Chapter

Introductory Chapter: *Pseudomonas aeruginosa* - Toward Omnipresence

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1. Master in evolving

Antibiotics are extensively used worldwide for treating predominantly gram-negative bacterial infections and also for treating certain gram-positive infections. While the precise mechanism of their bactericidal action is yet to be unraveled, aminoglycosides, for example, act by binding to the RNA component of ribosomes, leading to both mistranslation and ultimate inhibition of protein synthesis. The widespread use of other major classes of antibiotics has resulted in the emergence of resistant bacteria by expediting the course of its evolution [1, 2]. The emergence of resistance to antibiotics is of special concern in the treatment of infections, particularly of systemic nature, by gram-negative organisms narrowing down the options for antibiotic alternatives. The resistance mechanisms displayed by the bacteria can be classified into the following: (a) reduced uptake, (b) increased efflux, (c) enzymatic modification of drug, and (d) drug target modification. Whereas resistance to streptomycin, the first widely used aminoglycoside, is predominantly through mutations in drug targets (mostly in the ribosomal protein rpsL and also in rRNA), resistance to other aminoglycosides appears to utilize a variety of mechanisms. The question arises, whether antibiotic action facilitates the emergence of resistant mutants. For certain other classes of antibiotics that induce the bacterial SOS response either by direct DNA damage (e.g., ciprofloxacin) or through indirect means (e.g., ampicillin), it has been shown that the action of the antibiotic itself plays a significant role in the emergence of mutations that confer resistance. One such mechanism, mistranslation due to defects in the translation apparatus, can promote hypermutagenesis in a phenomenon called translational stress-induced mutagenesis (TSM) raising the possibility that aminoglycoside exposure, by promoting mistranslation, could also elevate mutagenesis. According to the current understanding, TSM is mediated by a low-level mistranslational corruption of the replicative DNA polymerase leading to episodic hypermutagenesis. Exposure of wild-type bacterial cells to sublethal concentrations of an antibiotic increases mutagenic translesion DNA synthesis in vivo, and exposure of certain mutants also increases spontaneous mutagenesis. Exposure of wild-type *Pseudomonas aeruginosa* PAO1 cells to sublethal concentrations of tobramycin and amikacin, two aminoglycoside antibiotics commonly used to treat *P. aeruginosa* infections, can elevate spontaneous mutagenesis leading to complications in treating cystic fibrosis patients [3].

2. Master in dominating

Cystic fibrosis (CF) is an autosomal recessive genetic condition among Caucasians, with an incidence rate of 1 in 2500 live births. The morbidity and

mortality associated with this disease condition are due to thickened lung secretions and subsequent creation of hypoxia and secondary infections predominantly by opportunistic pathogens. Bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia cepacia* complex have been in the limelight as the pathogens that affect CF patients with progression of lung disease ultimately leading to mortality. Interestingly, recent developments in high-throughput genomic techniques revealed the presence of several other bacterial species, which were hardly identified using conventional microbiological techniques. Enteric bacteria, such as *Prevotella*, *Bacteroides*, *Fusobacterium*, *Mycoplasma*, *Ralstonia*, *Veillonella*, etc., which do not normally appear in the laboratory cultures were identified and were found to have an impact on the CF microbiome [4]. This fluctuation in the CF microbiome may be due to transition of atypical species toward chronic mode of infection through formation of biofilms, dormancy, small colony variants, etc. The immunocompromised nature of CF patients predisposes them to a variety of infections, thereby increasing the need for antibiotics, alone or in combination, on a daily basis, at milligram levels. Such a continuous antibiotic pressure drives evolution of lung pathogens through the downregulation of acute-mode virulence factors in order to avoid unnecessary energy loss and expression of regulons associated with chronic mode of infection/colonization. Though the CF microbiome has been shown to consist of several species of bacteria, *P. aeruginosa* becomes the predominating one during the course of chronic colonization in the CF lung, thereby increasing its significance when considering appropriate treatment strategy [5].

Apart from the abovementioned bacterial species in the CF microbiome, mycobacteria, in general, are widespread organisms except tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*M. leprae*) pathogens which are obligate parasites always in need of a host. These bacteria are often involved in asymptomatic infections, are highly fastidious organisms showing resistance to antibiotics, and are able to survive for long periods in acids, alkali, detergents, etc. Non-tuberculous mycobacteria constitute all the other mycobacteria gaining importance in respiratory infections including the one resembling tuberculosis. Practically, overgrowth of pseudomonads and other predominant bacterial species in the lung makes it difficult to understand the existence of atypical bacteria in the case of CF lung infections. The inherent slow growth rate of mycobacteria adds to failures in preliminary detection of these bacteria. Once identified it requires a prolonged treatment regime for several months with combined antibiotics, which add stress to the CF lung environment, thereby resulting in a progressive deterioration of lung function with consequent emergence of resistant pathogens. Dominance by *P. aeruginosa* or few known predominant bacterial species in the CF lung is clinically beneficial in the sense that these outnumbered species may offer protection against more pathogenic species such as mycobacteria [6].

3. A friend or a foe?

Normally, tuberculosis is rare among CF patients, and it was found to complicate the CF disease condition. It is also interesting to know that the CF disease condition will not support growth of TB mycobacteria (*Mycobacterium tuberculosis*) and the risk of TB in these patients is high in areas with high prevalence. In addition, other chronic illnesses such as poorly controlled diabetes were considered as an additional risk factor among CF patients.

Among non-typical mycobacteria (NTM), *M. abscessus* is considered the most clinically virulent species. Isolation of NTM is common in CF patients before lung transplantation as revealed by data from a large US center. However, reports

mention high variability in infection rates predominantly with single species and rarely by two mycobacteria due to several factors from diversity in methodology, number of patients involved in the studies, geographical and racial differences, and the age factor, with some ambiguity in the case of gender basis. Adolescents and young adults (10–25 years age) are prone to NTM infections with rapidly growing strains infecting patients of all age groups. The slow-growing species *M. avium*, *M. intracellulare*, and other genetically related species are prevalent in North America, whereas the rapidly growing *M. abscessus* prevails in Western Europe and Israel. Infrequent prevalence was reported for *M. fortuitum*, *M. gordonae*, *M. kansasii*, *M. simiae*, *M. peregrinum*, and *M. malmoense* [7]. However, survival of CF patients infected with NTM before transplantation is reported to be similar to that of patients without NTM infection. Overall, the predominance of *P. aeruginosa* could help keep a check on infections by other pathogenic bacteria [8].

4. The concern

Huge genetic repertoire and mosaic genome structure of *P. aeruginosa* make it a versatile opportunistic pathogen in nosocomial settings, particularly in conditions involving burns and wounds, meningitis, endocarditis, and microbial keratitis. Interestingly, *P. aeruginosa* displays a common phenotype in the CF lung irrespective of the genetic content, which includes mucoidy, lipopolysaccharide modifications, lack of flagella and pili, upregulated antibiotic efflux, etc. New forms of emerging resistance in bacteria spread rapidly by intra- and interspecies acquisition of genetic content from the environment where community biofilms are common. In addition to being a threat to public health, highest resistance rates correlate with highest per capita antibiotic consumption of a nation.

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