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Review Article

Metabolic Adaptation and Antibiotic Resistance in Bacterial Pathogens

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ABSTRACT

Antibiotic resistance is a major worldwide health problem that compromises our ability to treat bacterial diseases. Antibiotic resistance is often ascribed to genetic mechanisms like antibiotic-inactivating enzymes, target modification and drug efflux, but there is growing evidence that bacterial metabolic adaptation also impacts antibiotic susceptibility, tolerance, persistence and the evolution of resistance. Metabolic activities are responsible for energy production, redox balance, membrane transport, biosynthesis and stress responses, and hence dictate how bacteria react to antimicrobial exposure. Altered antibiotic activity and bacterial survival may be caused by changes in glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation, amino acid metabolism and carbon utilisation. In addition, metabolic variability within bacterial populations and biofilms can result in physiological situations where some cells survive antibiotic treatment without being heritably resistant. This review highlights the biochemical and molecular processes of the interaction between bacterial metabolism and antibiotic resistance with special emphasis on energy metabolism, redox balance, membrane transport, stress adaption and persistence. It also covers developing treatment approaches such as metabolic adjuvants, disruption of biofilm metabolism, targeting bacterial energy pathways and metabolomics-guided development of antimicrobials. Understanding the metabolic basis of antibiotic reactions may aid in the creation of more effective treatment options. However, the effects of metabolic treatments are different depending on bacterial species, infection environment, antibiotic class and host circumstances, which needs to be carefully evaluated.

Keywords: *Antibiotic resistance; bacterial metabolism; metabolic adaptation; anti-microbial tolerance; oxidative stress; bacterial persistence; biofilms; metabolic reprogramming.*

INTRODUCTION

Antibiotic resistance develops when bacteria acquire or evolve mechanisms that enable them to withstand exposure to antimicrobial substances that would normally restrict their growth or kill them. The rise of resistant bacterial infections has led to a decline in the efficiency of traditional antibiotics and has hampered the management of infectious disorders. Resistant Gram-negative bacteria, such as carbapenem-resistant Acinetobacter baumannii, are listed in the World Health Organization's 2024 Bacterial Priority Pathogens List and resistant Enterobacterales, are among the high priorities for research and public health intervention[1]

The common causes for antibiotic resistance are based on genetic variables such as mutations in the antibiotic targets, creation of enzymes that inactivate the medication, decreased membrane permeability and expression of efflux pumps. These mechanisms are still fundamental. But susceptibility to microorganisms also depends on physiological and metabolic state of the cell. Metabolism supplies the energy, reducing equivalents, biosynthetic precursors and cellular resources essential for growth, maintenance and stress adaptation[2].

Recent studies have demonstrated that bacterial metabolism can influence multiple aspects of antibiotic action including drug absorption, target activity, death kinetics and the selection of resistance populations . The intricate link between metabolism and antibiotic resistance has been said [3] to emphasise the significance of metabolic state in understanding antimicrobial efficacy and resistance evolution.

Metabolic adaptability is the ability of bacteria to alter metabolic pathways in response to changes in the environment, availability of nutrients, host immune pressure and exposure to antimicrobials. These changes may enhance bacterial survival during therapy and, under certain conditions, promote the establishment or selection of heritable resistance. However, metabolic adaptation, antibiotic tolerance, persistence and genetic resistance are different processes and should not be confused[4].

This review covers the main biochemical pathways linking metabolic adaptation and antibiotic resistance and their importance for antimicrobial therapy, laboratory research and future medication development.

Bacterial Metabolism and the Basis for Antibiotic Susceptibility

Bacterial metabolism encompasses interrelated metabolic pathways that are responsible for energy generation, macromolecular biosynthesis, nutrient uptake, and cellular homeostasis maintenance. The main processes are glycolysis, tricarboxylic acid cycle, oxidative phosphorylation, pentose phosphate pathway, amino acid metabolism, and fatty acid synthesis.

The operation of these pathways influences antibiotic resistance because many antibacterial drugs target processes that are linked with active cell physiology. For example, beta-lactams impede cell-wall production, fluoroquinolones interfere with DNA replication, aminoglycosides interfere with protein synthesis, and certain antibiotics block folate metabolism. The efficacy of these medications is partly dependent on the rate of bacterial growth, target activity, intracellular drug concentration, and the organism's ability to respond to cellular injury. Thus bacteria developing fast in nutrient-rich environments may respond differently from bacteria under nutritional constraint, hypoxia or other stress conditions[5]. Metabolic pathways are also related. Changes in one pathway might influence the availability of substrates, lowering equivalents and energy for other cellular activities. A change in carbon utilisation, for example, can cause a change in respiratory activity, membrane energetics and buildup of antibiotics.

Importantly, metabolic adaptation is not necessarily accompanied by increased resistance . The activity of an antibiotic is augmented in certain metabolic conditions and depressed in others. The direction of the effect relies on the mechanism of action of the antibiotic, the bacterial species and the ambient conditions[6].

Antibiotic Resistance and Energy Metabolism

Glycolysis transforms glucose to pyruvate, producing ATP and reducing equivalents. The generated metabolites can feed into other pathways involved in energy production, biosynthesis, and redox control.

In the presence of antibiotics or nutritional limitation, bacteria can adapt the carbon absorption and redistribute the metabolic flow. These modifications can influence the rate of growth, biosynthetic activity and the stress responses of the cell. Lowered growth may lessen the activity of antibiotics highly linked to active cell-wall formation or other growth-dependent processes[7].

But sluggish growth is not a universal mechanism of resistance. Some antibiotics maintain killing activity against slowly growing bacteria, whereas others show altered killing kinetics in nutrient-limited environments. Moreover, certain metabolic conditions increase the lethality of antibiotics by either increasing the absorption of the medication or increasing cellular damage.

Thus, the link between carbon metabolism and antibiotic action is context-dependent. Studies of central metabolism should consider substrate availability, growth phase, antibiotic class and the physiological context in which the infection occurs [8].

The tricarboxylic acid cycle also produces reducing equivalents that fuel respiration and other metabolic processes. Oxidative phosphorylation uses an electron transport chain and proton motive force to generate ATP synthesis and membrane-related activities.

Changes in respiratory activity may affect antibiotic susceptibility through changes in membrane energetics, intracellular drug accumulation, and the ability to maintain cellular homeostasis. greater respiratory activity has been associated with greater aminoglycoside absorption and death in various bacterial systems . Respiratory constraint, in contrast, could decrease drug accumulation or change the cellular response to antibiotic exposure[9].

Bacterial cellular respiration has been shown to be intimately related to the action of numerous bactericidal drugs. Their work was crucial in establishing metabolism as a major factor of antibiotic activity and not simply a background mechanism supporting bacterial growth[10].

However, respiratory effects range among species and medication types. Some bacteria may depend on different electron acceptors or fermentative pathways , while others are highly sensitive to changes in respiration . Thus respiratory metabolism is a possible therapeutic target but interventions need to consider changes in bacterial physiology[11].

Likewise, ATP supplies energy for synthesis of macromolecules, membrane transport, protein quality control and cellular damage repair. There are various mechanisms by which changes in ATP availability can affect antibiotic susceptibility. Lower ATP levels may decrease the activity of several energy-dependent activities including some transport systems and be associated with lower growth and metabolic activity. In contrast, having sufficient energy stores may allow for stress responses, maintenance of membrane integrity, and recovery following antibiotic exposure.

ATP-dependent efflux pumps may contribute to resistance by decreasing intracellular concentrations of the antibiotic. Other transporters use proton motive force instead of direct ATP hydrolysis, which suggests that energy metabolism and drug transport are tightly coupled yet mechanistically diverse[12].

ATP and resistance are not linearly related. ATP depletion might impede defensive systems, but it might also limit the activity of processes targeted by antibiotics. Thus, ATP readings should be considered in the light of growth, membrane potential, respiration, and drug susceptibility data.

Redox Balance and Oxidative Stress

Redox homeostasis is crucial for bacterial survival as reactive oxygen species and other reactive intermediates can damage DNA, proteins and membrane lipids. Bacteria regulate these activities using antioxidant systems such as catalases, superoxide dismutases, peroxidases, and thiol-based redox systems.

The pentose phosphate pathway is particularly significant since it contributes to the generation of NADPH which is used for reductive biosynthesis and antioxidant defence. Thus, changes in carbon metabolism may affect the ability of a bacteria to cope with oxidative stress[13].

Antibiotic exposure may directly or indirectly alter redox balance. This may involve disturbance of respiratory metabolism, buildup of reactive intermediates, decreased antioxidant defences or damage to critical cellular components, depending on the medication and organism.

Bacteria might respond by enhancing antioxidant capacity, altering their respiratory routes, changing substrate utilisation or activating their stress-response mechanisms. These modifications may enhance survival in some environments, although the benefits are not uniform between species and antimicrobials[14].

The part that reactive oxygen species play in antibiotic-mediated death is still a topic of scientific controversy. Although oxidative damage may be involved in the action of some antibiotics in specific experimental systems, it should not be assumed that this is a universal mechanism of antibiotic killing.

Thus, the link between redox control and resistance needs to be studied extensively utilising complementary methodologies such redox measurements, metabolomics, genetic analysis, and direct detection of bacterial viability[15].

Drug Transport and Efflux, Membrane Energetics

The bacterial membrane is an important link between metabolism and antibiotic activity. It governs nutritional intake, ion balance, energy conservation, and the transport of antimicrobial drugs into and out of the cell.

The proton motive force (ion gradients and membrane potential) drives ATP generation, nutritional transport, motility and the activity of numerous membrane related proteins. So changes in membrane energetics can affect the sensitivity to drugs in bacteria.

Efflux pumps are of particular importance in this interaction. ATP hydrolysis is used by certain transport systems whereas others use proton or sodium gradients. Efflux pumps can lower intracellular levels of susceptible antibiotics, hence lowering therapeutic efficacy and, in some instances, contributing to multidrug resistance [16].

Efflux activity is also modulated by membrane composition, environmental stress and availability of metabolic energy. In Gram-negative bacteria, efflux mechanisms may cooperate with limited outer-membrane permeability to limit antibiotic accumulation.

These processes are of particular importance for organisms such as Pseudomonas aeruginosa, Escherichia coli and Klebsiella pneumoniae where combinations of permeability, efflux and antibiotic inactivating enzyme alterations can lead to clinically meaningful resistance phenotypes.

Metabolic interference with efflux is being explored as a potential avenue to restore antibiotic susceptibility. However, non-specific alteration of membrane energetics might also have consequences for host cells or trigger unpredicted bacterial responses. These methods consequently have therapeutic utility only if they are selective, safe and lead to improved antimicrobial outcomes[17].

Metabolic Adaptation, Antibiotic Tolerance and Persistence

Antibiotic resistance, tolerance and persistence are related but independent survival mechanisms.

Resistance is often marked by an increase in the minimum inhibitory concentration (MIC). Resistance can be acquired by

inheritable genetic alterations. Tolerance is the ability of a bacterial population to endure antibiotic exposure for a longer time, without necessarily having a higher MIC. Persistence is the ability of a subpopulation of cells to survive and to rebuild when the antibiotic is removed, often in the absence of stable genetic resistance [8].

Metabolic variability drives tolerance and persistence. Individual cells within a bacterial community can differ in growth rate, energy availability, respiratory activity, and stress-response activation. Low-activity cells may be less sensitive to drugs that require active growth or biosynthesis.

Thus, persister cells survive treatment and may contribute to recurrent infection, if conditions allow regrowth. This effect is particularly relevant in chronic infections because bacteria may be subjected to food limitation, immunological pressure and protracted antibiotic exposure.

However, persister cells are not simply described as low metabolism bacteria. There are a variety of physiological methods by which persistence can be achieved and metabolically active persisters have also been described . The link between metabolism and persistence is complex and is influenced by the organism, the antibiotic, and the experimental settings.

These phenomena must be distinguished in laboratory experiments. MIC values alone are not sufficient to define tolerance or persistence effectively; time-kill studies and appropriate regrowth analysis are required to examine survivability under antibiotic exposure[19].

Biofilms and Metabolic Diversity

Biofilms are organised microbial communities that are embedded in an extracellular matrix consisting of polysaccharides, proteins, extracellular DNA, and other substances. They are found on injured tissue, on medical devices and on a variety of biological surfaces.

Biofilm-associated infections are characterised by a matrix, changed microenvironment and physiological variety of bacterial cells that can impair antibiotic efficacy and make them difficult to remove. Gradients of oxygen and nutrients create zones of varying metabolic activity which result in subpopulations with different growth, respiration and resilience to stress.

In places where the water is deeper or nutrient-poor, slower growth and changes in metabolism may make some antibiotics less effective. However, alterations in extracellular matrix components and gene expression can influence medication penetration, cell protection and persisting infections.

Quorum sensing is a cell density-dependent communication that can govern biofilm formation, pathogenicity and metabolic adaptability in various bacterial species. Although quorum sensing itself is not a metabolic pathway, its regulatory crosstalk with cellular physiology makes it crucial for the metabolism-antibiotic response link. Possible approaches involve interfering with biofilm development, targeting metabolic weaknesses, enhancing antibiotic penetration, and using traditional antimicrobials in conjunction with compounds that alter biofilms. These approaches need to be validated as the biofilm responses are significantly different between species and conditions of infection[20].

Metabolic Adaptation and the Evolution of Genetic Resistance

Metabolic adaptability can thereby influence the evolution of resistance via alterations in bacterial growth, survival and exposure to selective pressure. Specifically, resistance mutations affecting important biological functions can burden bacteria with resistance mutations with fitness costs. These costs may sometimes be compensated by compensatory mutations and metabolic rearrangement, leading to increased bacterial fitness[2].

Metabolism may potentially influence the rate of expansion of resistant populations under antimicrobial pressure. Competition between susceptible and resistant cells can be influenced by nutrient availability, growth state and stress response. This means that the persistence or distribution of a resistance determinant could be influenced by the ecological environment.

Add additional dimension of horizontal gene transfer. Resistance genes may be located on plasmids and other mobile genetic elements, as well as factors for metabolism, stress responses or environmental adaption. However, the existence of metabolic alterations does not mean that they cause horizontal gene transfer directly.

It is vital to distinguish between metabolic adaptation which allows for transient survival and mechanisms which lead to lasting, heritable resistance. Metabolic treatments can enhance antibiotic efficacy but do not always prevent resistance evolution, and their long-term consequences need to be evaluated experimentally[21].

New Therapy Strategies

Metabolic adjuvants are chemicals that are designed to alter bacterial physiology to boost the activity of antibiotics. Depending on the drug and organism, these substances can affect the use of carbon, respiration, redox balance, or intracellular drug accumulation.

Research has focused on the utilisation of specific metabolites and metabolic inhibitors to improve antibiotic killing under certain conditions. Metabolic supplementation, however, does not reliably improve treatment outcomes. Some substrates may improve bacterial growth or decrease susceptibility whereas other substrates may enhance antimicrobial action in certain experimental conditions.

Future work should focus on repeatable mechanisms, dose-dependent effects, host safety, and validation in clinically relevant infection models.

Bacterial processes for generating energy are also attractive therapeutic targets since they are necessary for growth, maintenance and adaptability. Targeting specific metabolic enzymes or respiratory elements could compromise bacteria's defences and render it vulnerable to current treatments.

However, metabolic pathways are flexible and bacteria are able to compensate the loss of one pathway by switching to a different substrate or activating alternate processes for energy generation. The issue is to find metabolic vulnerabilities that are required under infection-relevant conditions, but sufficiently separate from host pathways to limit damage. Approaches to combat biofilms may involve the use of matrix disrupting chemicals, quorum sensing inhibitors and traditional antibiotics. Targeting physiological variations in subpopulations of biofilms could be a way to promote bacterial eradication, especially in cases of persistent or device-associated illness.

These techniques need to be tested on mature biofilms, different clinical isolates and realistic host habitats, and not just on planktonic laboratory cultures.

Metabolomics also allows for the global investigation of tiny chemicals involved in bacterial metabolism. Combined with transcriptomics, proteomics, genomic data and antimicrobial susceptibility tests, it can help to uncover metabolic signatures associated with resistance, tolerance and treatment response.

Systems biology will also be likely to identify combinations of metabolic pathways that are vulnerabilities of resistant pathogens. However, metabolomic fingerprints are influenced by culture conditions, sample preparation and analysis procedures. Standardisation and external validation are therefore a pre-requisite before such findings can be transferred to clinical diagnostics[22].

CONCLUSION

Metabolic adaptability is a major factor of bacterial responses to antibiotics. Alterations in central carbon metabolism, respiration, ATP availability, redox homeostasis, membrane energetics and biofilm physiology can influence antibiotic accumulation, cellular damage, survival and the selection of the resistant population. These pathways are also involved in the physiological variability underpinning antibiotic tolerance and persistence.

Antibiotic susceptibility is modulated in a non-uniform fashion by metabolism. It is influenced by the species of bacteria, the antimicrobial agent, environmental factors and the crosstalk between metabolic and genetic pathways. Future research needs to combine metabolomics, genetics, physiological measures and therapeutically relevant infection models to uncover robust metabolic vulnerabilities . This information can be used to design metabolic adjuvants, superior antibacterial combinations, and more effective ways to combat resistant bacterial infections.

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