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Review Article

Molecular Mechanisms of Bacterial Antibiotic Resistance

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Abstract

Antibiotic resistance is a prevalent threat to global health and humankind, guided by varied bacterial adaptations that reduce the efficiency of currently available and in-use antibacterial drugs. In 2021, we estimated 4.71 million deaths were associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR. Trends in AMR mortality over the past 31 years varied substantially by age and location. From 1990 to 2021, deaths from AMR decreased by more than 50% among children younger than 5 years, yet increased by over 80% for adults 70 years and older. In this mini review, we present an effective interpretation of the major molecular systems of resistance, including target alteration, drug inactivation mechanisms, horizontal gene transfer, clinical implications, and strategic solutions. Apart from these classical mechanisms, we also acknowledge adaptive physiological pathways, similar to biofilm formation and persistence, that contribute to antimicrobial treatment failures. Comprehending these mechanisms is crucial for conducting an improvement of modern antibiotics and stewardship programs.

Keywords: antimicrobial resistance, biofilm formation, horizontal gene transfer, multidrug resistance

1. Introduction

Bacterial antimicrobial resistance (AMR) is actually one of the most critical challenges in clinical management of many infectious diseases. The common resistance mechanisms arise from both genetic and epigenetic pathologies, such as mutations and molecular injuries, and the addition of resistance genes from different organisms, frequently under selective pressure from antibiotic exposure (Figure 1). AMR mortality decreased for children younger than 5 years in all super-regions, whereas AMR mortality in people 5 years and older increased in all super-regions. For both deaths associated with and deaths attributable to AMR, meticillin-resistant Staphylococcus aureus increased the most globally (from 261 000 associated deaths and 57 200 attributable deaths in 1990, to 550 000 associated deaths and 130 000 attributable deaths in 2021) [1]. By 2050, around 2 million people, the majority aged 70 and over, could die from drug-resistant infections each year [2]. Antibiotics and antibiotic biosynthetic pathways are believed to have evolved over millions of years, suggesting that antibiotic resistance is an equally ancient phenomenon (Figure 2) [3], [4]. The increase of multidrug-resistant organisms continues to affect the effectiveness of clinically essential drugs, which leads to serious morbidity and mortality and also to healthcare burdens.

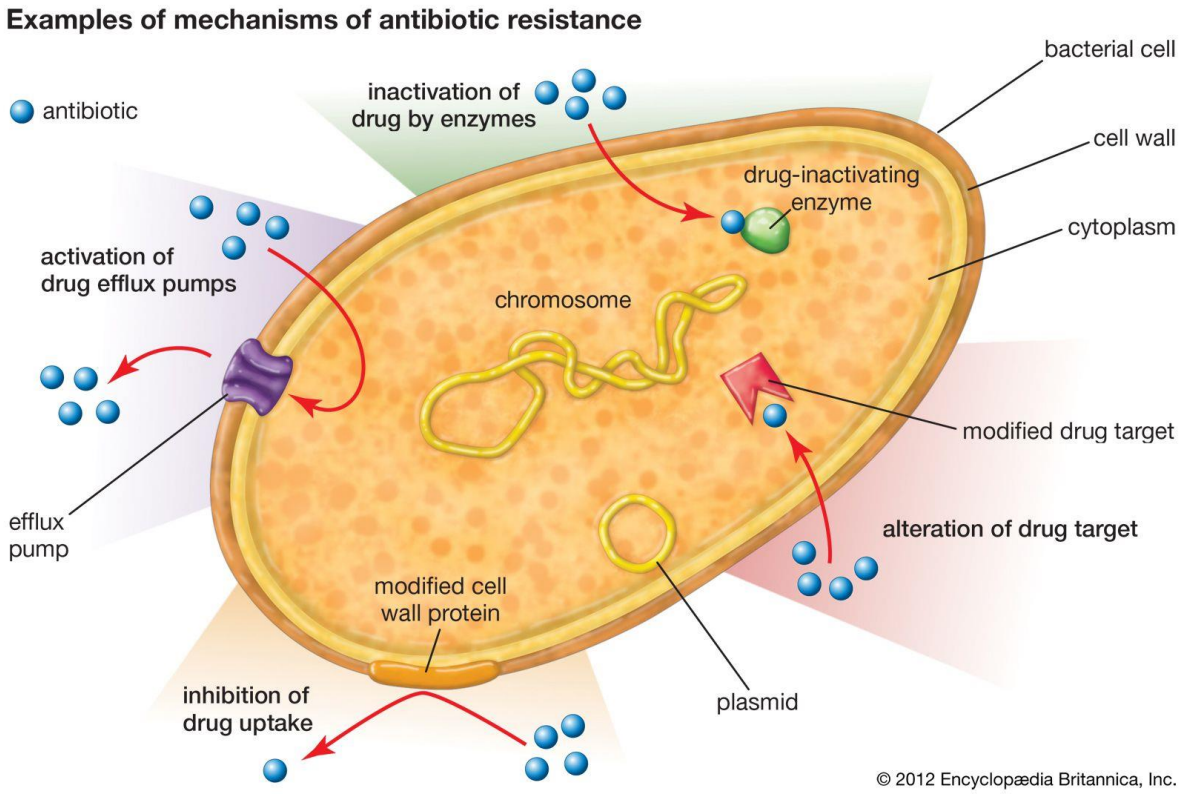

Figure 1. Mechanisms of antibiotic resistance in bacteria.
Source: Adapted from Encyclopaedia Britannica [5].

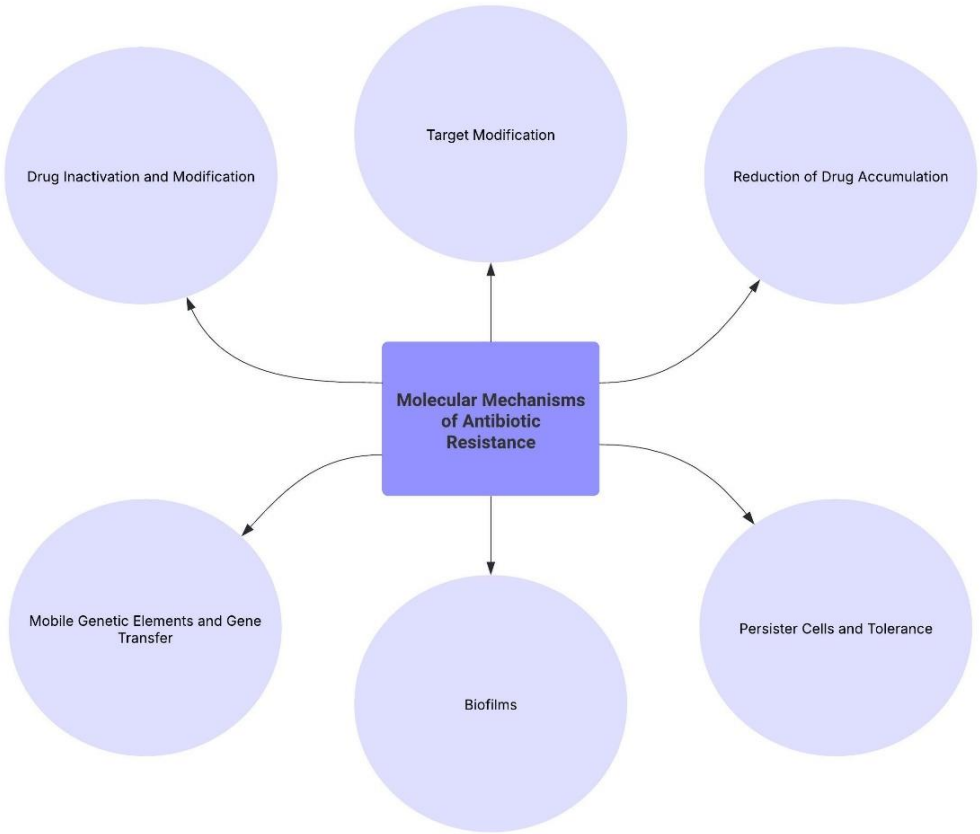

Figure 2. Six mechanisms of AMR.
Source: Created with Lucid.

2. Classical Molecular Resistance Mechanisms

2.1. Antibiotic Inactivation

One of the most common mechanisms is the enzymatic inactivation of drugs. One of the most pervasive ways is the production of beta-lactamases, which hydrolyse the beta-lactam ring crucial to penicillins, cephalosporins, and carbapenems. Correspondingly, enzymes that modify aminoglycosides through acetylation, phosphorylation, or adenylation reduce antibiotic binding to ribosomal targets. Antibiotic-inactivating enzymes can accomplish this task by one of two means: by eradicating the essential reactive center of the antibiotic or by modifying the drug in a manner that impairs target binding [6].

2.2. The Modification of Target

The alterations by bacteria in antibiotic targets that affect drug affinity. Mutations and unknown molecular alterations in ribosomal RNA and proteins confer resistance to aminoglycosides and macrolides, while changes in DNA gyrase or topoisomerase IV can lead to fluoroquinolone resistance. These modifications may originate through mutation or be carried on mobile gene elements. Modification of the antibiotic target is a resistance strategy that is increasingly prevalent among pathogens. Examples include resistance to glycopeptide and polymyxin antibiotics that occurs via chemical modification of their molecular targets in the cell envelope. Similarly, many ribosome-targeting antibiotics are impaired by methylation of the rRNA [7].

2.3. Decreasing of Antibiotic Accumulation

Decreased intracellular antibiotic concentration is another important resistance mechanism. For example, Gram-negative bacteria carry an outer membrane that inherently restricts the entry of multiple antibiotics. Alterations of porin expression can further limit uptake. There are two main ways in which porin changes can limit drug uptake: a decrease in the number of porins present, and mutations that change the selectivity of the porin channel [8]. Members of the Enterobacteriaceae are known to become resistant by reducing the number of porins (and sometimes stopping production entirely of certain porins). As a group, these bacteria reduce porin number as a mechanism for resistance to carbapenems [9]. Furthermore, efflux pumps actively eliminate a broad range of antibiotics from the cytosol, leading to multidrug resistance phenotypes.

3. Gene Transfer and Mobile Genetic Elements

The resistance genes are extensively disseminated via transposons, integrons, and plasmids. The complex process of antibiotic resistance genes (ARG) transmission via horizontal gene transfer (HGT) conjugation, transformation, transduction, and the more recently identified vesiduction is given in a review by Liu et al. [10]. Horizontal Gene Transfer (HGT) permits these elements to shift between different bacterial species, enabling rapid distribution of resistance genes within microbial strains. By examining how mobile genetic elements (MGEs) in Klebsiella pneumoniae serve as carriers of both virulence and resistance genes, Han et al. [11] summarize MGE types and how they contribute to the establishment of harmful strains such as carbapenem-resistant hypervirulent K. pneumoniae (CR-hvKP). Plasmid resistance determinants are often associated with multiple drug resistance phenotypes, presenting essential clinical problems.

4. Biofilms, Persister Cells, and Tolerance

4.1. Biofilms

Biofilms are organised bacterial communities that stick together and are embedded in an extracellular matrix, supplying resistance to antibiotics. For acute and chronic infections, underlying health conditions such as immunodeficiencies, diabetes, and cystic fibrosis can lead to commensal biofilm organisms becoming opportunistic pathogens, often manifesting as polymicrobial biofilm infections of the lungs, foot ulcers, bone and deep tissues, and indwelling medical devices [12], [13], [14], [15], [16]. These infections are refractory to treatment due to species diversity, variability of the infectious microenvironment [17], and the upregulation of virulence and resistance pathways via quorum sensing and metabolic interaction [17], [18], [19]. Furthermore, antimicrobial resistance is promoted through limiting drug penetration, the presence of dormant “persister”

cells, and the enhancement of horizontal gene transfer [20]. These result in either chronic, recurring disease or systemic life-threatening infection [21], [22].

4.2. Persister Cells and Tolerance

The multiple bacterial populations can produce persister cells that do not die and do not respond to the therapy of antimicrobial regimens. Persisters are largely responsible for high levels of biofilm tolerance to antimicrobials, but virtually nothing was known about their biology. Tolerance of Escherichia coli to ampicillin and ofloxacin was tested at different growth stages to gain insight into the nature of persisters. The number of persisters did not change in the lag or early exponential phase, and increased dramatically in the mid-exponential phase. Similar dynamics were observed with Pseudomonas aeruginosa (ofloxacin) and Staphylococcus aureus (ciprofloxacin and penicillin). This shows that the production of persisters depends on the growth stage [23].

5. Clinical Implications and Strategic Solutions

Antibiotic resistance mechanisms lead to a significant threat to global healthcare, resulting in severe medical therapeutic implications. This results in increased mortality and extended hospitalisations. Physicians could use second- and third-line agents, which can be more toxic medications. Infectious treatments could be delayed. Strategic solutions for healthcare systems in all countries are improving the programs of antibiotic stewardship, early diagnostics, and development of novel antibiotics and alternatives like bacteriophages and antimicrobial peptides.

6. Conclusion

Antibiotic resistance (AR) in bacteria is a crucial global health crisis and arises from massive overuse of antimicrobial drugs and a combination of ineffective structural, enzymatic, and physiological processes. These molecular mechanisms span from antibiotic inactivation, target modification, mobile gene transfers, biofilms, and persister cells to organised bacterial communities such as biofilms. Critical effective responses require a variety of approaches integrating molecular insights, clinical practice, and stewardship programs.

Author Contributions

All authors contributed to the conception, literature review, writing, editing, and final approval of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Antimicrobial Resistance (AMR), Ribonucleic Acid (RNA), Deoxyribonucleic Acid (DNA), Antibiotic Resistance Genes (ARG), Horizontal Gene Transfer (HGT), Mobile Genetic Elements (MGEs), Carbapenem-Resistant Hypervirulent K. Pneumoniae (CR-hvKP), Antibiotic Resistance (AR).

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Journal of Molecular Biosciences and Engineering

Review Article

Epigenetics: The Impact of Trauma on Gene Expression and Transgenerational Transmission

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Abstract

This study examines the relationship between childhood trauma and epigenetic changes in genes that regulate the stress response. Traumas such as violence or lack of control experienced at an early age can disrupt the long-term regulatory mechanisms of the hypothalamic-pituitary-adrenal (HPA) axis, leading to impaired stress responses. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs play an important role in the stress response by regulating gene expression without altering the DNA sequence. Genes such as FKBP5, MAOA, and NR3C1, which are important in stress regulation, are sensitive to childhood trauma; changes in their methylation and transcription levels affect neuronal function, synaptic plasticity, and emotional regulation. These modifications have been associated with increased psychiatric risks such as depression, post-traumatic stress disorder (PTSD), and antisocial behaviors. In addition, the intergenerational transmission of trauma is also considered; epigenetic changes that occur at an early age can be passed down through generations, increasing children's susceptibility to stress. The tissue specificity of epigenetic changes and the interaction between genetic and environmental factors are also important factors. Understanding these mechanisms provides a foundation for understanding the biological memory of childhood trauma and its impact on long-term health outcomes. At the same time, it suggests potential targets for early interventions and therapeutic strategies and provides guidance in understanding the psychological and physiological effects of trauma.

Keywords: epigenetics, trauma, genetic changes

1. Introduction

Trauma can affect individuals within a generation and future generations (transgenerationally) through biological and environmental influences. Recent studies suggest that environmental stressors can induce long-lasting epigenetic modifications that influence stress responsiveness and may contribute to the intergenerational transmission of trauma [1], [2]. The term epigenetics was first proposed by Conrad Hal Waddington in 1940. It refers to changes in gene expression without changes in the underlying DNA sequence. These changes are permanent but reversible. These changes occur through multiple molecular mechanisms (Figure 1), such as DNA methylation, hydroxymethylation, histone modifications, nucleosome positioning, 3D genome organization, and non-coding RNAs (ncRNAs). Collectively, all of these mechanisms biologically link stress-related genes to the ability to regulate gene expression, mediating long-term effects of trauma, and influencing health outcomes [3]. Early-life adversity has been shown to alter epigenetic regulation of stress-response genes, thereby increasing vulnerability to psychiatric disorders later in life [2], [4].

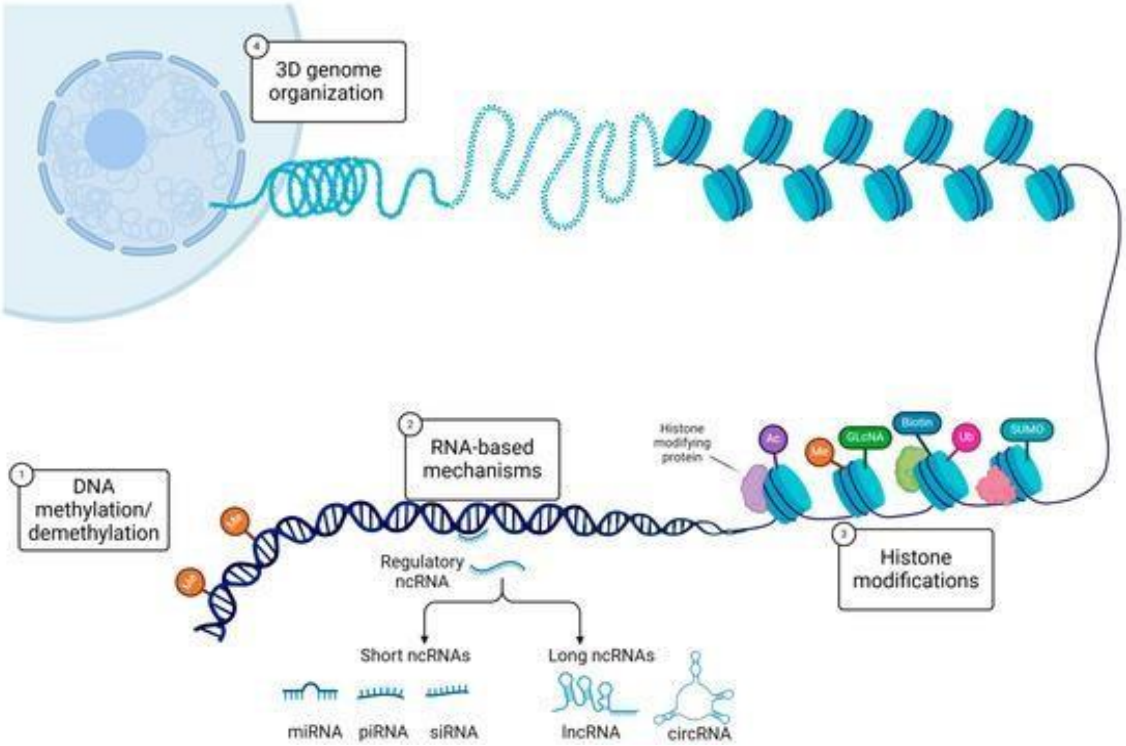

Figure 1. Epigenetic mechanisms in gene regulation: (1) DNA methylation and dimethylation. The addition or removal of methyl groups to the cytosine nucleotide, (2) RNA-based mechanisms, (3) Histone modifications are modifications that occur during translation, (4) 3D genome organization [5].

The mechanisms that regulate gene activity (epigenomes) change throughout life. Epigenetic marks are erased and re-established during early development. In adults, these genes change in response to environmental influences, for example, during inflammation and infection in immune cells, epigenetic changes cause genes to be activated or silenced. Research over the past decade has shown that exposure to environmental toxins and nutritional deficiencies can, in some cases, cause epigenetic changes that can be passed down through generations [5].

2. Epigenetic Mechanisms

2.1. DNA Methylation

DNA methylation is the most common epigenetic mechanism. This mechanism is the covalent attachment of methyl groups to the C-5 position of the cytosine ring of DNA by DNA methyltransferases. In plants, cytosines are located both symmetrically and asymmetrically, and methylation occurs here. In mammals, DNA methylation occurs predominantly at cytosines within CpG dinucleotides, although non-CpG methylation can also occur in specific cell types such as embryonic stem cells and neurons. More than 98% of methylation occurs in somatic cells. This also occurs at CpG dinucleotide in somatic cells. A quarter of all methylation appears in a non-CpG context in embryonic stem cells [6].

It was first discovered by Hotchkiss in 1944. When DNA methylation occurs in the promoter region, it usually acts as a repressor of gene transcription. DNA methylation represents one of the most extensively studied mechanisms through which environmental experiences become biologically embedded and influence long-term gene expression patterns [3]. DNA methylation is a key player in processes such as X chromosome inactivation, regulation of gene expression, and silencing of retroviral elements. During the process, the Tet enzyme (translocation) accelerates the formation of 5hmC (5-methylcytosine). It is then hydroxylated by Tet. It is then deaminated by AID/APOBEC enzymes. The deaminated molecule is removed by Tet enzymes by BER, which removes damaged or altered nucleotides and incorporates molecules (Thy, 5hmU, 5Fc, 5caC) that will be replaced by cytosine. Methylated cytosines are read by MBD (methyl-CpG) proteins and UHRF proteins, and either silence gene expression or enhance methylation during replication [7].

2.2. Non-Coding RNAs (ncRNAs)

Each of the RNA classes has specific cellular functions. Some of these functions involve chromatin remodeling during or after transcription in gene expression. The types of RNA that cause epigenetic modifications are microRNA (miRNA), small interfering RNA (siRNA), promoter-associated RNA (PAR), enhancer RNA, and non-coding RNA. The most common types of non-coding RNA are ncRNA and lncRNA. MiRNA and siRNA are involved in the regulation of approximately 50% of gene expression by degrading mRNA. PAR has been shown to have activating effects. This type of RNA enhances transcription [7].

2.3. Histone Modifications

Histone protein is a molecule that causes DNA to be transformed into nucleosomes and chromatin. Changes in histones affect chromatin structure. Histone modifications include acetylation, deacetylation, histone methylation, and histone phosphorylation. Histone acetylation occurs at lysine amino acids. Lysines in the histone core and tail can be acetylated. Histone acetylation generally relaxes chromatin structure, increasing DNA accessibility and promoting gene transcription. In the deacetylation process, chromatin is condensed by HDAC, and gene expression is repressed. Finally, histone phosphorylation occurs at serine and tyrosine residues located in the histone tail [8].

2.4. Stress and the HPA Axis

Trauma, especially childhood trauma, affects health. So why does it affect? Stress is classified into 3 categories: “good stress”, “tolerable stress”, and “toxic stress”. The central biological pathway that responds to stress is the hypothalamic-pituitary-adrenal (HPA) axis. Walter Cannon proposed the fight-or-flight model of stress response in 1914. Recent studies suggest that changes in the HPA axis are related to the process of coping with stress. Stress and trauma experienced during childhood alter the HPA axis. Stress also causes epigenetic effects on genes. These genes are as follows:

FKBP5 encodes FK506-binding protein 51 (FKBP51), a co-chaperone that regulates glucocorticoid receptor sensitivity and HPA-axis feedback. Gene expression is affected by genetic variants of FKBP5. For example, SNP rs1360780, which is associated with a change in the three-dimensional structure of a genetic locus, affects the physical contact between the transcription start site and hormones located in intron 2. These changes cause different variants of the FKBP5 gene to alter the sensitivity of the glucocorticoid receptor. Thus, HPA axis activity produced differences in the regulation of neuronal function and synaptic plasticity. Studies demonstrate that the rs1360780 risk allele (T) is associated with childhood trauma and increases the risk of many psychiatric disorders [9]. Allele-specific demethylation of FKBP5 following childhood trauma has been shown to alter glucocorticoid receptor regulation, providing a molecular explanation for gene–environment interactions in stress-related disorders [10].

The MAOA gene is located on the X chromosome and encodes MAO A and B, which break down dopamine, serotonin, and noradrenaline, genes related to the effects of childhood trauma. MAOA and MAOB regulate the degradation of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, thereby influencing cognition, emotion, and behavior. Brunner syndrome is caused by a point mutation in exon 8 of the MAOA gene and is characterized by aggressive behavior.

Different health outcomes seen after stressful life events have been associated with a variable number of tandem repeats (VNTRs) in the MAOA gene. VNTR is a short repeat of 20−100 nucleotides and is involved in the regulation of gene expression.

There are CCCCTCCCCCG and CTCCCTCCCCCG VNTRs located near the transcription start site of MAOA, which are associated with antisocial behavior in women after childhood trauma. Additionally, children who have the risky MAOA u-VNTR genotype and are maltreated in childhood are more likely to develop psychiatric disorders such as conduct disorders, antisocial personality, and violent crime in adulthood.

The NR3C1 gene is one of the genes studied in the HPA axis. Childhood trauma and stress alter the methylation of this gene. NR3C1 encodes the glucocorticoid receptor. Childhood trauma in humans increases NR3C1 methylation. One of the landmark studies in this field demonstrated increased methylation of the glucocorticoid receptor gene (NR3C1) in the hippocampus of suicide victims with a history of childhood abuse, suggesting long-term epigenetic programming of stress-response pathways [11].

In salivary DNA samples from a specific type of childhood trauma, parental loss, hypermethylation of CpGs near the NGFI-A binding site in the NR3C1 gene was observed in association with the L-allele (3 or 5 repeats) of the MAOA u-VNTR. Stress during adolescence further increases methylation of the NR3C1 gene. It has become clear that methylation within the NR3C1 gene promoter can be gender-specific. Increased methylation of the NR3C1 promoter has been associated with altered glucocorticoid receptor expression and dysregulated stress responses. Among survivors of the Rwandan genocide, men had a lower risk of PTSD [9]. Collectively, evidence indicates that childhood adversity influences stress-response pathways through epigenetic modifications of genes such as FKBP5 and NR3C1. These alterations contribute to dysregulation of the HPA axis and increase susceptibility to depression, anxiety, PTSD, and other psychiatric disorders [4], [12].

3. Transmission of Trauma from Generation to Generation

According to epidemiological studies, 70% of people have experienced at least one traumatic event in their lifetime, and 30% have experienced four or more. These statistics have caused concern, and researchers have investigated the causes, pathophysiology, and transmission mechanisms of trauma to address this concern.

There are two important mechanisms to explain the intergenerational transmission of trauma:

1. Socio-environmental transmission (parenting styles, discrimination, etc.)
2. Biological conditions (epigenetic inheritance) (Figure 2)

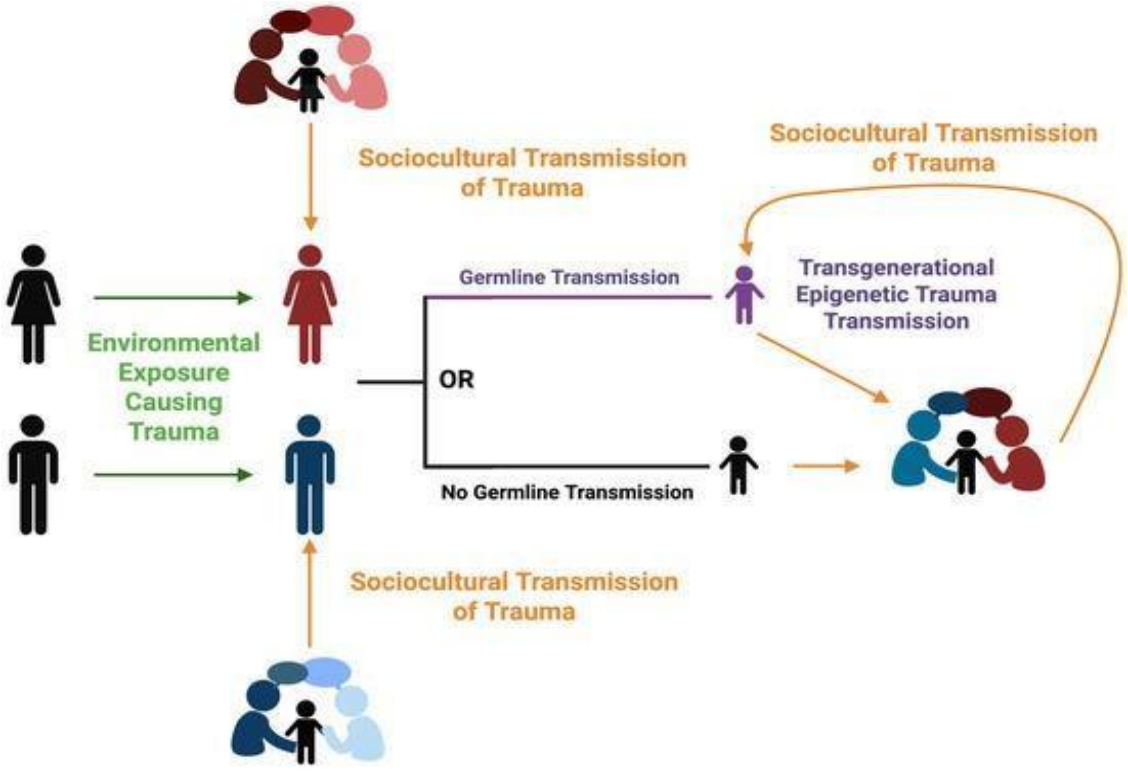

Figure 2. The rise and transmission of intergenerational trauma [13].

Studies have found that adults' maladaptive attachment styles increase the risk of transmitting trauma to their children. One of the important elements of the transmission of social trauma is the environment and external factors. These factors increase vulnerability to trauma and hinder the ability to cope with adversity. Factors such as poverty, discrimination, exposure to violence, and lack of social support increase the risk of trauma and limit the resolution of the issue. If such conditions persist frequently, their effects can be preserved across generations and passed on to other generations. For example, a child growing up in an area with high crime rates is more likely to experience trauma, such as being bullied, being sexually abused, etc. Such conditions create obstacles to trauma resolution. Unresolved traumas are more likely to be passed down from generation to generation [13].

The terms intergenerational and transgenerational have been proposed to more fully describe epigenetic inheritance. Intergenerational epigenetics are epigenetic changes that occur in both parents and offspring after exposure to environmental stressors. For example, if a pregnant woman drinks alcohol, both the fetus and the ovaries are exposed to the alcohol (Figure 3).

Transgenerational epigenetic transmission is the transmission of epigenetic modifications that cannot be caused by environmental exposure. These epigenetic changes must be transmitted directly from the parent's epigenome to the embryo.

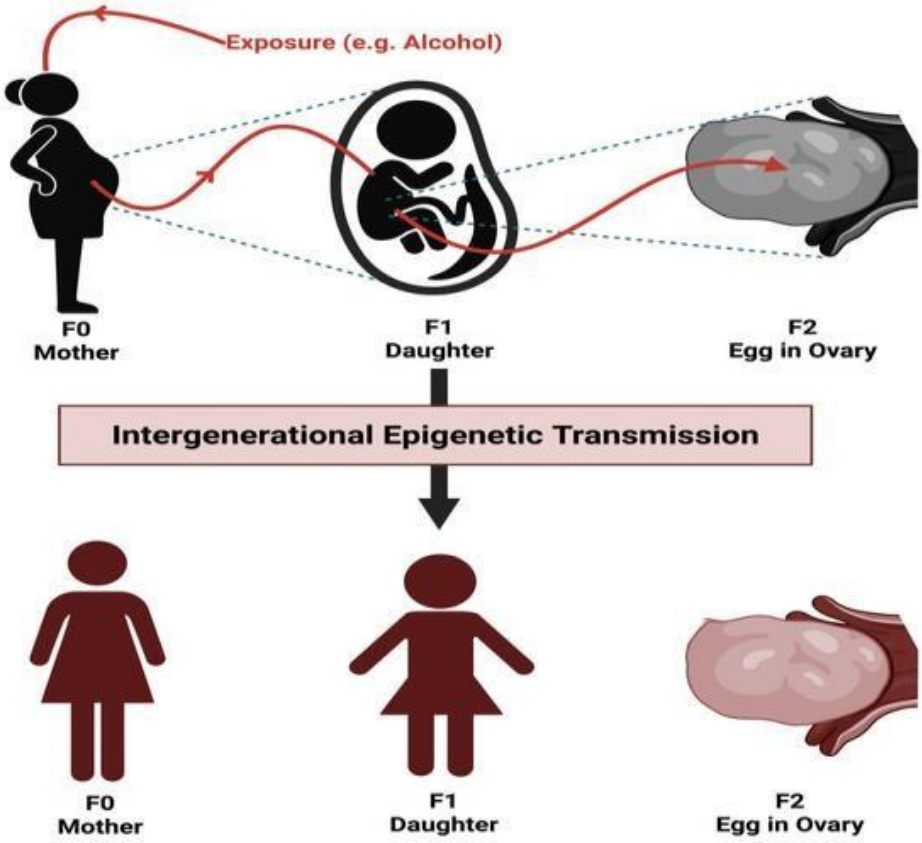

Figure 3. Mechanism of transmission of epigenetic trauma [13].

One of the most widely studied examples of intergenerational trauma involves Holocaust survivors and their descendants. Previous studies have shown that children whose parents survived the Holocaust are more likely to experience mental health difficulties than individuals without a family history of Holocaust exposure. The psychological effects of this trauma may persist across multiple generations. In addition to psychosocial influences, biological mechanisms have also been investigated. Yehuda et al. demonstrated altered methylation patterns of the FKBP5 gene in Holocaust survivors and their offspring, suggesting that severe trauma may affect epigenetic regulation of stress-response pathways across generations. These findings provide evidence that trauma transmission may involve both environmental and biological mechanisms [13], [14]. Although evidence supports epigenetic contributions to trauma transmission, environmental influences such as parenting behaviors, family dynamics, and social conditions also play significant roles in shaping outcomes across generations [15].

4. Conclusion

This review provides information on the effects of trauma on genes and the transmission of these effects to generations. Childhood traumas and stresses affect living organisms epigenetically and cause changes in gene expression. DNA methylation, dimethylation, histone modifications, and non-coding RNAs, particularly in genes such as FKBP5, MAOA, and NR3C1 that regulate the HPA axis, are involved in shaping stress responses and behavioral mechanisms. These changes have been linked to psychiatric disorders, stress sensitivity, and other health problems. The effects of trauma on genes are being investigated, and the processes involved in the mechanism of transmission from generation to generation are being identified. The mechanism

of epigenetic transmission is influenced by the interaction of living things with the environment, nutrition, age, and gender. Understanding epigenetic mechanisms offers important opportunities for the prevention of trauma-related diseases and the development of effective interventions. Future research should focus on studying in more depth the transmission of these mechanisms from generation to generation and their specificity in different tissues and cells. Epigenetic mechanisms are increasingly recognized as central contributors to the pathophysiology of stress-related psychiatric disorders, including depression, anxiety disorders, and PTSD [16]. Future longitudinal and multi-omics studies integrating epigenomics, transcriptomics, and environmental exposure data will be critical for elucidating the mechanisms underlying trauma-associated biological inheritance and for developing precision-based therapeutic interventions.

Author Contributions

Sama Akbarli conceptualized the study, conducted the literature review, and wrote the original manuscript. Chilanay M. Alakbarova reviewed and edited the manuscript. Both authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Hypothalamic-Pituitary-Adrenal (HPA), Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), Single Nucleotide Polymorphism (SNP), Variable Number of Tandem Repeats (VNTRs).

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Review Article

Psychosomatic Behaviors of People with Cardiovascular Diseases

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Abstract

The study of patient behavior models in cardiovascular diseases (CVD) and their proper management plays a crucial role in improving clinical outcomes. Patients' psychosocial status, levels of depression and anxiety, personality traits, lifestyle, and social support systems directly influence adherence to medical recommendations and disease progression. Research shows that integrating behavioral interventions with medical treatment reduces CVD burden, enhances patient quality of life, and minimizes the risk of disease complications. Psychosocial and cognitive-behavioral interventions decrease depression and anxiety levels, improve treatment adherence, and increase stress resilience. Lifestyle modifications, family and social support, educational programs, and technology-based interventions contribute to optimizing patient behavior models. This approach requires a multidisciplinary effort, ensuring individualized treatment planning and addressing patients' psychosocial and medical needs. The scientific novelty of the study lies in the comprehensive assessment of multidimensional factors affecting patient behavior and demonstrating the impact of behavioral interventions integrated with medical treatment on clinical outcomes. The findings are significant for optimizing patient behavior management strategies and enhancing the effectiveness of rehabilitation programs in clinical practice.

Keywords: cardiovascular diseases, patient behavior models, behavioral interventions, psychosocial factors, cognitive-behavioral therapy

1. Introduction

Cardiovascular diseases (CVDs) rank first among the causes of death worldwide. Today, they are considered one of the most important global public health problems and the leading cause of mortality across the world. The onset and progression of CVDs cannot be explained solely by biological factors; patients' behavioral patterns, psychological status, lifestyle habits, and social environment directly influence the course of these diseases. Epidemiological and clinical studies conducted in the 21st century show that patient behavior is one of the main components determining the effectiveness of medical interventions, and that disease management becomes more difficult unless this behavioral pattern is modified.

Behavioral models encompass the individual's health-related decision-making processes, level of motivation, attitude toward risk factors, adherence to treatment regimens, and self-management skills. The role of behavioral factors in the prevention of CVDs is particularly important, since most risk factors, such as smoking, unhealthy eating habits, physical inactivity, psychosocial stress, and harmful habits, are directly related to human behavior. According to the World Health Organization, at least 50% of CVD-related deaths could be prevented if appropriate behavioral changes were implemented [1].

The study of patient behavior in the context of CVDs requires a multidisciplinary approach. Research in cardiology, medical psychology, sociology, behavioral sciences, public health, and health management demonstrates that such factors as the patient's psychological preparedness for treatment, emotional state, level of social support, and health literacy significantly affect treatment adherence, adaptation to lifestyle changes, and long-term clinical outcomes.

At the same time, the strengthening of patient-centered approaches in modern healthcare systems has further increased the importance of behavioral models. The active participation of patients in decision-making about their own health, the enhancement of physician-patient collaboration, and the use of digital monitoring technologies have created new opportunities for managing behavioral change.

Thus, the scientific analysis of patients' behavioral models in the context of CVDs is fundamentally important not only for improving health at the individual level but also for reducing disease burden at the population level, optimizing healthcare costs, and enhancing the effectiveness of preventive strategies.

2. Anatomy and Physiology of the Cardiovascular System

The role of behavioral factors in the etiology of cardiovascular diseases (CVDs) is multidimensional and complex. Modern research shows that modifiable behavioral habits account for a large proportion of CVD risk, and that the formation of healthy behavioral models is one of the main targets for reducing disease burden at the population level. Large-scale epidemiological studies on atherosclerosis, hypertension, heart failure, and ischemic heart disease reveal that factors such as smoking, eating patterns, level of physical activity, and stress management have a fundamental impact on clinical outcomes.

The concept of a healthy lifestyle includes components such as nutritional behavior, physical activity, sleep patterns, and abstinence from harmful habits. Unhealthy nutrition, particularly the excessive consumption of saturated fats, trans fats, and high-sodium foods, leads to disturbances in the lipid profile, functional destabilization of the vascular endothelium, and activation of inflammatory processes. In contrast, scientifically validated dietary models such as the Mediterranean diet and the DASH diet, which are rich in antioxidants, whole grains, and plant-based fats, support cardiovascular function [2].

Physical inactivity is one of the primary behavioral risk factors that increases the likelihood of CVD. According to the World Health Organization (WHO), at least 150 minutes of moderate-intensity physical activity per week slows the process of atherosclerosis, helps regulate body weight, and increases insulin sensitivity. Moreover, physical activity enhances myocardial resilience and regulates the levels of stress hormones [3].

Smoking is considered one of the behavioral factors that most significantly increases CVD risk. Nicotine and other toxins increase oxidative stress in the vascular endothelium, promote the destabilization of atherosclerotic plaques, and raise the risk of thrombosis. Studies have shown that the risk of myocardial infarction decreases by more than 50% within 12 months after smoking cessation [4].

It is now widely accepted in the scientific community that chronic stress plays an important role in the development of cardiovascular diseases. Long-term elevated levels of stress hormones cortisol and adrenaline enhance the effect of catecholamines, leading to disruption of vascular tone, increased blood pressure, and the development of metabolic syndrome. At the same time, stress indirectly affects behavioral models: higher stress levels increase the likelihood of smoking, reduce physical activity, trigger emotional eating, and disturb sleep patterns.

Psychosocial factors such as depression, anxiety, social isolation, and low social support are among the key determinants that increase CVD risk [1]. Mechanisms such as decreased serotonin levels, imbalance in the autonomic nervous system, and impaired immune responses during depressive states accelerate the development of cardiovascular diseases. Additionally, patients with depression tend to adhere less to treatment, have lower levels of physical activity, and experience more difficulty adapting to healthy eating behaviors.

Behavioral factors interact with each other and often create a cascade effect. For example, physical inactivity leads to weight gain, increased body weight raises insulin resistance, which in turn increases the risk of hypertension and atherosclerosis. At the same time, stress increases the tendency to consume high-calorie foods, facilitating the development of metabolic disorders.

A systematic analysis of the interaction between behavioral factors in the development of CVDs shows that risk management is possible not only through targeting individual habits, but through comprehensive behavioral interventions.

3. Behavioral Factors and Patient Adherence in Cardiovascular Diseases

Patient adherence to treatment is considered one of the most important determinants in the management of cardiovascular diseases. The chronic nature of CVDs requires long-term pharmacotherapy, lifestyle changes, and self-management skills. For this reason, even small decreases in adherence levels can have serious consequences for clinical outcomes. Globally, approximately 40–60% of patients with CVD do not fully comply with their prescribed treatment regimens, which leads to increased mortality, hospitalizations, and acute cardiac events [5].

The reasons for non-adherence are multifactorial and related to the patient, the treatment process, and the social environment. The most common causes include:

- **Complexity of pharmacotherapy:** Adherence decreases when multiple medications must be taken daily.
- **Concerns about side effects:** Patients may stop treatment by prioritizing perceived risks over benefits.
- **Lack of perception of disease severity:** Mild or absent symptoms may cause patients to consider treatment unnecessary.
- **Lack of motivation and psychological resistance:** Especially in the presence of depression and anxiety.
- **Low social support:** Family and social environment positively influence adherence.
- **Financial difficulties:** High medication costs limit regular use for many patients.

The clinical consequences of non-adherence have been clearly identified in large-scale studies. Poor adherence is associated with exacerbation of heart failure, recurrent myocardial infarction, loss of blood pressure control, and increased overall mortality. For example, according to AHA 2022 data, only 50% of patients with hypertension adhere consistently to their medication regimen, and the risk of stroke is doubled in this group [6].

Health literacy also plays an important role in shaping adherence behavior. The patient's level of knowledge about the disease, understanding of the purpose and mechanism of action of medications, and ability to interpret medical information largely determine their attitude toward treatment. Studies show that patients with CVD who have higher health literacy are more successful at maintaining blood pressure, lipid profile, and blood glucose levels within target ranges.

Self-management skills are also among the core components of adherence behavior. Measuring blood pressure at home, monitoring diet, tracking physical activity, and using reminder systems for medication intake contribute to improved clinical outcomes. The application of digital health technologies, mobile apps, smartwatches, and telemonitoring systems has opened new possibilities in this field.

Physician-patient communication is one of the principal psychosocial factors in determining adherence levels. Studies show that being listened to carefully by the physician, having questions answered, and implementing a shared decision-making model significantly improve adherence [7]. A clear explanation of treatment goals, potential side effects, and available alternatives in simple language ensures more active patient engagement in the treatment process.

Psychological factors play a crucial role in shaping patient behavior and determining patients' approach to treatment, adherence to medical recommendations, and level of engagement in rehabilitation. Among these factors, depression, anxiety, and personality traits are particularly noteworthy. In the context of cardiovascular diseases, these factors may alter behavioral patterns and directly influence disease outcomes.

Depression and anxiety are common psychological disorders among cardiac patients. Studies indicate that 20–40% of patients with chronic heart diseases experience clinical levels of depression [1]. Depression reduces motivation, limits daily activity, minimizes physical exercise, and weakens medication-taking discipline, thereby significantly reducing treatment effectiveness. For example, patients with depressive tendencies are more likely to forget to take their medication or miss scheduled check-ups, which contributes to disease progression.

Anxiety is characterized by feelings of fear and worry regarding the patient's future health status. High levels of anxiety reduce pain tolerance, increase the risk of cardiovascular events, and impair psychosocial functioning [8]. Depression and anxiety often interact, reinforcing each other and negatively affecting behavior and engagement in treatment. Therefore, psychological support and cognitive-behavioral therapy play an important role in positively modifying patients' behavioral models.

Personality traits are another key psychological factor that determines patients' behavioral patterns and attitudes toward illness. In the context of coronary heart disease, Type A and Type B personality patterns have been widely studied [9].

Individuals with Type A personality traits tend to be highly ambitious, impatient, aggressive, and sensitive to time pressure. These patients often have higher levels of stress hormones, which increases the risk of cardiovascular events. Type A individuals may struggle with adherence to treatment recommendations, as they tend to minimize symptoms and prioritize work and activity over rest and treatment.

Type B personality, by contrast, is characterized by calmness, balance, and greater resilience to stress. Such patients perceive symptoms more adequately, are more compliant with medical advice, and exhibit more positive behavior in the treatment process. Taking personality traits into account allows clinicians to develop individualized approaches and tailor psychological support strategies.

Research also shows that personality traits influence the ability to utilize social support. For example, Type B patients benefit more from social networks and family support, maintaining emotional balance and actively participating in treatment. In this context, a psychological assessment that identifies personality type is important for predicting behavioral patterns and individualizing treatment strategies.

Depression, anxiety, and personality traits directly shape patient behavior. Medical staff who apply individualized approaches that consider these psychological factors can increase treatment effectiveness, accelerate rehabilitation, and reduce the risks associated with chronic disease.

Not only psychological factors, but also social and cultural determinants play an important role in the formation of patient behavior. Social factors shape patients' health-related decisions, treatment adherence, attitudes toward medical procedures, and overall engagement in rehabilitation. In this context, social determinants include family support, peer environment, economic status, level of education, and societal attitudes toward the healthcare system.

Support from family and the close environment directly influences patient behavior. Studies show that family members' awareness of treatment and their psychosocial support increase adherence and stabilize the patient's emotional state. For example, in patients with chronic heart disease and diabetes, family support strengthens health behaviors by providing supervision of medication intake and psychological motivation.

The role of the family is also evident in reducing stress and anxiety. Social support systems provide emotional comfort, reduce levels of depression and fear, and thereby increase the likelihood of adherence to medical recommendations [10]. Thus, psychosocial support received from the immediate environment is one of the main determinants of patients' behavioral models.

Patients' socioeconomic status determines their health behaviors and access to medical resources. High income and stable economic conditions facilitate access to quality healthcare, increase participation in preventive check-ups, and support regular medication use. Conversely, low socioeconomic status reduces the ability to adhere to treatment, limiting access to medications and physician consultations.

Educational level is another important determinant of patient behavior. Education increases patients' knowledge about the disease, improves their ability to correctly understand medical procedures, and enables more effective use of health services [11]. For instance, highly educated patients are more likely to take medications correctly, follow treatment plans carefully, and implement lifestyle changes more quickly.

Patient behavior is also influenced by cultural and social belief systems. Attitudes toward illness, preferred treatment methods, and perceptions of alternative medicine vary across cultures. In some societies, beliefs that illnesses have natural or divine causes may lead to caution or mistrust toward medical procedures. This is particularly observed in developing countries and rural areas.

Social belief systems also shape how patients respond to stress and disease symptoms. Individuals who receive support from social networks comply better with medical procedures and implement lifestyle changes more effectively. Conversely, social pressure and stereotypes may negatively affect attitudes toward treatment.

Patient behavior can be understood not only through individual social factors but also through their interactions. For example, high socioeconomic status combined with strong family support maximizes

adherence and reduces levels of depression and anxiety. In contrast, low educational level and limited social support negatively affect attitudes toward medical procedures and behavioral patterns.

Various methods are used in medical psychology to assess the impact of social determinants on patient behavior. Social support scales, economic status questionnaires, quality-of-life assessments, and cultural belief inventories help determine patients' social environment and its influence on behavior [10]. These data are crucial for developing individualized approaches, planning psychosocial interventions, and optimizing treatment strategies.

Chronic diseases, particularly cardiovascular diseases, diabetes, and chronic pain, clearly demonstrate the interaction between patient behavioral models and social determinants. In such patients, family support, social networks, and educational level directly influence the course of the disease. For example, in diabetes, family support and medical awareness increase medication adherence and prevent complications. Patients with heart disease cope better with stress and maintain quality of life thanks to social support.

Therefore, planning individual- and group-based interventions that take social factors and behavioral determinants into account is important in medical practice. Social support programs, disease education, psychosocial therapy, and family-based work are priority directions in this context [12].

Social factors are among the main determinants in the formation of patient behavior. Family and close social support, economic and educational status, and cultural and social belief systems directly influence patients' attitudes toward medical procedures, adherence to treatment, and psychosocial state. Medical approaches that consider the interaction of these factors enable optimization of health outcomes.

Regulation of behavioral models in patients with cardiovascular diseases is an important area of clinical practice. Patients' lifestyle, psychological state, and social environment directly influence the course of their disease. Therefore, integrating psychosocial and behavioral interventions into treatment strategies accelerates rehabilitation and improves disease outcomes.

Psychosocial interventions are aimed at reducing depression, anxiety, and stress levels in CVD patients. Cognitive-behavioral therapy (CBT) is one of the most widely used forms of such interventions. CBT teaches patients to analyze their thoughts and behaviors, modify maladaptive beliefs, and develop healthy behavioral models [13].

Studies show that CVD patients undergoing CBT experience reduced levels of depression and anxiety, improved medication adherence, and increased physical activity. Psychosocial interventions also enhance self-confidence and strengthen patients' sense of responsibility for their health. By increasing resilience to stress, cognitive-behavioral interventions help reduce the risk of cardiac events.

Lifestyle modification is one of the core behavioral interventions for CVD patients. This includes healthy nutrition, regular physical activity, avoidance of smoking and alcohol, and adherence to medical recommendations. Lifestyle interventions reduce cardiometabolic risk factors and slow disease progression.

For example, regular aerobic exercise improves cardiac function in CVD patients, normalizes blood pressure, and enhances psychosocial well-being. Healthy eating and caloric restriction improve lipid profiles, normalize body weight, and reduce inflammatory processes. Lifestyle interventions can be implemented individually or in groups. Group programs provide social support and increase the sustainability of behavioral change.

Patient education is one of the most effective interventions for changing behavior. Educational programs provide comprehensive information about the disease, treatment methods, preventive measures, and lifestyle changes [11]. Studies show that well-informed patients are more compliant with medication, treatment plans, and preventive examinations. Educational interventions also improve self-management abilities and reduce stress and anxiety. These programs can be delivered through individual counseling, group sessions, brochures, and electronic media.

Support from family and social environment strengthens adherence to behavioral changes in CVD patients. Studies show that family support and social networks facilitate medication adherence, implementation of lifestyle changes, and compliance with medical advice. Family-based interventions stabilize patients' psychosocial state and reduce levels of depression and anxiety. Social support also improves quality of life

and minimizes risk behaviors associated with the disease [10]. These interventions may include group therapy, family seminars, and support through social networks.

In modern practice, technology-based interventions such as mobile applications, online platforms, and telemedicine support behavioral changes in CVD patients. Mobile apps provide information and monitoring related to medication intake, physical activity, and diet, and send reminders. Telemedicine and online consultation services provide continuous medical support, increase adherence, and reduce psychosocial stress. These approaches are particularly beneficial for patients living in remote areas and ensure continuity of medical supervision.

Behavioral interventions for CVD patients play a significant role in improving psychosocial and medical outcomes. Lifestyle changes, cognitive-behavioral therapy, family and social support, and technology-based interventions increase treatment adherence, reduce depression and anxiety levels, improve quality of life, and optimize disease outcomes.

To increase the effectiveness of these interventions, individualized approaches, assessment of the patient's psychological state and social circumstances, and continuous monitoring of the treatment plan are essential. Behavioral interventions not only improve adherence to medical recommendations but also enhance patients' ability to cope with disease and their overall quality of life.

4. Conclusion

The results of the study show that understanding and appropriately managing behavioral models in patients with cardiovascular diseases (CVDs) play a decisive role in improving clinical outcomes. Patients' psychosocial status, levels of depression and anxiety, personality traits, lifestyle, and social support systems directly determine their adherence to medical recommendations and disease outcomes. In this regard, systematic investigation of the impact of psychological and social factors on patient behavior and the integration of behavioral interventions with medical treatment are of high scientific and practical significance.

The scientific novelty of this work is manifested primarily in three directions. First, it provides a comprehensive assessment of the psychological, social, and personality determinants of behavioral models in CVD patients and analyzes their interaction with clinical outcomes. Previous research has typically examined psychosocial or medical factors separately, whereas this study employs a multidimensional approach. Second, the work demonstrates, on scientific grounds, the effect of integrating behavioral interventions in parallel with medical treatment on disease progression and clinical outcomes. Third, it evaluates the effectiveness of technology-based tools (mobile applications, telemedicine) in managing patients' behavioral models, which can be regarded as an element of scientific innovation.

The practical significance of the study lies in the formulation of concrete recommendations that can be used directly in clinical practice. The findings show that examining individual behavioral models of CVD patients and planning interventions that consider their psychosocial, social, and personality-related factors increases treatment adherence, reduces the risk of complications, and improves quality of life. This requires a multidisciplinary approach by medical personnel and the application of individualized strategies.

Furthermore, the results can be applied in disease prevention and rehabilitation of patients with chronic CVDs. For example, individualized psychosocial and behavioral programs designed for patients can optimize medication adherence, physical activity, and dietary behavior, while reducing levels of depression and anxiety. At the same time, the planned use of family and social support mechanisms enhances psychosocial well-being and reduces disease burden. This approach is also socioeconomically beneficial for patients with chronic CVDs, as it shortens hospital stays and ensures more efficient use of medical resources.

In conclusion, this study emphasizes the scientific and practical importance of investigating and managing behavioral models in patients with CVDs. Its scientific novelty lies in the comprehensive assessment of multidimensional factors influencing patient behavior and in demonstrating the impact of integrating behavioral interventions with medical treatment. Its practical significance is reflected in planning individual- and group-based interventions in clinical practice, rehabilitating patients, and optimizing disease outcomes. This approach serves both as a guiding principle for medical personnel and as an effective strategy for improving the health and quality of life of patients with CVDs.

Author Contributions

The author solely contributed to the conception and design of the study, literature review, data analysis and interpretation, manuscript drafting, revision, and final approval of the manuscript.

Conflict of Interest

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Abbreviations

Cardiovascular diseases (CVDs), Dietary Approaches to Stop Hypertension (DASH), World Health Organization (WHO), American Heart Association (AHA), Cognitive-Behavioral Therapy (CBT).

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Review Article

New Treatment for Alzheimer's Disease: Tau-Targeting Drugs and Therapies

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Abstract

Alzheimer's disease is a neurodegenerative disorder, the most common form of dementia in older people, and is characterized by synaptic loss and brain atrophy. The first part to be damaged during the disease is the hippocampus, which is the memory center, and then the cerebral cortex, which controls logical and social behavior. Alzheimer's disease is pathologically characterized by the formation of tau neurofibrillary tangles and amyloid-β plaques in the brain. The formation of intracellular neurofibrillary tangles, the main cause of tauopathies, begins with the accumulation of hyperphosphorylated tau protein isoforms. These isoforms cause neuronal death and contribute to the development of complex neurodegenerative diseases such as Alzheimer's, Parkinson's, and other neurodegenerative diseases. Many of the treatments developed for Alzheimer's disease have focused on amyloid-β plaques, but since these treatments have failed to halt the progression of the disease, attention has been focused on tau pathologies. However, clinical trials of many drugs have been discontinued due to toxicity and failure to demonstrate the desired effect. Most of the tau-targeted agents currently being tested are immunotherapies. New research presents various potential approaches for preventing cellular toxicity resulting from tau aggregation. These include many methods, such as preventing toxic tau aggregation and post-translational modifications of tau protein, and developing tau-targeted immunogens. Since the accumulation of tau tangles is a major cause of Alzheimer's, it is significant to investigate therapies that restore normal tau mechanisms and prevent tau accumulation. In recent years, nanoparticle-based drug delivery technologies have offered promising opportunities for treating this disease.

Keywords: Alzheimer's disease, dementia, neurodegenerative disorder, tau protein, amyloid-β plaques, tau-targeted immunotherapy

1. Introduction

Approximately 57 million people worldwide suffer from dementia, and this number is expected to reach 139 million by 2050. 60–70% of these cases are caused by Alzheimer's disease (AD). In addition, Alzheimer's and related diseases cost the healthcare system hundreds of billions of dollars each year. Over the years, many treatments have been developed for Alzheimer's disease, with initial research focusing on amyloid-β, the main component of plaques that accumulate in the brain. However, immunotherapies have often been ineffective or have had harmful effects on the body. Therefore, the presence of tau pathology in several neurodegenerative diseases, including Pick's disease and primary age-related tauopathy (PART), has made tau an attractive therapeutic target. Tauopathies are a group of neurodegenerative diseases characterized by abnormally phosphorylated tau protein. Although significant progress has been made in the study of tau pathologies in tauopathies, how the tau protein causes neuronal death has not yet been fully elucidated. Also, the clinical efficacy of tau-targeted therapies has not yet been fully proven, and many trials are currently ongoing. One of these trials, antisense oligonucleotides, has shown promising results. The positive results of these experiments could help develop tau-targeted drugs for the treatment of Alzheimer's disease in the future and pave the way for treatments for other types of dementia [1], [2].

2. The General Overview of Tau Pathologies in Alzheimer's Disease

Alzheimer's is the most common age-related neurodegenerative disease, and extracellular plaques composed of amyloid-β and intracellular tangles composed of hyperphosphorylated tau protein are two major pathological hallmarks of this decline. Tau is a protein associated with microtubules and has many functions, including maintaining the stability of microtubules in neurites, normal microtubule structure in neurons, and establishing connections between axons. In Alzheimer's disease and many other neurodegenerative diseases called "tauopathies," tau proteins are a major component of intraneuronal and glial fibrillary changes. Tau protein has been evaluated as a promising target for the development of therapeutic pathways because it has a broad pathological role in many neurodegenerative diseases. Thus, when tau undergoes various modifications, it can lead to microtubule destabilization, neuronal dysfunction, and cell death. Although a different set of modifications is observed in each neurodegenerative disease, Alzheimer's disease is the most common of these. There are various forms of tauopathies, one of which is a disruption of the 3R:4R ratio of tau protein, which normally has a precise balance between the four-repeat (4R) and three-repeat (3R) isoforms. Several other isoforms of tau can also have a significant impact on the aggregation of Alzheimer's disease. Recently, García-Escudero and colleagues discovered a truncated tau isoform unique to humans, resulting from the retention of intron 12. This process leads to the formation of a truncated tau protein supplemented with 18 additional amino acids and a sharp decrease in the aggregation ability of that isoform. This tau isoform has a similar biochemical composition and ability to bind to microtubules as the others, but the resulting variation stabilizes the tau protein and is therefore thought to play a beneficial role [3], [4].

Tau proteins also play a role in establishing various connections between other cytoskeletal elements and proteins. Thus, although the significance of tau pathology in Alzheimer's disease was not previously fully understood, the numerous mutations identified in the tau gene that lead to pathological aggregation of tau protein, the formation of FTDP-17, and the gradual damage of neocortical areas have proven that disruption of tau function alone can initiate neurodegenerative processes. Therefore, a deeper study of the characteristics of the spread of tau-related neuroinflammation in tauopathies is crucial to clarify the role of immunotherapies as potential therapeutic targets in the treatment of Alzheimer's disease and other tauopathies. Despite previous suspicions, the fact that mutations in the tau gene lead to abnormal aggregation of tau and the development of FTDP-17 has shown that tau dysfunction is sufficient to cause neurodegenerative diseases. In Alzheimer's disease, the major pathological effects of the tau protein create major changes in the progression of the disease. Tau's role in enhancing axonal transport is undeniable, demonstrating its importance for message transmission within the brain [3], [5], [6].

3. Molecular Mechanism of Tau Pathologies

Tau is a protein associated with microtubules located in the q12 and q21 regions of human chromosome 17. This protein has six major isoforms in the human brain. The isoforms can arise in different ways, one of which is the alternative splicing of exons 2 and 3, which creates isoforms with no (0N), one (1N), or two (2N) extra segments. Also, alternative splicing of exon 10 produces isoforms with three (3R) or four (4R) repeats. In a healthy brain, a 1:1 ratio of 3R and 4R isoforms is observed. This 3R:4R ratio change is associated with abnormal splicing of exon 10. Tau is divided into four functional domains: an amino-terminal projection domain, a proline-rich region, a microtubule-binding domain, and a carboxyl-terminal domain. The microtubule binding region contains repeats that bind to heterodimers of α- and β-tubules, which form polymerized microtubules and thus facilitate axonal transport. Studies in wild-type mice have shown that 63 different posttranslational modifications of the tau gene have been identified, including truncation, glycation, and oxidation. The most common posttranslational modification of tau is phosphorylation, as the longest isoform of Tau in the human brain has 80 serine and threonine residues and 5 tyrosine residues, which have a high phosphorylation capacity. Thus, tauopathies are a group of clinically, morphologically, and biochemically heterogeneous diseases characterized by the accumulation of fibrillated tau protein. Alzheimer's disease is considered a secondary tauopathy because it causes NFTs of the tau gene, which are found in amyloid plaques, mainly in fibril forms composed of amyloid-β (Aβ) peptide. From a mechanistic perspective and with regard to potential treatment, tauopathies have been shown to be highly heterogeneous and to be associated with other pathological conditions, which may have additive or synergistic effects. From a pathogenetic perspective, tauopathies are clinically apparent in up to 80% of elderly individuals. There is also an interaction between Aβ and tau genes in Alzheimer's. Although Aβ is known to cause tau pathology, the toxicity of Aβ has been shown

to be dependent on the tau gene. In the coming years, it is expected that more information will be obtained about tauopathies and the interaction between Aβ and tau [7], [8], [9], [10].

4. Tau-Targeted Drugs and Modern Therapeutic Strategies

Although rapid technological advances have opened up new possibilities for treating neurodegenerative diseases, the number of drugs that have shown success in clinical trials for tau-related neurodegenerative disorders is still in the minority. There are also some methods known to science, including studies in cellular and animal models showing that siRNAs targeting tau significantly reduce tau pathologies in P301S tau transgenic mice. A group of drugs that inhibit tau aggregation has also been identified, the most common of which is methylene blue. A special intranasal hydrogel is used to deliver this drug to the brain. Another therapeutic strategy is to prevent tau degradation, which can be achieved through the ubiquitin-protease system, the endosome-lysosome system, and the autophagy-lysosome system. Proteolysis-targeting chimeras targeting tau have been developed that can reduce total tau and phosphorylated tau levels in mouse models of tauopathy by inducing proteasome-mediated degradation. To promote lysosomal targeting of tau, lysosome-targeted chimeras and antibody-based PROTACs have also been generated. Recent studies have generated a specific pathogenic tau-specific autophagy that enhances autophagic flux and clears pathological tau, which reduces cognitive impairment in mice with Alzheimer's disease. In addition, several drugs have been developed that target tau hyperphosphorylation, including lithium and phosphate modifiers. Long-term lithium administration reduces amyloid plaque formation and tau hyperphosphorylation in transgenic mice that overproduce Aβ and tau. Significant advances have been made in immunotherapies for the treatment of tauopathies in recent years. However, studies in mice have shown that immunizations cause various side effects, including axonal damage and encephalomyelitis.

Also, nanoparticles have a number of superior properties compared to other drugs and therapies, including increased drug efficacy, better adaptation to the biological environment, and more precise targeting of brain areas affected by Alzheimer's disease. Thus, nanoparticles successfully cross the blood-brain barrier, achieving higher drug concentrations in areas affected by Alzheimer's disease. The use of nanotechnology in targeted therapy for Alzheimer's disease has great potential and could revolutionize the search for treatment options [6], [11], [12], [13], [14].

5. Conclusion

This review provides information on the role of tau protein in Alzheimer's disease and its use as a therapeutic target. Although amyloid-β-based therapies have long been used in the treatment of Alzheimer's disease, the low clinical efficacy of these treatments has made tau pathologies a more promising target. The significant role of abnormally phosphorylated and aggregated tau protein in neuronal death has demonstrated that tauopathies play a central role in neurodegenerative processes. In recent years, the molecular mechanisms of the disease have been further investigated as a result of the information obtained about tau isoforms, posttranslational modifications, and Aβ–tau interactions. Also, new therapeutic approaches such as antisense oligonucleotides, siRNAs, PROTACs, and drugs that inhibit tau aggregation have shown promising results in the treatment of the disease. However, many of these approaches are still in the clinical trial stage, and their effectiveness has not been fully proven. Consequently, tau-targeted therapeutic approaches have enormous potential for the treatment of Alzheimer's disease and other types of dementia. Continuing clinical research in this area may lead to the development of more effective and disease-modifying treatments in the future.

Author Contributions

The author is responsible for all aspects of this review article, including conceptualization, literature search, critical analysis, manuscript writing, revision, and final approval of the submitted version.

Conflict of Interest

The author declares no competing interests.

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Abbreviations

Alzheimer's disease (AD), Primary Age-Related Tauopathy (PART), Neurofibrillary Tangle (NFT), Amyloid Beta (Aβ), Ribonucleic Acid (RNA).

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Review Article

The BRCA1 and BRCA2 Mutation Spectrum in Women with Ovarian Cancer: Clinical, Pathogenetic, and Prognostic Features

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Abstract

This article comprehensively analyzes the clinical, pathogenetic, and prognostic features of the mutation spectrum observed in BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer. The main aim of the study is to determine the role of BRCA1/2 gene mutations in the mechanisms of ovarian cancer, their impact on the clinical course of the disease, and their significance in predicting treatment outcomes. Studies show that pathogenic mutations in the BRCA1 and BRCA2 genes lead to disruption of DNA repair by homologous recombination, which results in loss of genome stability and an increased risk of malignant transformation. Clinically, ovarian cancer in BRCA-mutation carriers may be diagnosed at an earlier age, be associated with high-grade serous histological type, and be accompanied by familial cancer syndromes. From a prognostic perspective, patients with BRCA1/2 mutations are highly sensitive to platinum-based chemotherapy and PARP inhibitors, which allows for improved survival rates. In addition, the type and localization of the mutation may have different prognostic significance in terms of the risk of disease recurrence and long-term clinical outcomes. Consequently, molecular-genetic analysis of the BRCA1 and BRCA2 genes in ovarian cancer has important scientific and practical significance in terms of selecting personalized treatment strategies, early screening of individuals at risk, and optimizing the prognosis of the disease.

Keywords: ovarian cancer, BRCA1, BRCA2, gene mutations, pathogenesis, clinical features, prognosis, personalized treatment

1. Introduction

Ovarian cancer is considered one of the most aggressive and highly lethal malignant diseases of the female reproductive system. This disease ranks first in terms of mortality among gynecological oncological pathologies and is often characterized by being diagnosed at late stages. The non-specificity of clinical symptoms, the lack of clear clinical signs in the early stages, and the limitations of effective screening methods make the timely detection of ovarian cancer difficult. It is for this reason that studying the molecular-genetic basis of the disease has become one of the priority research directions in modern oncology [1].

Scientific research conducted in recent decades has shown that hereditary genetic factors play an important role in the pathogenesis of ovarian cancer. Pathogenic mutations, particularly in the BRCA1 and BRCA2 genes, are associated with a significantly increased risk of ovarian and breast cancer. These genes perform key functions in maintaining genome stability, repairing DNA damage, and regulating the cell cycle. As a result of the loss of functional activity of the BRCA1 and BRCA2 genes, DNA repair mechanisms are disrupted, genetic instability occurs, and the likelihood of malignant transformation of cells increases.

The occurrence and spectrum of BRCA1 and BRCA2 gene mutations in the case of women suffering from ovarian cancer differ according to various factors such as population, ethnicity, and hereditary cancers. Numerous investigations reveal the fact that a considerable number of cases of hereditary ovarian cancer are associated with mutations of these genes. Mutations in the BRCA1 gene are marked by early age of disease

manifestation, histological diagnosis of high-grade serous subtype, and aggressive character of the disease development. In contrast, BRCA2 mutations are revealed much later in life and may possess various distinctive features [2].

In connection with the emergence of molecular genetics, it has become possible to analyze mutation spectra in the BRCA1 and BRCA2 genes more accurately. The mutation spectra include base changes, small insertions/deletions, and major restructuring of the genome. The nature of the mutation and its localization play an important role in the pathogenesis and clinical aspects of the disease. In this regard, sequence analysis of the BRCA1 and BRCA2 genes is not only diagnostic, but also has prognostic and predictive significance.

The identification of BRCA mutations in clinical practice has led to the development of new approaches to the management of ovarian cancer. Thus, high sensitivity to platinum-based chemotherapy is observed in BRCA mutation carriers. In addition, the introduction of PARP inhibitors based on the principle of synthetic lethality has significantly increased the effectiveness of treatment in these patients. These drugs cause the accumulation of DNA damage in cells with impaired BRCA function, resulting in the selective destruction of tumor cells. Thus, the detection of BRCA1 and BRCA2 gene mutations has become one of the key indicators in the selection of personalized treatment strategies.

The role of BRCA mutations in prognostic terms is also being extensively studied. Several scientific studies. It suggests that overall and disease-free survival rates may be higher in BRCA-mutation-positive ovarian cancer patients. However, this advantage may vary depending on the type of mutation, treatment strategy, and clinical stage. At the same time, detailed analysis of the mutation spectrum is of particular importance in terms of relapse risk and long-term clinical outcomes [3].

All these points illustrate that studying the clinical, pathogenetic, and prognostic features of the mutation spectrum in the BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer is one of the current and strategically important directions of modern oncology. This topic is of great importance both in terms of deepening fundamental scientific knowledge and in terms of early diagnosis, risk assessment, and the application of effective treatment models in clinical practice. As a result, the molecular genetic study of the BRCA1 and BRCA2 genes serves as one of the most important pillars of personalized medicine in relation to ovarian cancer treatment and presents wide perspectives for future research.

2. Prevalence and Structure of BRCA1/2 Mutations in Ovarian Cancer

Analysis of the mutation spectrum in BRCA1 and BRCA2 genes in patients with ovarian cancer reveals that not only does it increase the likelihood of developing this disease, but it also affects its course, biology, and therapy. As shown in modern oncogenetics, ovarian cancer caused by BRCA mutations differs considerably from sporadic forms in terms of its molecular and clinical characteristics [4].

An analysis of the frequency of mutations in BRCA1 and BRCA2 genes proves that these abnormalities predominantly occur in high-grade serous ovarian carcinomas. Based on various international research, mutations in one of the genes, BRCA1 or BRCA2, can be found in 10–20% of cases among patients with ovarian cancer. It is worth mentioning that mutations in the BRCA1 gene happen more often and correlate with the early age at the moment of disease onset. The reasons for such high frequency are connected with the broad range of functions fulfilled by BRCA1 in cells – regulation of cell division and response to damage to the DNA [5].

Special attention should also be paid to the structure of the mutation spectrum. Alongside point mutations, small deletions, insertions, and genome rearrangements are quite common. In particular, frameshift and nonsense mutations cause the synthesis of functional protein to stop, completely losing the tumor-suppressor function of the gene. These types of mutations play a significant role in shaping the more aggressive molecular phenotype of ovarian cancer [6].

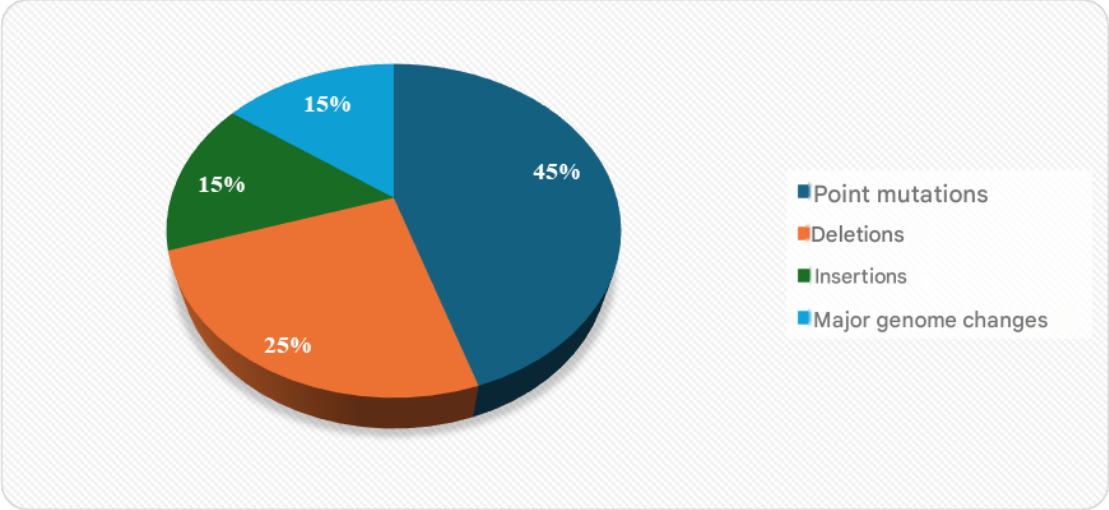

Figure 1. Distribution of mutation types in the BRCA1 and BRCA2 genes.
Source: *Author's own elaboration based on [7].*

Figure 1 illustrates the relative distribution of the main types of mutations found in the BRCA1 and BRCA2 genes in women diagnosed with ovarian cancer. As can be seen from the diagram, point mutations account for the largest share of the mutation spectrum. Deletions, insertions, and large genomic alterations are observed less frequently but play an important role in disrupting the functional activity of genes [5]. This diversity reflects the molecular heterogeneity of BRCA-mutation-associated ovarian cancer and has a significant impact on the pathogenesis of the disease, as well as on the characteristics of response to treatment [8].

3. Pathogenesis of BRCA-Mutation-Positive Ovarian Cancer

From a pathogenetic perspective, the main mechanism of action of BRCA1 and BRCA2 mutations is related to the disruption of DNA repair through homologous recombination. Under normal conditions, these genes maintain genome stability by ensuring the accurate repair of double-strand breaks. However, the failure of this mechanism as a result of mutation leads to the activation of alternative, error-prone DNA repair pathways. As a result, the mutation load in cells increases, chromosomal aberrations accumulate, and a favorable molecular environment for malignant transformation is formed [9].

This is one of the most important mechanisms determining the characteristics of these tumors. Despite their high growth rate, these tumors are also characterized by a high sensitivity to those drugs that induce damage to DNA. The peculiarity of these tumors is their aggressive nature, as well as sensitivity to treatment. These features are characteristic of BRCA-positive ovarian tumors [10].

4. Clinical Features and Histological Classification

As a result of the clinical analysis, it was concluded that, among the BRCA1 mutation carriers, there is a prevalence of diagnosis before menopause and a frequent presence of a positive family history for breast or ovarian cancer. Among patients carrying the BRCA2 mutation, the disease develops somewhat later and may follow other clinical courses. The above findings were determined due to the functional specificity of genes and their impact on intracellular signaling pathways [11].

Ovarian cancer associated with the presence of BRCA mutations mostly presents as a high-grade serous tumor. The probability of the occurrence of BRCA mutations among other histological subtypes of cancer (e.g., endometrioid or mucinous) is much lower. This fact indicates that BRCA mutations are closely associated with specific tumor biological phenotypes and increases the importance of molecular classification in clinical practice.

Table 1. Distribution of histological types of ovarian cancer according to BRCA-mutation status.

Histological type	BRCA-mutations positive (%)	BRCA-mutations negative (%)
High-grade serous carcinoma	70–80	40–50
Endometrioid carcinoma	8–12	15–20
Clear cell carcinoma	3–6	10–15
Mucinous carcinoma	1–3	10–12
Other rare histological types	2–5	5–8

Source: *Compiled by the author based on data from [12].*

5. Treatment Responses and Future Research Directions

Prognostic analyses suggest that patients with BRCA1 and BRCA2 mutations may have a more favorable response to treatment than BRCA-negative patients. Particularly high sensitivity to platinum-based chemotherapy regimens allows for longer disease-free survival in this group of patients. This condition is explained by the inability of BRCA-mutation-positive tumor cells to effectively repair DNA damage.

The introduction of PARP inhibitors into clinical practice in recent years has marked the beginning of a new phase in the treatment of BRCA-mutation-associated ovarian cancer. Based on the principle of synthetic lethality, these drugs cause the selective destruction of tumor cells by blocking the additional DNA repair pathway in cells with impaired BRCA function. As shown by the data of clinical trials, PARP inhibitors increase the probability of disease-free survival and lower the chances of recurrence.

Nevertheless, there are exceptions to a favorable treatment response even among patients with BRCA mutations. These include the nature of the mutation itself, its location in the gene structure, and the existence of other molecular alterations. Thus, the presence of secondary "reversing" mutations may lead to the functional recovery of BRCA and the acquisition of resistance to the applied medications.

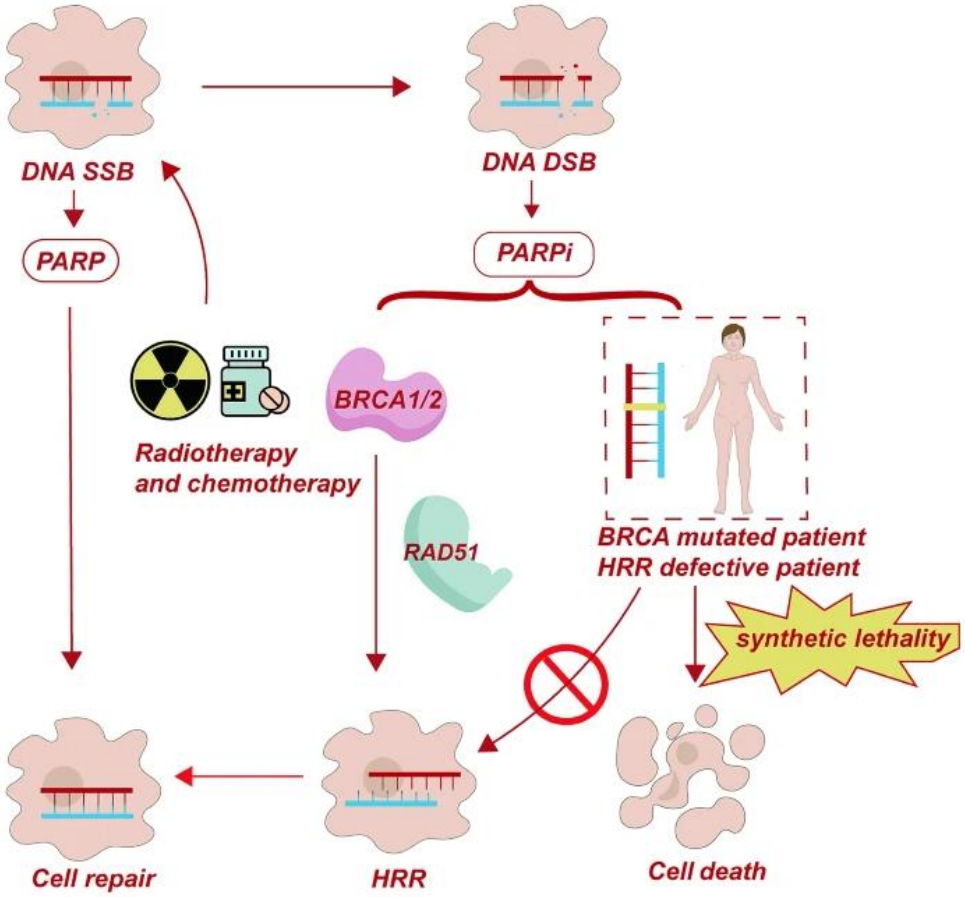

Figure 2. Mechanism of synthetic lethality of PARP inhibitors in the setting of BRCA1/2 mutation [13].

Figure 2 illustrates the repair of DNA single-strand breaks (SSB) under normal conditions by the PARP enzyme and the repair of double-strand breaks (DSB) by homologous recombination (HR) involving the BRCA1/2 and RAD51 proteins. When mutations exist in the BRCA1 and BRCA2 genes, the homologous recombination mechanism is disrupted, and the cell is unable to effectively repair DNA damage. The administration of PARP inhibitors (PARPi) also blocks the alternative DNA repair pathway, which leads to the accumulation of DNA damage and ultimately selective cell death, synthetic lethality in tumor cells carrying the BRCA mutation. Radiotherapy and chemotherapy enhance the effectiveness of this mechanism by further contributing to increased DNA damage.

Analysis of the available scientific literature exhibits that although the role of BRCA1 and BRCA2 gene mutations in ovarian cancer has been extensively studied, there are still open questions. The majority of studies were done retrospectively, while there is a lack of information about certain groups of patients. Nevertheless, the results concerning the influence of other homologous recombination-related genes other than BRCA genes on the progression of the disease have not been finalized yet.

Among the priorities for future research, the comparative analysis of the mutation pattern within diverse ethnicities, an understanding of the interaction of mutations within BRCA genes with other molecular alterations, and a better prediction of the prognosis of the disease based on the molecular markers are worth mentioning.

6. Role of BRCA1 and BRCA2 Mutations in the Molecular Genetic Mechanisms of Ovarian Cancer

The BRCA1 gene and BRCA2 gene mutations are associated with the progression of ovarian cancer. The two genes have significant roles, particularly in the maintenance of genomic stability and the repair of DNA damage. The two mutations cause instability of the genomes, making them more susceptible to cancer formation. In addition, these gene mutations are important in choosing suitable treatment options that are highly sensitive to such drugs as PARP inhibitors [14].

7. Conclusion

The obtained data demonstrate that the spectrum of mutations of the BRCA1 and BRCA2 genes in patients with ovarian cancer is an important factor for understanding the processes of formation of the disease, its progression, and further therapy. The important contribution of the mentioned genes in DNA repair by homologous recombination suggests their mutations to be one of the important molecular markers of ovarian cancer.

It follows from the total results of the research that BRCA1 mutations tend to be found in early years, be of high-grade serous histological type, and possess the aggressive nature of the clinical picture. As for BRCA2 mutations, they have somewhat different clinical manifestations and tend to predict better treatment results and prognosis in some cases. The character of mutations and the sites of their localization have a great influence on pathogenetic properties of ovarian cancer and the tendency to relapses.

From the clinical point of view, patients with BRCA mutations have a higher sensitivity to the platinum and PARP inhibitors. This is justified by the synthetic lethality concept and proves that the BRCA mutations represent a key factor in predicting the efficacy of such types of therapy. Therefore, the introduction of molecular-genetic tests into medical practice leads to a significant increase in the efficiency of the personalized approach in the treatment of this pathology.

At the same time, numerous sources indicate that not all patients with mutations in their BRCA genes are characterized by identical therapeutic effects. Other genetic changes, reversion mutations, and heterogeneous molecular characteristics of the tumors could be among the mechanisms underlying the formation of therapy resistance in such patients. Hence, there should be not only the consideration of BRCA status but also the HRD problem from a broader point of view in treating ovarian cancer.

Accordingly, a detailed examination of the spectrum of mutations within the BRCA1 and BRCA2 genes in women suffering from ovarian cancer represents a significant problem for further research in terms of prevention and therapy improvement. Further research needs to be done on a comparative study of mutations in various population groups, the role of genes that are involved in the HR pathway apart from BRCA, and

additional prognostic factors. Such a strategy would help enhance the molecular-based treatment model of ovarian cancer.

Author Contributions

The author confirms responsibility for the conception and final approval of the manuscript.

Conflict of Interest

The author declares no competing interests.

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Abbreviations

Breast Cancer 1 Gene (BRCA1), Breast Cancer 2 Gene (BRCA2), Deoxyribonucleic Acid (DNA), Double-Strand Break (DSB), Single-Strand Break (SSB), Homologous Recombination (HR), Homologous Recombination Deficiency (HRD), Poly (ADP-ribose) Polymerase (PARP).

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Review Article

CRISPR Technologies in Biotechnology: Mechanisms, Applications, Advantages, Risks, and Future Prospects

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Abstract

CRISPR technology is an innovative technique in the field of genetic engineering. It facilitates the precise modification of DNA. The defence mechanism of bacteria against viruses served as the model for CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). Jennifer Doudna and Emmanuelle Charpentier were awarded the 2020 Nobel Prize in Chemistry for the development of the CRISPR-Cas9 system in 2012. The method cuts and modifies DNA using guide RNA and the Cas9 enzyme. The Cas9 enzyme slices the target site on DNA after the guide RNA (gRNA) finds it. Genetic engineers can introduce the desired modification (deletion, insertion, or substitution) as the cell attempts to repair this incision. This procedure is quick, inexpensive, and very accurate. CRISPR has several uses, including the treatment of genetic disorders like sickle cell anaemia, cancer immunotherapy, the prevention of viruses like HIV, the development of resilient crop types in agriculture, and the manufacture of new species in biotechnology. CRISPR is more effective and simpler than previous methods (ZFN, TALEN); however, it encounters challenges such as off-target effects (unintended incisions) and ethical issues (editing human embryos).

Keywords: CRISPR, Cas9 enzyme, gRNA

1. Introduction

Gene editing (also called genome editing) is a set of modern techniques used to modify the genetic material, i.e., DNA, of plants, animals, and microorganisms. Through these methods, it is possible to add, delete, or modify DNA sequences in certain, pre-selected parts of the genome [1]. Genome editing technologies developed in recent years have made it possible to quickly and economically make specific, predetermined changes to the genomes of various cells and organisms. These technologies are based on an approach called "targeted genome engineering" and enable highly precise modification of specific regions of the genome. The most widely used platforms in modern genome engineering include CRISPR/Cas9, TALEN (Transcription Activator-Like Effector Nucleases), ZFN (Zinc Finger Nucleases), and meganucleases [2].

This process is not carried out through natural reproduction, but artificially through human intervention. The result is genetically modified organisms (GMOs) as a form of genetic engineering. The most widely used genome editing method currently is CRISPR-Cas9 technology [1].

"CRISPR-Cas9 is a tool that has the potential to revolutionize biomedicine by permanently altering the human genome to treat genetic diseases." – Emmanuelle Charpentier [3].

The 2020 Nobel Prize in Chemistry was awarded to E. Charpentier and J. Doudna for their discovery of CRISPR technology. Genetic modifications that once seemed possible only in science fiction movies have now become a reality thanks to CRISPR. This technology offers hope for the treatment of genetic diseases caused by small changes in the genome and opens up great opportunities to improve people's quality of life [3]. Currently, more than 6,000 monogenetic diseases are known worldwide, and CRISPR/Cas-based therapies are considered a promising approach in the treatment of these diseases. Clinical studies conducted in recent

years have shown that CRISPR technology can show effective results in the treatment of sickle cell anemia, β-thalassemia, and some hereditary retinal diseases [2].

The discovery of CRISPR technology arose from an important scientific need in genetic research. Programmable nuclease systems, such as ZFN and TALEN, used before CRISPR had high technical complexity, an expensive manufacturing process, and limited flexibility. Therefore, scientists needed to develop new technologies that could modify specific parts of the genome more precisely, quickly, and effectively. This need was met with the discovery of CRISPR in the immune system of bacteria. Bacteria use this mechanism to cut and neutralize the DNA of viruses that infect them [3]. The CRISPR/Cas system functions as an adaptive immune defense mechanism in bacteria. Viral DNA fragments are stored in the bacterial genome as "spacers" and allow for recognition of those sequences during subsequent infections. CRISPR RNA (crRNA) and trans-activating crRNA (tracrRNA) synthesized from the CRISPR locus direct the Cas9 enzyme to specific target DNA, ensuring the cleavage of foreign genetic material [2].

Once CRISPR's DNA-cutting mechanism was understood, this system became a powerful tool for gene editing. The CRISPR-Cas system recognizes a precise target in the genome through guide RNA (gRNA), and the Cas enzyme cuts the DNA at that point. The molecular basis of genome editing is the generation of double-stranded DNA breaks and the repair of these damages through intracellular DNA repair mechanisms. Two repair systems are mainly involved in this process: Non-Homologous End Joining (NHEJ) and Homology-Directed Repair (HDR). NHEJ is a rapid but error-prone mechanism, which results in the loss of gene function. On the other hand, HDR enables more precise gene correction by utilizing a donor DNA template. CRISPR is a more precise, cost-effective, and straightforward system than previous gene editing technologies due to these features [3].

CRISPR technology is significant because of its many uses. This approach creates new opportunities for researching the genetic traits of different organisms and treating genetic illnesses. Therefore, CRISPR is regarded as a significant turning point in the advancement of today's biology and medicine [2], [3].

The possibilities of genome engineering have been considerably extended in recent years by novel techniques based on CRISPR technology, such as base editing, prime editing, and epigenome editing. These technologies are regarded as one of the primary instruments for personalised medicine in the future since they enable more precise genetic alterations without causing double-strand breaks [2].

2. Historical Development of CRISPR Technologies

CRISPR clustered regularly interspaced short palindromic repeats were initially identified in the DNA sequences of the Escherichia coli bacterium and subsequently characterised by Ishino et al. from Osaka University (Japan) in 1987. The discoverers of these challenging-to-study DNA fragments were unable to comprehend their origin or significance within the bacterial cell, despite the fact that the sequencing process required several months. Despite the fact that the biological function of the CRISPR system had not yet been clarified in the early work in this field, scientists had already proposed a method to utilise the information encoded in CRISPR loci in medical research. This method involved genotyping a variety of bacterial strains, initially Mycobacterium tuberculosis and eventually Streptococcus pyogenes. As it turned out, CRISPR loci had a high degree of polymorphism in different strains of the same species of pathogenic bacteria, which enabled the identification of bacterial strains in clinical conditions [4].

In 1995, Francisco Mojica of the University of Alicante (Spain) made a breakthrough in the understanding of the biological function of CRISPR loci when he discovered analogous structures in the archaeal genome of Haloferax mediterranei. Their existence in two evolutionarily distant domains of life indicated the significant functional importance of these elements and provided a motivation for additional research. Mojica observed the similarity between the elements he described in archaea and the DNA repeats that had been previously identified in bacterial genomes. He was one of the first scientists to propose that these unusual loci contain fragments of foreign DNA and are, in fact, a component of the immune system of bacteria and archaea. In the same year as Mojica, two other laboratories simultaneously reached similar outcomes, thereby announcing the beginning of an era of active investigation into this remarkable natural phenomenon. Viral DNA fragments ("spacers"), which are 17-84 bases in length, are grouped into clusters in intergenic regions and separated by short palindromic repeats, in accordance with the theory of the prokaryotic immune system. These fragments represent a library of potentially harmful genetic information. At first, it was believed that the operation of

such a system would be facilitated by the mechanism of RNA interference. Nevertheless, Marraffini and Sontheimer's publication experimentally demonstrated for the first time that the immune system of prokaryotes actually targets foreign DNA, not mRNA. Consequently, the use of such a system in the laboratory could serve as a potent tool for genomic editing. Interestingly, later studies demonstrated that some of the described CRISPR systems do work with RNA molecules directly and, therefore, can be used to deactivate specific transcripts inside the cell in a selective way [4].

Rodolphe Barrangou and Philippe Horvath, two French food scientists, worked with yoghurt cultures of the bacterium Streptococcus thermophilus for the Danish company Danisco in 2007. Their research provided the first experimental information regarding the mechanism of action of the CRISPR system. Scientists have been able to trace the historical development of the bacterial acquisition of spacers at the CRISPR locus in response to viral attacks by bacteriophages, as a result of the company's extensive collection of bacterial strains collected since the 1980s. The addition of new spacers in this work caused acquired immunity to the corresponding new types of bacteriophages in S. thermophilus: an observation which subsequently led to the authors obtaining one of the first patents in this area and the start of bacterial cultures' "vaccination" with the use of CRISPR-based technology by Danisco in 2005 [4].

At present, CRISPR repeats have been detected in the majority of archaeal genomes and nearly half of the bacterial genomes that have been studied. However, they have not been observed in eukaryotic or viral DNA sequences. One of the earliest publications on the subject suggested the presence of CRISPR repeats in mitochondria, and the same article also, for the first time, described CRISPR in cyanobacteria. The authors used a set of previously published data on the sequencing of mitochondrial plasmids from Vicia faba L. beans, and their conclusions were further cited by Mojica et al., but these observations were not confirmed in later studies [4].

The search for early articles on the topic is currently complicated by the fact that a variety of abbreviations were used for CRISPR by individual scientific groups during early discoveries. The name CRISPR, as used today, first appeared in the work of Jansen et al. in 2002 and was proposed by Mojica in correspondence between two collaborating scientific groups. The same publication was the first to identify the existence of genes associated with CRISPR repeats (referred to by the authors as Cas1-4, CRISPR-associated genes). These genes were found to be located near CRISPR loci of various prokaryotes, and two of them contained motifs characteristic of helicase and nuclease. This supported the authors' hypothesis about the non-random association of the Cas genes with the CRISPR locus and their involvement in DNA metabolism. Also in 2002, a team of scientists led by Eugene Koonin from the NCBI Institute (Bethesda, USA) identified the same gene region, but at that time, the association of these genes with CRISPR sequences could not be determined. From the moment the genes associated with the CRISPR system were first discovered to the present day, an extraordinary abundance and diversity of genes have been found in prokaryotic cells, including helicases, nucleases, polymerases, and others. Proteins associated with this system can be assigned either to adaptive modules (primarily Cas1 and Cas2, which play a role in immunity acquisition) or effector modules (involved in the recognition and degradation of mobile genetic elements and their direct elimination); additionally, some supplementary and regulatory proteins associated with the system have also been identified. Currently, a classification method is accepted in which all known CRISPR-Cas systems are divided into 2 classes and 6 types, which are further divided into numerous subtypes. At the time of writing this review, Makarova et al. had identified more than 30 subtypes. The main difference between the classes is that the effector module of Class 1 systems is represented by a complex of several proteins, while in Class 2, it is a single multidomain protein (Cas9, Cas12, or Cas13) [4].

Of all the known Cas proteins, the most studied are those belonging to the directional cutting system of foreign DNA (and, as it was later discovered, in some cases, RNA); these are called "genetic scissors" and include the nuclease Cas9. This protein was first identified in a paper by Bolotin et al. in the context of its association with CRISPR repeats and was initially named Cas5 (other alternative names are Csn1 and Csx12). Furthermore, the authors identified the presence of the HNH motif (His–Asn–His), which is also found in other nucleases. Another significant observation made by Bolotin et al. was the discovery of a specific pattern in the nucleotide sequences on one side of the identified spacers of the CRISPR sequences, although the role of this phenomenon was only revealed in later studies. Currently, short motifs that are not present in the original spacers of the CRISPR locus but

are adjacent to the protospacers are called PAMs (protospacer-adjacent motifs). Protospacers are DNA fragments that are attacked by the immune system of prokaryotes and are identical to the corresponding spacers in the CRISPR locus except for the PAM motif. These motifs are important at the stage of recognition of potentially dangerous genetic information; their presence at the end of the sequence signals that the DNA fragment is foreign and needs to be destroyed, while the DNA sequences stored in the CRISPR locus as spacers and not containing PAM motifs are not attacked by the prokaryotic immune system [4].

It turned out that a critical element in the CRISPR-Cas9 system is a short RNA molecule, a processed product of transcription from the CRISPR locus, which directs proteins of the prokaryotic immune system to foreign molecules containing genetic information. A group of researchers led by John van der Oost from Wageningen University in the Netherlands identified the existence of these types of RNA molecules and named them crRNA (CRISPR-associated RNA). It was also noted that the initial result of transcription from the CRISPR locus is a pre-crRNA precursor molecule consisting of various interstitial segments and repeats, which are subsequently cleaved into separate fragments. In the study led by Virginijus Siksnys (University of Vilnius, Lithuania), it was shown that the length of the 20-base pair true "guide" crRNA sequence, complementary to the target DNA, is necessary and sufficient for the nuclease activity of the CRISPR-Cas complex, even if the interstitial region at the CRISPR locus is represented by a longer nucleotide sequence. This publication was one of two in vitro studies, carried out in parallel and independently in competing laboratories, that described, for the first time, how the Cas9 enzyme uses crRNA to attack foreign DNA [4].

The final and significant component of the CRISPR-Cas9 system, which makes it impossible to create a functional CRISPR-Cas9 system in a laboratory setting, is another short RNA molecule discovered by Emmanuelle Charpentier's group in 2011 in connection with its role in crRNA processing. This molecule, essential for nuclease activity, was named tracrRNA (trans-activating CRISPR RNA). Subsequent studies, ultimately confirmed by a Nobel Prize, demonstrated tracrRNA's role in the cleavage mechanism of target DNA. It was also proposed at the time that two RNA molecules, crRNA and tracrRNA, could be combined into one chimeric molecule (sgRNA-single guide RNA), which greatly facilitated the practical use of the CRISPR-Cas9 system in subsequent applications [4].

3. Molecular Basis of the CRISPR/CAS9 Mechanism

CRISPR/Cas systems are divided into two main classes based on the structure and functional properties of the Cas proteins: Class I (types I, III, and IV) and Class II (types II, V, and VI). While Class I systems are composed of complexes consisting of several Cas proteins, in Class II systems, genome editing is carried out by a single Cas protein. The CRISPR/Cas9 system, which belongs to Class II due to its simpler structure, is the most widely studied and most widely used system in genetic engineering.

The two main components of the CRISPR/Cas9 system are guide RNA (gRNA) and the Cas9 endonuclease protein. The Cas9 protein, which was first used in genome editing, was derived from the bacterium *Streptococcus pyogenes* and is called SpCas9. This protein is a 1368 amino acid, multidomain DNA endonuclease that is capable of creating double-strand breaks in target DNA. It is precisely because of this property that Cas9 is called "genetic scissors" [5].

The Cas9 protein is structurally composed of two main parts: the recognition (REC) lobe and the nuclease (NUC) lobe. The REC lobe encompasses the REC1 and REC2 domains and is primarily responsible for binding guide RNA. The NUC lobe consists of domains that interact with RuvC, HNH, and PAM. The RuvC and HNH domains create double-strand breaks by cutting each strand of DNA separately. The PAM (Protospacer Adjacent Motif) interaction domain enables Cas9 to recognize and bind to target DNA. Without the PAM sequence, Cas9 cannot bind to DNA, which ensures the high specificity of the system [5].

Guide RNA consists of two parts - CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA). crRNA is 18–20 nucleotides long and recognizes and pairs with the target DNA sequence. tracrRNA consists of RNA loops that act as a structural support for the Cas9 protein. In genome editing technologies, these two RNAs are artificially combined to create a single guide RNA (sgRNA), which allows targeting of almost any gene [6].

CRISPR/Cas9 technology relies on the interaction of guide RNA (sgRNA) and the Cas9 endonuclease protein to make precisely targeted changes in the genome. Initially, an active complex is formed when the sgRNA attaches to the Cas9 protein. This complex searches for PAM (Protospacer Adjacent Motif) sequences as it travels throughout the cell's DNA. Once the PAM is found, the sgRNA pairs with the target DNA sequence, and the Cas9 protein is activated at that point [6].

The HNH and RuvC domains of the activated Cas9 protein cut both strands of DNA, creating a double-strand break. After this break, the cell activates its natural DNA repair mechanisms. As a result, the function of the gene may be disrupted, altered, or a new genetic sequence may be added. Thus, CRISPR/Cas9 technology allows for highly precise genetic modifications to be made in any area of the genome [6].

The CRISPR/Cas9 system was first discovered in bacteria as a defense mechanism against viral DNA. However, this system later became a revolutionary tool in genetic engineering. While the classic CRISPR/Cas9 technology enabled genome editing with high precision, one of its main drawbacks was the inability to regulate genes in a reversible manner and without damaging DNA [6].

To overcome this problem, MIT professor Jonathan Weissman and his colleagues created new modifications of the Cas9 protein - the CRISPRoff and CRISPRon systems. These systems are not based on classical DNA cleavage, but rather regulate gene activity through epigenetic mechanisms. The CRISPRoff system turns off the activity of genes by adding epigenetic marks to certain gene regions with the help of guide RNA, while CRISPRon removes these epigenetic changes and reactivates the genes [7].

Studies have shown that these changes remain stable during cell division and can even be inherited. Scientists have tested this system on stem cells, artificially turning off genes and transforming those cells into neurons and other differentiated cell types. The results showed that the silenced genes were not activated even after cell differentiation [7].

Thus, the molecular basis of CRISPR/Cas9 technology is not limited to DNA cutting alone, but also allows for the control of gene expression at the epigenetic level. This technology holds great promise in the study of genome functions and, especially, in the treatment of genetic and neurodegenerative diseases such as Alzheimer's disease [7].

4. Application Areas of CRISPR Technologies in Biotechnology

CRISPR/Cas9 genome editing technology has revolutionized the fields of biology and medicine in a short time since its discovery. This technology is currently widely applied in numerous fields such as gene therapy, disease treatment, medical diagnostics, gene activation, and gene silencing. In the future, CRISPR technologies are expected to be further improved and become a key tool in the treatment of many hereditary and infectious diseases.

4.1. CRISPR/Cas9 in Gene Therapy

The CRISPR/Cas9 system is considered one of the most effective and widely used technologies for genome editing in recent years. This system is based on the defense mechanism of bacteria and archaea against foreign genetic material and was later adapted for use in genetic engineering [8], [9].

The main components of CRISPR/Cas9 technology are single-guide RNA (sgRNA) and the Cas9 endonuclease enzyme. The sgRNA recognizes a specific DNA sequence and directs the Cas9 enzyme to that site, resulting in a double-strand break in the target DNA [8].

After this break, the cell's natural DNA repair mechanisms are activated. Genome editing occurs mainly through two mechanisms: non-homologous end joining (NHEJ) and homology-directed repair (HDR). During the NHEJ mechanism, DNA is repaired imprecisely, and insertions or deletions can occur, while the HDR mechanism allows for more precise genetic changes when a suitable DNA template is available [9].

CRISPR/Cas9 technology is used in gene therapy in two main ways. In the first approach, CRISPR components are introduced directly into the body and genome editing is performed in vivo. In the other approach, cells taken from the patient are edited in the laboratory and then returned to the body, which is called ex vivo gene therapy [9].

CRISPR/Cas9 technology has shown promising results in the treatment of various genetic diseases. For example, in some experimental studies, this system has been used to correct mutations caused by diseases such as hereditary tyrosinemia, and a reduction in disease symptoms has been observed [9].

However, there are also some challenges in the clinical application of CRISPR technology. One of the main challenges is the efficient delivery of the editing system to the target cells and the occurrence of off-target effects related to the generation of off-target changes [8].

4.2. CRISPR in Cancer and Infectious Diseases

CRISPR/Cas9 technology has opened up important prospects for the research and treatment of cancer and infectious diseases. Since cancer is a disease caused mainly by genetic changes, genome editing technologies are widely used to study the molecular mechanisms of tumors [8].

The CRISPR system allows us to study the function of genes involved in the development of tumor cells and change their activity. In addition, CRISPR technology is used to create cancer models, which allows us to study the mechanisms of tumor formation and test new drugs [8].

CRISPR/Cas9 technology is also being used in the study of infectious diseases. For example, in some studies, the CRISPR system has been used to target the genome of the hepatitis B virus to reduce viral replication [10]. The cccDNA structure that causes the hepatitis B virus to remain in a stable form in cells allows the virus to persist for a long time. The CRISPR system can help reduce infection by disrupting this viral DNA [9].

However, for the clinical application of CRISPR technology, it is important to address issues such as delivering the gene editing system to target tissues and reducing off-target effects [8].

4.3. CRISPR in Medical Diagnostics

During the COVID-19 pandemic, CRISPR technology has been used not only as a potential treatment tool but also as a rapid and accurate diagnostic method. One of the most important achievements in this field has been the SHERLOCK™ CRISPR SARS-CoV-2 test kit. The test in question has received Emergency Use Authorization from US federal agencies for use in laboratory settings. The SHERLOCK system allows for the detection of the virus's genetic material with high sensitivity. In addition, the subsequently developed STOPCovid diagnostic test is also based on a CRISPR-based approach and is considered an effective method for rapid detection of the virus [5].

Another CRISPR-based COVID-19 diagnostic method is the DETECTR system developed by Mammoth Biosciences. Similar to the SHERLOCK and STOPCovid tests, the DETECTR method uses the genetic material recognition (search) feature of Cas proteins. This system mainly uses the naturally occurring Cas12 and Cas13 nucleases and identifies the viral RNA with high accuracy [10].

The diagnostic applications of CRISPR technology are not limited to COVID-19. Similar diagnostic systems based on the search function of Cas proteins have also been developed for the detection of infectious and genetic diseases. In early 2021, research led by Dr. Kiana Aran of Cardea Bio combined three Nobel Prize-winning technologies - graphene, transistors, and CRISPR to create a very small chip. This chip has the ability to detect pathogenic single-nucleotide polymorphisms (SNPs) [5].

It should be noted that approximately 50% of disease-causing mutations in humans are associated with SNPs. In this regard, the development of such CRISPR-based diagnostic technologies is considered an important scientific achievement in the field of modern medical diagnostics [5].

5. Advantages of CRISPR Technology

CRISPR-Cas9 is one of many gene editing technologies available to researchers. While it can be an extremely industrious approach for inducing changes to genetic material, it, like any other gene editing application, has several advantages and disadvantages that should be taken into consideration when designing an experiment [11].

5.1. Fast and Flexible Design

Specifically, CRISPR-Cas9 gene editing requires two components: the Cas nuclease and a guide RNA. In some cases, researchers prefer to use the two-part crRNA-tracrRNA system, while in others they use sgRNA. After the guide RNA and endonuclease bind to each other, they form a ribonucleoprotein (RNP) complex. It's within this complex that the guide RNA can bind to the target sequence, and editing can occur [11].

5.2. Multiplexed Gene Editing

CRISPR-Cas9 can edit multiple genes simultaneously when the sgRNAs used are designed to target different genetic regions. This makes CRISPR-Cas9 gene editing an attractive and efficient approach for manipulating multiple locations in the genome [11].

5.3. Cost-Effectiveness

For the reasons mentioned above, CRISPR-Cas9 can be extremely cost-effective compared to other gene editing approaches requiring protein engineering, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). The simplicity of CRISPR-Cas9, relying largely on 2 molecules to induce edits, as well as the flexibility available in designing sgRNAs to bind to any/numerous target(s), means that researchers can start editing quickly and make adjustments easily [11].

6. Disadvantages of CRISPR Technology

6.1. Delivery Limitations

Successful delivery of CRISPR-Cas9 to cells is necessary to perform the desired gene editing. As with many other gene editing applications, delivering the Cas9/gRNA complex to a sufficient number of cells can be challenging because all components must be delivered to the cells at the correct concentrations and at the correct point in the cell cycle. CRISPR reagent delivery methods include electroporation, lipofection, microinjection, nanoparticles, and viral plasmids [11].

6.2. Efficiency Limitations

Another necessary limitation to consider when using the CRISPR-Cas9 gene editing method is that gene editing activity may not occur once the Cas9/gRNA complex is taken up by cells. This is especially true when the goal is to insert or insert material into a gene, a process based on homologous directed repair (HDR). However, researchers have made significant progress in improving HDR efficiency rates with CRISPR. To read more about improving CRISPR-Cas9 gene editing efficiency, check out the DECODED article, improving efficiency of homology-directed repair (HDR) [11].

6.3. Off-Target Effects

Off-target effects occur when undesirable changes occur as a result of the Cas9 nuclease editing a non-targeted part of the genome. Off-target effects are a major concern for CRISPR-Cas9 experiments and can be difficult to predict. Efforts have been made to improve in silico off-target prediction tools as well as to reduce off-target effects by improving Cas9 nucleases [11].

7. Genome Editing for Human Germline

The editing of human germline cells with CRISPR-Cas9 is prohibited for various safety reasons. However, the application of CRISPR-Cas9 to somatic cells with the aim of transferring desired characteristics to our lives is increasing. Many phenotypic traits have a genetic component independent of the environment. By exploiting this characteristic, CRISPR-Cas9 could be used to enhance athletic performance, prevent violent behavior, or reduce addiction. While gene therapy is generally used to the benefit of patients, in the future, the criminal justice system may require recidivism or dangerous criminals to correct their violence-related genes using genome editing technologies. One of the biggest dilemmas here is obtaining informed consent for a minor if the intervention is performed during zygote development. This would give parents or guardians the right to make decisions on behalf of minors for non-health-related reasons. Moreover, from a social perspective, some genetically enhanced populations or individuals may have certain advantages over others in

terms of various traits such as mental and physical capacity. Therefore, the use of CRISPR-Cas9 in genome enhancement should be seriously discussed both socially and morally [12]. The potential use of CRISPR-Cas9 for genome editing in human germ cells has raised serious ethical debates. Until 2015, all therapeutic applications in humans were performed on somatic cells using genome editing technologies. However, in 2015, the editing of the human germline performed by Chinese scientist Huang and his team with CRISPR-Cas9 raised new social, moral, and bioethical issues [12].

8. Future Perspectives

Over the past decade, significant progress has been made in the use of CRISPR, both as a tool and as a treatment method. As discussed, CRISPR-Cas has become very effective as a screening tool, but it would benefit from better genome coverage, more refined gRNA designs, and analyses that can distinguish between multigene transcripts. Clinically, as we have previously noted, CRISPR-based editing has proven effective in developing cell therapies for both ex vivo and in vivo applications. Despite the clear applications of CRISPR-based editing, several challenges remain (see Key Questions). These current challenges (e.g., immune responses, application, off-target effects, DNA damage, etc.) stem from the fact that nature optimized CRISPR nucleases to function as a bacterial defense system, not for precise genome editing; this means that much more work needs to be done to make these systems suitable for precise editing in humans. Furthermore, significant genomic heterogeneities exist within the human population, complicating treatment development. To optimize targeted activity and minimize off-target effects, gRNAs specifically designed for the patient's genetic makeup may be needed. In addition, to accelerate the development of CRISPR-based therapies, various methods for precise control of Cas9-based systems are being developed, and new editors (e.g., base and prime editors) are being created. Also, we are seeing an increase in translational dCas9-based technologies that enable dose and temporal control of a therapeutic target without double helix breaks, thus overcoming the current challenges associated with Cas9. Especially considering how far CRISPR technologies have advanced since their discovery only a decade ago, we anticipate that further engineering strategies over the next decade will better minimize and optimize the system, allowing for the development of transformational in vivo applications [13].

9. Conclusion

Considered one of the most transformative discoveries in modern molecular biology and biotechnology, the CRISPR-Cas9 methodology has created a fundamental scientific turning point in the field of genome editing. Analysis of scientific sources and conducted research clearly demonstrates that this system is based on the natural adaptive immune defense system that bacteria have developed against viral attacks during their evolution, and allows for highly precise, targeted modification of the genetic code. This innovative technology promises broad future prospects in both fundamental theoretical experiments and practical applications, as it allows for highly efficient and point-wise manipulations of the genome at specific coordinates.

The results of scientific research show that the CRISPR-Cas9 mechanism has a much simpler structure, superior accuracy rating, and a more universal application area compared to the classical genome editing methods used before it, including homologous recombination, zinc finger nucleases, and TALEN systems. In particular, the ability to perform parallel changes on several different genetic regions in the same time frame, i.e., the multiplexing function, is the most fundamental advantage that distinguishes this management system from other methodological approaches. This process, which takes place at the molecular level, is carried out by directing the nuclease enzyme called Cas9 to a specific DNA site designated as a target via a special single-stranded RNA molecule that acts as a guide. At that specific point, a double-strand break is created by the Cas9 enzyme, and immediately thereafter, the cell's own internal DNA repair mechanisms, non-homologous end joining and homology-directed repair pathways, are activated. Using these regeneration pathways, unwanted genes can be completely deactivated, existing mutations can be corrected, or new genetic sequences can be integrated into the genome, making the CRISPR-Cas9 system the most efficient genome editing tool in biology.

Simultaneously, this methodology has significantly accelerated the advancement of gene therapy in the field of health and medicine, thereby enabling the creation of innovative treatment strategies for the radical treatment of hereditary genetic diseases and the complete removal of certain viral infections from the body, particularly those that cause chronic diseases, such as Hepatitis B.

In spite of these accomplishments, the practical application of CRISPR-Cas9 technology is plagued by significant ethical dilemmas and technical challenges. The risk of off-target effects is one of the primary issues, as the system occasionally induces unknown mutations and cuts in other unanticipated, non-target DNA regions. Scientific research is being conducted in an effort to enhance the safety and specificity of the technology, as these types of random alterations have the potential to cause harm to the body.

Numerous next-generation methodologies are currently being developed to enhance and optimise CRISPR technology from a scientific perspective. Particularly, the incorporation of bioinformatics programmes and artificial intelligence tools into CRISPR design systems contributes significantly to the more precise identification of target genes and the reduction of off-target effects. At the same time, new generation genetic engineering modifications, such as the inactive Cas9 protein, base editing based on direct nucleotide replacement, and prime editing, which offers more complex editing capabilities, guarantee safer and more flawless genetic manipulations in the future.

In conclusion, CRISPR-Cas9 technology, as one of the most remarkable achievements of modern biological science, has had a strong global impact on both the development of fundamental laboratory research and the expansion of applied fields such as agriculture, medicine, and biotechnology. Further improvement of this technology in the future and the formation of completely safe application mechanisms will play a decisive role in the complete treatment of hereditary genetic pathologies, ensuring food security on a global scale, and the creation of completely different innovative directions of the biotechnology industry.

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The author conceived the study, conducted the literature search, analyzed and synthesized the collected information, and wrote, reviewed, and approved the final manuscript.

Conflict of Interest

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Abbreviations

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), Guide RNA (gRNA), Human Immunodeficiency Virus (HIV), Transcription Activator-Like Effector Nucleases (TALEN), Zinc Finger Nucleases (ZFN), Genetically Modified Organisms (GMOs), Deoxyribonucleic Acid (DNA), CRISPR RNA (crRNA), Trans-Activating crRNA (tracrRNA), Non-Homologous End Joining (NHEJ), Homology-Directed Repair (HDR), Histidine–Asparagine–Histidine (HNH), Protospacer-Adjacent Motifs (PAMs), single guide RNA (sgRNA), Recognition (REC), Nuclease (NUC), Single-Nucleotide Polymorphisms (SNPs).

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