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DNA Repair Mechanisms in Multi Drug Resistant Bacteria: Impact on Genome Stability and Antibiotic Resistance

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ABSTRACT

Conventional antibiotics are becoming less effective as the global health crisis of multidrug-resistant (MDR) bacterial infections worsens. The function of bacterial DNA repair systems in promoting MDR is a quickly developing paradigm, despite the well-established nature of conventional resistance mechanisms such as efflux pumps and drug-inactivating enzymes. The present understanding of how DNA repair pathways, which are necessary for the stability of the genome, paradoxically promote adaptive mutagenesis and horizontal gene transfer under antibiotic stress is summarized in this review. In important MDR pathogens, we investigate the complex interactions among repair mechanisms, stress reactions, and resistance evolution. The regulatory crosstalk with other bacterial systems and the potential of DNA repair inhibitors as novel therapeutic adjuvants are two examples of significant knowledge gaps that are highlighted. We wrap up by going over potential future directions for focusing on DNA repair to re-sensitize MDR bacteria and prolong the effectiveness of current antibiotics.

INTRODUCTION

One of the most urgent global health issues of the twenty-first century is the unrelenting emergence of multidrug-resistant (MDR) bacteria, which poses a threat to the fundamentals of contemporary medicine. According to projections, MDR infections could surpass the cancer mortality rate and push routine medical procedures back into a high-risk, pre-antibiotic era by 2050, resulting in up to 10 million annual deaths if effective intervention is not implemented (1). Understanding and combating traditional mechanisms, such as the enzymatic inactivation of medications, the alteration of antibiotic targets, and the overexpression of efflux pumps that remove harmful substances from cells, has been the main focus of the fight against resistance for many years (2). Although these tactics are important, they frequently take a reactive stance toward resistance that has already developed rather than tackling the underlying mechanisms that initially create this diversity.

The discovery that bacterial genome plasticity, which is expertly controlled by DNA repair systems, is inextricably linked to the emergence and evolution of antibiotic resistance is causing a paradigm shift. Once praised as devoted protectors of genomic integrity, these repair pathways are now recognized to have two distinct personalities. The very mechanisms that maintain genetic stability can be weakened to support genetic diversity under the deadly and mutagenic pressure of antibiotics. Bacterial populations can effectively "engineer" their own survival through this stress-induced response, which speeds up the acquisition of resistance mutations and promotes the horizontal transfer of resistance genes (3). Specifically, the induction of error-prone repair pathways serves as a bet-hedging strategy, whereby the long-term advantage of producing adaptive traits under extreme selective pressure is exchanged for the short-term cost of more mutations. The goal of this review is to summarize and assess the novel idea that DNA repair is a proactive, dynamic driver of resistance evolution in MDR pathogens

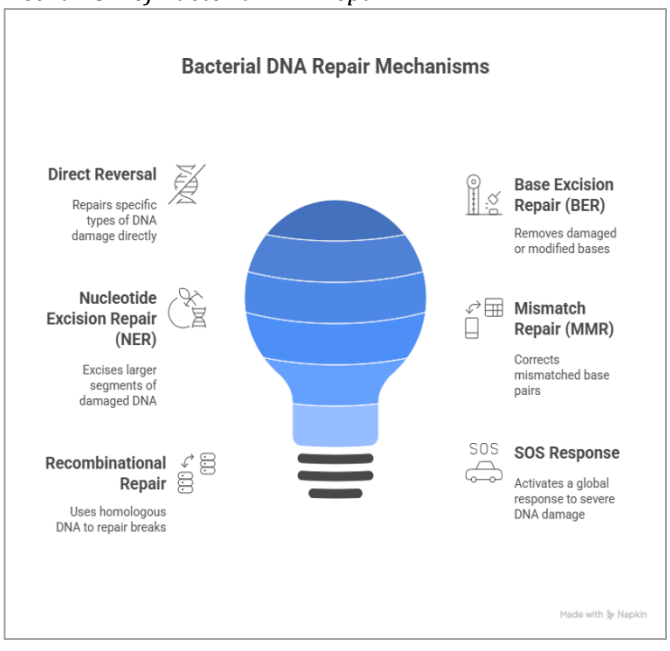
rather than just a housekeeping function. We will break down the distinct repair pathways that are triggered by various antibiotic classes, ranging from direct reversal to the intricate SOS response, and explain how they contribute to the development of mutator phenotypes and the effective integration of foreign genetic material. Our goal is to offer a thorough framework for comprehending bacterial adaptability by examining the complex interactions among DNA damage, repair, and stress response networks. The development of DNA repair inhibitors as innovative therapeutic adjuvants intended to impede resistance evolution and re-sensitize MDR bacteria to traditional antibiotics will be the main focus of our final evaluation of the ground-breaking translational potential of this knowledge.

OVERVIEW OF BACTERIAL DNA REPAIR SYSTEMS

Bacteria have developed an advanced and multi-layered arsenal of DNA repair mechanisms to survive in genotoxic environments, such as those produced by antibiotic assault. From single-base alterations to disastrous double-strand breaks, these pathways can repair a variety of DNA lesions with exceptional specificity and effectiveness. Although the stability of the genome depends on the combined activity of these systems, stress can alter their fidelity and regulation, generating a molecular furnace for evolutionary adaptation. A number of key bacterial DNA repair pathways repair genomic damage, which is represented in **Figure 1.0**. The six major pathways shown are direct reversal, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), recombinational repair, and the SOS response. Each repair process acts on a specific type of DNA damage, from mismatched bases to double-strand breaks. Together, these systems deliver accurate DNA replication and protect bacteria against genotoxic stress.

Figure 1

Mechanism of Bacterial DNA repair



Major DNA Repair Pathways

Each of the core pathways that make up the bacterial DNA repair toolkit is specific to a particular kind of damage:

Direct Repair

Since it repairs damage without deleting any nucleotides, this is the most straightforward and energetically efficient tactic. For example, photolyases directly split cyclobutane pyrimidine dimers produced by UV light using energy from visible light (4). Similar to this, damaging lesions such as 1-methyladenine and 3-methylcytosine can be directly demethylated by the AlkB family of α-ketoglutarate-dependent dioxygenases, returning the undamaged base without the need for a repair intermediate (5).

Base Excision Repair (BER)

The main mechanism for repairing minor, non-helix-distorting base lesions brought on by oxidation, alkylation, or deamination is BER. An abasic (apurinic/apyrimidinic or AP) site is created when a group of DNA glycosylases identifies and removes particular damaged bases. After an AP endonuclease cleaves this site, DNA polymerase I processes and fills the resulting single-nucleotide gap, and DNA ligase then seals the backbone (6).

Nucleotide Excision Repair (NER)

NER deals with large, helix-distorting adducts that prevent replication and transcription. The UvrA-UvrB complex looks for DNA distortions in bacteria. UvrA confirms the damage, UvrB melts the surrounding DNA, and UvrC cuts the lesion on both its 3' and 5' sides. UvrD helicase eliminates the resultant oligonucleotide, and DNA polymerase I fills the void (7).

Mismatch Repair (MMR)

Base-base mismatches and tiny insertion-deletion loops that evade DNA polymerase proofreading are fixed by MMR, a post-replication proofreading technique. The newly synthesized, unmethylated DNA strand is incised by the latent endonuclease MutH after the MutS protein homodimer identifies the mismatch and recruits MutL. Replication fidelity is then increased by 100–1000 times by excising and resynthesizing the error-containing strand (8).

Recombinational Repair

DNA double-strand breaks (DSBs), one of the most deadly types of DNA damage, are primarily repaired by this mechanism. The RecA protein, which forms a nucleoprotein filament on single-stranded DNA, is at the center of the process. In order to make an accurate repair, this filament infiltrates a homologous DNA sequence, usually the sister chromosome. In order to create the single-stranded DNA needed for RecA loading, the broken DNA ends must be resected by the RecBCD or AddAB complexes (9).

SOS Response

The cellular response to significant DNA damage is coordinated by the SOS response, a global, inducible network. RecA nucleoprotein filaments aid in the autocleavage of the LexA repressor when replication forks stall and single-stranded DNA is produced. The error-prone translesion synthesis (TLS) polymerases Pol IV (DinB) and Pol V (UmuD'2C) are among the more than 40 unlinked genes involved in DNA repair that are derepressed by LexA inactivation. These TLS polymerases significantly increase the rate of mutations and promote

adaptive evolution under stress, but they do so with decreased fidelity, allowing replication to continue past blocking lesions (10).

Comparative Insights

The DNA repair environment is dynamic and can vary greatly between MDR and antibiotic-sensitive strains. In chronic and MDR isolates of pathogens such as P. aeruginosa and A. baumannii, hypermutator phenotypes which are frequently caused by defects in the MMR system (e.g., mutS or mutL mutations) are remarkably overrepresented (11). This implies a clear evolutionary connection between successful resistance emergence and elevated genomic instability. Moreover, DNA repair is intricately linked to other cellular stress responses and does not function independently. For example, aminoglycoside-induced oxidative stress can trigger the SOS response directly, establishing a molecular link between genotoxic stress and metabolic disruption that increases the risk of mutagenesis (12).

ANTIBIOTIC-INDUCED DNA DAMAGE AND ACTIVATION OF REPAIR PATHWAYS

Although many antibiotics do not directly damage DNA as their primary mechanism of action, they often cause a series of cellular events that lead to significant genotoxic stress. It is essential to comprehend this indirect pathway to DNA damage because it triggers the bacterial repair mechanisms that eventually propel the evolution of resistance.

Mechanisms of DNA Damage by Antibiotics

Different mechanisms are used by several major antibiotic classes to cause DNA lesions:

Fluoroquinolones

These medications, like ciprofloxacin, directly target topoisomerase IV and DNA gyrase, trapping them in a covalent bond with DNA. The transcription machinery and replication fork are physically blocked by this "cleavage complex." Irreversible double-strand breaks (DSBs), one of the most deadly types of DNA damage, occur when a replication fork strikes this stabilized complex (13).

β-Lactams

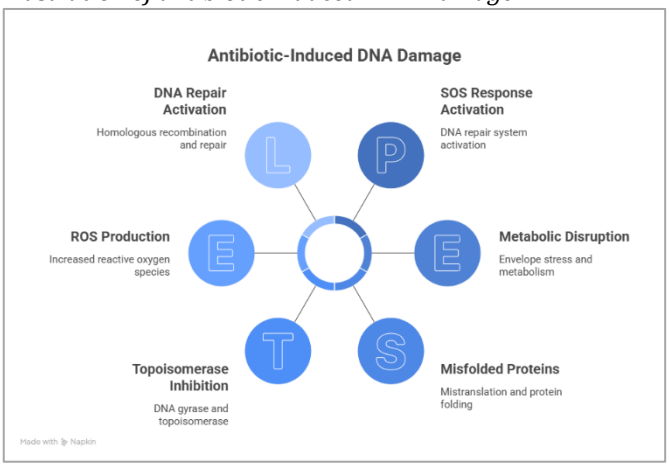
β-lactams interfere with the synthesis of cell walls by blocking the proteins that bind penicillin. This sets off a fruitless cycle of cell wall remodeling attempts that results in envelope stress induction and metabolic disruptions. One significant effect is an increase in intracellular reactive oxygen species (ROS), such as hydroxyl radicals, which lead to oxidative DNA damage, including base modifications, single-strand breaks, and 8-oxoguanine lesions (14).

Aminoglycosides

By attaching themselves to the decoding center's 16S rRNA, these bactericidal antibiotics result in mistranslation and misfolded proteins. When these abnormal proteins are incorporated into the membrane, the electron transport chain is disrupted, which causes a sharp increase in ROS production. All macromolecules, including DNA, suffer extensive oxidative damage as a result of this oxidative burst, which is comparable to that brought on by β-lactams (15). Figure 2.0 shows pathways relating to the molecule generation of antibiotics in inducing DNA damage in bacteria. Antibiotics generate oxidative stress (ROS generation), inhibit topoisomerases, and disrupt metabolism and protein folding. These stresses cause DNA damage that triggers repair mechanisms, such as homologous recombination and the SOS response. Collectively, these processes display the response of bacterial cells to antibiotic pressure in order to maintain genomic integrity.

Figure 2

Illustration of antibiotic induced DNA Damage



Activation of DNA Repair Systems

Antibiotic-induced DNA lesions serve as potent signals that trigger matching repair pathways, starting a fight for survival that may have unforeseen evolutionary repercussions.

SOS and Recombinational Repair

The SOS response is strongly triggered by the DSBs produced by fluoroquinolones. In order to enable LexA autocleavage and the complete activation of the SOS regulon, RecA attaches itself to the single-stranded DNA produced at the broken ends. Concurrently, the sister chromatid is used as a template by the homologous recombination machinery (RecBCD/RecA) to precisely repair the breaks. One of the main defenses against this drug class is this coordinated response (16).

ROS-Mediated Repair Activation

The oxidative base lesions caused by β-lactams and aminoglycosides are primarily handled by the Base Excision Repair (BER) pathway. Glycosylases like MutM (Fpg) specifically recognize and initiate the repair of 8-oxoguanine. Critically, the oxidative stress itself and the resulting stalled replication forks can also induce the SOS response, creating a link between metabolic stress and error-prone repair. This "ROS-mediated repair activation" functions as an adaptive signal, priming the bacterial population for evolution under drug stress (17).

Case Studies

Key MDR pathogens exhibit the interaction between repair activation and antibiotic-induced damage:

- ***E. Coli:*** Treatment with ciprofloxacin strongly triggers the SOS response, which results in mutagenesis that is dependent on Pol IV (DinB). This can lead to "collateral resistance," which is

resistance to other, unrelated antibiotics in addition to fluoroquinolones themselves (18).

- ***A. baumannii:*** RecA and error-prone polymerase genes are upregulated in MDR strains when exposed to carbapenems, a β-lactam class of antibiotics. This pathogen's success can be attributed to its improved repair and mutagenic capacity, which makes it easier to select mutations that confer higher-level resistance (19).
- ***S. aureus:*** The SOS response to fluoroquinolone exposure in S. aureus upregulates genes involved in biofilm formation in addition to encouraging mutagenesis. This illustrates how phenotypic resistance mechanisms can be induced by DNA damage, making treatment even more challenging (20).

DNA REPAIR–MEDIATED MUTAGENESIS AND THE EVOLUTION OF ANTIBIOTIC RESISTANCE

There are two sides to the activation of DNA repair systems during antibiotic stress. Despite being necessary for survival, these pathways directly speed up the evolution of antibiotic resistance by actively creating the genetic diversity that natural selection relies on.

Error-Prone Polymerases and Mutator Phenotypes

The SOS-regulated translesion synthesis (TLS) polymerases are central engines of stress-induced mutagenesis.

Mechanism of Action

Pol IV (DinB) and Pol V (UmuC) are enlisted to get around DNA lesions where high-fidelity replicative polymerases are stalled. Because of their loose active sites and lack of proofreading activity, these polymerases have a high synthesis error rate, which hinders replication and cell survival (21). SOS-induced TLS can cause mutations throughout the genome in a single round, possibly affecting genes that provide resistance.

Hypermutator Phenotypes

Strains with faulty MMR systems, such as mutS mutants, are frequently responsible for chronic bacterial infections, especially those caused by *P. aeruginosa* in patients with cystic fibrosis. The likelihood of spontaneously developing resistance mutations against all administered antibiotics is significantly increased in these "hypermutators" due to their permanently elevated mutation rate, which is 100–1000 times higher than wild-type (22).

Recombination and Horizontal Gene Transfer

DNA repair systems are vital for both acquiring foreign resistance genes and repairing the host's genome.

Plasmid and Gene Stabilization

One of the main pathways to MDR is the acquisition of a plasmid containing multiple resistance genes. However, the plasmid must replicate and stabilize in the new host for establishment to be successful. In order to resolve plasmid multimers and integrate resistance cassettes from mobile elements such as integrons and genomic islands into the chromosome, which guarantees their stable inheritance, RecA-mediated homologous recombination is essential (23).

Facilitating Gene Acquisition

The direct role of recombinational repair in horizontal gene transfer is highlighted by studies in *A. baumannii*, which demonstrate that inhibition of RecA dramatically lowers the bacterium's ability to acquire and incorporate new antibiotic resistance genes from the environment (24).

Mutational Rescue under Stress

The traditional understanding of mutations as entirely random occurrences is called into question by the idea of "stress-induced mutagenesis." According to this theory, bacterial populations that are subjected to lethal stress can trigger controlled processes that raise their rate of mutation only during that time.

Adaptive Mutagenesis

A "mutational rescue" mechanism is provided by this process. The population responds to the antibiotic challenge by dynamically increasing its genetic diversity rather than waiting for an already-existing resistant mutant. The likelihood of a resistant clone emerging is increased by this controlled rise in genomic instability rather than a directed mutation (25). Because the urgent need for a mutation that confers survival outweighs the risk of accumulating harmful mutations, the induction of error-prone repair represents a calculated evolutionary gamble. This paradigm emphasizes that DNA repair systems actively participate in the evolutionary arms race between bacteria and antibiotics rather than merely acting as passive protectors of the genome.

GENOME STABILITY VS. EVOLVABILITY: A PARADOX OF RESISTANCE

The need to preserve genomic information (stability) and the need to evolve to meet new challenges (evolvability) are fundamentally at odds. The core of this paradox is DNA repair systems. High-fidelity repair predominates under typical circumstances. Error-prone pathways are upregulated under stress, which shifts the balance in favor of evolvability. This balance can be adjusted by epigenetic regulation, such as DNA adenine methylation, which can affect the expression of genes involved in repair and stress response (26).

TARGETING DNA REPAIR PATHWAYS: A NEW FRONTIER IN ANTIMICROBIAL THERAPY

DNA repair is a desirable therapeutic target due to its pivotal role in resistance evolution. The plan is to create adjuvants that disarm the adaptive mechanisms of bacteria.

Current DNA Repair Inhibitors

Key repair node-targeting small-molecule inhibitors are being developed. These consist of substances that interfere with the SOS response, LexA proteolysis inhibitors, and RecA inhibitors (such as suramin) (27).

Synthetic Lethality and Combination Therapies

Synthetic lethality, which kills the bacterium by blocking a DNA repair pathway and another target (like a primary antibiotic), is a promising tactic. An SOS inhibitor and a fluoroquinolone, for instance, can enhance the antibiotic's action and prevent the emergence of resistance (28).

Advanced Tools and Future Directions

In bacterial populations, CRISPR-Cas systems can be designed to specifically disrupt genes encoding RecA or error-prone polymerases. Furthermore, it is possible to design peptide nucleic acids (PNAs) to inhibit the expression of important repair genes (29).

DNA REPAIR AS A BIOMARKER OF RESISTANCE AND TREATMENT OUTCOME

According to transcriptomic research, MDR strains frequently exhibit unique expression signatures for DNA repair. Error-prone polymerase, lexA, and recA gene overexpression can be a biomarker for increased adaptive potential and treatment failure risk. These upregulated repair transcripts can be directly detected from clinical samples using quantitative PCR and RNA-seq assays, offering a quick prognostic tool. Precision medicine may be made possible by incorporating DNA repair activity data into diagnostic pipelines, which would direct the selection of antibiotic combinations according to the evolvability profile of the bacterium (30).

INTERPLAY BETWEEN DNA REPAIR AND BACTERIAL STRESS ADAPTATION NETWORKS

The global network of cellular stress includes DNA repair. Osmotic shock, nutrient starvation (stringent response), and oxidative stress (OxyR/SoxR regulons) can all alter the expression of DNA repair genes, preparing the bacterium for genotoxic stress (31). A subset of DNA repair genes is regulated by the stationary phase sigma factor RpoS, which connects genome maintenance and general stress adaptation. Nutrient stress is linked to mutagenesis through the direct stimulation of Pol IV expression by the stringent response alarmone (p)ppGpp. One stressor exposure (such as bleach) can increase DNA repair systems, offering cross-protection against antibiotics' DNA-damaging effects. This phenomenon has consequences for disinfection procedures (31).

EVOLUTIONARY AND ECOLOGICAL PERSPECTIVES ON DNA REPAIR–DRIVEN RESISTANCE

According to phylogenetic analyses, successful MDR pathogens such as A. baumannii have repair genes that have undergone specific adaptations, such as gene acquisitions and duplications, which may have optimized their adaptive responses. Along with resistance genes, plasmids frequently carry their own DNA repair systems (such as umu operons), which can be transferred and instantly increase the recipient's capacity for mutagenicity (32). Bacteria with elevated stress and repair responses may be selected for by sub-inhibitory concentrations of antibiotics, heavy metals, and biocides in the environment, which could pre-adapt them for clinical resistance (33).

DNA REPAIR IN BIOFILM-ASSOCIATED RESISTANCE

Oxidative stress, nutrient gradients, and enhanced antibiotic tolerance are characteristics of the biofilm microenvironment. When compared to planktonic cells, biofilm cells show increased SOS and BER responses (34). Biofilms that repair poorly may produce resistant mutants. Additionally, repair mechanisms help persister cells, a dormant subpopulation that is resistant to antibiotics, survive and repopulate the infection (35). One tactic against chronic infections is to interfere with DNA repair in biofilms, such as by using RecA inhibitors, which can make the biofilms more sensitive to antibiotic treatment and stop the emergence of resistant variants (36).

KNOWLEDGE GAPS AND FUTURE PERSPECTIVES

Unresolved Questions

The precise function of non-coding RNAs in post-transcriptionally controlling repair genes under stress (37) and the interplay between the host's DNA repair machinery and CRISPR-Cas systems (an adaptive immune system) during plasmid acquisition (38) are important unanswered questions.

Emerging Research Directions

In order to map the global repair-resistance interface, future research will integrate multi-omics (genomics, transcriptomics, and proteomics). In order to forecast resistance outbreaks, artificial intelligence can simulate the intricate dynamics of repair-mediated adaptation (39). One important therapeutic frontier is the logical development of adjuvants that target repair for combination therapy (40).

DISCUSSION

According to this review, DNA repair systems are at the heart of the MDR crisis. They enable the stable acquisition of resistance genes through recombination and supply the genetic diversity required for resistance evolution through error-prone repair. There is substantial translational potential. Repair gene expression signatures may develop into useful biomarkers for anticipating treatment failure and directing stewardship, while DNA repair inhibitors may interrupt the cycle of resistance evolution.

Effective countermeasures must be developed by combining the fields of microbiology, structural biology, genomics, pharmacology, and computational modeling.

Limitations of This Review

We recognize that there is currently a dearth of clinical and in vivo data that definitively connects particular repair activities to patient outcomes. Moreover, non-canonical repair mechanisms may be overlooked in favor of canonical pathways. There is an immediate need to validate these ideas in a larger variety of bacterial models and clinical contexts.

CONCLUSION

Bacteria's DNA repair pathways are an intricate adaptive network that guarantees their survival. These systems are used to create genetic diversity under antibiotic pressure, which directly contributes to the development of multidrug resistance. They serve as a catalyst, encouraging adaptive mutations, and a shield, preserving the integrity of the genome.

Converting this knowledge into clinical tools must be the main goal of future initiatives. This entails creating point-of-care diagnostics for repair biomarkers, high-throughput screening for strong and targeted DNA repair inhibitors, and verifying these approaches in intricate infection models. Innovative tactics are needed to combat antibiotic resistance. We can create a new class of "anti-evolution" medications by comprehending and focusing on the very mechanisms that enable bacteria to adapt and

evolve their DNA repair machinery. The effectiveness of our current antibiotic arsenal could be restored with this multidisciplinary approach, protecting public health for coming generations.

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