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Epigenetic and Metabolic Reprogramming Driving Multidrug Resistance in Clinically Relevant Gram-Negative Bacteria

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ABSTRACT

Multidrug-resistant (MDR) Gram-negative bacteria owing to epigenetic and metabolic modifications as well as genetic alterations are a major global health concern. This review aims to clarify besides classical genetic factors the roles of epigenetic mechanisms and metabolic reprogramming in antimicrobial resistance. It focuses on epigenetic mechanisms such as DNA methylation, nucleoid-associated proteins, small regulatory RNAs and phase variation that alter gene expression and lead to antimicrobial tolerance. In parallel, it highlights metabolic adaptations such as changes in carbon metabolism, redox homeostasis, efflux systems, biofilm formation, and persistence pathways that contribute to bacterial survival under antibiotic stress. The review emphasizes the role of metabolic state transitions in phenotypic resistance and virulence in clinically relevant pathogens like *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Host-pathogen interactions, clinical environmental pressures, and stress-induced regulatory networks that lead to both transient and stable resistance are also discussed. The importance of advances in multi-omics technologies for identifying non-genetic predictors of resistance is emphasized. In summary, the interplay between epigenetic and metabolic plasticity offers a novel paradigm for predicting resistance evolution and designing new therapeutic strategies, for example by targeting bacterial metabolism and epigenetic systems as alternatives to conventional antibiotics.

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Key words: Tricarboxylic acid (TCA), Deoxyribonucleic acid, Phase variation, Genetic mutation transcriptional inhibitors, *Pseudomonas aeruginosa*.

INTRODUCTION

The emergence of multidrug resistant (MDR) Gram-negative bacteria is an alarming rising threat and represents one of the most urgent challenges in modern medicine, as the efficacy of almost all classes of existing antibiotics is compromised. Historically, antimicrobial resistance has been associated mainly with fixed genetic mechanisms, such as chromosomal mutations, horizontal gene transfer and the acquisition of resistance plasmids [1,2]. While these genetic determinants are of utmost importance, there is growing evidence that they are not enough to explain the rapid adaptability, phenotypic heterogeneity and transient resistance behaviors displayed by many clinically relevant pathogens. This has led to a paradigm shift towards recognizing the role of non-genetic processes, especially epigenetic regulation and metabolic reprogramming, as major players in antimicrobial tolerance and resistance [3,4]. Complex regulatory networks allow Gram-negative bacteria to sense and respond rapidly to environmental stresses such as antibiotic exposure, nutrient limitation, oxidative stress and host immune pressure. A. For clinically significant pathogens including *aeruginosa*, *K. pneumoniae*, and *E. coli*, which normally exist in a changing environment that favors the growth of genetically similar but phenotypically diverse populations. These adaptive responses often involve reversible changes in gene expression, metabolic flux and cellular homeostasis that enhance survival without permanent genetic alterations [5,6]. Epigenetic regulation plays a central role in controlling virulence-associated transcriptional programs, stress responses, biofilm formation and antibiotic resistance. Heritable or reversible phenotypic states can be established through phase variation, DNA methylation patterns, nucleoid-associated proteins and small regulatory RNAs . In parallel, metabolic rewiring allows bacteria to augment energy production, redox homeostasis, and biosynthetic pathways under antibiotic stress, thereby supporting resistance-associated phenotypes like efflux pump activity, persistence, and intracellular survival [7,8]. Importantly, epigenetic and metabolic processes are not independent but are highly interconnected. Epigenetic changes and metabolic status are linked by complicated feedback loops, and metabolic signals also affect the epigenetic regulation of gene expression [9,10]. This

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convergence may explain the persistence of infections despite appropriate antibiotic therapy and the rapid emergence of resistance during therapy [11,12]. Understanding the interplay between metabolic processes and epigenetic control gives key insight into the complexity of bacterial resistance development. These systems together constitute a regulatory system that makes bacteria more resistant to drugs. Additional studies in this area could reveal new therapeutic targets to break these regulatory connections and render multidrug-resistant Gram-negative bacteria more susceptible to antibiotics. [13,14]. This review aims to summarize the current knowledge of the concerted interaction between metabolic reprogramming and epigenetic regulation in the development of multidrug resistance in Gram-negative bacteria. From a systems biology, molecular microbiology and clinical research point of view, this work uncovers new concepts beyond classical genetic resistance and can provide new opportunities for therapeutic intervention. [15,16].

Epigenetic Mechanisms Contributing to Multidrug Resistance in Gram-Negative Bacteria

Epigenetic regulation, an underappreciated but important level of control of the antimicrobial resistance phenotype of Gram-negative bacteria, Epigenetic processes, in contrast to permanent genetic mutations, permit rapid reversible changes in gene expression that can be propagated over multiple generations, and allow bacteria to rapidly evolve in response to antibiotic pressures [17,18]. These processes are important for the generation of phenotypic heterogeneity, survival under adverse conditions and emergence of subpopulations with multidrug resistance [19,20]. DNA methylation is one of the most well characterized epigenetic processes in bacteria, and is catalyzed by adenine and cytosine methyl transferases. DNA methylation regulates gene expression by modulating the accessibility of promoters to the binding of transcription factors and by controlling the processes of DNA replication and repair. Heterogeneous methylation by phase-variable DNA methyl transferases in bacterial populations results in divergent expression of genes involved in resistance, virulence factors and stress responses in a number of Gram-negative pathogens. This epigenetic variability enables cell groups to survive exposure to antibiotic resistance, being a reservoir for the development of resistance [21,22]. Nucleoid-associated proteins (NAP) such as H-NS, Fis, IHF, and HU are involved in epigenetic regulation through modifying chromosome structure and global transcriptional sceneries [23,24]. These

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proteins can switch on or off large groups of genes, including those for biofilm formation, outer membrane permeability and expression of efflux pumps. Changes in NAP activity under antibiotic or environmental stress to develop tolerance to different antimicrobial agents have been described to cause widespread transcriptional reprogramming [25,26]. The other important epigenetic layer is small regulatory RNAs (sRNAs) that are known to modulate both mRNA stability and gene translation post-transcriptionally that are associated with antibiotic uptake, efflux systems, metabolic adaptation and stress responses. sRNA mediated networks have been directly implicated in adaptive resistance and persistence to antibiotic therapy in pathogens such as Pseudomonas aeruginosa and Escherichia coli [27,28]. Mechanisms such as phase variation, i.e., reversible ON - OFF switching of gene expression, contribute to increased epigenetic diversity of bacterial populations [29, 30]. This stochastic switching may have the ability to alter surface structures, porins and resistance determinants, allowing bacteria to be able to resist antibiotics and host immune defenses at the same time [31,32]. Comparative analysis of epigenetic mechanisms in multidrug resistance (MDR) is listed in Table 1 [33-36]. These epigenetic mechanisms allow Gram-negative bacteria phenotypes to be rapidly modulated in response to antimicrobial pressure in the absence of permanent genetic mutations. Multidrug resistance is based on epigenetic regulations allowing for long-term adaptation and can be a useful target for new therapeutic interventions that challenge bacterial plasticity rather than simply inhibit growth [37,38].

Table 1. Comparative Analysis of Epigenetic Mechanisms in Multidrug Resistance (MDR).

Mechanism	Mode of Action	Speed of Effect	Stability	Role in MDR
DNA Methylation	Addition of methyl groups to CpG islands leading to transcriptional repression	Relatively slow	High (heritable through cell division)	Promotes long-term drug resistance by silencing tumor suppressor genes and drug sensitivity regulators
microRNA (miRNA)	Small non-coding RNAs that bind to mRNA, inhibiting	Fast	Moderate (dynamic and reversible)	Regulates MDR-related genes such as drug efflux transporters and apoptosis

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	translation or inducing degradation			pathways
Nucleoid-Associated Proteins (NAPs)	DNA-binding proteins that alter chromosomal architecture and gene accessibility	Moderate	Moderate to high depending on environmental conditions	Enable global transcriptional adaptation in bacteria, contributing to antibiotic resistance

Metabolic Reprogramming as a Driver of Antibiotic Tolerance and Resistance

Metabolic re-programming has been recognized to contribute to Gram-negative antibiotic tolerance and multidrug resistance pathogenesis. Bacterial metabolism is a regulatory determinant of bacterial responses to antimicrobial stress, in addition to serving as an energy source and a biosynthetic precursor. Antibiotics impose a high metabolic cost, forcing the bacteria to rearrange their metabolic machinery to maintain redox balance, energy homeostasis and survival in stressful environments [39,40]. Remodeling of central carbon metabolism is one of the most prominent metabolic responses associated with antibiotic resistance. Alterations in the pentose phosphate pathway, the tricarboxylic acid (TCA) cycle, and glycolysis have all been demonstrated to impact susceptibility to various classes of antibiotics. [41,42] (Figure1) [43]. Subsequent antibiotic treatment may induce a switch to fermentative or low energy metabolic states with reduced ROS production and prevention of oxidative damage by downregulating TCA cycle activity. These metabolic changes are often encountered in tolerant and persisted cells. [44,45] Another important aspect of metabolic reprogramming is redox homeostasis. Gram-negative bacteria respond to antibiotic-induced oxidative stress by altering intracellular NADH/NAD+ ratio and upregulating antioxidant defenses. This includes the activation of NADPH generating pathways and upregulation of antioxidant enzymes, both of which promote bacterial survival and contribute to transient resistance phenotypes. These redox modifications affect cellular defense and stress-response signaling pathways and persistence mechanisms. [46,47] Efflux pump activity is one of the main resistance mechanisms in Gram-negative bacteria and is also closely associated with energy metabolism. [48,49] The energy consumption of proton motive force-driven multidrug efflux systems, especially those in the resistance

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nodulation-division (RND) family, is well documented. [50,51]. Metabolic rewiring in bacteria enhances membrane potential and energy supply, leading to improved efficiency and reduced intracellular antibiotic accumulation [52,53]. The metabolic reprogramming is also involved in biofilm formation which is highly associated with antimicrobial resistance. Metabolic characteristics of cells within biofilms include oxygen limitation, nutrient gradients, and metabolic heterogeneity. Which leads to conditions that promote slow growth or dormancy, which is less sensitive to antibiotics by nature. In addition, metabolic cross-feeding in biofilm communities promotes collective resistance and persistence [54,55]. These metabolic changes highlight the importance of bacterial metabolic plasticity in the emergence of antibiotic tolerance and resistance. Metabolic reprogramming is a promising therapeutic avenue to be explored in the development of novel active treatment strategies to re-sensitize Gram-negative bacteria to existing antimicrobials by enabling them to survive in antimicrobial stress conditions and evolve MDR phenotypes [56,57].

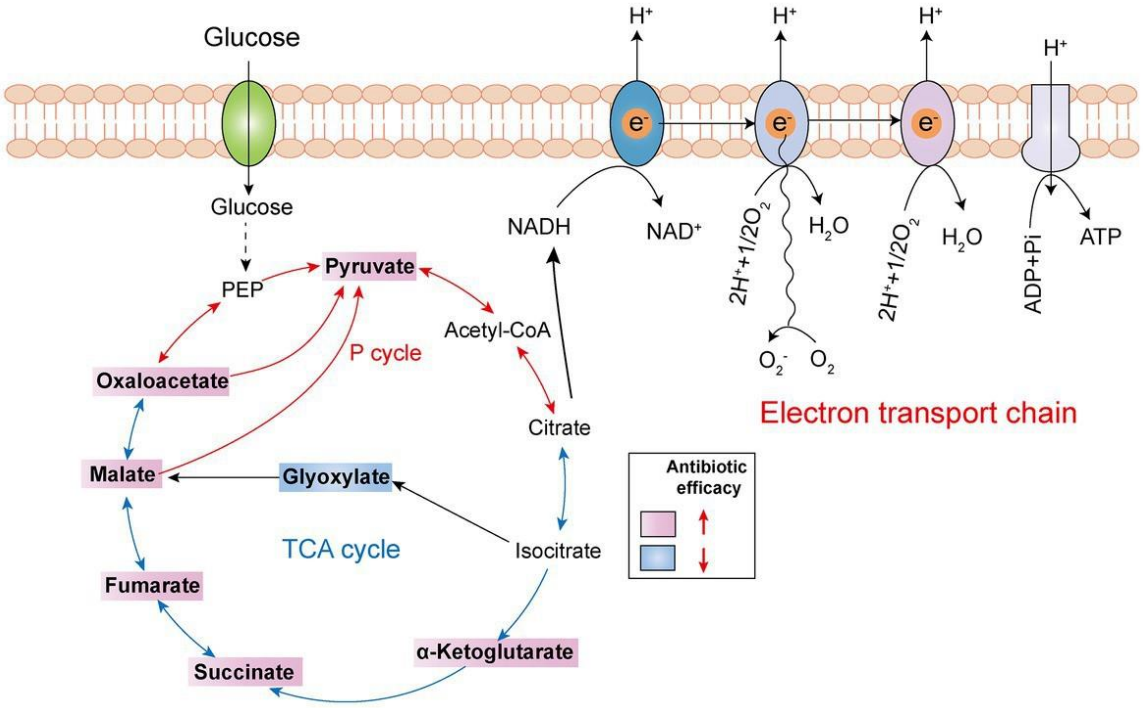

Figure 1. Metabolic Reprogramming in Gram-Negative Bacteria Linking Central Carbon Metabolism, TCA and Glyoxylate Cycles to Antibiotic Tolerance [43].

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Interplay Between Epigenetic Regulation and Metabolic Plasticity in Clinically Relevant Pathogens

The reciprocal control between epigenetic regulation and metabolic plasticity is one of the central axes of the adaptive mechanisms of clinically important Gram-negative pathogen, such as Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli. DNA methylation, nucleoid-associated proteins and phase variable gene expression that restore the central carbon flux, redox equilibrium, and energy distribution under antibiotic stress are direct effects of epigenetic changes that can directly modify the transcriptional activity of metabolic genes [58,59]. For example, promoter region methylation of efflux pump can increase drug extrusion and regulate upregulation of glycolytic and tricarboxylic acid metabolism enzymes, thus helping bacteria survive under nutrient-limited and oxidative conditions [60,61]. But the changes in metabolic states may give feedback to the epigenetic regulation. Altered pools of intracellular metabolites including adenosyl methionine, acetyl-CoA, and NAD+/NADH. These changes control the activity of DNA methyl transferases and histone-like protein modifications which in turn modify gene expression programs associated with virulence, biofilm formation and persistence. This crosstalk is bidirectional and creates a soft regulatory circuit that allows for the emergence of long-term stable multidrug resistance phenotypes and transient antibiotic tolerance. [62,63]. In particular, clinical isolates frequently show coordinated changes between metabolic states, including aerobic respiration, anaerobic fermentation, and states of adaptation to oxidative stress, often due to epigenetic remodeling. [64,65]. This interaction provides a molecular basis for how non-genetic plasticity can promote both short-term survival and long-term resistance evolution. Hence, targeting nodes at the interface of epigenetic control and metabolic adaptation, such as metabolite-dependent methyl transferases or energy-coupled efflux systems, represents an opportunity to disrupt mutual reinforcement of tolerance and resistance of high-risk Gram-negative pathogens. Future research that integrates single-cell and system-level investigations will be critical to understand the temporal dynamics of these interactions in relevant clinical settings. [66]. Recent findings have illustrated the complex relationship between metabolic plasticity and epigenetic regulation in clinically relevant pathogens. Examples of epigenetic mechanisms relevant for the regulation of gene expression without changing the underlying DNA sequence. These systems allow viruses to rapidly respond

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to environmental changes and stress acquired from their hosts by changing their metabolic pathways. For example, secondary metabolism crucial for virulence, adaptation and survival in fungal infections has been shown to be under epigenetic regulation [67]. In addition, some histone modifications, such as H3K4 methylation, are directly involved in the regulation of genes associated with cellular processes and pathogenicity, thereby enhancing the ability of infections to adapt to host environments. Furthermore, epigenetic modifications also allow long-term adaption and infection success and contribute to phenotypic plasticity by enabling reversible changes in gene expression that are maintained even after removal of environmental cues [68]. Importantly, recent studies have shown that metabolic states and intermediates can modulate epigenetic enzymes, thereby implicating a bidirectional relationship between metabolism and epigenetic control. Metabolite availability changes can alter the epigenetic landscape, resulting in dynamic reprogramming of gene expression and metabolic pathways. The complexity of this network highlights the importance of epigenetic–metabolic interaction in the pathogen's adaptation, virulence and persistence, making this a suitable target for the development of novel antimicrobial strategies. [69,70]

Insights from Multi-Omics Approaches and Clinical Environments

Improvements in multi-omics technologies have afforded an integrated view of the epigenetic, transcriptional and metabolic modifications that underpin multidrug resistance phenomena in Gram-negative bacteria, therefore substantially expanding our knowledge. Transcriptomics and small RNA profiling has identified whole genome regulatory RNA and gene expression networks that regulate expression of metabolic enzymes, virulence factors and efflux pumps. [71]. Metabolomics studies reveal rapid changes in central carbon metabolism, amino acid pools, redox cofactors and energy generation pathways underlying antibiotic tolerance. Epigenomics and proteomics further explain the post-translational adaptations and patterns of gene modification via DNA methylation that stabilizes these adaptive features [72]. Single cell studies show that there is high heterogeneity within bacterial communities and in subpopulations in different metabolic or epigenetic states that may sustain lethal antibiotic conditions. This heterogeneity has been related to stochastic epigenetic changes, and it is on the basis of this heterogeneity that stable phenotypes are maintained in clinical isolates [73]. Other pressures in

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the clinical setting, such as nutrient and host immune restrictions and recurrent exposure to antibiotics, condition the bacterial epigenetic and metabolic responses. The integration of multi-omics data with clinical metadata provides relevant information on adaptive responses and potential biomarkers of resistance and can be used to design specific therapeutic interventions [74]. As shown in table 2.

Table 2. Overview of Multi-Omics Approaches and Clinical Environmental Pressures onMDR Gram-Negative Bacteria.

Omics Approach	Key Insights	Clinical Relevance
Transcriptomics	Identification of efflux pump regulation, stress response genes, sRNAs	Reveals targets for transcriptional inhibitors
Metabolomics	Shifts in central carbon metabolism, redox balance, and energy allocation	Explains metabolic adaptations under antibiotic stress
Proteomics	Protein abundance and post-translational modifications	Highlights enzymes critical for resistance and persistence
Epigenomics	DNA methylation patterns, nucleoid-associated protein activity	Links epigenetic changes to stable and transient resistance
Single-Cell Analyses	Heterogeneity in gene expression and metabolic states	Identifies tolerant subpopulations and phenotypic variability
Clinical Environment	Nutrient limitation, host immune pressures, repeated antibiotic exposure	Drives adaptation and selection of MDR phenotypes

Significant advances in the understanding of the mechanisms of multidrug resistance in Gram-negative infections have been achieved through several genomic and whole-genome sequencing (WGS) studies. As an illustration of the significance of porin loss as a resistance mechanism showed that disruption of the outer membrane porins ompK35 and ompK36 in Klebsiella pneumoniae decreased membrane permeability and contributed to carbapenem resistance [75] Similarly, it was found that increased blaKPC copy number in conjunction with ompK35/ompK36 disruption boosted resistance to new β-lactam/β-lactamase inhibitor combinations, offering insight into the genomic evolution of carbapenem resistance in clinical isolates.[76] Comparative genomic analyses of Pseudomonas aeruginosa revealed alterations in

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regulatory genes including mexR and nalC, which led to MexAB-OprM efflux pump overexpression and multidrug resistance[77].

Conclusion and Future Perspectives

The development of multidrug resistance in Gram-negative bacteria is central to epigenetic control and metabolic flexibility. Epigenetic modification is a stringent and flexible network that regulates metabolic gene expression and dynamic metabolic status to facilitate bacteria to adapt to various stressful environments. High impact bacteria of clinical relevance, including Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli exploit this interaction to acquire transient, persistent and stable resistance phenotypes. The complexity and heterogeneity of these adaptive responses have started to emerge as a result of newly emerging multi-omics technologies, and single-cell analyses and systems biology approaches which have provided new insights into the previously uncharted territory of the non-genetic drivers driving resistance. These findings point to the need to look beyond conventional antibiotic strategies and develop therapies that, in addition to epigenetic regulators, attack metabolic pathways. Some of the proposed interventions include metabolite-dependent methyltransferase inhibitors, regulators of the energetics underlying efflux pumps, and swamping metabolic plasticity by seeking disruptive paths that sensitize resistant populations to antibiotic therapies. Future integrated analyses of longitudinal clinical studies and high-resolution omics datasets will be warranted to map temporal dynamics of epigenetic metabolic dialogues. Together, they will improve the predictive modelling of resistance evolution, personalized antimicrobial therapy and contribute to the development of new generations of tools to fight such infections involving the multidrug-resistant Gram-negative species.

Future research directions should focus on:

1. Map the temporal and spatial dynamics of epigenetic–metabolic interactions during infection using single-cell and longitudinal multi-omics techniques.
2. Identifying key regulatory nodes that connect metabolism to epigenetic remodeling when antibiotic stress is present.
3. Integrating host-pathogen metabolic interactions to understand how the host environment shapes bacterial adaptive resistance.

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Potential therapeutic strategies including

1. The development of metabolite-dependent inhibitors that specifically target bacterial methyl transferases and other epigenetic enzymes.
2. The systems of energy metabolism that support efflux pump function and biofilm persistence are upset.
3. Pharmacological "metabolic reprogramming" to reduce bacterial adaptability and impose susceptible states.
4. Combination therapies that mix conventional antibiotics with drugs that interfere with metabolic adaptation or epigenetic switching.

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