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Epigenetic Regulation and Metabolic Adaptation in the Emergence of Multidrug Resistance Among Clinically Significant Gram-Negative Pathogen

Shaymaa F Abbas
Department of Pharmacology, Alzahraa College of Medicine, University of Basrah, Basra, Iraq.

Saifali J. Aljabran
Department of Pharmacology, College of Medicine, University of Basrah, Basra, Iraq.

Dhuha E. Omran
Department of Pharmacology, Alzahraa College of Medicine, University of Basrah, Basra, Iraq.

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Abstract

The swift development of multidrug-resistant (MDR) Gram-negative microbes has emerged as a key health problem in the world, greatly reducing the efficacy of the available antimicrobial treatments. Among the most designable effective pathogens that cause severe healthcare-associated and community-acquired infections, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii can be named. Historically, genetic processes, such as horizontal gene transfer, chromosomal mutation, enzymatic inactivation of antibiotics, and overexpression of efflux pumps, have been recognized as the major causes of antibiotic resistance in these organisms. Nevertheless, there is increasingly strong evidence of a significant role of non-genetic regulatory mechanisms in controlling adaptation and survival of bacteria to antimicrobial pressure.

In the recent past, research on epigenetic regulation and metabolic adaptation has been noted as critical factors in the development and maintenance of MDR in Gram-negative

pathogens. Flexible gene expression in bacteria is made possible through epigenetic processes, such as DNA methylation, phase variation, and nucleoid-associated protein activity, but does not change the genome sequence. These processes bring about simple and reversible phenotypic alterations in bacteria, which enables the populations to produce phenotypic diversity and increase their ability to endure the environmental exposure as a consequence of antibiotic exposure.

Simultaneously, metabolic adjustment has also been much more highly appreciated as a pivotal determinant in bacterial tolerance and resistance towards antibiotics. When exposed to antimicrobial agents, significant changes are commonly induced on the central metabolic pathways, such as carbon metabolism, energy production, and oxidative stress responses. Such metabolic changes may affect the growth rate of bacteria, the cellular dynamics, and the membrane dynamics, which have an eventual impact on antibiotic susceptibility. Moreover, the metabolic reprogramming can also enhance the development of persister cells, subpopulations with a transient antibiotic tolerance, which can lead to the long-term expansion of stable resistance in the form of long-term mechanisms.

Critically, metabolic processes and epigenetic regulation are thought to be very linked. The expressions of genes in metabolic pathways can be regulated by epigenetic modifications and intracellular metabolic states may affect epigenetic regulation systems via the provision of important metabolites. This bidirectional interaction creates a complicated regulatory network that increases the adaptability of bacteria to the antibiotic pressure and is favorable to the emergence of multidrug resistance.

The purpose of the review is to obtain a complete picture of the present-day knowledge on epigenetic regulation and metabolic adaptation of clinically significant Gram-negative bacteria and their contributions to the development of multidrug resistance. Besides, the therapeutic implications that have been discussed in the review with regard to targeting these regulatory systems and emerging strategies that could play a role in the development of novel antimicrobial interventions are discussed. Better insight into these processes can possibly be used to discover new methods to address MDR infection and enhance the efficacy of future antimicrobial treatment.

Keywords: Multiple myeloma; Extramedullary disease; Paraspinal mass; Retrovertebral tumor; MRI; Plasmacytoma; Neurosurgery

Introduction

The problem of the rapid development and the further dissemination of the multidrug-resistant (MDR) bacteria is one of the most urgent issues of contemporary medicine. There has been an alarming rate of healthcare-associated and community-acquired infections caused by gram-negative pathogens, which exemplarily develop and sustain resistance to more than one group of antibiotics (1,2,3). Most commonly, such clinically significant Gram-negative bacteria as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii are involved in the pathogenesis of pneumonia, bloodstream infections, UTIs, and wound infections. The rising numbers of cases of MDR strains among these organisms have greatly restricted therapeutic choices, resulting in increased morbidity, mortality, long hospitalization and higher cost of health care across the globe (4,5,6).

Historically, well characterized genetic processes that include horizontal gene transfer, mutation and overexpression of efflux pumps, and enzyme inactivation of antibiotics have been identified to play a significant role in the development of antibiotic resistance in bacteria. Recent developments in microbial genomics and systems biology have however indicated that non-genetic regulatory systems can also be crucial in bacterial adaptation and survival in cases of antibiotic stress. Epigenetic regulation and metabolic adaptation have become some of these mechanisms that have contributed to the evolution and maintenance of multidrug resistance in Gram-negative pathogens (7,8,9).

Epigenetic regulation in bacteria Epigenetic regulation of bacteria is a process where there is a change in gene expression, but the underlying DNA sequence remains unchanged. Such regulatory mechanisms are typically entailed in the DNA methylation, variation of phases and the actions of nucleoid-associated proteins that control the structure of chromosomes and transcriptional availability. These processes allow bacteria to switch between the expression profile of genes quickly in reaction to environmental pressures such as antimicrobial agent exposure. Epigenetic changes can be used to produce phenotypic heterogeneity in bacterial populations to survive under unfavorable circumstances, leading to the development of resistant or tolerant subpopulations (10,11,12).

Simultaneously, metabolic adaptation is also vital to help bacterial cells to survive antibiotic pressure. Exposure to antibiotics frequently causes extensive metabolic alterations in bacterial metabolism, such as energy generation, central-carbon

metabolism, oxidative stress-response, and nutrient use. Such metabolic changes have the potential to decrease the vulnerability to antibiotics through mechanisms such as retarded cell growth, membrane physiological alterations, or increase in stress-response systems to safeguard important cellular processes. Accumulating data indicate a role of metabolic reprogramming in the development of antibiotic tolerance and the stabilization and evolution of genetic resistance mechanisms (13,14,15).

Notably, epigenetic control and metabolic adaptation do not exist in isolation of each other; instead, they are more than closely interrelated processes which combine to influence the way bacteria react to environmental stresses. Epigenetic changes may have an effect on the expression of metabolic genes, and metabolic conditions may have an effect on the work of epigenetic regulators, which can form a dynamic regulation system that promotes the survival and adaptation of bacteria under antibiotic conditions (16,17,18).

Due to the increasing risk of MDR Gram-negative pathogens, the mechanism of interaction between epigenetic regulation and metabolic adjustments has become a research priority. The information about these regulatory networks can provide new therapeutic options and new approaches to the antibiotic resistance. This review thus examines the existing knowledge of epigenetic processes and metabolic changes in the development of multidrug resistance in clinically significant Gram-negative bacteria with an emphasis on recent developments and their future prospects in antimicrobial development (19,20,21).

Clinically Important Gram-Negative Pathogens and the Global Burden of Multidrug Resistance

Gram-negative bacteria are a significant category of causative agents of hospital-acquired and community-related infections of a broad range. Clinical significance is mostly due to the existence of complex outer membrane which inherently decreases the permeability to antibiotics and the exceptionally high genetic plasticity that supports the uptake of resistance determinants. Over the past decades, multidrug-resistant (MDR) Gram-negative pathogens have emerged as a crucial social health issue, especially in the intensive care units with susceptible patients frequently being exposed to broad-spectrum antibiotics (22,23,24).

Some of the clinically most significant Gram-negative microorganisms include Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii. Some of the most common infections that these pathogens are believed to cause are urinary tract infections, ventilator-associated pneumonia, bloodstream infections, and wound infections. It is primarily because they can adapt to hostile environments quickly and gain resistance to a variety of antimicrobial agents that has enabled them to be highly successful as opportunistic pathogens. An example is E. coli and K. pneumoniae exhibiting extended-spectrum 2 -lactamase (ESBL) which have become common in both hospital and community environments, making the use of 2 -lactam antibiotics less efficient. Likewise, P. aeruginosa and A. baumannii have proved to have an extraordinary ability to grow resistant to carbapenems, in which case the later are regarded as the last-line antibiotics against a serious infection (25,26,27).

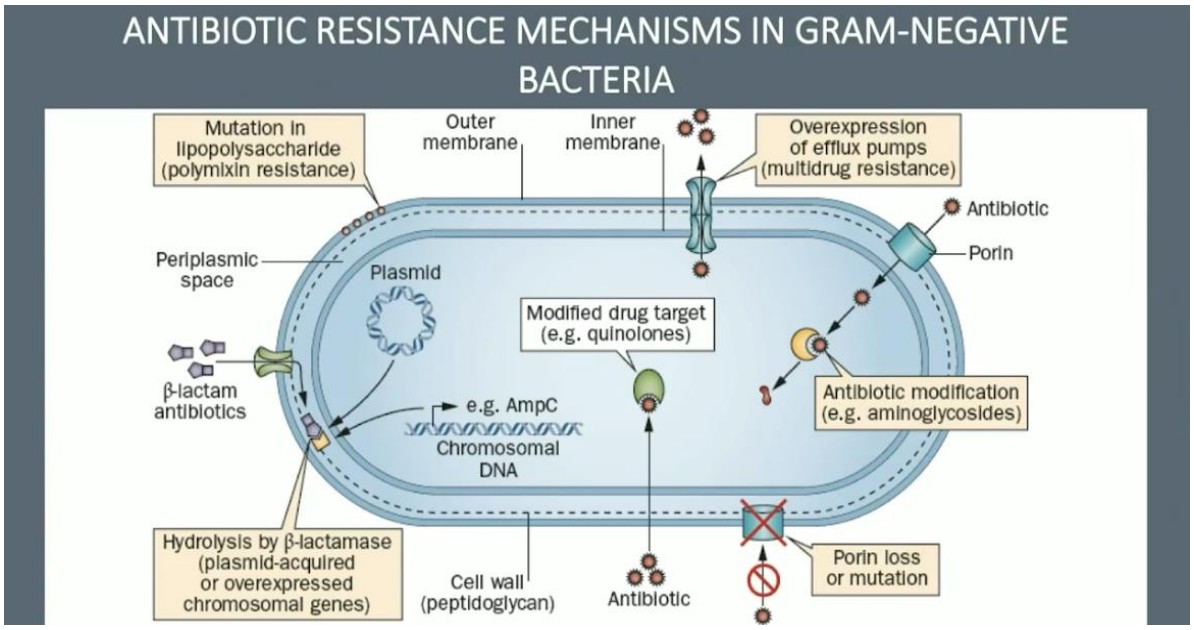

Fig 1: MDR Gram-Negative Infections

The dissemination of mobile genetic factors including plasmids, transposons and integrons which possess antibiotic resistance genes has further exacerbated the global burden of MDR Gram-negative infections. These factors enable horizontal gene transfer between populations of bacteria that increases the spread of resistance among other species and geographical locations. Moreover, the positive selection pressure due to the overuse or misuse of antibiotics in medical and agricultural practice leads to the development of antibiotic-resistant strains (29,30).

MDR Gram-negative bacteria infections are clinically linked with increased mortality rates, extended hospitalization and increased health care spending. The scarcity of effective antibiotics has compelled clinicians to use older and more toxic antibiotics like colistin or polymyxins as an alternative, and this argument further explains the urgency in learning the mechanisms behind the development of resistance. Therefore, the definition of the key Gram-negative pathogens implicated in MDR infections and their resistance patterns are all necessary measures in the development of effective measures of therapy and prevention (30,31,32).

Table 1. Major clinically significant Gram-negative pathogens associated with multidrug resistance (33,34).

Bacterial species	Common infections	Major resistance mechanisms	Clinical significance
Escherichia coli	Urinary tract infections, sepsis	ESBL production, efflux pumps	Leading cause of community and hospital infections
Klebsiella pneumoniae	Pneumonia, bloodstream infections	Carbapenemases (KPC, NDM), ESBLs	Major cause of hospital outbreaks
Pseudomonas aeruginosa	Ventilator-associated pneumonia, burn infections	Efflux pumps, porin loss, enzyme production	Highly adaptable opportunistic pathogen
Acinetobacter baumannii	ICU infections, wound infections	Carbapenem resistance, biofilm formation	Notorious for hospital-acquired MDR infections

Epigenetic Regulation in Gram-Negative Bacteria

Epigenetic regulation has played out as a significant process through which bacteria can speedily modify the expression of their genes in relation to environmental alterations without modifying their DNA backbone. Despite being a study that has traditionally been linked to eukaryotic organisms, there is an emerging body of work that shows that bacterial cells also utilize epigenetic mechanisms to control important physiological processes, such as virulence, stress responses, and antibiotic resistance. Epigenetic regulation in Gram-negative pathogens offers another point of control allowing them to adapt to exposure to antibiotics and other unfavorable conditions within a short period of time (35,36,37).

DNA methylation is one of the major epigenetic processes used in bacteria. The DNA methyltransferases introduce methyl groups on to particular bases, usually on adenine or cytosine bases leading to modifications that affect the DNA-protein interactions and transcriptional activity. DNA adenine methylation that is mediated by Dam (DNA adenine methyltransferase) in Gram-negative bacteria is important in the regulation of gene expression, DNA replication, and mismatch repair. Notably, the antibiotic resistance, stress response, and virulence factors genes could be modified by methylation patterns and this affects bacterial survival under antimicrobial pressure (38,39,40).

The other interesting phenomenon regarding epigenetics is the phenomenon of phase variation which is a reversible switching mechanism by which certain genes may be expressed or silence in bacteria. Phase variation can be as a result of the modification of DNA methylation or modification of repetitive DNA sequences and this leads to the phenotypic diversity within bacterial populations. This heterogeneity allows only part of the cells to endure the stressor in the environment like antibiotics, and due to this heterogeneity, it is more likely that resistant phenotypes will develop and be maintained (41,42,43).

Furthermore, nucleoid-associated proteins (NAPs) are important regulators of bacterial epigenetics controlling accessibility and structure of genes and chromosomes. H-NS, Fis and IHF are proteins that are interacting with the DNA and organize the bacterial chromosome to control the transcriptional networks. The proteins may control the expression of metabolism, virulence, and antimicrobial resistance associated genes, thereby, making the bacteria adaptable (44,45,46).

All these epigenetic processes enable Gram-negative bacteria to actively control gene expression to produce a phenotypic variance without necessarily having to mutate their genomes in a permanent manner. This plasticity gives an advantage of survival in a dynamic environmental condition, such as exposure to antibiotics. With ongoing discoveries of the complexity surrounding the nature of bacterial epigenetic regulation, it has become increasingly apparent that the processes are instrumental in the development and maintenance of multidrug resistance (47,48,49).

Table 2. Major epigenetic regulatory mechanisms in Gram-negative bacteria (50,51).

Epigenetic mechanism	Key components	Functional role	Impact on antibiotic resistance
DNA methylation	DNA methyltransferases (e.g., Dam)	Regulates gene expression and DNA replication	Modulates expression of resistance and stress genes
Phase variation	Reversible gene switching	Generates phenotypic diversity	Enables survival of resistant subpopulations
Nucleoid-associated proteins	H-NS, Fis, IHF	Chromosome organization and transcription control	Influences virulence and resistance gene expression
Epigenetic gene regulation networks	Interaction of regulatory proteins and methylation patterns	Coordinated cellular responses to environmental stress	Supports adaptive responses to antibiotics

Metabolic Adaptation as a Driver of Antibiotic Resistance

It has emerged that Metabolic adaptation is an essential factor in the survival of bacteria in the presence of antibiotics. Exposing Gram-negative pathogens to antimicrobial agents may result in the alteration of metabolic pathways, and bacteria cells can maintain the needed physiological processes without any detrimental effect of antibiotics. These alterations in metabolism enable bacteria to survive in an adverse environment and can also contribute to both the transient development of the temporary resistance to antibiotics and the eventual development of the intractable multidrug resistance (52,53,54).

Among the fundamental processes of metabolic adaptation, one should mention reprogramming of central carbon metabolism. Some of these are the routes which the bacteria tend to alter under pressure of antibiotics such as glycolysis, tricarboxylic acid (TCA) cycle and pentose phosphate pathway. These changes can have an impact on cellular energy production, redoxation and biosynthesis. An example of this is that, to prevent the formation of reactive oxygen species (ROS), which are a by-product of exposure to antibiotics, blocking the TCA cycle or changing it to the alternative metabolic processes may inhibit the formation of reactive oxygen species (ROS). There is a decrease in oxidative stress, which helps the bacteria in lowering susceptibility to antimicrobial treatment (55,56,57).

In addition to the energy metabolism, in most of the cases, the mechanism of respiration and electron transfer is also altered by the antibiotic stress in the bacterial cells. Alterations in respiratory activity can alter membrane potential and intracellular ATP such that the uptake and effectiveness of particular antibiotics is altered. A low rate of metabolism or a transition into the low-energy stage of physiological state may decrease the efficiency of antibiotics that are active against growing cells, which is also among the factors that cause antibiotic tolerance.

The other important attribute of metabolic adaptation is in the form of regulation of nutrient intake and consumption. The gram-negative bacteria have control over the uptake of carbon sources, amino acids among other nutrients to respond to environmental conditions. It is this metabolic flexibility that allows bacterial populations to endure nutrient-restrained environments such as infected tissues as well as retain cellular functions that are needed to survive and adapt (58,59,60).

Moreover, metabolic adaptation is directly linked with the development of persister cells the subpopulation of bacteria that becomes temporarily tolerant to antibiotics, but which does not have permanent genetic resistance. Such cells tend to exhibit a disturbed metabolic condition of low growth rates and low metabolic activity. Though not bearing permanent resistance mutations, persisters are more likely to survive during antibiotic treatment, hence a higher likelihood of genetic resistance will in due course be found in the population (61,62,63).

The recent developments in the metabolomics and systems biology have produced new information about the role of metabolic networks in determining antibiotic susceptibility. These studies have shown that metabolic pathways are capable of regulating the activity of the efflux pumps, membrane transport systems and stress response pathways which are significant in antibiotic resistance. Therefore, the manipulation of bacterial metabolism is suggested as one of the potential approaches to increasing antibiotic effectiveness and defeating MDR infections (64,65).

Altogether, metabolic adaptation is a complex process of survival, which allows Gram-negative pathogens to resist the pressure of antibiotics. A further insight into the role of metabolic reprogramming in the formation of antibiotic tolerance and resistance can offer useful prospects of creating new antimicrobial drugs to interfere with the metabolic networks of bacteria (66,67).

Interaction Between Epigenetic Regulation and Metabolic Pathways in the Development of Multidrug Resistance

Multidrug resistance in Gram-negative bacteria is coming to be seen as the outcome of interactions between complex sets of regulatory systems and not the activity of single mechanisms. The connection between epigenetic regulation and metabolic pathways is one of the most significant of these interactions and it is involved in determining how bacteria respond to antibiotic stress. The inter-relationship of these systems allows the rapid change of bacteria to the new environment because the co-ordinated genes expression is linked to cellular metabolic conditions (68,69).

The expression of genes that take part in metabolic pathways can directly be affected by epigenetic processes like DNA methylation and activity of nucleoid-associated proteins. Epigenetic regulators are able to regulate the expression of

enzymes involved in central carbon metabolism, energy production, and stress response pathway by changing the availability of DNA to transcriptional machinery. This regulation flexibility enables bacterial cells to narrow down metabolic activity to internal environmental factors such as exposure to antimicrobial agents (70,71).

On the other hand, the epigenetic regulatory processes can also be affected by the metabolic states in the bacterial cell. The availability of important metabolites that are either epigenetic enzyme cofactors or substrates are determined by cellular metabolism. As an illustration, changes in intracellular concentrations of S-adenosylmethionine (SAM), a key donor of methyl group can have a direct impact on DNA methylation patterns. The flux alterations can thus modify the global gene expression patterns via epigenetic alterations (72,73).

The combination of metabolism and epigenetics regulation plays a role in the heterogeneity of phenotype in bacteria. Amongst the representatives of one and the same bacteria, the levels of metabolic activity and the epigenetic condition may produce subpopulations that are characterized by specific physiological traits. Part of these cells can exhibit a higher resistance to antibiotics and this is an advantage of survival in antimicrobial therapy. These tolerant cells may also overtime develop genetic mutations or develop resistance determinants and eventually result into stable multidrug resistant strains (74).

Moreover, combined metabolic and epigenetic network control is involved in a variety of processes related to resistance, such as biofilm formation, efflux pump activity and stress response networks. An example of such microbial communities is biofilms which are highly structured micro communities with altered metabolic states and unique gene expression patterns. Epigenetic processes aid in the regulation of genes related to the development of biofilm and the metabolic changes to sustain the survival of cells in these protective structures. All of these variables contribute to great diminishment of antibiotic penetration and efficacy (75,76).

Knowledge regarding the relationship between epigenetic control and metabolic processes presents instrumental information on the intricacy of bacterial resistance development. These systems do not operate in isolation but create a system of regulation that increases the adaptability of bacteria to antibiotics. With further investigation in this field ongoing, new potential therapeutic targets that will disrupt these regulatory interactions and revert antibiotic susceptibility in multidrug-resistant Gram-negative pathogens may be discovered (77,78).

Therapeutic Implications and Emerging Strategies to Combat Multidrug Resistance

The emergence of a multidrug-resistant (MDR) Gram-negative strain has put a strain on the available treatment methods, compelling the development of novel approaches to treatment, beyond the usual development of antibiotics. Traditional strategies of finding new antimicrobial agents have not been sufficient enough because bacteria develop resistance to counteract these medicines very fast. Recent studies have therefore moved in the direction of knowledge of the regulatory mechanisms that facilitate the adaptive response of bacteria to target new therapeutic targets, such as epigenetic regulation and metabolic reprogramming (79).

A potential solution is the attack on bacterial metabolic pathways to make them more vulnerable to antibiotics. Given that metabolic adaptation has been identified to be important in the survival of bacteria in response to the presence of antibiotics, interfering with the most important metabolic functions will reduce bacterial defenses and enhance treatment outcomes. As an illustration, the presence of central carbon metabolism, respiration, or energy production inhibitors can predispose bacterial cells to the available antibiotics. It has also been shown that altering metabolic state of bacteria like elevating metabolic activity during treatment can result in improved bactericidal activity of some antibiotics (80).

The other strategy that is emerging is the creation of agents which disrupt the epigenetic regulatory processes. Since the expression of genes that determine virulence and antibiotic resistance is affected by DNA methylation and the presence of nucleoid-associated proteins, the regulation of these systems can lead to the disruption in bacterial adaptation. Despite the early research stages on epigenetic-based therapies in bacteria systems, emerging evidence indicates that it is possible to modify gene expression patterns by controlling the activity of methyltransferase, or chromosomal regulatory proteins, to make it less resistant or less virulent.

Another strategy in combating the MDR pathogens is combination therapy. The combining effect of several drugs with different mechanisms of action limits the possibility of bacterial

resistance. As an example, the use of metabolic inhibitors or efflux pump inhibitors in conjunction with traditional antibiotics could be very helpful to enhance antimicrobial efficacy. In the same vein, adjuvant therapies meant to destabilize the responses of bacteria to stress or even biofilm development can increase the penetration and activity of antibiotics (81,82).

The development of systems biology, genomics, and metabolomics has also given new means of finding potential drug targets in the bacterial regulatory networks. These technologies enable researchers to examine international variations in genes expression and metabolic action during antibiotic exposure, and assist to determine weak points in bacterial cells. Moreover, other treatment methods, including bacteriophage treatment, antimicrobial peptides, and immune-based treatment are receiving more interest as to be used as a supplement to first-line antibiotic therapy (83,84).

In general, the further study of the molecular processes of bacterial adaptation, such as epigenetic regulation and metabolic remodeling, has provided new opportunities in ways to fight MDR Gram-negative infections. A combination of these findings with therapeutic design can result in an improved therapeutic strategy that has the potential to overcome the current increasing problem of antibiotic resistance (85).

Conclusion

The issue of multidrug resistance in Gram-negative pathogens has become one of the major challenges to international population health. Both the genetic mutations and the transfer of horizontal genes are necessary that together with the complex regulatory systems that regulate the expression of the genes and physiological functions in the cells facilitate the ability of these organisms to quickly adjust to the pressure of antibiotics. Epigenetic control and metabolic adjustment have become essential factors of antibiotic resistance development and maintenance in clinically significant Gram-negative bacteria in the past few years.

Bacteria can regulate the expression of genes in response to environmental stresses dynamically via epigenetic processes, including DNA methylation, phase variation, and nucleoid-associated protein. Through these mechanisms, bacterial populations can produce phenotypic variations without being subjected to genetic changes at the level of genetic sequences, making some subpopulations to have a higher chance of surviving exposure to antibiotics. Concurrently, metabolic adaptation enables bacterial cells to alter central metabolic pathways, energy generation and responses to stress differently to facilitate survival, when under antimicrobial pressure.

Notably, the interplay between the epigenetic control and the metabolic networks forms a very well-coordinated system that promotes the adaptability of bacteria. Epigenetic modification may play a role in the expression of metabolic genes, and metabolic conditions may play a role in the regulation of epigenetic regulation activity by providing essential metabolites. This reciprocal interaction leads to the formation of tolerant and stable bacterial subpopulations which in the long run transform to stable multidrug resistance bacteria.

The knowledge of these interrelated mechanisms can be useful in defining the complexity of the development of antibiotic resistance. It further indicates the shortcomings of the conventional methods that aim solely at inhibiting the growth of bacteria or particular resistance genes. Alternatively, antimicrobial approaches in the future can be more useful by attacking larger regulatory webs that govern bacterial adaptation and survival.

Recent developments on molecular biology, genomics, and metabolomics have greatly widened our understanding of bacterial regulatory mechanisms with new potential targets of therapy being made available. Those strategies that cause intervention and disruption of metabolic pathways, epigenetic regulation, or a combination of antibiotics and metabolic and regulatory inhibitors can serve as promising opportunities to restore the activity of antibiotics.

Conclusively, to mitigate the issue of multidrug resistance that is a worldwide problem, one needs to have a thorough insight into the various mechanisms through which bacteria can survive when subjected to antibiotic pressure. Further studies on the functions of epigenetic control and metabolic adjustment will be necessary to develop new therapeutic strategies that will be able to manage MDR Gram-negative infections and ensure the future of the antimicrobial treatment.

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