined. Using single particle electron cryo-microscopy, we have demonstrated that Protein E forms a stable inhibitory complex with both E. coli MraY and SlyD by physically blocking access to the active site of MraY. The structure of this three-protein complex has additionally allowed us to derive new functional insight for both SlyD and MraY. Overall, the work provides exciting implications for the development of novel therapeutics.