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Plasma Combined with Drugs: Synergistic Mechanisms for Eliminating Cancer Cells

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Abstract: With the continuous advancement of cancer treatment methods, plasma combined with drug therapy has garnered widespread attention as an emerging therapeutic strategy. This paper elaborates on the generation and characteristics of plasma, as well as its mechanisms of action on cancer cells when used alone, including the production of reactive oxygen and nitrogen species, and damage to cancer cell membranes, and organelles. It emphasizes the synergistic mechanisms observed when plasma is combined with various anticancer drugs (e.g., chemotherapeutic agents, targeted drugs, and immunotherapies). The analysis focuses on enhancing drug uptake, promoting the activation of drug action targets, and improving the tumor microenvironment. These insights provide a theoretical basis for optimizing plasma-drug combination therapy for cancer.

Keywords: Plasma; Anticancer drugs; Synergy; Enhancement mechanisms

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1. Introduction

Cancer is one of the major diseases posing a severe threat to human health worldwide. While traditional cancer treatments, such as surgery, radiotherapy, and chemotherapy, have achieved notable success to some extent, they still face significant limitations, including toxicity to normal tissues, tumor recurrence, and metastasis. In recent years, plasma technology has brought new hope for cancer treatment due to its unique physical and chemical properties, which enable the generation of diverse reactive species that directly destroy cancer cells. Furthermore, plasma combined with drugs demonstrates synergistic potential, offering the possibility of improving therapeutic outcomes and reducing drug-related toxicity. Therefore, studying the mechanisms by which plasma and drugs synergistically eliminate cancer cells holds significant theoretical and clinical importance.

2. Generation and characteristics of plasma

Before delving into the synergistic mechanisms of plasma combined with drugs for eliminating cancer cells, it

is essential to first understand the basics of plasma itself. This section focuses on two key aspects: how plasma is generated and its unique physical and chemical characteristics. These insights not only provide a foundation for understanding the independent effects of plasma on cancer cells but also lay the groundwork for further exploration of its combined mechanisms with drugs.

2.1. Methods of plasma generation

Plasma is an ionized gas composed of charged particles (positive ions, negative ions, and electrons), photons, and neutral particles (atoms, molecules, free radicals, and active groups), and it is macroscopically electrically neutral. Compared with the usual three states of matter (solid, liquid, and gas), plasma differs fundamentally in both composition and properties, earning it the designation as the "fourth state of matter." Plasma contains a variety of active particles, such as high-energy electrons, ions, free radicals, excited gas atoms and molecules, and photons [1].

In practical applications, whether in laboratory research or clinical disease treatment, there are multiple methods for generating plasma. Among these, gas discharge methods are the most common, including dielectric barrier discharge, radiofrequency discharge, and microwave discharge. Other methods include laser-induced and plasma jet techniques. The core principle of these methods involves applying energy to specific gases, causing ionization of gas atoms or molecules, and transforming them into a plasma state, thereby creating the foundation for various applications.

2.2. Physical and chemical characteristics of plasma

Plasma exhibits significant characteristics such as high temperature, high energy, and high reactivity. Among its many properties, the generation of reactive oxygen species (e.g., hydroxyl radicals, superoxide anions) and reactive nitrogen species (e.g., nitric oxide, nitrogen dioxide) is a key factor in inducing biological effects. These reactive species, due to their strong oxidative properties, can chemically react with various biomolecules in cancer cells, such as lipids in cell membranes, intracellular proteins, and nucleic acids, leading to structural and functional damage, ultimately causing cell injury or death.

Additionally, physical factors generated by plasma, such as electric fields, magnetic fields, and ultraviolet radiation, can also affect cancer cells. These factors may alter membrane potential or impact internal metabolic processes, thereby exerting various effects on cancer cells.

3. Mechanisms of plasma acting alone on cancer cells

After understanding the generation and characteristics of plasma, it becomes crucial to investigate its mechanisms of action when used independently against cancer cells. This section discusses two primary aspects:

(1) How reactive oxygen and nitrogen species generated by plasma mediate damage to cancer cells.

(2) The direct effects of physical factors in plasma on cancer cell membranes and organelles.

Clarifying these mechanisms provides a deeper understanding of the intrinsic principles of plasma's anticancer properties, offering critical theoretical support for subsequent studies on its combination with drugs.

3.1. Cell damage mediated by reactive oxygen and nitrogen species

Reactive oxygen and nitrogen species produced by plasma are highly aggressive and can directly target critical organelles in cancer cells, including cell membranes, mitochondria, and nuclei. This triggers a series of severe

damage responses, such as lipid peroxidation, protein oxidation, and DNA damage.

Specifically, hydroxyl radicals can chemically react with unsaturated fatty acids in the cell membrane, compromising membrane integrity and causing leakage of intracellular substances. Superoxide anions can penetrate the cell and induce oxidative stress reactions in mitochondria, disrupting normal energy metabolism. Reactive nitrogen species interact with DNA bases, forming DNA adducts, ultimately leading to genetic mutations and pushing cancer cells toward apoptosis.

3.2. Direct effects on cancer cell membranes and organelles

In addition to the effects of reactive species, physical factors such as electric fields and ion flows in plasma can also directly influence cancer cell membranes. Plasma treatment can increase membrane permeability, leading to an imbalance in ion exchange inside and outside the cell, disrupting the intracellular ionic equilibrium and impairing normal physiological functions.

Furthermore, plasma impacts intracellular organelles such as mitochondria and the endoplasmic reticulum, altering their structures and causing functional impairments. This hinders processes such as energy supply, material synthesis, and transport, collectively driving cancer cells toward death from multiple angles.

4. Synergistic mechanisms of plasma combined with chemotherapeutic drugs

In cancer treatment, identifying more effective strategies is crucial. While the independent mechanisms of plasma acting on cancer cells have been clarified, the synergistic mechanisms when combined with chemotherapeutic drugs have become a new focus of research. This chapter analyzes these synergistic principles in depth, addressing three critical aspects: enhancing drug uptake, activating drug targets, and synergistically inducing apoptosis. The aim is to reveal how this combination therapy overcomes the limitations of traditional chemotherapy and paves new pathways for improving cancer treatment efficacy.

4.1. Enhancing drug uptake

The efficacy of chemotherapeutic drugs depends on their ability to enter cancer cells. However, cancer cells often develop resistance mechanisms that significantly hinder drug uptake, adversely affecting chemotherapy outcomes. Plasma treatment offers a novel solution to this problem by disrupting the integrity of the cancer cell membrane and increasing its permeability. This creates more efficient pathways for chemotherapeutic drugs to enter cancer cells [2]. For example, studies have shown that in the combined treatment of lung cancer cells with plasma and cisplatin, the uptake of cisplatin by cancer cells was significantly increased, thereby enhancing its cytotoxic effect and improving overall anticancer efficacy.

4.2. Activating drug targets

Some chemotherapeutic drugs exert their anticancer effects by acting on specific cellular targets, such as DNA repair proteins or tubulin. The reactive species generated by plasma can uniquely modify or activate these targets, enhancing the efficacy of drug-target interactions. For instance, plasma treatment can oxidize DNA repair proteins in cancer cells, inhibiting their repair functions [3]. Consequently, the cancer cell's ability to repair DNA damage is reduced, amplifying the DNA-damaging effects of chemotherapeutic drugs and ultimately enhancing their anticancer effectiveness.

4.3. Synergistically inducing apoptosis

Both plasma and chemotherapeutic drugs have unique pathways for inducing apoptosis in cancer cells. When used in combination, they produce significant synergistic effects, greatly increasing the extent of apoptosis. Specifically, plasma can activate apoptotic signaling pathways within cancer cells, such as mitochondrial and death receptor pathways, prompting the self-destruction of cancer cells. Meanwhile, chemotherapeutic drugs inhibit the expression of anti-apoptotic proteins, reducing the cell's ability to resist apoptosis [4]. Together, these mechanisms complement each other, making cancer cells more susceptible to apoptosis and improving the overall therapeutic effect, thereby offering greater survival prospects for patients.

5. Synergistic mechanisms of plasma combined with targeted drugs

The combination of plasma and targeted drugs has shown tremendous potential in the evolving field of cancer treatment. This chapter explores the synergistic mechanisms of this combination, focusing on three dimensions: improving the tumor microenvironment, enhancing the specificity of targeted drug binding, and overcoming resistance to targeted drugs. These insights provide a solid theoretical basis for clinical applications and advance cancer treatment toward greater precision and efficacy.

5.1. Improving the tumor microenvironment

The efficacy of targeted drugs is largely influenced by the tumor microenvironment. Common conditions such as hypoxia and increased interstitial pressure in tumor tissues often weaken the action of targeted drugs. Plasma offers a potential solution to these challenges by modulating cytokines and angiogenic factors within the tumor microenvironment [5]. For instance, plasma treatment can reduce the expression of vascular endothelial growth factor (VEGF) in tumor tissues, inhibiting angiogenesis. This not only decreases the nutrient supply to tumor cells but also optimizes blood flow and oxygenation within the tumor, enabling targeted drugs to more effectively kill cancer cells and improve overall treatment outcomes.

5.2. Enhancing the specificity of targeted drug binding

Targeted drugs often work by binding to specific receptors or markers on the surface of cancer cells to exert their anticancer effects. Plasma treatment can play a unique role in this process by altering the molecular conformation on the surface of cancer cells or changing the expression levels of relevant molecules, ultimately making targeted drug binding more effective. For example, in the treatment of EGFR-positive cancer cells with plasma combined with epidermal growth factor receptor (EGFR) targeted drugs, plasma can increase the expression of EGFR on the cancer cell surface. This significantly enhances the binding affinity between the targeted drug and the cancer cells, improving the cytotoxic effects and opening new avenues for cancer therapy [6].

5.3. Overcoming resistance to targeted drugs

While targeted drugs are widely used in cancer treatment, resistance developed by cancer cells poses a major challenge. Plasma combined with targeted drugs offers a promising solution to this issue through multiple pathways. On one hand, plasma can suppress the expression and activity of resistance-related proteins within cancer cells, restoring their sensitivity to targeted drugs. On the other hand, reactive species generated by plasma can directly act on drug-resistant cancer cells, bypassing their resistance mechanisms and enhancing the

cytotoxicity of targeted drugs. This dual approach provides new strategies and directions for improving cancer treatment outcomes [7].

6. Synergistic mechanisms of plasma combined with immunotherapeutic drugs

With continuous innovations in cancer treatment, the combination of plasma and immunotherapeutic drugs has emerged as a promising direction. This chapter focuses on the synergistic mechanisms underlying this combination, analyzing its principles in depth. By activating the immune system to overcome tumor immune evasion, increasing tumor antigen exposure to enhance immune cell recognition and synergistically boosting immune cell cytotoxicity, these mechanisms provide essential theoretical support and practical guidance for optimizing cancer immunotherapy strategies and improving treatment outcomes.

6.1. Activating the immune system

Immunotherapeutic drugs work by activating the immune system to identify and eliminate cancer cells. However, tumor cells often develop immune evasion mechanisms, limiting the efficacy of these drugs. Plasma can serve as an immunological adjuvant by activating immune cells (e.g., dendritic cells and T lymphocytes) and modulating the secretion of cytokines (e.g., interleukins and interferons), thereby enhancing the body's antitumor immune response [8]. For example, plasma treatment can promote the maturation of dendritic cells and their antigen-presenting capabilities, effectively activating T lymphocytes and enhancing the efficacy of immunotherapeutic drugs.

6.2. Increasing tumor antigen exposure

Tumor antigens on the surface of cancer cells are key targets for recognition and attack by the immune system. However, tumors often deploy complex mechanisms to conceal or downregulate these antigens, evading immune surveillance and attack. Plasma treatment offers an effective solution to this issue [9]. It can disrupt the structural integrity of the tumor cell membrane, exposing previously hidden intracellular antigens and improving immune cells' efficiency in recognizing and killing tumor cells. Furthermore, reactive species generated by plasma can chemically modify tumor antigens, enhancing their immunogenicity and further optimizing the effects of immunotherapy, opening new directions for cancer immunotherapy.

6.3. Synergistically enhancing immune cell cytotoxicity

In cancer treatment, the combined application of plasma and immunotherapeutic drugs exhibits unique advantages. Their synergistic effects significantly enhance immune cells' cytotoxic activity against cancer cells. Specifically, plasma can upregulate the expression of activating receptors on immune cell surfaces, strengthening their cytotoxic functions and enabling more effective attacks on cancer cells [10]. Simultaneously, immunotherapeutic drugs can inhibit immune checkpoints, relieving the suppression of immune cells and fully unleashing their activity. When used together, these mechanisms drastically enhance immune cells' ability to destroy cancer cells, offering better treatment outcomes and recovery prospects for patients while advancing the development of cancer therapies.

7. Conclusion

In summary, plasma combined with drug therapies demonstrates significant synergistic mechanisms in cancer

treatment. By enhancing drug uptake, activating drug targets, improving the tumor microenvironment, overcoming drug resistance, and activating the immune system, the combination of plasma with chemotherapeutic, targeted, and immunotherapeutic drugs holds promise for improving treatment efficacy and providing new hope for cancer patients.

However, plasma-assisted drug therapies are still in the research phase, with many issues yet to be resolved, such as the optimal treatment parameters for plasma, the safety of combination therapies, and their long-term efficacy. Future efforts should focus on conducting further fundamental research and clinical trials to optimize plasma-based combination therapy protocols. This will advance the application and development of this emerging therapeutic strategy in clinical cancer treatment, providing more effective tools for precision oncology.

Disclosure statement

The author declares no conflict of interest.

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