Review Article

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EPIGENETIC REPROGRAMMING AND METABOLIC PLASTICITY IN MULTIDRUG-RESISTANT BACTERIA: EMERGING MOLECULAR TARGETS TO OVERCOME ANTIBIOTIC TREATMENT FAILURE

Ali Hassanen Ali*

National Centre of Hematology, Mustansiriyah University, Baghdad, Iraq.

*Corresponding Author: Ali Hassanen Ali

National Centre of Hematology, Mustansiriyah University, Baghdad, Iraq.

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ABSTRACT

Multidrug-resistant (MDR) bacteria and their rapid global spread has become one of the most significant challenges to the health of the population and has significantly weakened the efficacy of traditional antibiotic treatment, resulting in a high morbidity, mortality, and healthcare expenses. In spite of the fact that classical genetic mechanisms, including the target modification, the enzymatic drug deactivation, and the efflux pump overexpression, were known as the main causes of resistance, the mechanisms are not able to describe the complexity of the failure in antibiotic treatment which is observed in clinical practices. There is mounting evidence to support the idea that non-genetic adaptive strategies are important in the surviving of bacteria under antibacterial pressure. Here in this review, we give a critical overview of how epigenetic reprogramming and metabolic plasticity contribute to the selection of phenotypes that relate to multidrug resistance in bacteria. These mechanisms allow bacterial genome epigenetic regulation, such as DNA methylation, phase variation, and regulation by the nucleoid-associated protein, which is rapid and reversible and does not modify the underlying DNA sequence. The processes produce phenotypic heterogeneity in bacterial populations, which facilitates antibiotic tolerance, persistence and frequent infections. Simultaneously, metabolic plasticity enables MDR bacteria to be able to restructure metabolic pathways in real time, to enter low-energy or dormant states, and to evade antibiotic-directed processes, which increases the antibiotic resistance and survival chances. Notably, the arising crosstalk between epigenetic regulation and metabolic networks as the key axis of adaptation in MDR bacteria is emphasized in this review. The two-way communications among these two regulatory layers not only orchestrate stress responses, but also stabilize adaptive phenotypes, and also cause treatment failure in the absence of stable genetic resistance. We also explain the new molecular targets and intervention approaches to disrupt epigenetic and metabolic changes, such as epigenetic regulators, metabolic regulators and combination therapy to restore the activity of antibiotics. This review takes a systems view of multidrug resistance in bacteria by incorporating existing information on the topics of genetics, epigenetics, and metabolism. The comprehension of epigenetic reprogramming and metabolic plasticity interaction opens up new prospects of developing novel antimicrobial interventions that may overpower antibiotic treatment failure and solve the increasing global problem of the MDR bacterial infections.

KEYWORDS: Notably, the arising crosstalk between epigenetic regulation and metabolic networks as the key axis of adaptation in MDR bacteria is emphasized in this review.

1. INTRODUCTION

The issue of multidrug-resistant (MDR) bacteria is one of the most urgent health-related issues of the twenty-first century worldwide.[1,2] The extensive and frequent and non-selective use of antibiotics in clinical, agricultural, and environmental spheres has increased the evolution of bacterial populations that can endure exposure to more than one antimicrobial agent.[3,4]

Consequently, traditional antibiotic treatments are gradually becoming ineffective, with resulting longer infections, increased morbidity and mortality, and significant cost to the health care systems of many countries across the globe. Although decades of studies have aimed to clarify the classical forms of resistance, such as target alteration, enzymatic drug inactivation, and overexpression of efflux pumps, these reasons are no longer believed to be the ultimate causes of the exceptional adaptability and persistence of MDR bacterial pathogens.[5,6]

Over the past few years, an increasing body of evidence has shown that stable genetic mutations are not the only factors that contribute to bacterial survival in the presence of antibiotic stress but that the process is extremely complex and highly dependent on reversible and dynamically adaptive mechanism. Epigenetic reprogramming has become a major but understudied source of bacterial phenotypic diversity and antibiotic resistance among these processes.[7,8] In contrast to the permanent genetic changes, epigenetic changes allow bacteria to easily adapt the expression pattern of genes within a specific environmental pressure without altering the cellular DNA genome.[9,10] This regulatory plasticity permits the bacterial populations to form heterogeneous phenotypes some of which can be transiently or persistently resistant to antimicrobial agents and hence improve the ability to survive under exposure to antibiotics.[11]

Epigenetic regulation is going hand in hand with metabolic plasticity, which has become a core topic of study as an intrinsic adaptive mechanism among MDR bacteria. Metabolic plasticity means that there is a response of bacterial cells to adjust their metabolic pathways based on nutrient availability, host-derived signals, and antibiotic-induced stress. The antibiotics tend to cause a metabolic constraint because of disturbance in the necessary biosynthetic pathways or energy generation, whereby the bacteria have to alter their metabolic condition.[12] Such metabolic responses have the potential to decrease the susceptibility to antibiotics, enhance tolerance and persistence, and make survival in unfavorable conditions, such as existing in infected host tissues, possible on a long-term basis. Notably, metabolic reprogramming has been reported to affect not only the rates of bacteria growth, but also the effectiveness of antibiotic killing, indicating that metabolism is closely correlated with the effect of treatment.[13]

The meeting of epigenetics re-programming and metabolic plasticity offers an attractive paradigm of comprehending the failure of antibiotic treatment outside conventional resistance models. There is growing evidence that epigenetic regulators have the potential to directly control metabolic gene networks, and thus integrate adaptive metabolic responses in response to antibiotic challenge. On the other hand, epigenetic regulation can be affected by metabolic states by providing important metabolites that act as cofactors or substrates of epigenetic enzymes.[14] This bidirectional crosstalk allows the MDR bacteria to adjust physiological conditions in order to obtain survival, virulence, and resistance in the rapidly changing environments. These integrated regulatory networks can be the reason bacterial subpopulations that do not succumb to the effects of antibiotics despite no traceable resistance-conferring mutations are so persistent.[15]

The identification of epigenetic and metabolic changes as the primary agents of MDR bacteria that are resistant to drugs has important implications in the creation of new treatment options. By attacking these adaptive systems, it can provide a chance to interfere with the innate bacterial resilience processes instead of targeting key cellular processes, resulting in the development of resistance quickly. The use of epigenetic modifiers and metabolic pathway inhibitors are now under investigation as an adjunctive treatment to increase antibiotic effectiveness and minimize resistance to therapy.[16] Nevertheless, the multifaceted and multilayered nature of epigenetic and metabolic regulatory systems in bacteria require an integrative and broad-range knowledge base to discover feasible molecular targets.[17]

This review is a synthesis of existing information on epigenetic reprogramming and metabolic plasticity in multidrug-resistant bacteria, their respective and combined contributions to antibiotic resistance and treatment failure.[18] The article aims to offer a conceptual framework on which future research and therapeutic innovation should be based through critical review of emerging evidence and identification of key regulatory pathways. Finally, a better understanding of the molecular interaction of epigenetic control and metabolic response can lead to the next generation antimicrobial approaches that can counteract the increasing incidence of multidrug-resistant bacterial infection.[19,20]

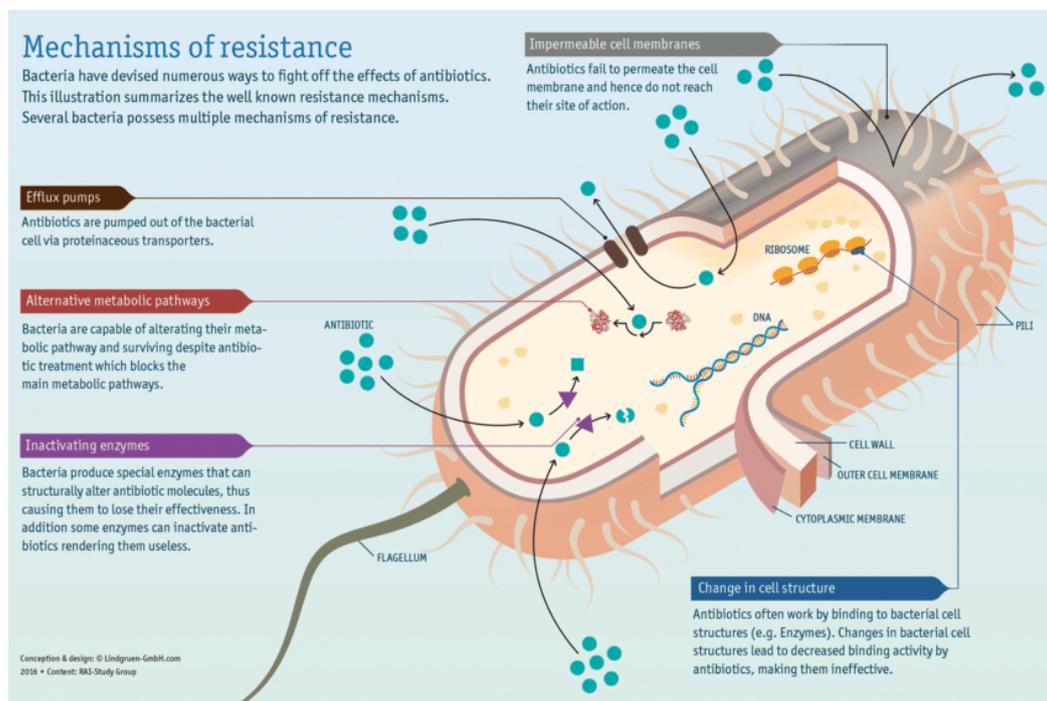## 2. Multidrug Resistance in Bacteria: Current Landscape

Multidrug resistance (MDR) of bacteria has become a vital issue of contemporary medicine, which has essentially nullified the efficacy of antimicrobial treatment, which previously revolutionized the treatment of infectious diseases.[21] The concept of MDR is usually characterized as the resistance of bacterial pathogens to a variety of antibiotic agents, including drugs that are usually regarded as the last-line medications.[22] The high increase and spread of MDR bacteria in the world have led to higher instances of failure in treatment, high hospitalization, high healthcare expenses and high rates of infection related morbidity and death. These results indicate that there is an urgent need to research in more depth the mechanisms that have supported bacterial resistance beyond the traditional paradigms.[23]

Clinically significant MDR pathogens may also include Gram positive and Gram-negative, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus spp., carbapenem-resistant Acinetobacter baumannii, Pseudomonas aeruginosa and the production of extended-spectrum 5 -lactamase (ESBL) in Enterobacteriaceae. The infections brought about by these organisms have become very hard to control in most of the health facilities where the only solution to the problem is the toxic or less effective drugs. This crisis is further aggravated by the emergence of extensively drug-resistant (XDR) and pan-drug-resistant (PDR) strains and this leaves the frightening prospect of the incurable bacterial infections.[24,25]

Conventionally, the pathogenic multidrug resistance has been ascribed to a group of well characterized molecular pathways which directly intervene with the effects of antibiotics. Enzymatic inactivation is one of the most common, in which bacteria synthesize enzymes that degrade or chemically modify the antibiotic molecules before they reach their cellular targets.[26]

β-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferases are some of the most common enzymes that neutralise antibiotics before they get into their cellular targets. Target modification is another significant resistance mechanism where drug affinity and efficacy are minimized by structural changes in antibiotic-binding sites including subunits of the ribosome or penicillin-binding proteins. Such mutations usually occur via the point mutations, or by the acquisition of other target genes.[27]

**Figure A. Cell-Level Mechanisms of Multidrug Resistance in Bacteria.**

Besides these mechanisms, bacteria often use mechanisms that restrict the intracellular accumulation of antibiotics.[28] The decrease in permeability of the bacterial cell envelope, especially in Gram-negative bacteria, limits entry of the antibiotic via changes in the expression levels or the structure of porins. In addition to this resistance mechanism, multidrug efflux pumps play an active role in pumping out a broad spectrum of antimicrobial agents out of the cell and thereby avoiding the achievement of lethal intracellular concentrations.[29] Efflux systems are overexpressed by most MDR pathogens and cause not only antibiotic resistance but also disinfectant and host-derived antimicrobial tolerance. Although these classical mechanisms of resistance can offer a starting point to understand MDR, they are not complete in their explanations of the complexity and heterogeneity that is evident in bacterial responses to the use of antibiotics.[30] The growing body of knowledge has indicated that bacterial populations possess dynamic and reversible resistance phenotypes which cannot be explained only through stable genetic mutations.[31] The presence of such phenomena as antibiotic tolerance and persistence enables subpopulations of bacteria to endure brief exposure to antibiotics without inheriting heritable resistance.[32] These phenotypic forms may again repopulate during antibiotic pressure release and this forms a significant contribution to treatment failure and an infection relapse.[33]

Evolutionarily, the genetic basis of MDR development and dissemination is persistently influenced by the high selective pressure exerted under the influence of antibiotic use, and the outstanding genetic plasticity of

bacteria. Horizontal gene transfer systems such as conjugation, transformation, and transduction, enable the spread of resistance determinants among and between species and ecological niches in rather short periods. The work of mobile genetic elements including plasmids, transposons, and integrons is at the center of this process, as they allow the deposition of multiple resistance genes in one bacterial genome.[34]

Notably, the present situation of multidrug resistance is becoming more and more understood as a multifactorial condition that cannot be limited to fixed genetic determinants. Epigenetic modulation, metabolic reprogramming and adaptive regulatory responses are currently being suggested to play a role in determining bacterial survival responses to antibiotic stress. These processes equip bacteria with the ability to quickly change their physiology with regards to changing conditions thus supplementing classical resistance mechanisms.[35] It is imperative to comprehend MDR in this wider biological context to reveal new weaknesses and generate new effective treatment methods that would allow overcoming the failure of antibiotic treatment.[15,36]
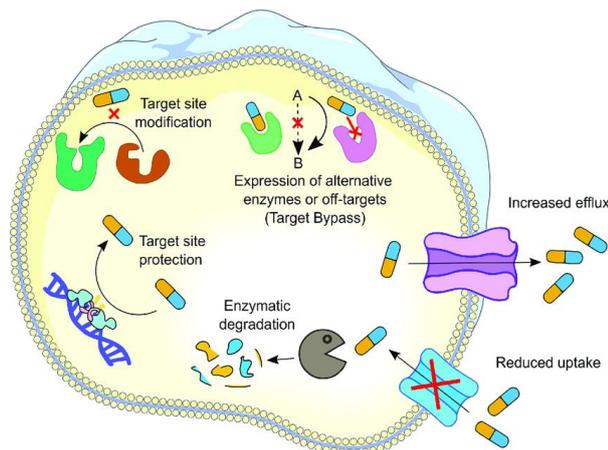
Figure B: Representative Unicellular Multidrug-Resistant Bacterial Pathogen.

3. Bacterial Epigenetics: Mechanisms and Regulatory Roles

Traditionally, the regulation of bacterial genes was studied mainly in terms of the classical genetic processes, such as mutations, transcriptional control in the form of operons, and horizontal gene transfer. Nonetheless, over the last twenty years, the understanding in this regard has been radically altered as there is mounting evidence that an epigenetic regulatory system is also used by bacteria to adjust gene expression in an active, reversible way.[37,38] Bacterial epigenetics can be defined as a process of heritable modification in gene expression or cellular phenotype without an underlying modification in sequence that can enable rapid phenotypic response to changing environmental factors, such as exposure to antibiotics.[39]

DNA methylation is one of the best-researched epigenetic processes in bacteria and is key in the regulation of transcription, DNA replication, DNA repair, and host-pathogen interactions. Epigenetic regulation in bacteria is mainly dependent on DNA methyltransferases and nucleoid-associated proteins unlike in eukaryotes where epigenetic regulation is usually through histone modifications, chromatin remodeling. Methylation of DNA usually takes place at adenine or cytosine bases and it is facilitated by certain enzymes like DNA adenine methyltransferase (Dam) and DNA cytosine methyltransferase (Dcm). These alterations have the potential to change the binding affinity of transcription factors and regulatory proteins, and hence altering gene expression in the genome of the bacterium.[40,41]

The peculiar element of bacterial epigenetics is the process of phase variation where stochastic and reversible epigenetic fluctuations produce phenotypic heterogeneity within clonal populations. Phase-variable DNA methylation systems enable subpopulations of bacterial cells to alternate through alternate expression of genes, that generate diverse phenotypes, which increase population level survival in stressful conditions. Epigenetic heterogeneity is especially beneficial during an antibiotic exposure, as there is a higher chance that some proportion of the population will acquire a tolerant or persistent phenotype that can survive exposure to antimicrobials.[42,43]

Alongside the DNA methylation, nucleoid-associated proteins (NAPs) can be regarded as the other important epigenetic regulatory layer in bacteria. H-NS, Fis, HU, and IHF proteins affect the manner in which the bacterial chromosome is organized and utilize global transcriptional programs. NAPs regulate the expression of genes needed to respond to virulence, stress responses, metabolic adaptation, and resistance to antibiotics, by changing the topology and access of DNA. Notably, the rapid reprogramming of bacterial transcriptional landscapes by alterations in NAP expression or activity does not need genetic mutations.[44,45]

The environmental sensing and stress adaption are also closely related to epigenetic regulation in the bacteria. The exposure to antibiotics has the potential to serve as a strong selective and regulatory cue, which induces epigenetic remodeling and changes the expression of resistance-related genes, efflux systems, and stress response pathways. Such epigenetic reactions are usually reversible and the bacteria can also revert to a vulnerable state after removal of antibiotic pressure. The plasticity also makes it more difficult to detect and predict resistance phenotypes in a clinical environment since epigenetically mediated resistance might not be revealed in a typical genomic analysis.[46,47]

It is important to note that there are no isolated cases of bacterial epigenetic mechanisms but rather they are connected to larger regulatory networks, such as metabolic and signaling pathways. Epigenetic alterations

have the ability to precisely adjust the expression of metabolic genes, and metabolic states have the ability to regulate the activities of epigenetic enzymes via the presence of methyl donors and cofactors. This networked regulatory framework outlines the significance of epigenetics as one of the key units of bacterial flexibility and robustness.[48,49]

Table 1: Major Epigenetic Mechanisms in Bacteria and Their Regulatory Functions.

Epigenetic mechanism	Key components	Primary regulatory roles	Relevance to antibiotic resistance
DNA adenine methylation	Dam methyltransferase	Regulation of gene transcription, DNA replication, phase variation	Modulates expression of resistance genes and stress response pathways
DNA cytosine methylation	Dcm methyltransferase	Control of transcription and genome stability	Influences antibiotic tolerance and phenotypic heterogeneity
Phase-variable methylation systems	Phasevarions	Generation of reversible phenotypic diversity	Promotes survival of subpopulations under antibiotic pressure
Nucleoid-associated proteins	H-NS, Fis, HU, IHF	Chromosome organization and global transcriptional control	Regulates efflux pumps, virulence factors, and stress adaptation
Epigenetic memory	Stable yet reversible expression states	Persistence of adaptive phenotypes	Contributes to recurrent infections and treatment failure

All these epigenetic mechanisms offer a formidable regulatory toolkit to the bacteria, facilitating quick and reversible environmental stress responses, such as antibiotics treatment. Bacterial epigenetics is also important in determining resistance phenotypes by producing phenotypic variation and orchestrating the expression of genes in response to stress. Knowledge of these regulatory layers is thus necessary to help explain the complexity of multidrug resistance as well as to discover new therapeutic targets that interfere with adaptive epigenetic changes without creating significant selective pressure to genetic resistance.[50,51]

4. Epigenetic Reprogramming in Antibiotic Stress Response
Antibiotic exposure can be deemed as an influential source of environmental stress that may significantly modify bacterial regulatory networks. In addition to the process of genetic selection of mutations resistant to antibiotics, antibiotic pressure may induce fast and reversible gene expression alterations through epigenetic reprogramming. This is an adaptive process in which bacterial populations can endure temporary or intermittent antimicrobial stress without undergoing any permanent genetic changes. Epigenetic reprogramming is thus more and more being taken as an important mechanism involved in the development of antibiotic tolerance, persistence, and treatment failure.[52,53]

The change of the patterns of DNA methylation is one of the most important characteristics of the epigenetic reprogramming that occurs under the influence of antibiotic exposure. There is also an indirect effect of antibiotics on the action of DNA methyltransferases, which results in changes in the level of methylation of promoter regions and regulatory elements. Such modifications have the ability to up-regulate genes of stress responses, efflux systems, DNA repair and survival pathways and down-regulate the growth-related processes. Notably, these transcriptional changes facilitated by epigenetics may happen over a short period of time, allowing bacteria to evolve in a generation.[54,55]

Epigenetic reprogramming also plays a role in the development of phenotypically different subpopulations of clonal communities of bacteria. Certain proportion of cells under antibiotic stress can be transiently in a dormant state with a high stress tolerance and antibiotic resistance. These cells are also known as persisters which are not genetically resistant but are programmed to endure lethal concentrations of drugs through epigenetic mechanisms. After the removal of antibiotic pressure, persister cells have the potential to transform back to a susceptible state and recolonize the site of infection, which results in relapse and chronic infection.[56]

Along with the DNA methylation, alterations in the activity of the nucleoid-associated proteins are also important in the epigenetic responses to stress. Transcriptional programs can rewire throughout the world on the basis of antibiotic induced changes in DNA topology and chromosomal organization. With these adaptations, bacteria can coordinate the expression of genes and balance survival costs and minimum energy usage. These international regulatory changes suggest how efficient epigenetic reprogramming can be as a survival mechanism.[57]

More importantly, the epigenetic responses to antibiotics have the capacity to produce some form of epigenetic memory, in which responses to antimicrobial agents are determined by previous exposure. Such memory effect can increase survival of bacteria during repeated treatment with antibiotics and makes eradication difficult. All these results show that antibiotic stress is not only a selective force but also a regulatory signal that

can reorganize the phenotypes of bacteria by reprogramming of the epigenetics.[57,58]

5. Metabolic Plasticity in Multidrug-Resistant Bacteria

Metabolic plasticity is the capacity of bacteria to dynamically change their metabolic networks to meet challenges posed by the environment such as exposure to antibiotics. The metabolic adaptation of multidrug-resistant bacteria is critical in lowering the effect of antibiotics and survival chances in unfavorable environments. Antibiotics can also exert metabolic stress, i.e. targeting key biosynthetic pathways or energy generating mechanisms and causing the bacteria to switch to other metabolic states less susceptible to antimicrobial killing.[20,59]

A switch to low-energy or dormant metabolism is one of the characteristics of metabolic plasticity in MDR bacteria. Low metabolic rate may lower the efficacy of antibiotics that depend on active cellular processes, e.g. synthesis of cell walls or translation of proteins. Bacteria can reduce their energy use and slack growth rate to a tolerant state that enables them to survive extended exposure to antibiotics. This metabolic inactivity is strongly related to persistence and it causes a lot of infection that is chronic and recurrent.[55,60]

The MDR bacteria may also divert the metabolic flows in order to avoid the antibiotics-mediated pathways. Alternative carbon use strategies, stimulation of stress-related metabolic enzymes, and the increased scavenging of host-produced nutrients allow bacteria to sustain the required functions despite the interference of antibiotics. Such metabolic adaptations do not only aid the survival but they can also regulate the redox state of cells and membrane potential, further affecting antibiotic uptake and activity.[44,61]

Notably, metabolic plasticity is not a passive reaction, but it is closely controlled by sophisticated regulatory and signaling pathways. The metabolic conditions have the ability to modulate the expression of resistance determinants, virulence factors as well as stress response genes.[25] Besides, bacterial metabolic strategies can be influenced by the metabolic environment of the host, e.g. nutrient availability, oxygen concentration, and immune-mediated stress, which influence treatment outcomes.[62]

The identification of metabolic plasticity as a cause of multidrug resistance has provided new avenues of therapeutic intervention. Directing their attacks on metabolic susceptibilities, as a novel entity, or as a part of the standard antibiotics, has the potential to sensitize MDR bacteria and overcome treatment failure. The metabolic adaptability of recalcitrant pathogens and thus the rational design of the next-generation antimicrobial strategies must therefore be understood.[84,63]

6. Crosstalk Between Epigenetic Regulation and Metabolic Networks

The most recent developments in bacterial systems biology have shown that epigenetics regulation and metabolic plasticity are not separate adaptive mechanisms but rather considerably intertwined in complex regulatory crosstalk. The interaction allows multidrug-resistant bacteria to organize gene expression, metabolic flux, and responses to stress in a very efficient way. This crosstalk is important to understand how bacteria are able to perform rapid phenotypic adaptation and survive under constant antibiotic pressure.[64]

Direct effects on the transcription of metabolic genes are exerted by epigenetic processes, especially DNA methylation and activity of nucleoid-associated proteins. Alterations in the dynamics of methylation may either activate or suppress full metabolic pathways enabling bacteria to adapt energy production, biosynthesis and redox equilibrium to antibiotics. As an example, downregulation of central metabolic pathways that is mediated by epigenetics can facilitate an energy-low state that increases bactericidal antibiotic tolerance. On the other hand, alternative metabolic pathways can be selectively activated in order to maintain critical cell processes in the event of disruption of major pathways.[45,12,65]

Metabolism, in its turn, has a strong impact on the epigenetic control. Numerous of these enzymes involved in epigenetics have metabolites as co-factors or substrates, which connects cellular metabolic condition to epigenetic regulation. Changes in the intracellular concentrations of methyl donors, including S-adenosylmethionine, may regulate the activity of DNA methylation and, thus, reconstruct transcriptional programs. This two-way interaction forms feedback connecting the adaptive phenotypes to the antibiotic pressure and stabilizes them.[66]

Epigenetic and metabolic regulatory integration is also a factor that leads to phenotypic heterogeneity in bacterial populations. The different metabolic patterns of subpopulations that differ in epigenetic states can contribute to the probability of survival of some cells during antibiotic exposure. This heterogeneity makes the treatment results more difficult and justifies the continuation of the infection even in the absence of stable genetic resistance.[55,67]

Table 2: Interactions Between Epigenetic Regulation and Metabolic Plasticity in MDR Bacteria.

Regulatory layer	Key components	Impact on metabolism	Contribution to antibiotic survival
DNA methylation	Dam, Dcm methyltransferases	Controls expression of metabolic genes	Promotes metabolic states associated with tolerance
Nucleoid-associated proteins	H-NS, Fis, HU	Alters global metabolic transcription profiles	Enables rapid metabolic reprogramming
Metabolic cofactors	SAM, ATP, redox metabolites	Modulate epigenetic enzyme activity	Links nutrient status to resistance phenotypes
Feedback loops	Epigenetic–metabolic coupling	Stabilizes adaptive states	Enhances persistence and treatment failure

Overall, the crosstalk between epigenetic and metabolic networks represents a central adaptive axis in multidrug-resistant bacteria, providing resilience against antibiotic interventions and highlighting novel targets for therapeutic disruption.[68]

7. Emerging Molecular Targets and Therapeutic Strategies

The increased awareness of epigenetic reprogramming and metabolic plasticity as the factor contributing to antibiotic resistance has widened the scope of possible therapeutic targets. Instead of simply killing bacteria or interfering with vital processes, newer approaches are also geared towards disrupting adaptive regulatory pathways that help bacteria to survive exposure to antibiotics. These methods can minimize selective pressure to be resistant, and enhance the effectiveness of long-term treatment.[22]

The interventions based on the epigenetics are a promising, yet to a large extent untapped, avenue. Epigenetically regulated resistance phenotypes may be disrupted by bacterial DNA methyltransferase inhibitors or nucleoid-associated proteins modulators, which would leave bacteria vulnerable to antibiotics. Epigenetic therapies can reduce the development of resistant mutations because they aim at regulatory flexibility as opposed to fixed resistance genes. The specificity and the safety of those interventions are however major challenges.[69]

Attacking Bacterial metabolism has also become popular as an adjunctive to the conventional antibiotic therapy. Antibiotic resistance MDR bacteria can be sensitised by disruption of metabolic pathways necessary to survive in times of stress (e.g., the persistence pathway or the dormancy pathway). The use of metabolic inhibitors can rejuvenate the effect of antibiotics by subjecting bacteria to more susceptible metabolically active conditions that can be killed by the antimicrobials.[70]

Another one of the most appealing approaches is combination therapies where epigenetic or metabolic modulators are combined with antibiotics. These methods are intended to inhibit the adaptive ability of bacteria at the same time, place antimicrobial pressure, which results in decreasing the possibility of failure of treatment and relapses. The recognition of context-specific weaknesses in epigenetic-metabolic networks is likely to be achieved by progress in systems biology, omics technologies, and computational modelling.[15]

Although this is promised, these strategies have practical constraints such as diversity of bacteria, interactions with hosts and off-target effects. However, attacking adaptive regulatory mechanisms is a paradigm shift in the antimicrobial treatment and it provides new hope of overcoming multidrug resistance.[18,70]

8. CONCLUSION AND FUTURE PERSPECTIVES

Multidrug-resistant bacteria is a growing menace to the general population in the world due to their extraordinary adaptation and survival in the presence of antibiotics. Although they still play an important role in classical mechanism of genetic resistance, they are not enough to explain the complexity of antibiotic treatment failure which is witnessed in clinical practice. The study of epigenetic reprogramming and metabolic plasticity is identified as the core drivers of bacterial resilience, which are closely interdependent and interconnected, allowing fast and reversible phenotypic adaptation without any genetic alteration.

Bacterial phenotype diversification is enabled by both epigenetic control and metabolic plasticity that enable bacteria to dynamically adjust gene expression and phenotypic heterogeneity, as well as provide tolerance, pathway rerouting and energy optimization. This interaction between these regulatory levels forms a powerful adaptive system of action, which increases persistence, encourages relapse, and decreases the efficacy of antibiotics. The understanding of resistance as an integrated network changes our perspective of resistance as simply a genetic phenomenon, instead of a process at the systems level.

Therapeutically, the ability to target the epigenetic and metabolic adoptions is promising to serve as an alternative to the traditional antimicrobial approaches. These methods can substitute the current antibiotics and mitigate the multidrug resistance burden though there are still significant obstacles such as specificity, safety, and translational feasibility. Further studies are required to further clarify the molecular mechanisms of epigenetic-metabolic communication, some of the circumstances underlying vulnerability, and innovative combination

therapy. Further development of such integrative knowledge can eventually lead to the emergence of next-generation interventions, which can be used to overcome the failure of antibiotic treatment.

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