INFINITY

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VARASTEGAN INSTITUTE FOR MEDICAL SCIENCES

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DIRECTOR-IN-CHARGE:

Reaching the sixth edition of the only English-language journal in the field of laboratory sciences is a testament to the tireless efforts of the authors' team and all those who have supported us along the way.

In today's fast-paced world, we have always strived to contribute a small part to enhancing the knowledge and awareness of our country's scientific community in the laboratory sciences field by providing up-to-date and practical scientific articles.

Finally, we cordially invite all professors, students, researchers, and those interested in the life sciences to collaborate with us on future journal issues.

Sincerely

Mahdieh Sadat Hosseini Nezhad

EDITOR-IN-CHIEF:

When I see a new cell under the microscope, it feels like discovering a new planet through a telescope because, in the world of medical laboratory sciences, there's always a new planet waiting to be discovered and this infinite world plays a pivotal role in healthcare, encompassing disciplines such as clinical biochemistry, microbiology, hematology, immunology, genetics, and medical biotechnology. Each article featured in this magazine represents a critical exploration of disease mechanisms, diagnostic techniques, therapeutic strategies, and advancements in medical technology.

I invite you all to join us in this endeavor. Whether you're a student researcher eager to share your findings or a reader curious about the latest breakthroughs, Infinity is here to inspire and inform. Let's embark on this journey together, where curiosity meets discovery and each page of Infinity brings us closer to unraveling the mysteries of laboratory sciences.

Thanks to our dedicated authors and reviewers for their invaluable contributions.

Nazanin Zeinab Arefipour

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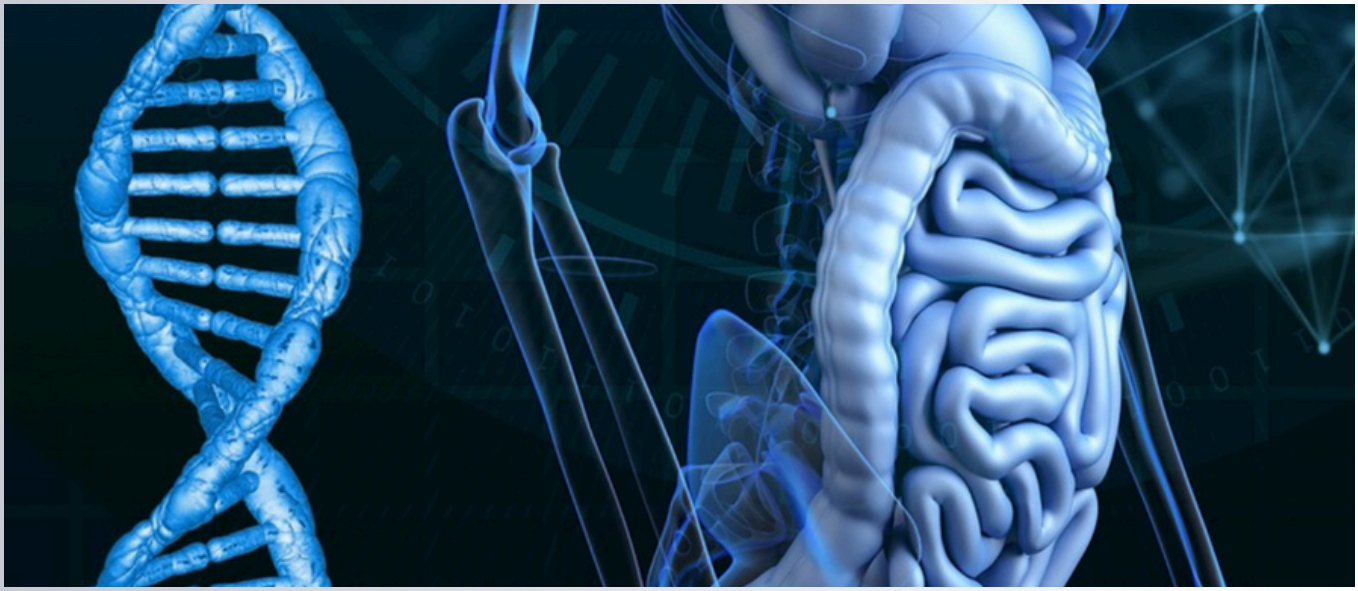
BIOCHEMISTRY

JANUARY 2025

1. Investigating the role of epigenetic biomarkers in colon cancer progression and response to treatment

Examining the significance of epigenetic biomarkers in the diagnosis, progression, and therapeutic potential of

COLORECTAL CANCER



Introduction

Colorectal cancer is recognized as one of the leading causes of cancer-related deaths worldwide. It is a multifactorial disease that is influenced by both genetic and environmental factors. Despite the importance of genetic alterations for its initiation and development, recent advances have highlighted the role of epigenetic mechanisms in cancer biology. Epigenetics involves heritable changes in gene expression that occur without actual changes in the DNA sequence. These changes include DNA methylation and histone modifications, which are implicated in the initiation and progression of cancer. Over the past two decades, many studies have identified epigenetic alterations as key molecular markers of cancer. Such alterations, which usually occur early in the development of the disease, affect almost all key pathways involved in tumorigenesis and are of great importance as clinically relevant biomarkers for diagnosis, prognosis, and prediction of treatment outcome.

Common epigenetic modifications in CRC

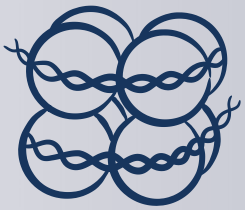
DNA methylation

DNA methylation is one of the most important epigenetic modifications that affects gene expression through the addition of a methyl group to cytosine, mainly at CpG dinucleotides catalyzed by DNA methyltransferases. Changes in DNA methylation may result in global hypomethylation of normally unmethylated regions, or hypermethylation can occur in gene promoter regions that predominantly affect tumor suppressor genes in cancer. For example, the CDKN2A, MLH1, and APC genes are implicated in CRC. Hypermethylation of CpG promoters is associated with silencing of these genes, whereas genome-wide hypomethylation serves as an early marker for colorectal cancer, associated with disease progression from adenomatous stages to advanced CRC.

Somatic methylation of the MLH1 promoter is an important epigenetic biomarker for colorectal cancers with loss of MLH1 and/or PMS2 protein expression in terms of management. The most common underlying mechanism for MLH1 inactivation is somatic biallelic promoter hypermethylation, which allows for the distinction between Lynch syndrome and sporadic MMR-deficient CRCs.

In addition, MLH1 hypermethylation, as well as BRAF mutations, is a hallmark of the serrated pathway in the development of colorectal cancers, thus linking it to serrated polyps and serrated adenocarcinomas.

Modification of Histones



Histone modulations, although not as studied as DNA methylation in the field of potential biomarkers, play a very important role in cancer pathogenesis, especially Colorectal Cancer (CRC).The extent to which histone modifications are being investigated is largely overshadowed by the technical challenges associated with quantifying the changes and their limited specificity across different cancer types. However, some histone modifications have been identified that can serve as valuable diagnostic and prognostic biomarkers in CRC.

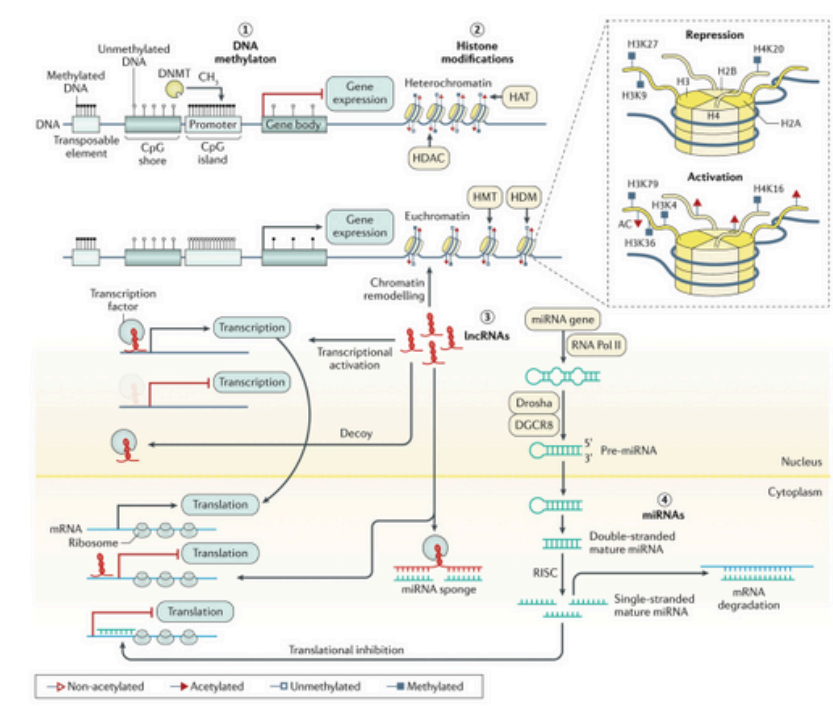
Histone acetylation and methylation have been extensively studied in the field of colorectal cancer progression (CRC) and patient survival outcomes. Some histone methylation markers, especially H3K4, H3K9, and H3K27, correlate with various clinical and pathological characteristics, including TNM staging and lymph node metastasis. In particular, H3K4 dimethylation (H3K4me2) and H3K9 trimethylation (H3K9me3) have been identified as independent prognostic indicators for the occurrence of hepatic metastasis in later stages.

Non-coding RNAs

Numerous scientific research studies have so far shown that non-coding RNAs, especially miRNAs and long non-coding RNAs (lncRNAs), can be used as potential biomarkers for diagnosis, prognosis estimation, and predicting therapy outcomes in colorectal cancer (CRC). However, compared to biomarkers associated with methylation changes, there is a wider need for approval for the clinical application of these ncRNA biomarkers.

MiRNAs have recently attracted a lot of attention as promising biomarkers, as they are small in size, have fewer numbers than protein-encoding genes, and are stable in various biological samples, including tissue, blood, and feces. Their identification and measurement can be done effectively using methods such as microarrays and RT-qPCR. In the past decade, research on miRNAs in Colorectal cancer has increased dramatically, especially in relation to their application as biomarkers, but there are still no well-designed studies with large groups of patients and independent approval. In particular, miR-31, along with miR-143 and miR-145, expressed simultaneously, has been identified as a tissue biomarker for predicting responses to promising treatment, while miR-106A in plasma may be useful for predicting responses to auxiliary chemotherapy in metastatic CRC.

lncRNAs are also emerging as potential biomarkers for CRC, although the exact number of functional lncRNAs remains unclear, and research is continuing in this area. Most studies have focused on lncRNAs in tissue samples, while others focus on blood, which indicates the potential of these biomarkers if they are non-invasive. Increased expression of HOTAIR lncRNA in the early stages of colon cancer is associated with TNM staging and patient survival. Similarly, increased CCAT1 expression in tumor and blood tissue indicates its role in early colon carcinogenesis and its association with the TNM stage and survival. The combination of HOTAIR and CCAT1 expression offers better sensitivity and diagnostic features for CRC than testing any lncRNA alone.



The primary epigenetic alterations associated with colorectal cancer (CRC)

Therapeutic potential of Epigenetics

Investigations into epigenetic alterations in cancer have yielded promising biomarkers and contributed to the development of novel anticancer agents, specifically epigenetic modifiers. These modifiers are reversible, making them more appealing as therapeutic targets than irreversible genetic alterations. Many epigenetic modifiers have been developed, including DNA methylation inhibitors and histone-modifying enzyme inhibitors; most of them have gained FDA approval for other indications besides CRC. It should also be noted that some dietary supplements, such as phenylbutyrate, a histone deacetylase (HDAC) inhibitor, have been proved to enhance the activity of cytotoxic agents in colorectal cancer (CRC). In most cases, clinical studies of epigenetic therapy have targeted patients with late-stage disease, among whom the benefit is generally small because of great heterogeneity and accumulation of genetic lesions. These treatments, therefore, may be more effectively used as adjuvant treatments at early stages of neoplasia, epigenetic alterations being considered early events in the sequence of carcinogenesis, and as such, the genomic burden imposed is relatively low. Moreover, the combination of epigenetic modulators with cytotoxic drugs in advanced-stage cancers may be able to re-establish the responsiveness of the tumor cells to other treatments, thus facilitating a reduction in the doses of cytotoxic drugs and increasing patients' tolerance.

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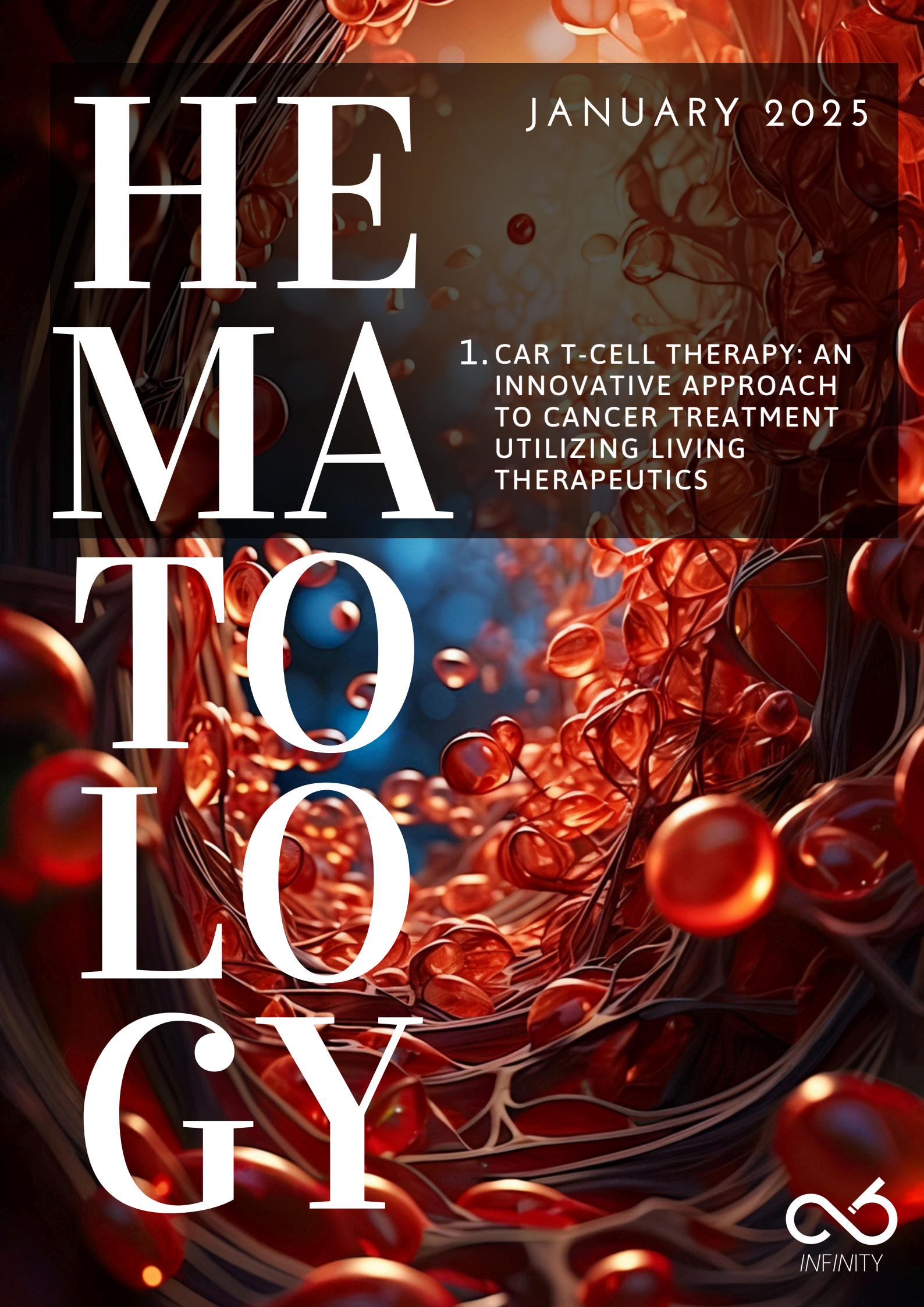
HEMATOLOGY

JANUARY 2025

1. CAR T-CELL THERAPY: AN INNOVATIVE APPROACH TO CANCER TREATMENT UTILIZING LIVING THERAPEUTICS



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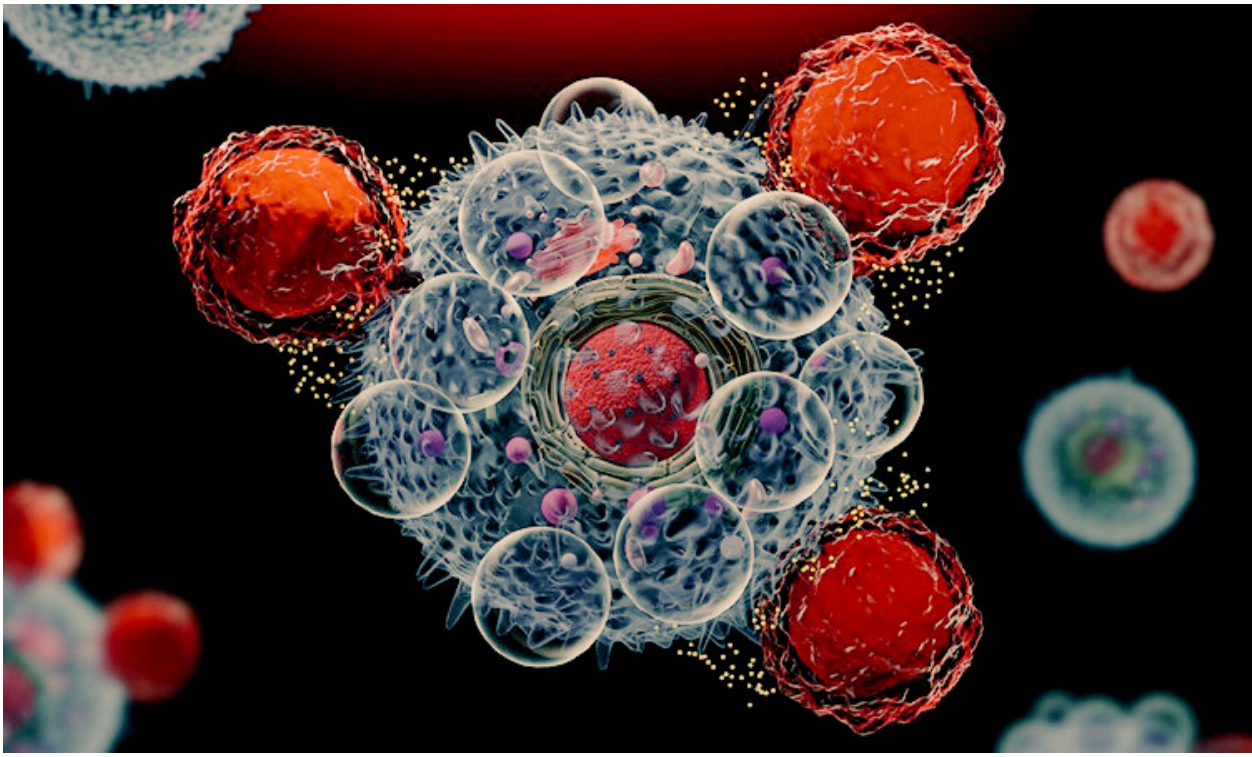
CAR T-CELL THERAPY

AN INNOVATIVE APPROACH TO CANCER TREATMENT UTILIZING LIVING THERAPEUTICS



Introduction

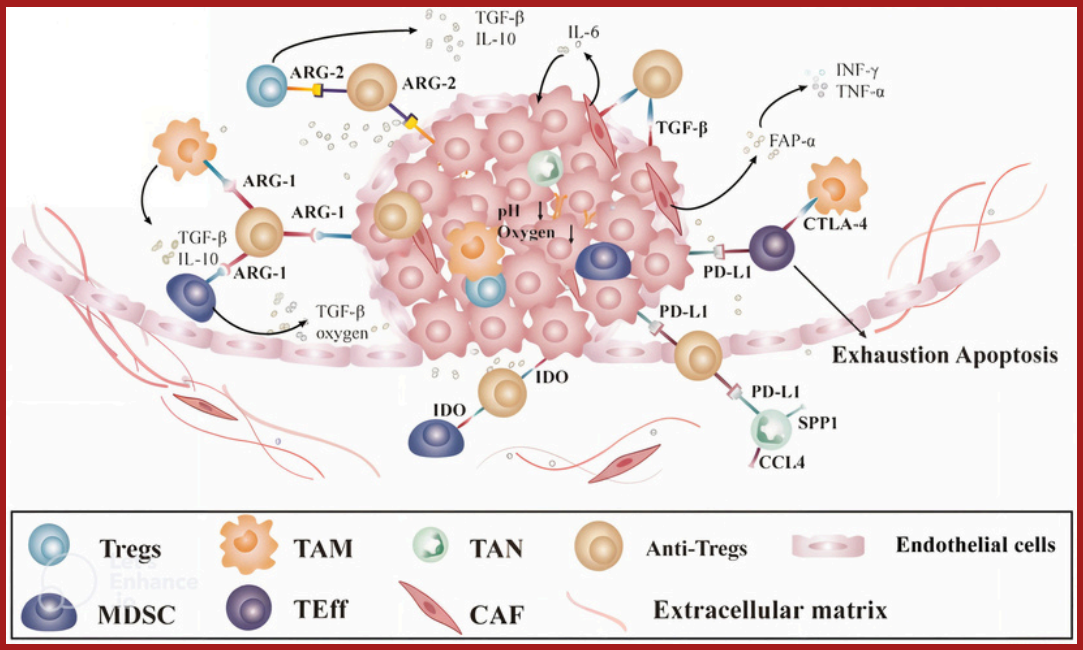
Chimeric antigen receptor (CAR) T-cell therapy is a promising new immunotherapy for cancer, demonstrating encouraging results in patients with B-cell leukemia and lymphoma. However, it faces several challenges, including high toxicity levels and limited anti-tumor activity. This study explores cancer immunotherapy, T-cell genetic engineering, and recent advancements in CAR T-cell methodologies to enhance efficacy in solid tumors and hematologic malignancies. Additionally, it addresses current issues associated with CAR T-cell therapy and discusses potential future therapies involving CAR T-cell-derived nanovesicles.

1. Solid tumors

Because tumors inhibit T-cell function, it is necessary to engineer cells that can overcome this repression. Clinical trials are evaluating the effectiveness of CAR T-cell therapies in treating solid tumors and targeting specific surface markers.

Several cell types involved in cancer treatment are described, including CAR T cells, CAE, CD276, CT041, BPX-601, hCD70, 4S CAR T, GFRA, EGFR, and CD133. Because tumors inhibit T-cell function, these cells must be engineered to overcome this suppression. Clinical trials are evaluating the effectiveness of CAR T-cell therapies in solid tumors and their targeted surface markers.

The immunosuppressive tumor microenvironment hinders CAR T-cell therapy for solid tumors



1.1 Pancreatic Tumors

Both in vitro studies and xenograft animal models demonstrate the therapeutic effectiveness of CAR T-cells against pancreatic tumors expressing αvβ6. T-cells engineered to express CXCR2 exhibit strong anti-cancer activity. Furthermore, co-stimulation with 4-1BB enhances these anti‑cancer effects by reducing PD-1 expression on tumor cells that express PD-L1. Clinical research indicates that CD133-CAR T-cells may decrease the risk of cancer metastasis.

1.2 Triple-Negative Breast Cancer (TNBC)

CAR T-cells have demonstrated efficacy in eradicating triple-negative breast cancer (TNBC) tumor cells, particularly MUC28z CAR T-cells. In xenograft models, these cells can inhibit TNBC cell proliferation and increase Th1 cell cytokine production. Furthermore, CAR T-cells can aid HRG1β in blocking breast cancer cell growth through HER family receptors, offering a potential therapeutic strategy against cancer resistance. Specific CAR T-cells show promise for breast cancer immunotherapy.

1.3 Thyroid Cancer

The initial investigation into CAR T-cell therapy for advanced thyroid cancer developed an ICAM-1- specific CAR T-cell that demonstrated preclinical efficacy. However, the clinical translation of this therapy may be hindered by factors such as elevated levels of soluble ICAM-1 in thyroid cancer patients and the potential for anti-ICAM-1 CAR T-cells to target one another. Alternative strategies that mimic T-cell receptor recognition through antibody-based CARs should be explored. Given that both carcinoembryonic antigen (CEA) and glial cell line-derived neurotrophic factor receptor alpha (GFRA4) are expressed in medullary thyroid carcinoma, this tumor type may be a suitable candidate for CAR T-cell therapy.

2. HEMATOLOGIC MALIGNANCIES

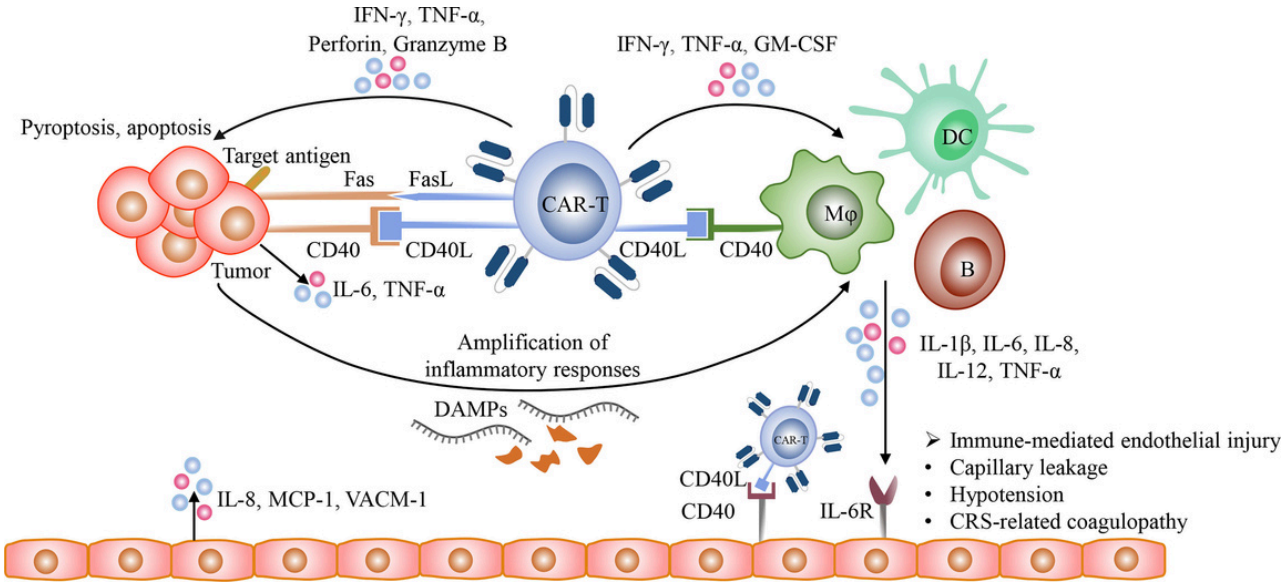
The development of CAR T-cell therapies has demonstrated significant promise in the treatment of hematologic malignancies. In comparison to other strategies, such as immune checkpoint inhibition and tumor vaccinations, CAR T-cell therapies often exhibit slower response times. Three FDA-approved CAR T-cell therapies have been specifically developed for acute lymphoblastic leukemia (ALL) and refractory diffuse large B-cell lymphoma (DLBCL).

In preclinical studies involving HL cell lines and mouse models, CAR T-cell therapies targeting CD30 have shown sustained antitumor responses. Additionally, patients with diffuse large B-cell lymphoma (DLBCL), B-cell acute lymphoblastic leukemia (B-cell ALL), and non-Hodgkin lymphoma (NHL) have reportedly exhibited favorable responses to anti-CD19 CAR T-cell therapy that incorporates a CD28 costimulatory domain, as stated by the National Cancer Institute (NCI).

Combination therapies utilizing cyclophosphamide and fludarabine have proven effective in achieving complete remission in patients with refractory B-cell lymphomas (BCLs). Furthermore, patients with nonHodgkin lymphoma (NHL) or B-cell acute lymphoblastic leukemia (B-ALL) who received anti-CD19 CAR T-cells with a 4-1BB costimulatory domain demonstrated significant antitumor responses. The overall response rate (ORR) to chemotherapy improved when fludarabine was incorporated into the conditioning regimen.

Anti-CD19 CAR T-cells have demonstrated promising results as adjuvant therapies following autologous or allogeneic hematopoietic cell transplantation (HCT) in ALL or B-cell NHL patients. Notably, axicabtagene ciloleucel has shown anticancer responses in refractory NHL when administered in conjunction with fludarabine and cyclophosphamide, as evidenced by phase I and II trials. Current clinical trials are investigating this combination therapy in patients with DLBCL.

The NCI has successfully administered anti-CD19 CAR T-cells to patients with DLBCL, B-cell ALL, and NHL, leading to complete remission in refractory BCLs. The combination therapy of cyclophosphamide and fludarabine has significantly enhanced the overall response rate.



The mechanisms of CAR-T cells in Hematologic malignancies

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JANUARY 2025

Immunology

- The use of natural killer cells in the treatment of endometriosis
- Target therapy by disguising tumor-fighting antibodies for lung cancer

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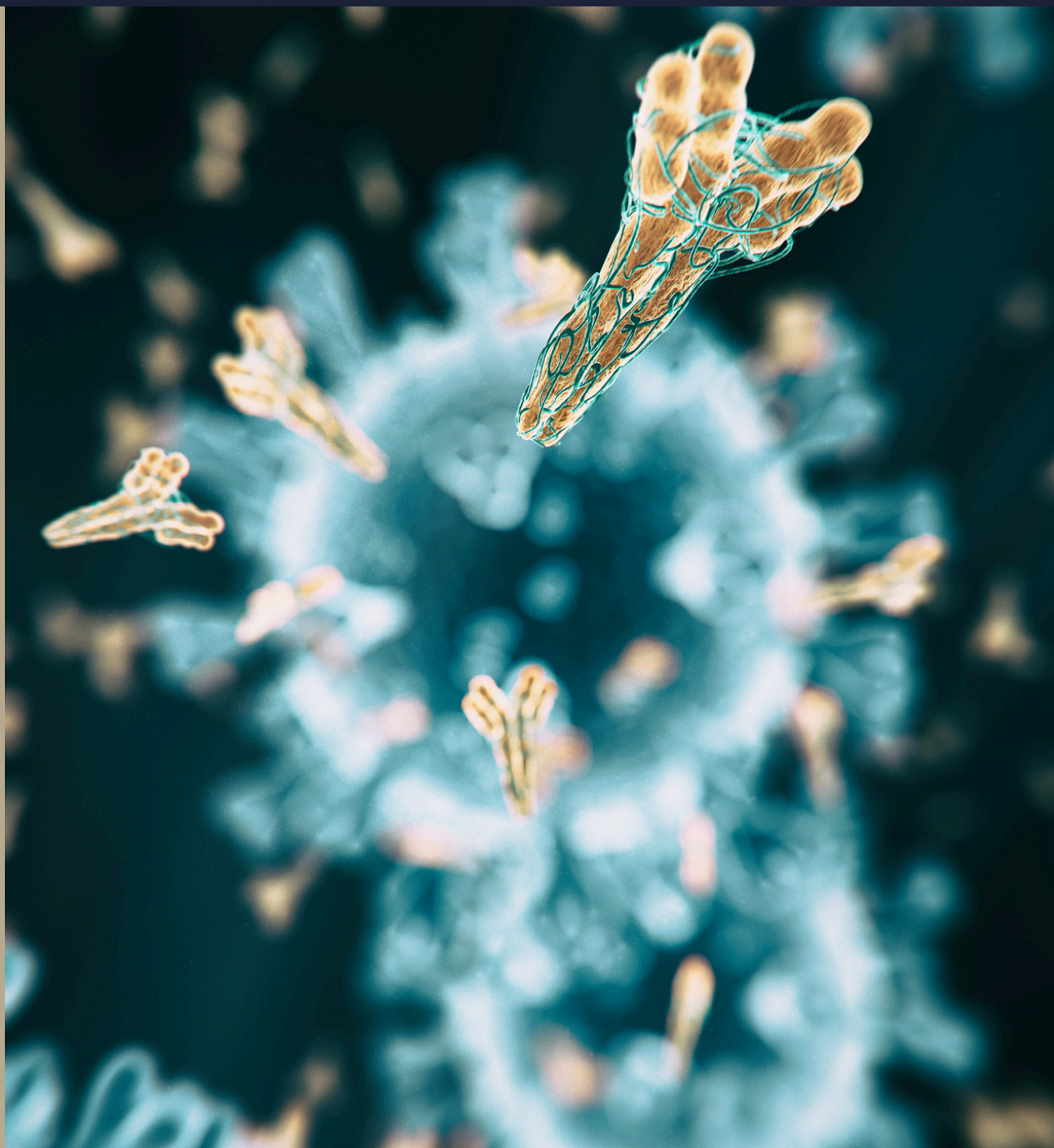
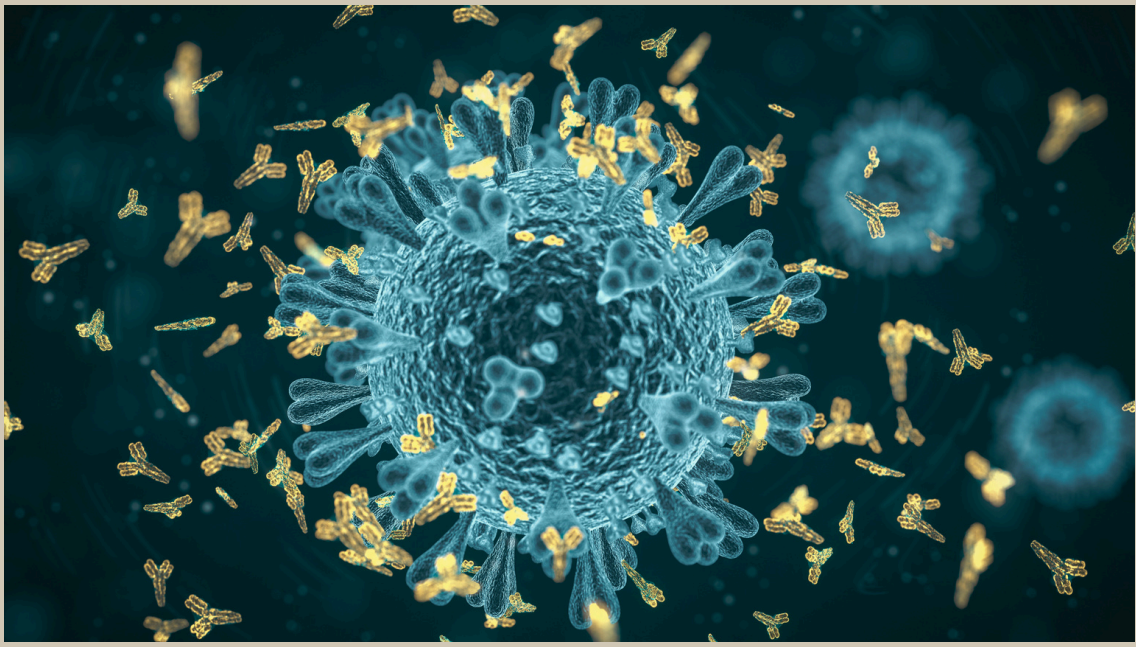


THE USE OF NATURAL KILLER CELLS IN THE TREATMENT OF ENDOMETRIOSIS

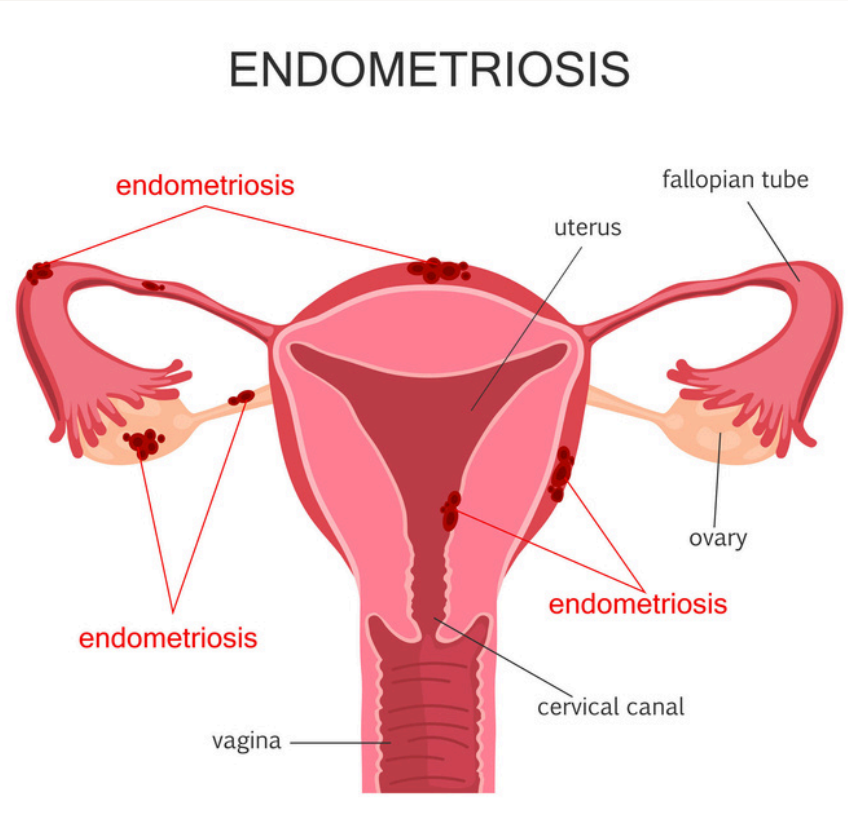


Introduction

Endometriosis is one of the most common gynecological conditions, affecting millions of women worldwide today. It occurs when endometrial tissue, similar to the lining of the uterus, grows outside the uterus. This misplaced tissue can lead to a variety of symptoms, including pelvic pain, irregular bleeding, and infertility. Although the exact cause of endometriosis remains unknown, it is believed to result from a combination of factors, including genetic predisposition, hormonal imbalances, and immune system dysfunction. One area of particular interest is the role of natural killer (NK) cells immune cells that help regulate the body's response to foreign invaders. Research has indicated that women with endometriosis often exhibit abnormalities in their NK cell function, suggesting a potential link between immune dysfunction and the development of the disease. Gaining a deeper understanding of the role of NK cells in endometriosis could pave the way for new therapeutic approaches.

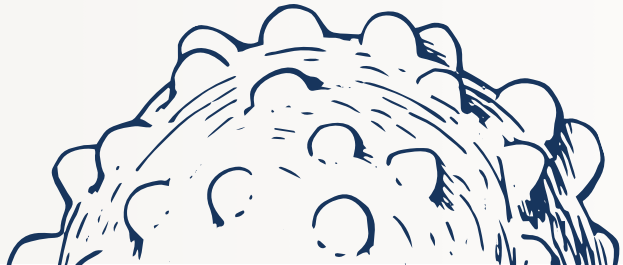
Endometriosis: A Complex Pathophysiological Condition

Endometriosis, characterized by the growth of endometrial tissue outside the uterus, is a complex condition with an uncertain etiology. Several theories have been proposed to explain its development, including retrograde menstruation, metaplasia, and hematogenous or lymphatic spread. Contributing factors to endometriosis include immune dysfunction, hormonal influences, and cellular characteristics. The role of the immune system is particularly significant, as it typically eliminates foreign tissue. However, in cases of endometriosis, the immune response is impaired, allowing endometrial tissue to survive and proliferate. Hormonal factors, particularly estrogen, can further promote the growth of this tissue. Additionally, endometrial cells may exhibit enhanced survival and growth capabilities. The development of endometriosis is likely the result of a complex interplay among these factors. Further research is essential to fully elucidate its pathogenesis and to develop more effective treatment options

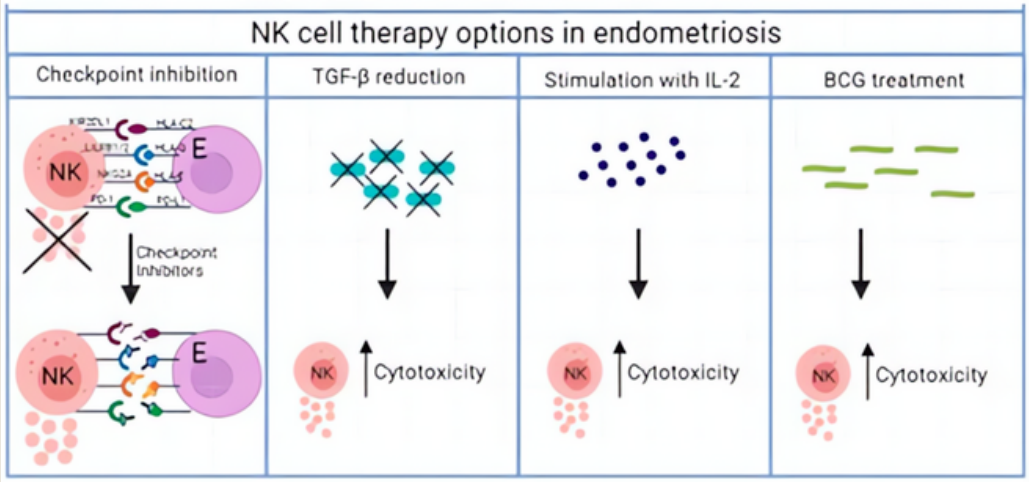


NK Cells and Fertility in Endometriosis

Natural killer (NK) cells are vital in regulating the immune response and can impact fertility. Studies have revealed that women with endometriosis often exhibit abnormal NK cell activity, characterized by reduced cytotoxicity and altered cytokine production. These changes can compromise the body's ability to support pregnancy and contribute to infertility. Natural Cytotoxicity Receptors (NCRs), like NKp46, are expressed on NK cells and regulate their function. Abnormalities in NCR expression, particularly NKp46, have been associated with infertility in women with endometriosis.



Lower NKp46 levels may contribute to diminished NK cell activity and impaired immune function. Cytokine production is also dysregulated in endometriosis. Elevated levels of certain cytokines, such as IFN-γ and TNF-α, have been observed in women with endometriosis. These cytokines can promote inflammation, angiogenesis, and the growth of endometrial tissue.



Different NK cell therapy options in endometriosis

NK Cell Therapy for Solid Tumors : A Promising Approach

While primarily utilized for hematological cancers, the potential of (NK) cell therapy for treating solid tumors is currently under active investigation. NK cells target tumor cells based on the "missing-self hypothesis," which allows them to recognize and eliminate cells that lack self-major histocompatibility complex class I (MHC-I) molecules. In adoptive NK cell therapy, NK cells are isolated, stimulated, expanded, and administered intravenously to patients. Cytokines like IL-2, IL-15, IL-12, and IL-18, or feeder cells, are used to support NK cell expansion and activation.

There are two types of adoptive NK cell therapy: autologous, which utilizes the patient's own NK cells, and allogeneic, which employs NK cells from external sources such as umbilical cord blood or induced pluripotent stem cells.

Ongoing clinical trials are assessing the safety and efficacy of NK cell therapy for solid tumors. Various strategies are being explored to enhance NK cell therapy, including cytokine-based therapy, such as IL-15, which activates NK cells without impacting regulatory T cells. Genetic modifications, such as chimeric antigen receptor (CAR) engineering, can also improve NK cell function by facilitating specific antigen binding and increasing tumor cell cytotoxicity.

NK cell therapy is typically administered intravenously; however, intraperitoneal administration may be considered for peritoneal diseases, such as endometriosis. Given the observed decline in NK cell function in patients with endometriosis, NK cell therapy may offer benefits for those experiencing persistent pain despite conventional treatments. Further research is essential to fully understand the effectiveness and current status of NK cell therapy in the treatment of endometriosis.

Conclusion

Endometriosis, a condition characterized by the abnormal growth of endometrial tissue, is associated with impaired NK cell function. NK cells, which are essential for immune regulation and fertility, can be targeted through NK cell therapy, a promising approach for treating endometriosis. However, further research is necessary to evaluate the effectiveness of this treatment strategy.

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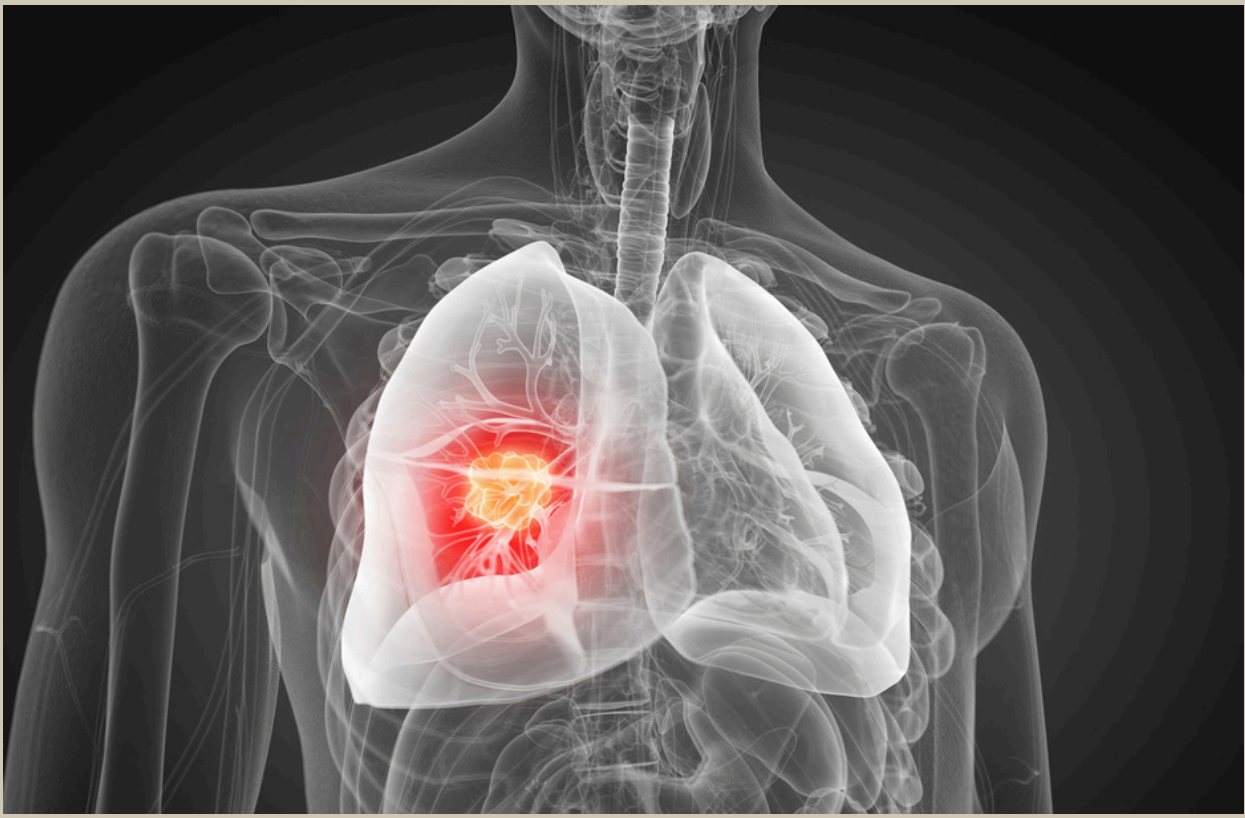
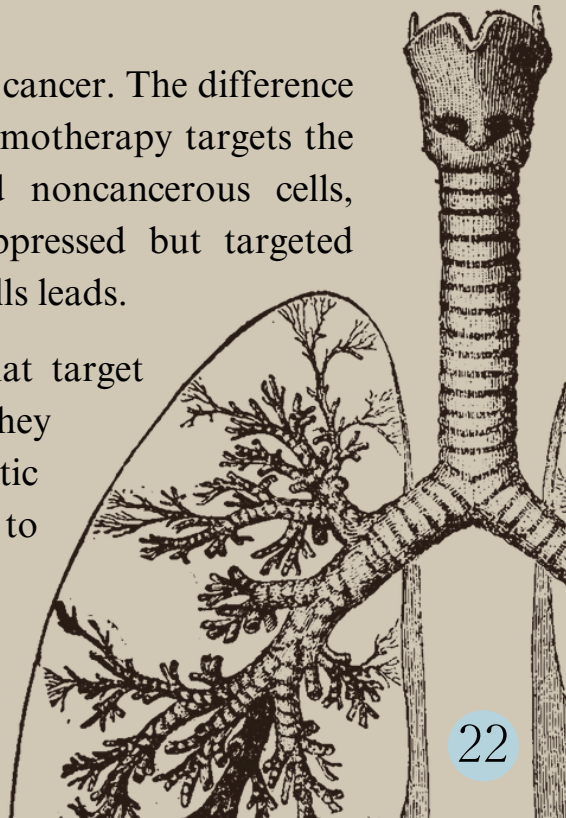
Targeted Therapy for LUNG CANCER



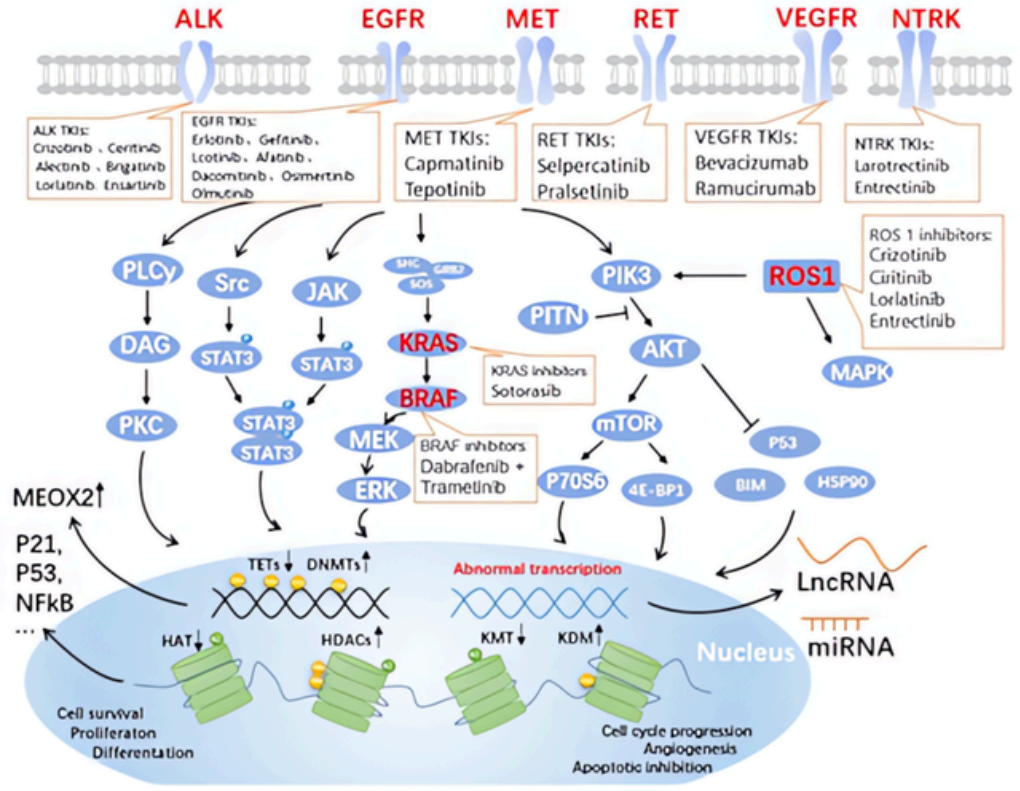
Targeted therapy is a type of cancer treatment that uses specific drugs to inhibit the growth and division of cancer cells. This approach disrupts key molecules cancer cells rely on for growth and survival.

Targeted therapy, like chemotherapy, uses drugs to treat cancer. The difference between chemotherapy and Targeted therapy is that chemotherapy targets the growing cells in the body, including cancerous and noncancerous cells, meaning that useful non-cancerous cells are also suppressed but targeted therapy drugs toward specific characteristics of cancer cells leads.

Targeted lung cancer treatment is the use of drugs that target specific molecules that affect growth and development. They affect the spread of cancer and destroy it. Certain genetic mutations are responsible for lung cancer. According to studies, these drugs are often the treatment of choice It is for people who are in the advanced stages of lung cancer.



Generally, targeted treatment of lung cancer has a higher response rate and has a long-term effect.



Genes and pathways associated with targeted drugs for NSCLC

Types of lung cancer targeted drugs

There are different drug categories for lung cancer targeted treatment. Each of these categories has a receptor, they target a mutation or a path in the cell. In the following, these categories are explained based on their purpose or target.

Purpose: growth of tumor blood vessels

Cancerous tumors need constant blood to grow. Angiogenesis inhibitors are a type of long-acting drug that targets the blood vessels that support cancer cells. By blocking the growth of these blood vessels, this targeted therapy can slow down the growth of lung cancer We may call these drugs VEGF inhibitors.

It is very likely that the doctor will prescribe bevacizumab or ramucirumab for targeted therapy Lung cancer prescribes.

Purpose: EGFR mutations

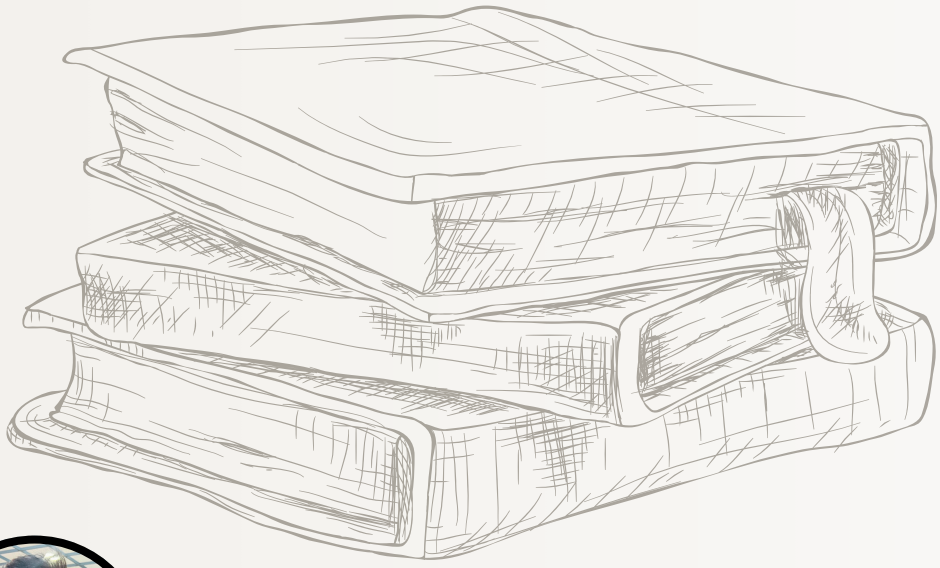
Epidermal growth factor receptor (EGFR) is a protein outside cells that controls their growth and division EGFR genetic mutations can cause excess EGFR in cells It causes cancer to grow faster. EGFR inhibitors prevent cell growth and division Cancer cells block EGFR signals. Some common EGFR inhibitors for lung cancer include Afatinib and Osimertinib. The side effects of this type of treatment can be so severe that doctors advise people to stop using it Prevent EGFR inhibitors.

Purpose: ALK gene mutation

ALK is a protein that supports cell growth. Some people with lung cancer have mutations in the ALK gene. ALK inhibitors are drugs that treat cancers. Some people can use them after or instead of chemotherapy some examples of these drugs are: Alectinib and Brigatinib.

Purpose: 1ROS gene mutation

According to a recent study, 1ROS inhibitors are a targeted lung cancer treatment for people suffering from a type of lung cancer known as adenocarcinoma. Adenocarcinoma is the source of 50 to 60% of lung cancer in people who do not smoke. If the doctor detects the 1ROS mutation, he may prescribe one of the following drugs: Lorlatinib and Crizotinib.



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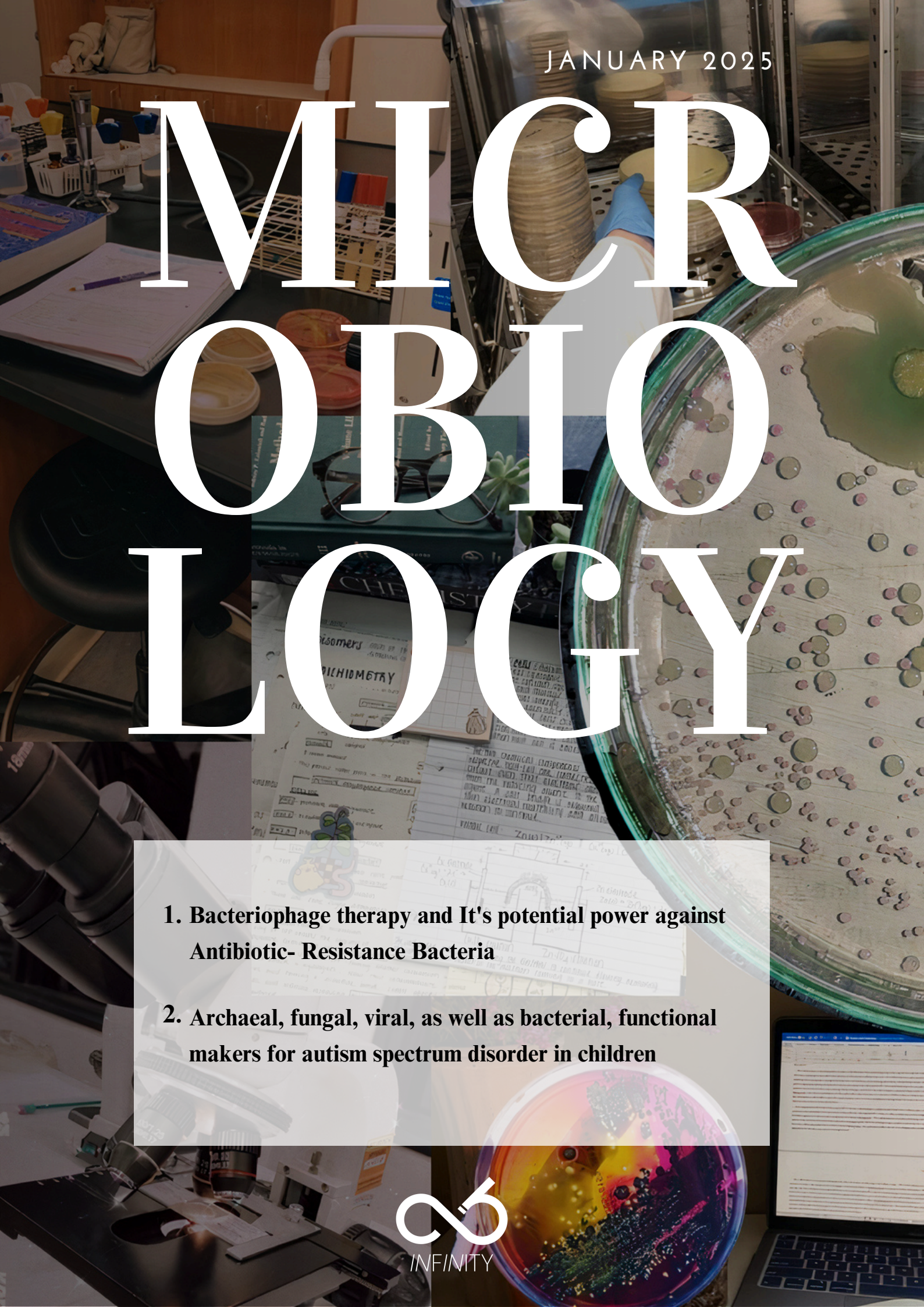


JANUARY 2025

MICROBIOLOGY

1. **Bacteriophage therapy and It's potential power against Antibiotic- Resistance Bacteria**

2. **Archaeal, fungal, viral, as well as bacterial, functional makers for autism spectrum disorder in children**

INFINITY

Bacteriophage Ttherapy

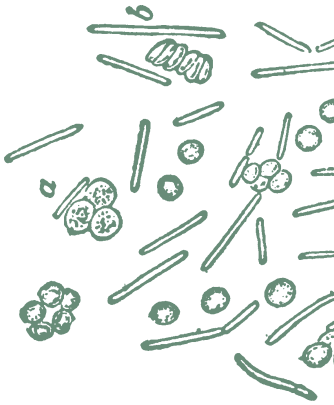
And Its Potential Power Against Antibiotic-Resistant Bacteria

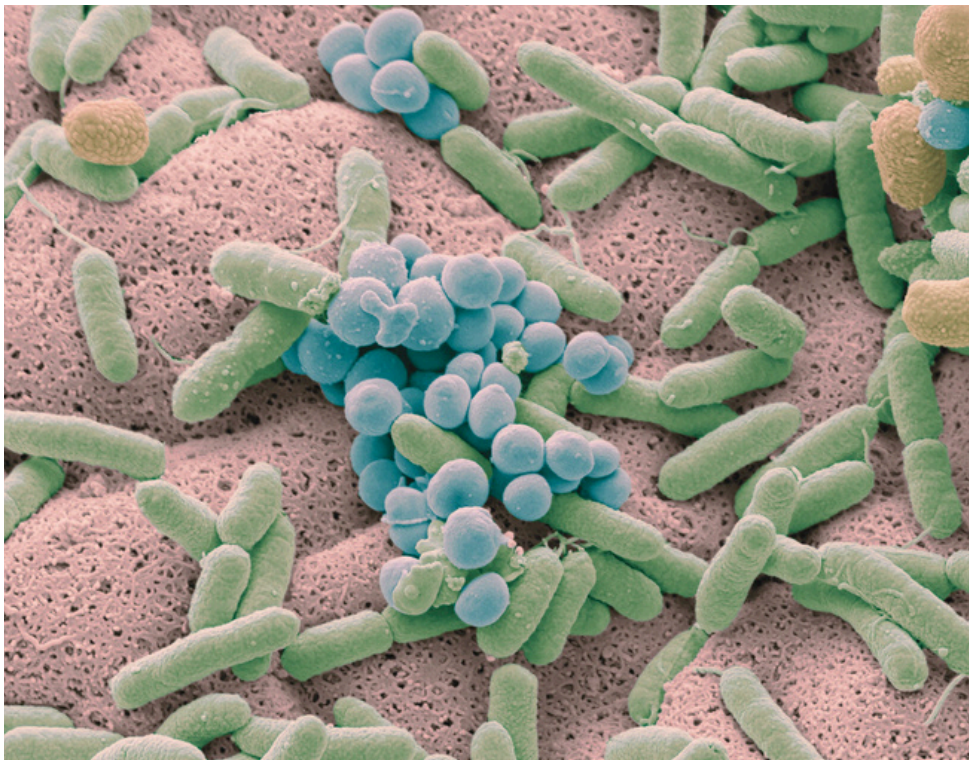
Introduction

Today, the emergence of antibiotic-resistant bacteria is considered a very important and worrying challenge all over the world. In this context, the World Health Organization published several highly antibioticresistant pathogens as critical priorities.

They are called antibiotic-resistant ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and Enterobacter species) pathogens. Due to the acquisition of antibiotic resistance genes by these bacteria, the treatment of their infections has failed and the rate of death caused by them has increased. Therefore, following the concerns created by them, the focus on the use of (bacterio) phage therapy as an alternative to traditional antibiotics has been increasing over the years. Phages, which are defined as bacterial viruses, are the most abundant organisms on the earth. Therefore, the use of the power of phages will be investigated by focusing on their effects on antibiotic resistance of bacteria

ESKAPE Bacteria



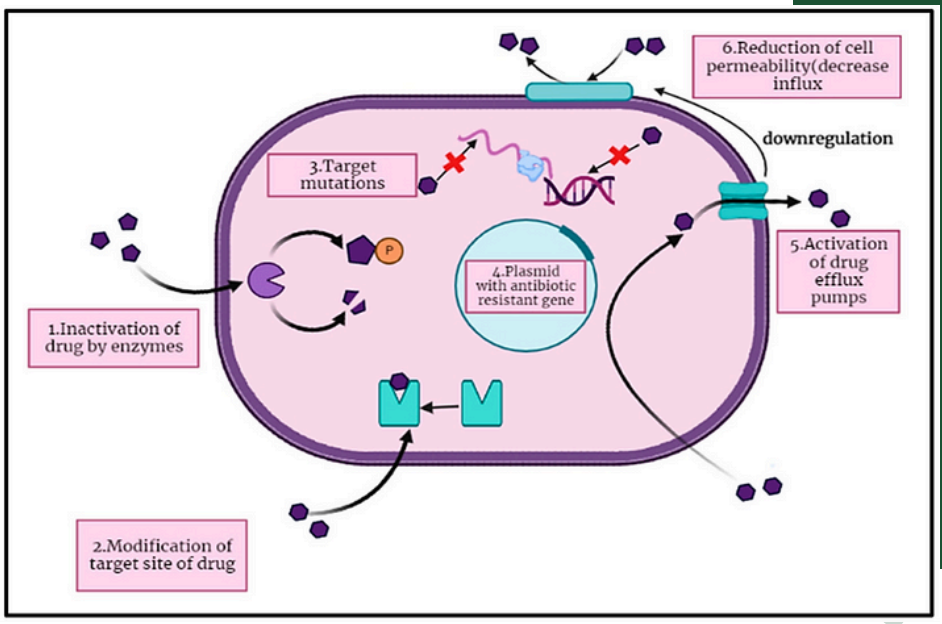


ESKAPE pathogenic bacteria are considered multidrug-resistant bacteria, which include *Enterococcus faecium (E), Staphylococcus aureus (S), Klebsiella pneumonia (K), Acinetobacter baumannii (A), Pseudomonas aeruginosa (P),* and Enterobacter species (E). Members of these bacteria, which are opportunistic in hospitals, are the main threat to health-care-related infections. Overall, these gram-positive and gram-negative bacteria are capable of causing infection in a wide range of patients due to the production of multiple virulence factors like biofilm production, adhesion, and antibiotic resistance mechanisms. Most of the bacteria in this group, which are classified as critical cases by the World Health Organization, can cause blood, urinary and respiratory infection.

Antibiotic-Resistant in Bacteria

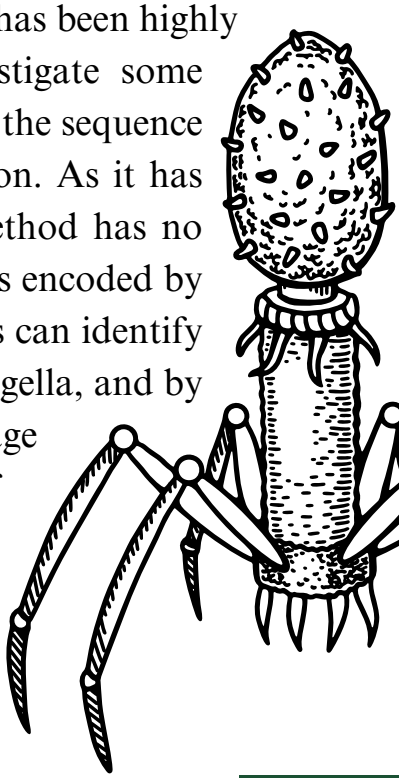
Antibiotic resistance has been an increasing trend in the past several decades, so it has become a critical issue in public health. This phenomenon is happening in many bacteria, and in this way, the effect of antibiotics against them is greatly reduced. In general, the mechanisms of antibiotic resistance can be divided into several groups, such as changing or inactivating the drug, modifying the binding site of the antibiotic, using efflux pumps, changing the permeability of the outer membrane to prevent the intracellular accumulation of antibiotics, and forming a biofilm. Also, a series of antibiotic resistance genes may be located on genetic elements such as chromosomes, plasmids, and transposons.

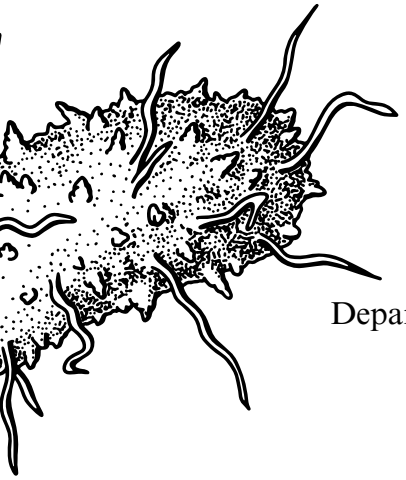
Phage therapy



Different mechanisms of antibiotic resistance in bacteria

Phages, which are introduced as bacterial viruses, are widely found in various environments such as sewage pipes. Phages exhibit common viral characteristics such as intracellular replication, relatively small genomes, apply the host machinery for replication, and host specificity. In terms of morphology, these viruses have different forms, but the most well-known of them is the double-stranded DNA (dsDNA) tailed phages. Also, phages are classified into two groups lytic and lysogenic based on their replication cycle. The use of bacteriophages to treat bacterial infections has been started many years ago. Moreover, in recent years, due to the emergence of antibiotic-resistant bacteria and the problems caused by them, the use of new antimicrobial approaches, such as bacteriophage therapy, has been highly regarded. For the clinical use of phages, it is necessary to investigate some characteristics, including determining the host range and determining the sequence of the phage genome to identify the phage species and its purification. As it has been confirmed in animal studies and human clinical trials, this method has no side effects and no pathogenicity. In this method, phages and enzymes encoded by them, such as endolysins, are used to destroy bacteria. These enzymes can identify specific adhesins on bacterial structures such as peptidoglycan and flagella, and by binding to them, degrade the cell wall of the bacteria. In addition, phage depolymerases recognize the exopolysaccharide structures matrix of the biofilm and digest them. Therefore, this action disrupts the biofilm of bacteria and eradicates them .





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FUNCTIONAL MICROBIAL MARKERS

(ARCHAEAL, FUNGAL, VIRAL, AND BACTERIAL) FOR AUTISM SPECTRUM DISORDER IN CHILDREN

Background

Autism Spectrum Disorder (ASD) is thought to result from both genetic and environmental influences. Recent research indicates that the gut microbiome, which consists of the bacteria and other microorganisms in the gut, may significantly impact ASD by affecting the communication between the gut and brain, as well as immune functions. Studies have found that children with ASD often have different gut microbiota compared to those without the condition. Some treatments, such as fecal microbiota transplants from healthy individuals, have reported improvements in symptoms.

While most studies have concentrated on bacteria, emerging technologies are highlighting the need to also investigate other microorganisms, such as archaea, fungi, and viruses. More research is necessary to understand how these various microorganisms interact and their roles in the development of ASD.

About the study

In this study, researchers recruited children under 12 years old, both neurotypical and those with Autism Spectrum Disorder (ASD), from a psychiatric clinic from December 2021 to December 2023. ASD diagnoses followed the DSM-5 criteria, while neurotypical children were matched for age and sex and screened for autism traits using a specific quotient.

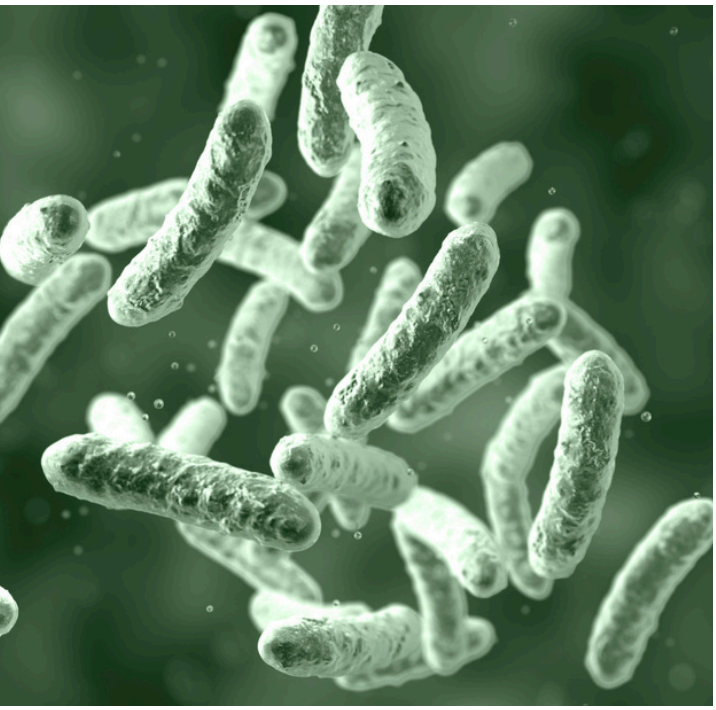
Children with certain conditions or who had recently used probiotics, antibiotics, or specific medications were excluded from the study. Detailed profiles were created for participants, including information on demographics, health conditions, medications, parental factors, and diet. Validation of findings involved separate groups for ASD cases from both a hospital and the community, alongside comparisons with cohorts for Attention Deficit Hyperactivity Disorder (ADHD) and atopic dermatitis.

Stool samples were collected to analyze microbial DNA and RNA, with extraction and sequencing carried out using advanced technology. The analysis of microbial profiles was conducted using specific software tools, and machine learning models were developed to assess the relationships between microbial data and various phenotypes. These models were tested on independent groups to confirm their reliability.

Study results

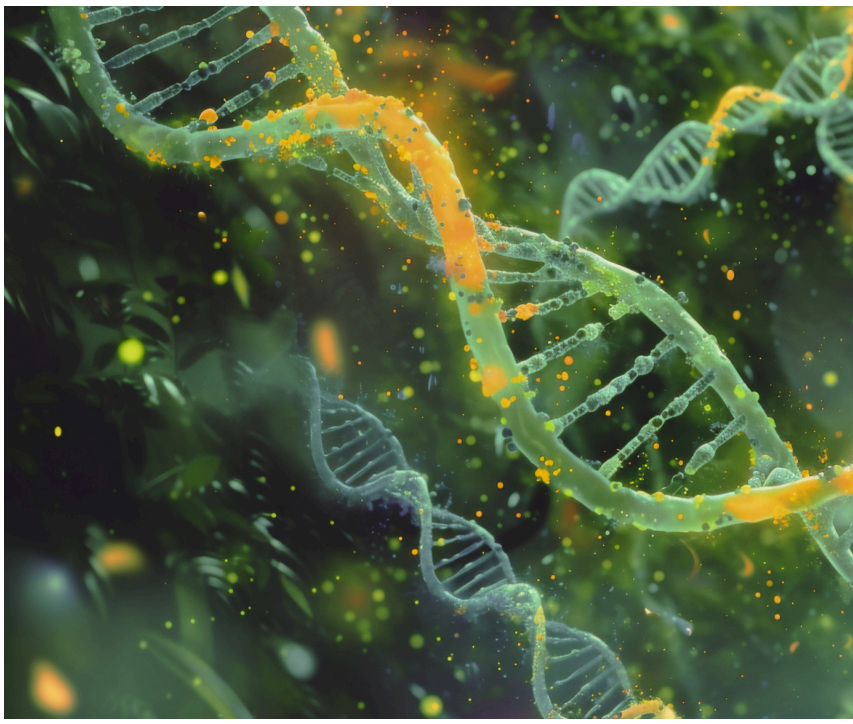
The study recruited 1,627 children aged 1-13, of whom 24.4% were female, from five different groups. Researchers collected extensive data on various factors, including age, sex, body mass index, diet, and health conditions. They performed metagenomic sequencing on fecal samples from these children, including 709 diagnosed with Autism Spectrum Disorder (ASD) and 374 neurotypical controls.

To validate their findings, they used additional samples from a hospital cohort (172 samples: 82 ASD and 90 neurotypical) and a community cohort of younger children (116 ASD and 60 neurotypical). They also analyzed 237 additional fecal samples from children with Attention Deficit Hyperactivity Disorder (ADHD) and atopic dermatitis to test the specificity of their results.



The research found that host phenotype factors accounted for 17.1% and 15.7% of the variation in microbiome pathways and microbial genes, respectively, with an ASD diagnosis being the most significant factor influencing these variations. They identified 27 differential genes (23 decreased and 4 increased) and 12 pathways linked to ASD, with notable reductions in pathways related to ubiquinol-7 and thiamine diphosphate biosynthesis in children with ASD.

The study evaluated microbial markers for diagnosing ASD, finding that a model based on microbial pathways had the best predictive ability (area under curve or AUC of 0.87). A combined model from various microbial kingdoms showed even better performance (AUC of 0.91). They identified 31 microbial markers, including specific bacteria and biosynthesis pathways, that contributed to diagnosis.

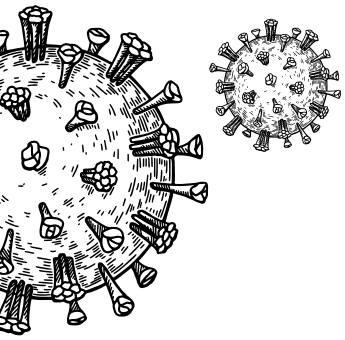


The external validation confirmed the panel's effectiveness, showing AUC values between 0.55 and 0.87 in different cohorts, with a strong performance (AUC of 0.89) in a younger group. The panel was reproducible across various populations, demonstrating its robustness and applicability. When tested in non-ASD groups (children with ADHD and atopic dermatitis), the panel showed lower specificity, underscoring its effectiveness for ASD. Notably, the reduced levels of genes associated with ubiquinol-7 and thiamine diphosphate biosynthesis were consistently linked with ASD across different cohorts.

Conclusions

This study examined more than 1,600 metagenomes from five different groups of participants. It found that certain species of archaea, fungi, viruses, and specific functional pathways in the microbiome can distinguish children with Autism Spectrum Disorder (ASD) from those who are typically developing (neurotypical).

A model that utilized 31 markers from various kingdoms of life demonstrated strong accuracy in diagnosing ASD. The consistent results across different ages, genders, and groups highlight the markers' promise as useful diagnostic tools.



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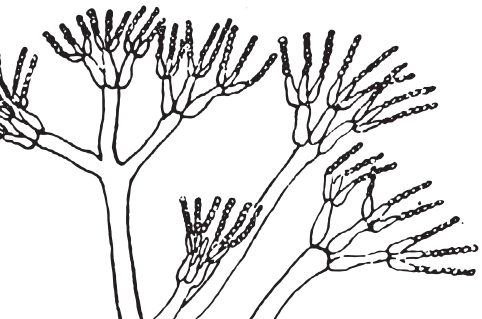
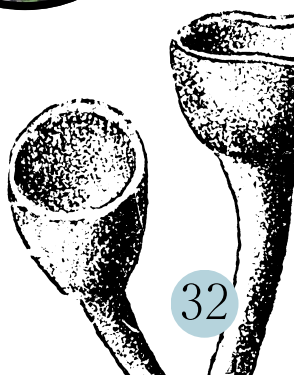




GENETICS

BIOTECHNOLOGY

JANUARY 2025

1. THE ROLE OF MICRORNAS IN B-CELLDEVELOPMENT AND FUNCTION
2. DRUG DELIVERY IN LUNG CANCER WITH ALGAL MICROROBOTS

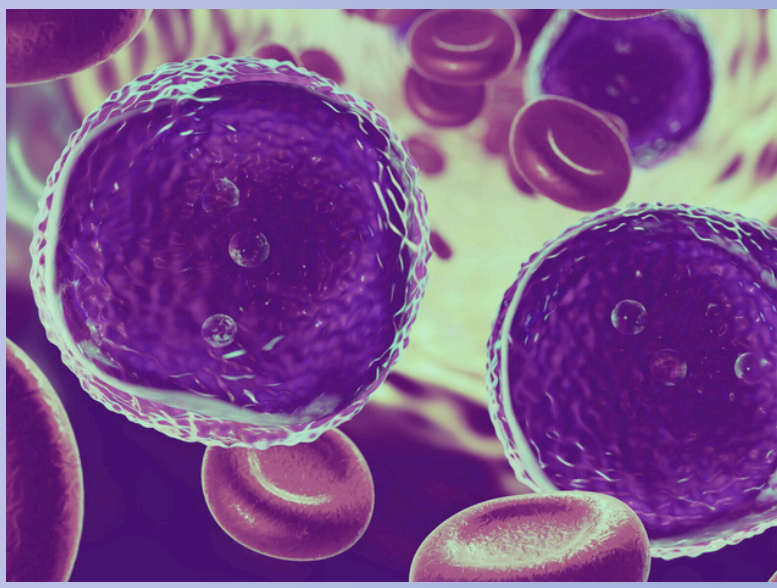
INFINITY

The Role of MicroRNAs in B-cell

Development and Function: Unveiling New Mechanisms in Immune Regulation

MicroRNAs (miRNAs) are short RNA sequences, typically about 22 nucleotides long, that do not code for proteins but play a significant role in controlling gene expression. By attaching to messenger RNA (mRNA), they can inhibit its translation or trigger its degradation. MiRNAs are crucial for the development and functioning of B-cells, affecting processes such as differentiation, immune system activity, and programmed cell death. Their roles also extend to autoimmune diseases and B-cell-related cancers like lymphoma.

Introduction to MicroRNAs and Their Function



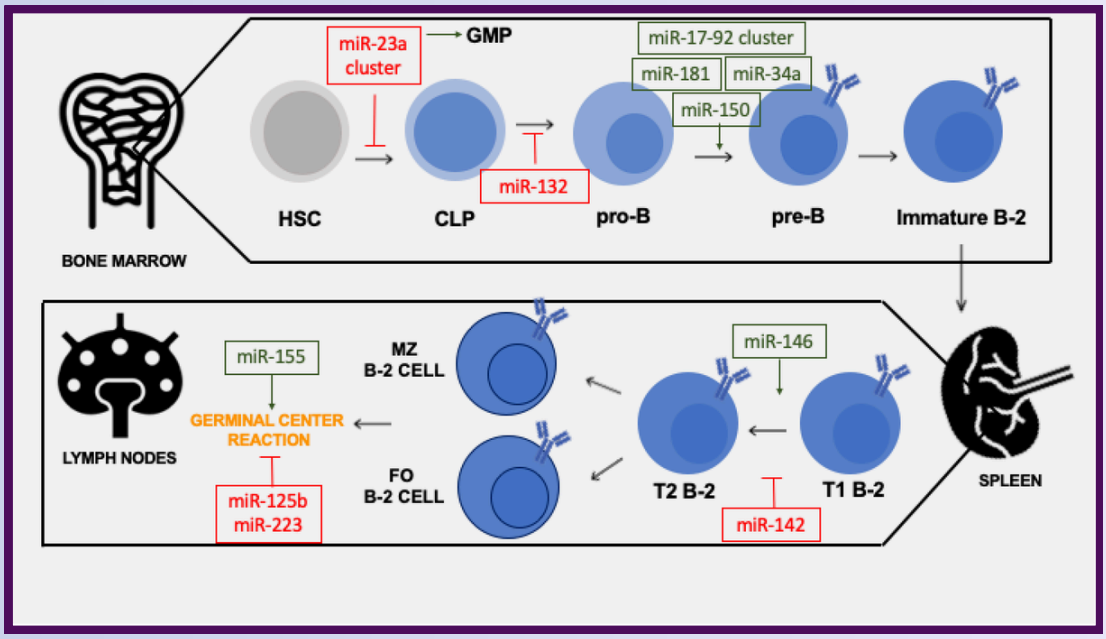
The production of miRNAs involves multiple steps. Initially, primary miRNAs (pri-miRNAs) are formed in the nucleus. These are processed into precursor miRNAs (pre-miRNAs), and finally into mature miRNAs in the cytoplasm. They primarily regulate gene expression by targeting the 3' untranslated regions (UTRs) of mRNAs.

In B-cells, miRNAs oversee critical functions including activation, proliferation, and apoptosis.

MicroRNAs in B-cell Development, Function and Apoptosis

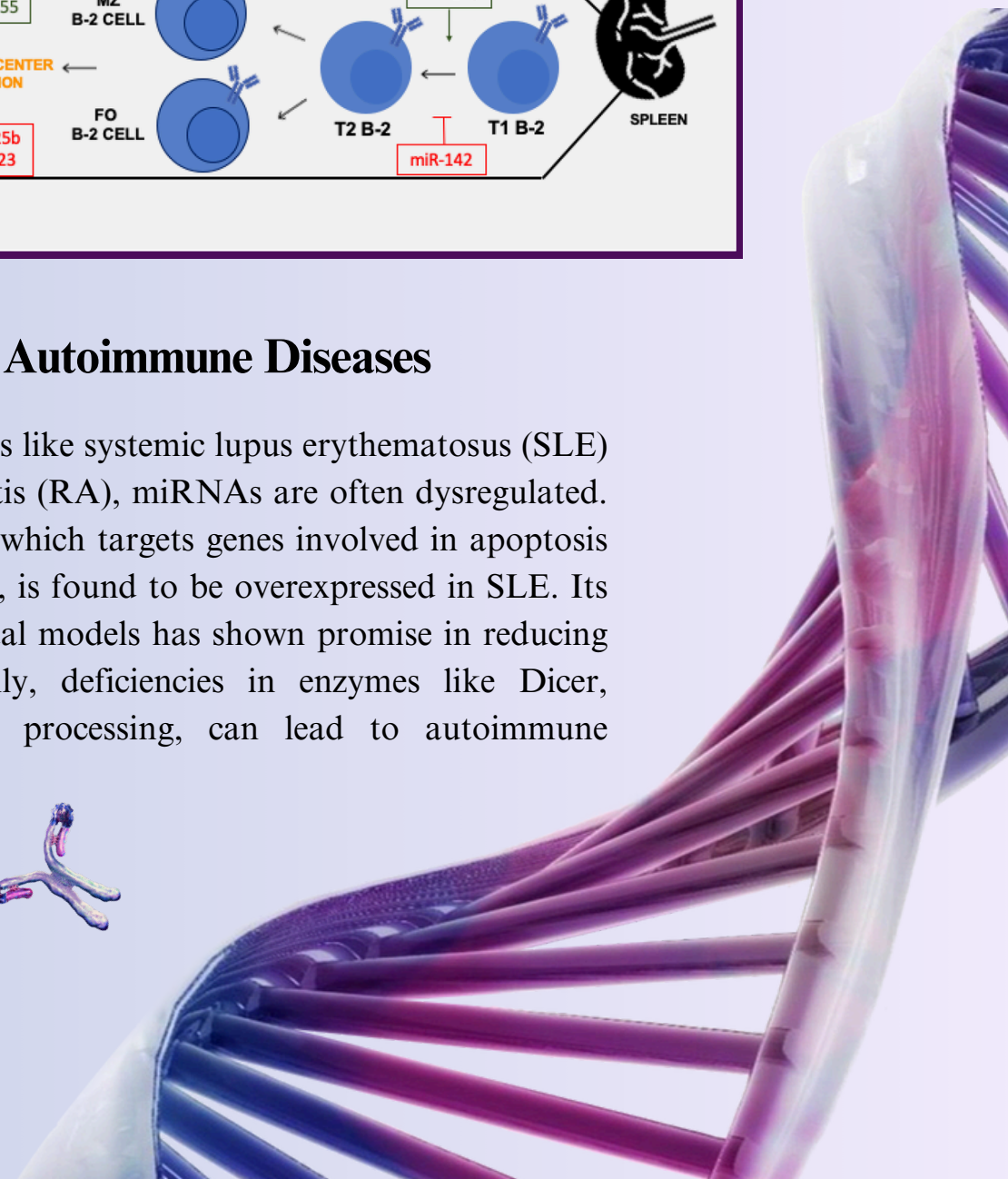
B-cell development, which begins in the bone marrow with hematopoietic stem cells, is a complex process involving stages that lead to the formation of antibody-producing cells in lymphoid tissues. Key miRNAs like miR-181a, miR-150, and the miR-17-92 cluster influence this development by ensuring proper differentiation and maintaining immune tolerance. Disruption in their regulation can result in autoimmune diseases or cancers.

Once matured, B-cells play an essential role in immune defense, particularly in producing antibodies and maintaining immune system balance. MiRNAs such as miR-155, miR-181b, and miR-125b are vital in regulating these processes. For instance, miR-155 is critical for B-cell activation and immune memory, while miR-125b supports cell survival by inhibiting apoptotic pathways.

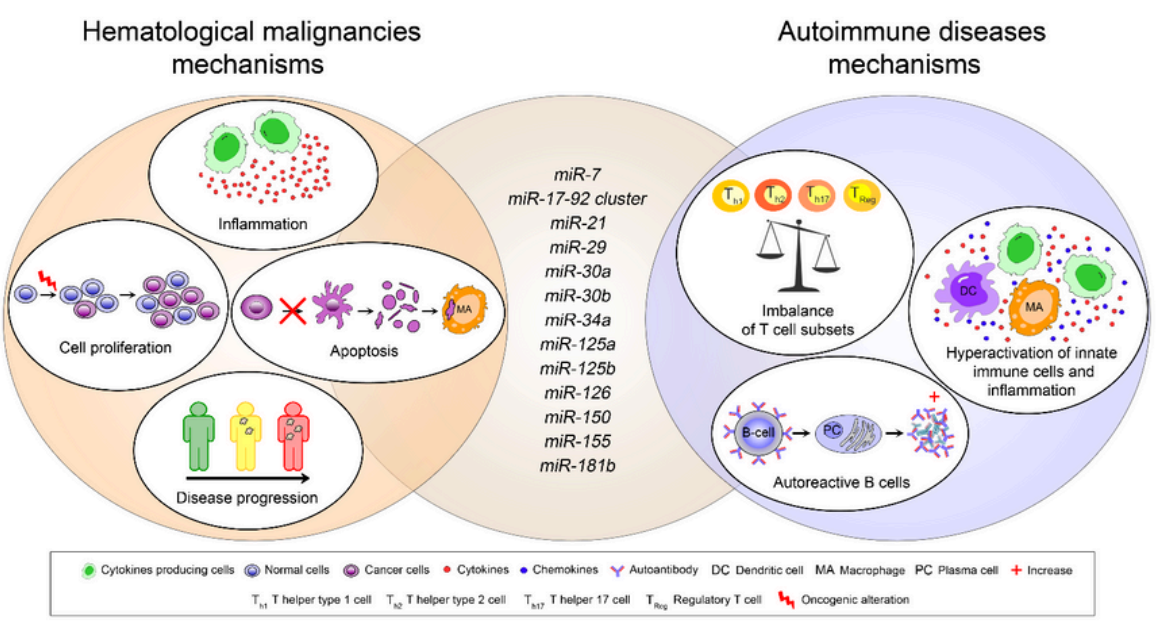


MicroRNAs and Autoimmune Diseases

In autoimmune diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), miRNAs are often dysregulated. For example, miR-21, which targets genes involved in apoptosis and cell differentiation, is found to be overexpressed in SLE. Its silencing in experimental models has shown promise in reducing symptoms. Additionally, deficiencies in enzymes like Dicer, essential for miRNA processing, can lead to autoimmune conditions.



MiRNA dysregulation is also a hallmark of B-cell lymphomas such as chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL). Certain miRNAs, like the miR-17-92 cluster, act as oncogenes by promoting cell survival and proliferation, while others, such as miR-34a, function as tumor suppressors.



Conclusion

Overall, miRNAs are pivotal in B-cell biology, influencing everything from their development and immune response to their role in disease. Research into their mechanisms offers promising avenues for developing new treatments for autoimmune diseases and B-cell malignancies, including diagnostic tools and targeted therapies.

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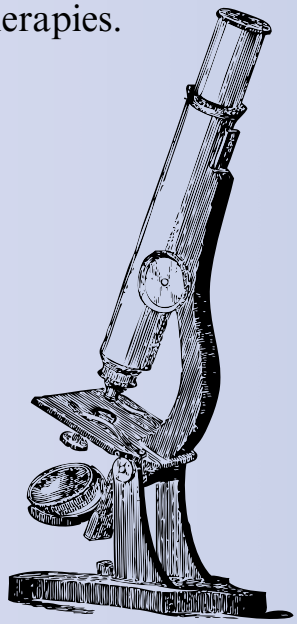


DRUG DELIVERY IN LUNG CANCER WITH ALGAL MICROROBOTS

Introduction:

Lung cancer is one of the most prevalent and lethal forms of cancer, characterized by the uncontrolled growth of lung cells that form a mass known as a tumor. This tumor can be malignant, indicating its potential to invade surrounding tissues and metastasize to other areas of the body. The primary risk factor for lung cancer is smoking, and its symptoms may include a persistent cough, shortness of breath, wheezing, chest pain, and unexplained weight loss.

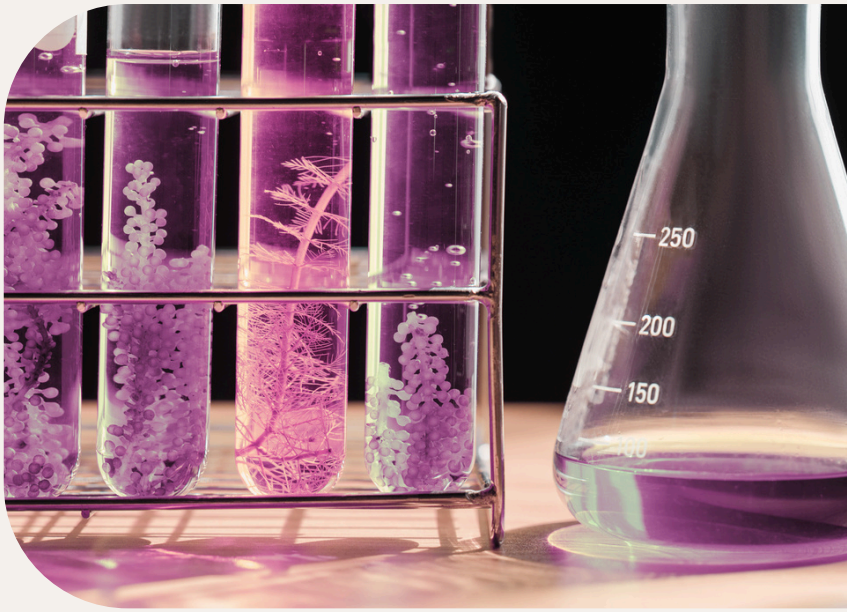
One of the most promising approaches in cancer treatment is targeted drug delivery, which enhances the effectiveness of medications while minimizing side effects. In this context, biohybrid microrobots derived from microalgae play a significant role as drug carriers. These microrobots, owing to their unique biological structure and specialized capabilities, can effectively transport drugs directly to cancer cells.

Algae possess advantageous biological properties and compatibility with the human body, allowing for more precise and efficient operation in the design of drug delivery systems.

Clinical trials:

In newly published research, biohybrid microrobots utilizing green microalgae have been developed to deliver chemotherapy directly to the lungs and treat lung metastases. Traditional artificial microrobots are often inefficient due to the presence of toxic compounds, such as heavy metals, and their limited ability to access various organs in the body. In contrast, biological microrobots, which incorporate flagellated microalgae, can effectively reach target organs, exhibit lower toxicity, and are more cost-effective and easier to produce.

The microalga "Chlamydomonas reinhardtii", which is also utilized in the pharmaceutical industry, is camouflaged with nanoparticles coated in red blood cell membranes. This approach enhances the biocompatibility of the microrobot and helps prevent the patient's immune system from attacking both the microrobot and the chemotherapy drug as they are delivered to lung cells.



This method was tested by researchers on mice with lung cancer. By utilizing algae-based biohybrid microrobots, they delivered the drug directly to the mice's lungs via the trachea, thereby minimizing the side effects of chemotherapy on organ size. When the microrobots are introduced into the lungs, they can navigate and distribute the drug throughout the lung tissue. Additionally, they can evade destruction by immune cells in the lungs, allowing for the gradual release of the drug from the nanoparticles, which enhances its efficacy in the lungs.

By delivering chemotherapy more effectively to diseased lung tissues, the biohybrid microrobots significantly improved treatment outcomes by reducing lung tumors and increasing the survival rates of treated mice. The survival rate of mice treated with algae-based microrobots increased by 40%, extending the lifespan of these diseased mice from 27 to 37 days.Immune cells ultimately degrade the microbots into non-toxic components and eliminate them from the body.

Result:

Biohybrid microrobots offer a promising method for delivering drugs to the lungs in the treatment of pulmonary diseases. Researchers are exploring the application of this technology for various other lung conditions. Additionally, these microrobots, composed of microalgae, may serve as a foundation for developing bioengineered cancer therapies.

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FIRST TIME IN THE WORLD

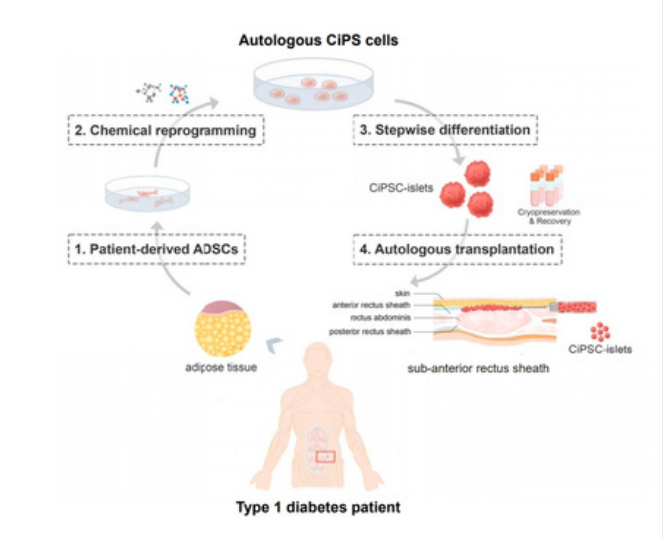
STEM CELLS REVERSE TYPE 1 DIABETES

A 25-year-old female patient with type 1 diabetes has demonstrated the ability to produce her insulin in less than three months following a pioneering stem cell transplant.

The research team, led by Deng Hongkui at Peking University, utilized cells extracted and reprogrammed from three individuals diagnosed with type 1 diabetes, transforming them into pluripotent stem cells. This approach represents an advancement over previous methodologies, as it incorporates small molecules to enhance control over the reprogramming process.

The researchers subsequently developed three-dimensional clusters of islets from these induced pluripotent stem (iPS) cells and conducted safety assessments in animal models. In June 2023, approximately 1.5 million islets were administered into the patient's abdominal muscles, a novel technique that facilitates monitoring through magnetic resonance imaging (MRI), in contrast to the conventional method of placement in the liver. Following a period of two and a half months, the patient exhibited the capacity to independently produce adequate insulin, successfully maintaining stable blood glucose levels within the target range for over 98% of the day for a duration exceeding one year.

Given that the subject had been administered immunosuppressants following a prior liver transplant, the researchers were unable to ascertain whether the induced pluripotent stem (iPS) cells contributed to a decreased likelihood of transplant rejection. Furthermore, even in the absence of transplant rejection, individuals with type 1 diabetes possess an autoimmune disorder, which presents a persistent risk of their immune system targeting the islet cells. Deng observed that this phenomenon was not evident in the subject due to her immunosuppressive therapy; however, the research team is actively engaged in the development of cells that can circumvent this autoimmune response.



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