

## Adaptive Antibiotic Resistance: Overview and Perspectives

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### Abstract

In reaction to the improved use of antibacterial materials, particularly in the 20<sup>th</sup> century, bacteria have developed mechanisms to surmount the efficacy of antibiotics and so become resistant. In fact, the evolution of the compulsive resistance of bacteria to antibiotics is great. Coevolution of microorganisms with environmental antibiotic materials has intensified the evolution of resistance mechanisms, which are usually classified into three types including intrinsic, acquired and adaptive resistance. Bacteria are either innately resistant or attain resistance to antibiotics in order to prevent access to drug targets, alterations in the construction and aegis of antibiotic targets and the direct change or inactivation of antibiotics. In adaptive resistance, the ability of bacteria to surmount antibiotic challenge without mutation is the focus. In this resistance, there is a transient nature. It occurs in response to some environmental conditions that are dependent on epigenetic phenomena for exhibition of permanent resistance. This review provides a summary of accessible information on adaptive resistance.

**Keywords:** Antibiotic resistance; Adaptive resistance; Bacterial resistance; Mutations; Epigenetics

### Introduction

Over the past decades, with the slow rate of development and introduction of new antimicrobial drugs, resistant clinical isolates were observed copiously. This has resulted in the production of ineffective and inappropriate antibiotics that are used to treat and control bacterial infections. The fantastic and potent ability of bacteria to acquire antibiotic resistance is more confusing to pharmaceutical scientists when analyzed from a development point of view [1].

Nevertheless, after the development and introduction of antibiotics into the clinic, this resistive force has significantly increased, culminating in a remarkable speed in the evolution and spread of resistance indications in bacteria. This is especially due to the fact that once bacteria acquire resistance to antimicrobial drugs, the resistance is lost at a relatively slow pace [2].

### Types of Antimicrobial Resistance

Coevolution of microorganisms with innate antibacterial materials has fostered the development of resistance mechanisms [3]. There are three basic types of antimicrobial resistance, including intrinsic, acquired, and adaptive. Intrinsic resistance contains all of the natural features or characteristics. There are three basic types of antimicrobial resistance, including intrinsic, acquired, and adaptive. Intrinsic resistance contains all of the natural features or characteristics of a special bacterium that limit the action of antibiotics.

Recent investigations have led to the recognition of many genes that are responsible for intrinsic resistance of bacteria to antibiotics of different categories, containing  $\beta$ -lactams, fluoroquinolones and aminoglycosides [4].

An example of this type of resistance is the biocide triclosan, which has widespread performance against gram-positive bacteria and many

gram-negative bacteria, but it is incapable of inhibiting the growth of members of the gram-negative genus *Pseudomonas*. This is because there is no susceptible target for triclosan in this bacterium [5]. In acquired resistance, an originally sensitive bacterium can become resistant by incorporating new genetic materials (transposons, plasmids, integrons, etc.) or as a result of mutations. In this way, bacteria are able to grow thin and proliferate in any new or changing environment [6]. Acquired resistance can occur by multiple mechanisms, which fall into three main types: first, those that minimize the intracellular concentrations of the antibiotic as a result of low penetration into the microorganism or the antibiotic efflux; second, those that change the antibiotic target by genetic mutation or post-translational alteration of the target; and third, those that emasculate the antibiotic by hydrolysis or modification [1,7,8].

### Adaptive Resistance of Bacteria

Bacteria can modify their transcription very quickly in response to changes around the milieu in order to enhance their chances of survival. Some of these changes confer on the bacterium a greater ability to withstand the challenges from antimicrobial drugs. There are many milieu indications that can show the acquisition of temporary resistance by a given antimicrobial compound, including ion densities, temperature, and very importantly, exposure to non-lethal doses of antibiotics [9].

In fact, bacteria acquire their adaptive capacity through mutability and a binding genetic plasticity that enables transfer of genes among bacteria [10].

Unlike intrinsic and acquired resistance, which are stable and can be transmitted vertically to subsequent generations, adaptive resistance has a unstable property and usually reverts at the liminal of the inducing status [9,11]. Unstable adaptation contains modulation of gene expression, which results in phenotypic changes due to changes in environmental markers that are sensed by the microorganisms [12]. If an environmental alteration would be encountered by a temporary or a

constant adaptation, it will depend largely on the power and duration of the selection force [13].

Considerable changes in the environment, as in the case of the sample of antibiotic treatment, can result in both unstable adaptations like metabolic changes, which would result in antibiotic resistant bacteria and permanent adaptations that sometimes give rise to bacteria that are antibiotic resistant [10,14]. The mechanisms of bacterial resistance to antibiotics vary amazingly and can be specific; in this way, the primary function in the cell is to resist the role of toxic materials, or non-specific action in cases where the resistant agent is a part of the other cellular functions but also exhibit a protective effect against antibiotics. The main mechanism of resistance contains the inactivation of the antibiotics by enzymes such as  $\beta$ -lactamases or aminoglycoside modifying enzymes. Additionally, resistance can be acquired *via* mutations that affect the intracellular target for a given antimicrobial drug [1]. In this paper, we focused on adaptive resistance, which was defined by [9] as 'a temporary increase in the ability of a bacterium to survive an antibiotic insult due to alterations in gene and/or protein expression as a result of exposure to an environmental trigger.' Unlike the other two types of resistance, adaptive resistance is dependent on the presence of antibiotics [1,9,15]. However, in a study, it was shown that adaptive resistance can also occur in the absence of known environmental stimuli [3].

## Genetic and Epigenetic Events Involve Adaptive Resistance of Bacteria

The choice of useful mutations or horizontal uptake of beneficial genes shows permanent genetic adaptations to an alteration in the environment. Any change in the environment is met by an interim or permanent adaptation, which largely depends on the ability and duration of the selection pressure. Actual changes in the environment, as in the case of antibiotic therapy, can result in both temporary capacity like metabolic alterations, which culminates in antibiotic tolerant bacteria [16] and permanent adaptations, which sometimes increase bacteria resistance to antibiotics [10,14].

In a research conducted to examine and study the adaptive resistance of bacteria to antibiotics, it was shown that it is very labile as it is mixed in a few generations of non-selective growth (without antibiotic). This also implies that adaptive antibiotic resistance is not produced by genetic alterations (which usually produce irreversible phenotypes), but possibly by epigenetic alterations, which are known to be less permanent [17,18]. Adaptive laboratory evolution experiences can be helpful in discovering the evolutionary potential of species in developing antibiotic resistance [13].

It has been suggested that a mix of epigenetic activities such as methylation and accidental gene expression, maybe responsible for the emergence of adaptive resistance [18-20]. In particular, it has been proposed that DNA methylation by the DAM methylase could be responsible for: i) the presence and heredity of different gene expression profiles [20-24] and ii) the mutability in expression observed in methylated genes. The function of the DAM methylase gene has been found to be relevant in the development of adaptive resistance [18]. Methylation is capable of generating both the heterogeneity and epigenetic heredity of gene expression plans essential for adaptive resistance to occur [25]. In addition, the reversion speeds to sensitive appearance are also very high. Once the microorganisms have become resistant, and the antibiotic is deleted from the milieu, a deduction as large as 95% of the bacterial crowd

becomes susceptible again "almost immediately" [18] or in less than 100 generations [17].

The significant point is that the rapid epigenetic alterations that take place in the transcription phase permit the population to remain alive long enough to become more constant and produce effective resistance. This action is stable from empirical observations, which shows that the bacterial populations that have been persistently exposed to antibiotics are continually resistant compared to populations that have not been exposed to antibiotics [18,25].

As regard antibiotic resistance, antibiotic selection force is the stimulus for the appearance of drug-resistant pathogens. This assertion which was formerly overlooked, further suggest that removal of the selection pressure, for example, by circulating patterns of antibiotics in clinical usage, would most probably induce a decrease in the resistance load [26,27]. The argument behind this opinion was that antibiotic resistance occurs at a fitness cost to those bacteria acquiring such new properties as a result of metabolic punishment from mutation of the necessary proteins that function as antibiotic receptors, as well as expression of multi-drug efflux pumps from re-engineering of the cell surface, or definition of a new enzyme that reduces or changes an antibiotic [26,28,29]. The ability for the bacteria to undergo genetic changes, provides the necessary drug-resistance genes; but, the development of mobile genetic elements is the key trait in global distribution of antibiotic resistance genes among bacteria [26,30].

Bacteria proliferating on surfaces such as biofilms exhibit adaptive resistance (frequently presented as tolerance) to antibiotics [31].

Adaptive mutation is one of the important resistance mechanisms that involves adaptive resistance of bacterial biofilm accumulations [32]. Adaptive mutations occur within the regulatory housekeeping genes targets of antibiotics, which are mostly oppositely pleiotropic (i.e., adaptive under some statuses, while harmful under others) [33].

Population structures, in specific biofilms, also show a very difficult structural instability for antibiotics in terms of their efficacy [34-36]. Primarily, because of the dynamic structure of the population, bacterial cells in the inner layers of the biofilm are less connected to environmental signals, and the toxic materials have a calm and restricted penetration. Due to this impermeability, gradients and harbors can be formed, which can facilitate the development of resistance. Moreover, peptides are also persistently secreted to the outer parts of the biofilm decreasing remarkably the toxic function of the antibiotics [34,37].

In summary, epigenetic heredity, population structure and heterogeneity, high mutation rates, gene amplification, efflux pumps, and biofilm formation are among the factors that have been reported as possible causes of the development of adaptive antibiotic resistance. Nevertheless, these concepts taken independently are not enough to arrest the rapid emergence of adaptive antibiotic resistance or to forestall its low consistency. New strains of resistant pathogens continue to appear, and none of the new approaches used to kill them (mixed antibiotics, sequential treatments, and efflux inhibitors) are completely efficacious [15].

As a result, adaptive antibiotic resistance can be considered as a barrier that permits rapid bacterial cell proliferation, due to temporary and unknown response to low antibiotic concentrations, while in the meantime the cell develops more effective and continual mechanisms that confer higher resistance to specific antibiotics.

## Author Contributions:

Kobra Salimiyan rizi has written the original text. Dr. K. Ghazvini has been in charge of the correct process of supervision and guidance. Mahdi kouhi Noghondar has helped to collect the informations.

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