Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/65/2024.LA18083

Metallic nanoparticles for tumor microenvironment modulation

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Abstract. Cancer is a complex, multifaceted disease influenced by genetic predispositions, lifestyle factors such as nutrition, exercise, and toxin exposure, as well as environmental conditions. A key element in cancer initiation, progression, metastasis, and therapeutic response is the tumor microenvironment (TME). Within the TME, immune cells like T cells, B cells, and immunoglobulins have a profound and direct impact on the growth and spread of tumor cells. As a result, effective regulation of the TME has become crucial for successful cancer treatment. Metal nanoparticles (MNPs), ranging from 1 to 100 nanometers, have shown great potential as agents for modulating the TME, delivering drugs, and improving cancer diagnostics. This discussion explores both the internal and external components of the TME, focusing on how MNPs influence the microenvironment. We highlight their targeting mechanisms and interactions with immune responses and tumor-associated inflammation. Due to their unique properties, MNPs offer distinct advantages in cancer therapy, and their range of applications continues to expand. This review underscores the potential of MNPs as a promising material in the future of cancer treatment.

Keywords: Cancer, Tumor microenvironment, Metal nanoparticles, immune response.

1. Introduction

A tumor is a mass of abnormal cells caused by physical, chemical, or biological problems. Cancer, a leading cause of death worldwide, is a type of tumor named malignant tumors. Common types of cancers include breast, lung, colon and rectum, and prostate cancers. In order to cure the deadly disease, treatments like radiotherapy, chemotherapy, hormonal treatments, targeted biological therapies, and immunotherapy are used. The TME is a really complex environment that plays a very essential role in cancer progression, invasion, metastasis, and resistance to therapy. This part of the era can be seen as a micro-ecosystem. The system consists of main components, including cancer-associated fibroblasts (CAFs), immune cells, extracellular matrix (ECM), blood vessels, and signaling molecules. Those related cells in the TME provide sources for the growth of cancer cells. The unstable structure of the system and the cancer cells can be prone to mutual exclusion, thus accelerating tumor progression and metastasis of their cells. For some conventional therapies, such as chemotherapy and radiotherapy, components of the TME may be overlooked in the process of targeting the killing of cancer cells as a

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therapeutic pathway. Moreover, potential adverse reactions the traditional therapy brought can affect the healthy tissues of the patient [1].

Researchers and scientists are searching for ways to make TME modulation easier and safer. New materials were found in order to induce an immune response and modify various tissues in the environment. Nanoparticles are one of the most promising choices. Nanoparticles (NPs) are the particles that exist in the natural world and are also made by human activities. The new material has a range of size from 1 to 100 nm. Because of their submicroscopic size, nanoparticles are widely used in medicine, engineering, catalysis, and environmental remediation. In general, there are three main types of nanoparticles: polymeric NPs, inorganic NPs, and lipid-based NPs (Table 1) [2]. Metal NPs are included in the inorganic nanoparticles. Metal nanomaterials enable intelligent drug delivery and real-time imaging of tumor cells by using their characteristics of light, heat, magnetism, force, and sound. Metal nanoparticles are uniquely suited to bring new vitality to the field of tumor diagnosis and treatments [3, 4]. In the paper, we investigated the potential of metallic nanoparticles for modulating the tumor microenvironment, summarized how metallic nanoparticles can effectively inhibit tumor growth, and explored the advantages and disadvantages of metallic nanoparticles in the field of healing.

Table 1. Main types of nanoparticles

Types of NPs	Examples of NPs	Properties of NPs
Polymeric NPs	Polymersome	Precise control of particle characteristics
	Dendrimer	Payload flexibility for hydrophilic and hydrophobic cargo
	Polymer micelle	Easy surface modification
	Nanosphere	Possibility for aggregation and toxicity
Inorganic NPs	Silica NP	Light, heat, magnetism, force and sound properties
	Quantum dot	Variability in size, structure and states
	Iron oxide NP	Toxicity and solubility limitations
	Gold NP	Stable drug carrier
	Silver NP	Formulation simplicity with a range of physicochemical properties
Lipid-based NPs	Liposome	High bioavailability
	Lipid NP	Payload flexibility
	Emulsion	Low encapsulation efficiency

2. Composition of tumor microenvironment

The tumor microenvironment refers to the complex environment that tumor cells need to rely on to survive. For example, ambient temperature and humidity can have a direct impact on the survival of cancer cells. Tumor cells are surrounded and influenced by a complex network of non-cancerous components, including the extracellular matrix (ECM) and various stromal cells, which together form the TME. Researchers have found and proven that tumor cells and stromal cells evolve together in two ways: either stromal changes lead to epithelial cell transformation, or transformed epithelial cells may

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paracrinely activate stromal cells. Tumor cells reconstitute the extracellular matrix and join other tumor growth bands, leading to further tumor invasion and spread. Studies on gene expression profiling have demonstrated that alterations in the tumor stroma can hasten the metastasis of tumor cells, and a shift from the stroma to the standard tumor classification can anticipate the changes that will transpire post-clinical practice and spread to other organs. TME is a general term for a series of physiological, biochemical, and immune changes in tumor cells and their surroundings that directly and seriously affect the development, metastasis, and response to treatment of tumors. It is an extremely complex ecosystem of tumor cells, immune cells, blood vessels, extracellular matrix (ECM), and various signaling molecules. It can be divided into two components: the first is the internal composition, and the second is the external composition. The internal composition is mainly divided into tumor cells, endocrine system, vascular system, and cytokines. The external components include the extracellular matrix (ECM), tumor-associated macrophages (TAMs), and other immune cells, such as natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and myeloid-derived suppressor cells (MDSCs), all of which have different roles and are indispensable in tumor composition.

The TME has a profound impact on tumor growth and metastasis. It is highly effective in promoting tumor growth, maintaining daily nutrient intake, enhancing immunosuppression, and growing more factors and cytokines. In addition, it can also promote tumor metastasis to other cells or other locations; the modification of stromal cells and ECM can also enhance the speed of tumor invasion and metastasis; there will be more new angiogenesis to further accelerate blood circulation; and in immune escape, some cells will cause tumor cells to escape immune cells to kill and counteract, which will give those malignant cells a chance to come back at any time and cause more serious damage to the human body.

3. Metal nanoparticles in Tumor microenvironment modulation

Metal nanoparticles can enhance anti-tumor immune responses by targeting immune cells in the tumor microenvironment, such as dendritic cells, macrophages, and natural killer cells. These nanoparticles are widely studied to improve the efficacy of tumor therapy due to their unique physicochemical properties and biocompatibility, and these particles can do this by altering the function of these immune cells or by providing immunomodulators. For example, several studies have shown how metal nanoparticles can enhance anti-tumor immune responses by modulating immunosuppressive cells in TME. In addition, metal nanoparticles can also play a role by altering the chemical environment of the TME, for example by modulating the pH, REDOX state, and metabolite levels of the tumor region to reshape the TME. These changes can promote the death of tumor cells and enhance the activity of immune cells. Metal nanoparticles modulate the tumor microenvironment through multiple mechanisms. For example, hollow MnO2 nanoparticles can decompose hydrogen peroxide in the tumor microenvironment, produce oxygen, thereby improving the hypoxic environment, and act as drug carriers to carry cytotoxic drugs, PD-1 antibodies, or anti-angiogenic drugs, significantly improving the therapeutic effect. In addition, metal-lophenol networks (MPNs) exhibit pH responsiveness and low toxicity in the tumor microenvironment, capable of inducing cancer immune escape while minimizing systemic side effects [5].

Metal nanoparticles can also influence the tumor immune system through a variety of mechanisms. For example, iron oxide nanoparticles inhibit tumor growth by inducing the polarization of pro-inflammatory macrophages in tumor tissue. In addition, metal nanoparticles can also generate reactive oxygen species through Fenton-type or Haber-Weiss-type reactions and induce cell death through oxidative stress. These mechanisms suggest that metal nanoparticles can act directly on tumor cells or indirectly by altering the tumor microenvironment. Nanoparticles can also enhance anti-tumor immune responses by modulating immunosuppressive cells and factors in the tumor microenvironment. For example, by targeting tumor-associated macrophages (TAMs) and modulating their function, anti-tumor immune responses can be enhanced. In addition, nanoparticles can inhibit tumor growth by inducing apoptosis and necrosis of tumor cells. For example, iron-core gold shell nanoparticles (Fe@Au) inhibit cancer cell proliferation through a mitochondria-mediated pathway. Metal nanoparticles can influence the tumor immune system through a variety of mechanisms. For example, iron oxide nanoparticles

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4. Metal nanoparticles for Drug delivery

The application of metal nanoparticles in cancer drug delivery is a highly active and growing area of research. These nanoparticles are widely studied for drug delivery systems in cancer therapy due to their unique physical, chemical, and photonic properties, as well as their ability to interact with biomolecules. Metal nanoparticles (such as gold, silver, platinum, etc.) not only show potential in drug delivery but also play an important role in diagnosis and treatment, such as directly fighting tumors through thermal ablation therapy or enhanced radiation therapy [7]. The size, shape, and surface chemistry of metal nanoparticles can be precisely controlled through synthetic techniques, which makes them safe and effective cancer drug carriers. For example, gold nanoparticles are widely studied in cancer therapy due to their excellent biocompatibility and unique optical properties. In addition, metal nanoparticles can also enhance the accumulation of drugs in tumor areas by using the tumor's enhanced penetration and retention effect (EPR effect) through passive targeting mechanisms.

Active targeting strategies enhance the specificity of therapeutic nanoparticles by using ligands or antibodies that target specific tumor markers, thereby reducing the impact on normal cells and improving efficacy. For example, by combining chemotherapy drugs with magnetic nanoparticles and using an external magnetic field to guide these particles to the tumor site, efficient drug delivery can be achieved.

The role of metal nanoparticles in tumor drug delivery is mainly reflected in their unique physical and chemical properties and biological functions, which make them an important tool in the field of cancer therapy. Metal nanoparticles achieve effective tumor targeting and drug delivery through a variety of mechanisms, including passive targeting, active targeting, photothermal effect, photodynamic effect, and interaction with the tumor microenvironment. Passive targeting: Metal nanoparticles are passively targeted using the enhanced penetration and retention (EPR) effects of tumors. This effect is caused by the abnormal nature of tumor blood vessels and the high permeability of tumor tissue, allowing nanoparticles to enter the tumor more easily [8]. In addition, the design of the metal nanoparticles optimizes their circulation time and biological distribution in the blood, thereby increasing their chances of reaching tumor cells. Active targeting: By functionalizing ligands or antibodies to the surface of metal nanoparticles, it is possible to recognize and bind specific tumor markers, thereby enhancing their specificity to tumor cells [9]. For example, the use of antibodies against tumor-specific antigens or receptors to functionalize metal nanoparticles can improve the efficiency of drug targeting of tumor cells. Photothermal and photodynamic effects: Certain metal nanoparticles, such as gold and silver nanoparticles, can generate heat by absorbing light energy or kill cancer cells by activating the reactive oxygen species (ROS) produced. These effects can kill cancer cells without direct contact with the drug, reducing the toxic effects on normal cells. Modulating the tumor microenvironment: Metal nanoparticles can also inhibit tumor growth by altering the tumor microenvironment. For example, they may work by boosting immune responses in tumor areas or by modulating tumor-related inflammatory responses [10]. Versatility and tunability: Metal nanoparticles can not only serve as drug carriers but also integrate diagnostic and therapeutic functions to achieve simultaneous release and detection of drugs. This versatility opens up the possibility of personalized and customized cancer treatment.

5. Conclusion

Metal nanoparticles can combine with other therapeutic methods to inhibit the growth and metastasis of tumor cells, change the tumor microenvironment, and kill tumor cells. Moreover, metal nanoparticles

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are more stable than others, and the treatment process is more controllable. Furthermore, the application prospect of metal nanoparticles in the tumor microenvironment is very broad, and its potential is mainly reflected in the targeting and drug delivery. However, although metal nanoparticles show great potential in tumor therapy, there are still some challenges. For example, how to improve its biocompatibility and stability, how to overcome the recognition of the immune system and how to optimize its distribution and clearance in the body, and whether metal nanoparticles exist in the human body for too long will have certain toxicity and harm the health of the body need to be further solved. In addition, the results of clinical trials are often lower than those in animal models, which suggests that we need to deeply understand the characteristics of the tumor microenvironment and conduct targeted design and optimization on this basis. A number of technical and clinical translational challenges need to be overcome before its widespread use in cancer treatment can be truly realized.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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