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Advances in Tumor Inhibition by Repolarized M2 Macrophages

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Abstract. The tumor microenvironment (TME) plays a crucial role in the occurrence, growth, and metastasis of tumors. Tumor-associated macrophages (TAMs), derived from bone marrow precursor cells, exhibit functional plasticity by polarizing into either pro-tumor M2 or anti-tumor M1 phenotypes depending on the microenvironment. This paper explores the advantages and limitations of targeted drug delivery systems using nanocarriers for the repolarization of M2 macrophages into M1 macrophages within the TME. While passive targeted transport techniques allow drug-carrying nanomedicine to selectively accumulate in tumor regions, the efficacy is often hindered by the host's immune response and the inherent toxicity of certain nanomaterials. This review summarizes the current landscape of nanocarriers, emphasizing the need for future research to explore novel nanomaterials and expand the database of drug delivery systems to optimize therapeutic outcomes. Moreover, the potential of polarized macrophage-targeted therapies remains underexplored, suggesting a critical area for future breakthroughs.

Keywords: Tumor microenvironment; macrophage; polarization; targeting transport.

1. Introduction

Tumor Microenvironment (TME) refers to the occurrence, growth, and metastasis of tumors and the internal and external environment of tumor cells. TAM (Tumor-associated macrophage) is derived from the precursor cells in the bone marrow, whose main function is to phagocytosis of cell fragments or pathogens. Macrophages will be polarized in different directions under the action of different microenvironments and stimulating factors. Passive targeted transport technology is used to transport drug-carrying nanomedicine from the porous tumor vasculature to the tumor region, and the M2 macrophages are repolarized into anti-tumor M1 macrophages.

At present, there are various drug delivery materials, but some nanocarriers are toxic.

In this paper, the advantages and disadvantages of targeted transport and several common nanomaterials are summarized, which provides a reference for future optimization of nanomaterials. In the next research, more nanomaterials should be tried in the experiment, and the number of databases should be increased in order to better optimize the nano drug delivery therapy. There is also the problem of insufficient existing data that cannot be solved, and the future should focus on trying more nanomaterials to expand the database.

2. Targeted Transport

2.1. Passive Targeted Transport

The nanocarriers carrying drugs are injected into the body through porous vasculature in the form of injection. In this process, the drugs will pass through other organs in the non-tumor area, and most of the drugs will stay in other organs, and only a small part of the drugs can reach the tumor area. Wait for the carrier to dissolve in the body and the drug in the carrier to disperse. The storage of drugs with nanocoliters for passive targeted transport can prolong systemic circulation [1], which is related to the size of the carrier, material and vascular penetration, and therefore not suitable for the specified organs or tissues, and the therapeutic effect is not satisfactory (Figure1).

2.2. Active targeted transport

Applied to the designated area, the receptor binds to the ligand, does not retain the drug on other organs, and can transport sufficient amounts of the drug to the tumor area. Therefore, the overall treatment efficiency is greatly improved and the side effects are reduced. At the same time, active targeted transport can improve the compatibility of nanocarriers and tumor cells, and enhance the permeability of drugs. [1]

This drug delivery system still has some limitations, the active targeted delivery of drugs will be affected by the body's own immune system, not only need to overcome the interference of the immune system, reduction in TME and clearance in the blood. Part of the tumor will form near the blood vessels, and the tumor will rapidly spread through the blood vessels to absorb nutrients. Meanwhile, the blood vessels will have less nutrients and less oxygen, forming necrotic areas and preventing the arrival of nanomaterials (Figure1).

Secondly, the nanocarriers will dissolve before reaching the ideal region, so that the drug in the carrier is released early, resulting in a reduced survival rate of the drug, and may also show toxicity. Nanocarriers are essential if the drug delivery system is to fully exploit its advantages. At the same time, this is also the part that has many problems at present, which is crucial for how to choose the material, size and shape of the nanocarrier.

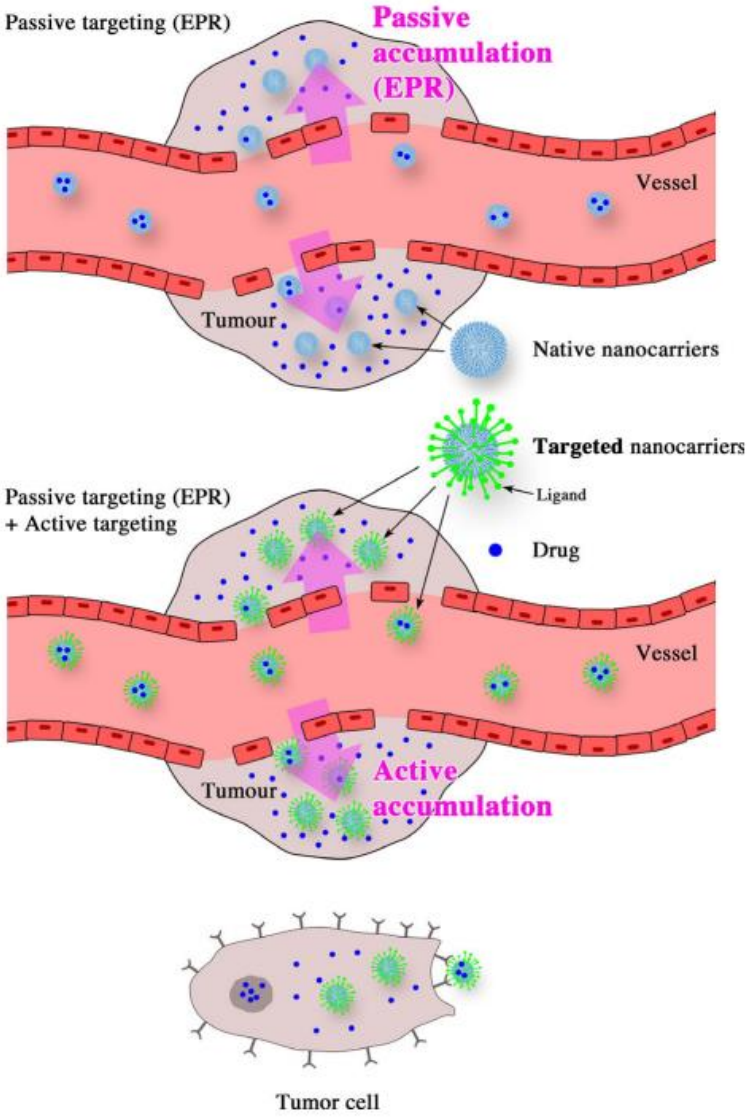

Fig. 1 The passive targeting (EPR) and the active targeting into a tumour [1].

3. Research Achievements and Challenges of Existing Nanomedicine Polarized M2 Macrophages

With the continuous promotion of nanomedicine as a carrier to depolarize M2 macrophages, more and more conclusions have been drawn after practice to continuously improve the drawbacks existing in polarized M2 macrophages. Affected by the autoimmune system, the body may reject nanomedicine, and a large number of drugs will have retention and fail to reach tumor tissues. Experimental PEG (PEG: Polyethylene glycol) is widely used because of its good biocompatibility and degradability [2]. However, due to the high plasticity of TMS, the phenotype of TMS in different tumor regions will be different, and there will be immunity to drugs, so more precise approaches are still needed [3]. The biggest challenge in this field is to reduce the toxicity of nanocarriers so that the human body does not reject nanomedicine.

Table1. Advantages and disadvantages of four different nanomaterials.

	Characteristics and disadvantages	Characteristics and disadvantages
liposome	Biocompatibility, safety, protection of drugs in the carrier from degradation, controlled release of drugs [4]. The production cost is high	Biocompatibility, safety, protection of drugs in the carrier from degradation, controlled release of drugs [4]. The production cost is high
Polymer nanoparticle	Small size, biocompatibility, low toxicity, low solubility, low bioavailability, resulting in reduced treatment efficiency [5].	Small size, biocompatibility, low toxicity, low solubility, low bioavailability, resulting in reduced treatment efficiency [5].
Metal nanoparticles	Biocompatibility, large surface area, can carry a variety of drugs, prolong the circulation time of drugs in the body [6] Small metal nanoparticles will agglomerate and lose activity	Biocompatibility, large surface area, can carry a variety of drugs, prolong the circulation time of drugs in the body [6] Small metal nanoparticles will agglomerate and lose activity
Graphene nanomaterials	With unique morphology, large surface area, small size [7], low cost and high toxicity to bacteria [8].	With unique morphology, large surface area, small size [7], low cost and high toxicity to bacteria [8].

At present, liposomes and polymer nanoparticles have been used in clinical practice because of their safety. However, the use of only a few nanomaterials is not enough to deal with the problem of complex diversification, resulting in insufficient research on the number of databases. Compared with other nanomaterials, metal nanoparticles have great potential. As shown in Table1, metal nanoparticles can effectively improve the treatment efficiency. Limited by the agglomeration and deactivation of small metal nanoparticles, studies have shown that secondary metabolites in plants can inhibit the agglomeration of metal nanoparticles [9]. Therefore, metal nanoparticles are extremely advanced nanomaterials and are expected to be applied in future targeted transport.

Protein nanometers are safer and more natural because they are obtained directly from tissues. Protein nanocarriers include animal protein and plant protein, which can be extracted from animal tissues and are more expensive than plant protein, but are therefore biocompatible and safer [10]. The liposomes in table1 do not belong to protein nanocarriers, but to artificial nanocarriers. However, the ideal nanocarriers are widely used in clinical treatment due to their advantages of good biocompatibility, non-immunogenicity, easy surface functionalization and so on [11].

4. Research Progress in Optimizing Targeted Transport

"Using living cells as carriers" - macrophages in immune cells. Macrophages can engulf and process foreign objects in the body, so they serve as a suitable camouflage. Using magnetic nanoparticles, the direction and distance of travel can be precisely determined by changing the magnetic field. Magnetic nanoparticles can be controlled by magnetic fields, and drug delivery can be made using infrared or ultrasonic waves [12].

Near-infrared light can penetrate the surface of the skin, and when the magnetic nanorobots absorb the light, they generate heat that causes the magnetic nanoparticles to release drugs.

According to the continuous attempts in the past few years, people have found a new optimization method - cell-mediated targeting [13]. Cell-mediated targeting is different from ordinary targeted transport in that the carrier is not loaded with drugs but cells that can phagocytic tumors, such as macrophages. Wait for the cells to spread to sufficient numbers before transporting them to the tumor area. This method can effectively reduce the toxicity and immunity of the human body, control the release, and effectively prolong the half-life.

However, since foreign cells containing drugs are injected into the body, if the mechanism of pathogenesis is not clear, it will cause harm to the human body, so further research and exploration of cell-mediated targeting are still needed.

5. Potential and Prospect in Clinical Treatment

Nanomaterials use nanomaterials as a carrier to deliver the drugs inside the tumor tissue, which greatly plays the role of the drugs in the carrier, and is a highly efficient tumor treatment method, which has been continuously optimized in scientific research in recent years, and is widely used in clinical treatment. There are many kinds of nano-drug carriers, so the advantages and disadvantages are different. This method of curing tumors has great potential, but the current nano-load is still limited, and it is necessary to constantly explore new types and expand the database.

6. Conclusion

This paper analyzes the advantages of the two types of targeted transport, but the therapeutic effect of targeted transport will be reduced due to the influence of the human body's own immune system. Therefore, the research should focus on the composition of nanomaterials, fill the loopholes in targeted transport, and improve the therapeutic effect. In future research, try more types of nanomaterials or find ways to optimize the shortcomings of all current nanomaterials. This part does not analyze the drug of polarized macrophages, and it may be possible to break through the current bottleneck from the composition of the drug. The future should focus on trying new nanomaterials to expand the database.

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