Developing Antibiotics with "Selfish DNA" Plasmids

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Plasmids are small circular double-stranded DNA molecules that are most commonly found in bacteria. They replicate independently of chromosomal DNA. Plasmids often encode genes that provide a survival advantage to the organisms(1). For instance, plasmids may carry genes that confer resistance to naturally occurring antibiotics, or may provide the organism the ability to selectively utilize particular nutrients that will aid in survival when food is scarce. However, the maintenance and replication of plasmids impose immense metabolic burden on the bacterial host, mainly in terms of reduced host growth and viability(2).

Plasmid numbers may vary from cell to cell depending on plasmid size, with smaller plasmids being more prevalent versus larger plasmids. Due to their low copy numbers, larger plasmids are at a risk of being excluded from some of the daughter cells during cell division, thus risking eventual attrition of plasmid-bearing cells in a bacterial population. Therefore, plasmids have employed diverse mechanisms to ensure their stable maintenance in cells. These are: (i) site-specific recombination systems, (ii) active partition systems, and (iii) plasmid addiction systems (PASs) preventing the survival of plasmid-free cells due to selective killing (3).

Dr. Tsang here presents an overview of the mechanisms of the plasmid addiction system that ensure that the "selfish DNA" plasmids are transferred to the daughter cells irrespective of the metabolic burden to the host. This review discusses in further detail the different kind of plasmid addiction systems at play in a variety of bacteria, in order to promote plasmid survival. Protein regulated systems, anti-sense RNA-regulated systems and restriction modification systems are the three broad categories of PASs. All the three PASs encode genes or RNAs that eventually cause cell death in plasmid-free cells by targeting essential cellular structures such as the cell membrane or chromosomal DNA.

Of particular interest are bacteria that carry both antimicrobial genes and PASs. These are often transferred horizontally across many different bacterial species and poses a threat to humans health. The article highlights examples of pathogenic microbes that acquired resistance to antibiotics during hospital visits. Finally, with the help of specific examples, Dr. Tsang effectively builds up an argument for utilizing PAS to develop novel antimicrobial agents (4). Development of antimicrobial resistance is one of the major issues facing infectious diseases today. According to the Centers for Disease Control, at least 2 million people become infected with antibiotic-resistant

bacteria and at least 23,000 people die each year due to those infections (5). Therefore, new and effective ways to overcome antibiotic resistance need to be implemented. Since PAS and antibiotic resistance often co-exist and are propagated by plasmids, targeting PAS offers a promising approach towards combating antibiotic resistance. This approach can be potentially adopted by pharmaceuticals in developing anti-bacterial programs.

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