

17.3.5 Targeting Nonessential Genes/Proteins

In a screening of the complete Keio collection that includes individual knock-out mutations in all nonessential genes of an *E. coli* strains, with 22 different antibiotics, 283 strains were identified to have increased sensitivity to at least one antibiotic (Liu et al. 2010). This strategy used in other organisms could identify potential targets that determine antibiotic resistance and that can be used to sensitize bacteria to antibiotics in the future. In a similar approach, Clatworthy et al., has proposed to target virulence factors to sensitize bacteria rather than identifying agents that are bactericidal (Clatworthy et al. 2007).

17.3.6 Bacteriophages

Bacteriophages are viruses with the capability of infecting and killing bacteria, which has been used clinically for a long time to treat both systemic and local bacterial infections in humans (Abedon et al. 2011). However, phages have also shown promise in sensitizing bacteria to antibiotics.

A study by Fischetti and co-workers showed synergy between the pneumococcal phage lytic enzyme Cpl-1 and antibiotics in clearing pneumococcal infection with antibiotic-resistant strains (Djurkovic et al. 2005). Comeau et al., described the phenomenon phage-antibiotic synergy (PAS) and showed that sublethal doses of antibiotics significantly increased the production of phage in *E. coli*, resulting in increased bacterial killing (Comeau et al. 2007). Similarly, low penicillin concentrations increased the lytic ability of phages in *Streptococcus thermophilus* (Verhue 1978), suggesting that bacteriophages and antibiotics can synergize both for bacteria that are sensitive and more importantly for bacteria that are resistant to antibiotics.

A unique and interesting approach was presented in a study by Yosef et al. (2015). By creating two phages, one lysogenic phage transducing CRISPR sequences that specifically targeted antibiotic-resistant plasmids into the bacteria in combination with a lytic phage that contains the same target sequence, treatment resulted in that infected bacteria became resistant to the lytic phage but sensitized to antibiotics, as the resistance plasmids were eliminated (Yosef et al. 2015).

17.4 Using and Strengthening the Human Immune System Against Resistant Bacteria

17.4.1 Strengthening Host Immune System Function

Antibiotics alone are never enough to treat an infection; they only act to tip the scale in favor of the immune system in an already ongoing battle. The studies described above all focus on the bacterial part of the treatment, i.e. how to