Bacteria-Phage Coevolution

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Co-evolution is the process of reciprocal adaptations and counter-adaptations between ecologically interacting species. In the case of bacteria-phage interactions, co-evolution is often seen as an "arms race" in which bacteria develops defense mechanisms in order to become resistant to phage infection and phage will evolve to overcome bacterial resistance mechanisms in order to achieve a successful infection. Bacterial defense systems against phage infection targets multiple phases of phage infection cycle: Phage attachment to cell surface, injection of phage genome DNA and phage replication.

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In order to initiate an infection, phages must attach successfully to their host by recognizing specific receptors present in the cell surface, this process is called adsorption. Bacterial receptors are a biochemically diverse group of molecules that includes proteins, polysaccharides and lipopolysaccharides that are efficiently recognized by phage receptor binding proteins (RBPs). In order to prevent phage adsorption, bacteria have evolved a series of mechanisms that prevents recognition of cell receptors by RBPs. One of these mechanisms includes the modification or elimination the cell receptor so that it can no longer be recognized by RBPs. To infect this receptor modified-host, phages can also modify their own RBPs or other proteins involved in attachment (like tail proteins) in order to recognize a new receptor. A second mechanism to prevent adsorption, is the reduction of the accessibility of the receptor to the RBPs through the production of a capsule or other exapolyssaccharides (EPS). In order to gain access to the receptors, some phages have acquired specific enzymes that degrades the extracellular matrix and exposes the cell receptors to RBPs.

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In case that phage adsorption is successful, bacteria can use restriction modification (R-M) systems as a second line of defense. R-M systems are typically composed by two enzymes, a restriction endonuclease that recognizes specific DNA sequences and targets the phage genome upon injection and a DNA methyltransferase that methylates the host DNA and protects it from the restriction endonuclease. In order to overcome R-M systems, phage have evolved a series of strategies that can be classified into passive and active strategies. In passive strategies, no additional factor present in the phage is required. These strategies include the elimination or reduction of restriction enzyme target sites, modifications of DNA topology that affects target recognition by restriction endonucleases and incorporation of modified bases like hydroxymethyl cytosine instead of cytosine or glycosylated DNA.

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In active strategies, an additional factor protects the DNA from restriction endonucleases. This factors can be already present in bacteria, like the use of host methyltransferase to protect the injected phage genome or they can be phage encoded. Phage encoded factors are variable and act in different ways. Phages can encode their own methyltransferases that

protects phage genome sites from host restriction endonucleases. Additionally, some phages can co-inject proteins, like DarA and DarB of P1 phage, that bind the DNA and masks restriction target sites or like in the case of the OCR peptide of phage T7 of *E.coli,* the co-injected protein mimics the restriction endonuclease target and sequester the restriction endonuclease.

Finally, many bacteria cannot prevent phage infection but can protect adjacent cells by inducing cell death before phage replication. However, many phages found the way to prevent cell death and allow successful phage replication.

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This continuous development of adaptations and counter-adaptations include genetic mechanisms such as point mutations in specific genes, genome rearrangements, and genomic exchange with other viral or microbial genomes to acquire new traits. This events influence directly the diversity of bacteria and phage populations playing an important role in microbial ecology and evolutionary processes.