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Analysis of the Selective Killing Effect of Microplasma on Specific Cancer Cell Lines

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Abstract: This article aims to deeply analyze the mechanism of the selective killing effect of microplasma on specific cancer cell lines. A comprehensive investigation of relevant literature expounds on the generation principle and characteristics of microplasma and its interaction process with cancer cells. The potential mechanisms of its selective killing of cancer cells are explored from multiple aspects including physics, chemistry, and biology, involving the generation of reactive oxygen and nitrogen species, damage to cell membranes, changes in intracellular signaling pathways, and immunomodulatory effects. Additionally, the existing problems in current research and future research directions are prospected, aiming to provide a theoretical foundation and reference for the further application of microplasma in the field of cancer treatment.

Keywords: Microplasma; Cancer cell line; Selective killing; Mechanism of action

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1. Introduction

Cancer, as one of the major diseases that severely threaten human health worldwide, has always been a hot and difficult topic in medical research regarding its treatment methods. Traditional cancer treatment methods, such as surgery, chemotherapy, and radiotherapy, have achieved certain results, but they are often accompanied by many side effects and limitations, such as damage to normal tissues and the development of drug resistance. In recent years, microplasma technology, as an emerging cancer treatment method, has gradually attracted attention due to its advantages of non-invasiveness, precise controllability, and potential selective killing effect on cancer cells, opening up new avenues for cancer treatment. Deep research on the mechanism of the selective killing effect of microplasma on specific cancer cell lines has important theoretical and practical significance for optimizing microplasma treatment technology and improving cancer treatment effects.

2. Generation and characteristics of microplasma

To understand the selective killing effect of microplasma on cancer cells, it is essential to delve into its generation mechanism and unique characteristics. This section first elaborates on how microplasma is generated under specific conditions and the characteristics of different generation methods. Then, it analyzes the physical and chemical properties that determine microplasma's unique behavior and potential biological effects when interacting with cancer cells.

2.1. Generation principle

Microplasma, confined to the millimeter to micrometer scale, is a type of low-temperature plasma that has become a hot research topic in recent years. Typically, microplasma has a scale below 1 millimeter, much smaller than traditional plasma, and can operate at atmospheric pressure, exhibiting numerous novel properties. Microplasma finds potential applications in various fields such as biopharmaceuticals, micro-machining, and micro-light sources, garnering widespread attention and research in recent years [1]. Its generation relies on specific gas environmental conditions where an electric field or radiofrequency energy of sufficient intensity is applied. This energy promotes the ionization of gas molecules, forming a plasma state containing various active particles like electrons, ions, excited atoms and molecules, and free radicals. The generation methods are diversified, including dielectric barrier discharge (DBD), radiofrequency discharge, and microwave discharge. DBD stands out due to its relatively simple device structure, easy operation, and stable microplasma generation at atmospheric pressure, making it widely used in specific scenarios. On the other hand, the radiofrequency discharge method excels in plasma density and energy control precision, achieving higher plasma density and precise energy regulation, meeting the experimental or application requirements for higher microplasma characteristics.

2.2. Characteristics

Microplasma exhibits unique and complex characteristics in both physical and chemical aspects. From the physical perspective, its electron temperature is relatively high, while the ion temperature remains low. This significant non-equilibrium state ensures the generation of a large number of active particles without significantly elevating the ambient temperature, providing a material basis for subsequent chemical and biological effects. Chemically, microplasma is rich in various reactive oxygen species such as O^{2-}, $OH\cdot$, H_2O_2 [2], and reactive nitrogen species like $NO\cdot$, $NO_2\cdot$, N_2O. These highly reactive substances can actively participate in oxidation, reduction, nitration, and other chemical reactions with surrounding substances, triggering biological effects on cells and significantly influencing their physiological states. Furthermore, advanced micro-machining techniques enable precise localization of the microplasma discharge region within microscopic scales, such as creating specifically sized and shaped microplasma sources. This achieves a highly localized and precise effect on cancer cells, offering a potential technical approach for cancer treatment.

3. Interaction process between microplasma and cancer cells

After clarifying the generation and characteristics of microplasma, further exploration of its interaction process with cancer cells becomes crucial [3]. This process involves multiple levels, from direct physical impacts to chemical reactions of active substances, and alterations in intracellular signaling pathways and immune responses. These levels intertwine, forming a complex network of microplasma's effects on cancer cells and profoundly influencing their fate.

3.1. Physical interaction

The initial interaction between microplasma and cancer cells occurs at the physical level. The electric field generated by microplasma affects the microenvironment of cancer cells, while physical factors like ion flow and electron impact directly target the cell membrane. As a critical barrier between the cell and its external environment, the integrity of the cell membrane is directly related to cell survival and functional normality. Under the influence of microplasma, ion flow and electron impact can alter the charge distribution on the cell membrane surface, leading to the phenomenon of electroporation. This manifests as the formation of temporary nanometer-to-micrometer-scale pores in the cell membrane, increasing its permeability and disrupting the balance of intracellular and extracellular material exchange. Consequently, this can gradually affect the cell's normal physiological functions and, in severe cases, lead to cell death.

3.2. Chemical interactions

The reactive oxygen and nitrogen species present in the microplasma play a crucial role in their interaction with cancer cells, exhibiting key chemical effects. These reactive species inherently possess highly active chemical reactivity, capable of rapidly initiating chemical reactions with lipid components on the cancer cell membrane, protein molecules, and various biological macromolecules within the cell, such as DNA, RNA, and enzymes. Specifically, the hydroxyl radical ($OH\cdot$), among the reactive oxygen species can attack unsaturated fatty acids on the cell membrane, triggering the process of lipid peroxidation and damaging the original structure and function of the cell membrane [4]. Simultaneously, hydroxyl radicals can also oxidize intracellular proteins, causing them to lose their normal biological activity, thereby interfering with intracellular signal transduction pathways and metabolic processes. On the other hand, reactive nitrogen species can alter the structure and function of proteins by nitrating amino acid residues, thus affecting biological behaviors such as cell proliferation and apoptosis, and playing a pivotal role in determining the fate of cancer cells.

3.3. Biological interactions

The effects of microplasma on cancer cells are not limited to the physical and chemical levels but also trigger a series of biological responses. After cancer cells are treated with microplasma, their internal signaling pathways change. For instance, some studies have found that microplasma treatment can activate apoptotic signaling pathways within cancer cells, such as the activation of caspase family proteases, promoting programmed cell death in cancer cells. Additionally, microplasma may affect the cell cycle regulation of cancer cells, causing them to stagnate in specific cell cycle stages, thereby inhibiting cancer cell proliferation [5]. Meanwhile, the interaction between microplasma and cancer cells may also trigger the body's immune response, such as the release of immune-modulating factors, attracting immune cells like macrophages and T-lymphocytes to gather at the cancer cell site, enhancing the body's immune clearance ability against cancer cells. This, to some extent, reflects the selective killing effect of microplasma on cancer cells, as normal cells typically do not elicit such a strong immune response.

4. Mechanism of microplasma's selective killing of specific cancer cell lines

After understanding the interaction process between microplasma and cancer cells, it is crucial to delve into the mechanism of its selective killing of specific cancer cell lines. This involves various factors such as the characteristics of cancer cells themselves, microplasma action parameters, and the microenvironment of cancer

cells. These factors are interrelated and synergistic, collectively determining whether microplasma can precisely target specific cancer cell lines, providing a critical basis for further optimizing the application of microplasma in cancer treatment.

4.1. Biological characteristics differences of cancer cells

From the perspective of the cell membrane, there are differences in phospholipid types, cholesterol content, and the distribution and types of membrane proteins, which directly determine the rate and selectivity of material exchange in and out of cells. These differences are closely related to the response of cancer cells to microplasma action [6]. For example, the permeability of certain cancer cell membranes may be low, limiting the entry of reactive substances generated by microplasma into the cells, thereby affecting the killing effect.

In terms of metabolism, different cancer cell lines exhibit variations in glycolytic intensity, the proportion of aerobic respiration, and the synthesis and decomposition rates of lipid metabolism. This results in significant differences in the metabolic detoxification ability of cancer cells when responding to reactive substances produced by microplasma.

The activity status of signaling pathways is crucial. The activation or inhibition of pathways like MAPK and PI3K-Akt directly determines the sensitivity of cells to microplasma. Some cancer cell lines, rich in antioxidant enzymes, can effectively neutralize the oxidative damage caused by microplasma, exhibiting lower sensitivity [7]. In contrast, other cancer cell lines may be more susceptible to damage under microplasma action due to special receptors on the cell membrane mediating the influx of several ions, disrupting intracellular homeostasis, or overactivation of key signaling pathways. These factors collectively constitute the key basis for the selective killing of cancer cells by microplasma, providing an important theoretical foundation for the development of cancer treatment strategies.

4.2. Regulation of microplasma action parameters

The action parameters of microplasma play a critical role in the killing process of cancer cells, where factors such as discharge power, action time, and gas composition significantly affect the killing effect and selectivity. Precise regulation of these parameters can achieve effective control over the type, quantity, and energy distribution of active particles generated by microplasma, thereby optimizing the killing effect and selectivity for different cancer cell lines.

In terms of discharge power, moderately increasing the discharge power typically promotes the generation of more reactive oxygen and nitrogen species by microplasma, enhancing the killing efficacy against cancer cells. However, excessively high discharge power beyond a reasonable range may cause unnecessary collateral damage to surrounding normal tissues while killing cancer cells.

Regarding gas composition, adjustments can alter the composition and proportion of active substances in microplasma, matching the sensitivity characteristics of different cancer cell systems. For instance, adding a moderate amount of oxygen to the gas can increase the production of reactive oxygen species [8]. For cancer cell lines that exhibit higher sensitivity to oxidative stress, such changes in gas composition can significantly enhance the killing effect of microplasma. Conversely, for cancer cell lines more sensitive to reactive nitrogen species, precise adjustments to the gas composition can increase the production of reactive nitrogen, achieving better cancer cell killing.

Additionally, the duration of action cannot be ignored. Reasonably extending the action time of microplasma

can expose cancer cells to more active particles, enhancing the killing effect. However, excessively long action times may also trigger other negative effects, requiring fine optimization based on specific cancer cell lines and experimental conditions. In conclusion, in-depth research and precise regulation of microplasma action parameters possess significant potential value for cancer treatment.

4.3. Influence of microenvironmental factors

The microenvironment surrounding cancer cells is highly complex, encompassing various aspects such as the extracellular matrix, intercellular interactions, and local physiological and biochemical conditions. These factors, acting together, significantly affect the selective killing efficiency of microplasma on cancer cells. Within the special environment of tumor tissue, cancer cells intertwine with surrounding stromal cells, immune cells, and vascular endothelial cells, forming an intricate network system [9]. Unique conditions such as hypoxia, acidosis, and high expression of specific growth factors and cytokines are common occurrences. Taking hypoxic conditions as an example, cancer cells under such environments undergo a metabolic shift from aerobic respiration to anaerobic metabolism with enhanced glycolysis, leading to adaptive adjustments in numerous signaling pathways. These changes may alter the sensitivity of cancer cells to microplasma, either increasing or decreasing it. Simultaneously, during its interaction with cancer cells, microplasma also exerts a reactive effect on the aforementioned factors within the cancer cell microenvironment [10]. For instance, reactive species generated by microplasma may alter the local redox state, subsequently influencing cytokine secretion and metabolite accumulation. This further fine-tunes the survival status of cancer cells and their sensitivity to microplasma, ultimately profoundly impacting the selective killing effect of microplasma on specific cancer cell lines.

5. Conclusion

The selective killing effect of microplasma on specific cancer cell lines is a complex and potential research field. Through an in-depth exploration of the principles and characteristics of microplasma generation, as well as its interaction processes and mechanisms with cancer cells, we have gained a preliminary understanding of its possibilities and advantages as a novel cancer treatment method. However, current research remains in its infancy, facing numerous key issues and challenges that need to be addressed. Future studies require further elucidation of the detailed molecular mechanisms underlying the selective killing of cancer cells by microplasma, optimization of treatment parameters and equipment design, and strengthening of preclinical and clinical trial research to comprehensively evaluate its efficacy and safety. Simultaneously, active exploration of combination therapy modes with other treatment methods is essential. This will provide a solid theoretical foundation and technical support for the clinical application of microplasma technology in the field of cancer treatment, potentially offering more effective, safe, and personalized treatment options for cancer patients, and driving the development and progress of cancer therapy.

Disclosure statement

The authors declare no conflict of interest.

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