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REVIEW ARTICLE

Trends of Gold Nanoparticle-based Drug Delivery System in Cancer Therapy

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Following surgical removal of malignant tumors, chemotherapeutic intervention usually is subsequently applied in patients with advanced stages of cancer. Most chemotherapeutic drugs are intravenously injected into patients, leading to systemic cytotoxicity in organs and tissues, including healthy tissue and tumors. Currently, it has been demonstrated that gold nanoparticles can easily penetrate blood vessels and tissue barriers into tumor foci, which indicates gold nanoparticles as a more effective drug carrier with great merits in reducing cytotoxicity and economic burden in patients. Moreover, gold nanoparticles display several unique characterizations with multiple functions in therapeutics, imaging, and surface modification, suggesting gold nanoparticles may become effective antitumor drug carriers. In this review article, we discuss the limitations and applications of gold nanoparticles in surface modification, targeting strategy, and safety considerations.

1. Introduction

Cancer is the leading cause of death worldwide. According to the United States cancer statistic reports, one of every four deaths in the United States is caused by cancer.[1] Chemotherapeutics are commonly used in current practice to treat cancer via intravenous administration but also to elicit toxicity to normal cells, leading to severe side effects in patients. Therefore, a new and improved therapeutic method to target tumor foci coupled with enhanced cytotoxicity on cancer cells and decreased side effects is needed. Recently, inorganic nanoparticles such as gold nanoparticles (GNPs) have been explored and exploited as a promising candidate for various biotechnology applications because of their unique characterizations.

GNPs have been used as nanobiomaterials for molecular imaging and drug delivery in recent years.[2] Gold nanoparticle conjugates express unique properties such as increased binding affinity and selective targeting to specific tissue or cells when delivered systemically.[3] Because gold nanoparticles can be modified in different ways by binding specific receptors coupled with various forms of therapeutics, there is a wide range of research and nanoparticle-based therapeutic methods under development for cancer.[4,5] The delivery of GNP-conjugated drugs have a higher perfusion rate in targeting tumor foci, leading to reducing antitumor drug dosage for treatments and lower toxicity to normal tissues coupled with less side effects.

In this review, we discuss various drug delivery systems of GNPs in cancer, including targeting approaches, modified conjugates and safety issue using nanoparticles in GNP-based drug delivering system.

2. Nanotechnology and nanomedicine

Nanotechnology is continuously being extended in the field of medicine to reach maximum therapeutic possibility and reduce side effects of clinically used agents. The history of nanotechnology began in the 1950s, when the first polymer drug conjugate was successfully schemed by Jatzkewitz,[6] followed by the liposome discoveries of Bangham and Horne,[7] and Bangham et al[8] during the mid 1960s. Current nanotechnology applications in medicine led to the emergence of a new domain in science known as nanomedicine, offering some exciting prospects such as improvement in diagnosis, monitoring, prevention, and treatments of disease using selectively active drug carriers, diagnostic agents, and pharmaceutical moieties to a target site.[9] Various types of nanoparticles

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have been used in biomedical applications, including drug delivery, molecular imaging, and combined therapy and diagnosis.

In the field of medicine, nanotechnology is the basis of nanocarriers (i.e., nanoparticles, polymeric micelles, liposomes, dendrimers, and carbon nanomaterials) and drug conjugates no larger than 200 nm.[10–13] One of the key discoveries observed by Matsumura and Maeda[14] in the 1980s revealed that nanoparticles could accumulate in tumors, leading to the scientists' interest in the application of nanoparticles as antitumor carriers. In normal or healthy tissue, the vascular endothelial layer is highly deployed and arranged with a barrier function in preventing the passage of molecules. With tumor progression, neovasculatures are formed and characterized as highly disordered vascular endothelial layer with large gaps between cells, resulting in leaks and propensity for the passage of molecules. Therefore, the unique abnormal structure, loose pattern, and less integrity of the vascular endothelial layer of cancerous blood vessels contribute to greater permeability and then facilitate the increased deposition of substances/particles onto solid cancerous tissue, phenomena termed as the enhanced permeability and retention effect (EPR).[14–16] Because EPR effect increases nanoparticle accumulation in solid tumor sites by passive targeting, nanoparticles as drug carriers exhibit a significant effect on enhanced therapeutic efficacy with reduced side effects and cytotoxicity to other tissues and organs (Figure 1).[17,18]

3. Gold nanoparticles

In general, gold nanoparticles are synthesized by the chemical reduction of chloroauric acid (HAuCl4) using reducing agents. Gold nanoparticles exhibit a combined feature of chemical, physical, optical, and electronic properties and may be applied as a new platform to bring about benefits in various fields, such as medicine.[19–25] Because of the unique property of a wide range of core sizes from 1 nm to 150 nm, GNPs can be easily modified with controlled dispersal. Therefore, GNPs have a great potential to be used as a drug delivery system for efficient drug transport into different cell types (Figure 2). Because of the ease of functionality and tailoring surface of GNPs, modified GNPs gain accessibility and effectiveness to target cancerous tissues by either active or passive targeting mechanistic system.[26,27] The size of GNPs determine the optical property in UV absorbance, and the color from red or blue.[28] The GNP surface is one of the most stable and easily functionalized platforms for further modifications such as adding substance or molecules forming a specific monolayer to prolong stability and enhance dispersion in organic media, and for further conjugations of targeting probes or drugs.[29] Gold nanoparticles have brought about a new direction and theological ideas to build better and more effective diagnostic and therapeutic agents for different biomedical-based applications in the current biotechnology industry. Currently, two of the nano-based products are under investigating in clinical trials with United States Foot and Drug Administration approval (Table 1).

4. Targeting approaches

It has been well documented that the passage or unloading of antitumor drugs onto targeted tumor sites relied on several permeating mechanisms including passive targeting, active targeting, or a combination. Active targeting uses GNPs that are preconjugated with various probes or targeting agents including antibodies, small molecules, or peptides to locate and attack tumors. Passive targeting is simply taking advantage of the EPR effect to deposit antitumor drugs to tumors (Figure 3), which is a common characteristic of nanoparticle-based drug delivery to cancer.[30] To enhance antitumor drug targeting to tumor coupled with better therapeutic efficacy, most nanoparticle-based carriers are theoretically labeled with tumor targeting probes. Previous studies suggests that the optimal size of nanocarriers for attacking tumors

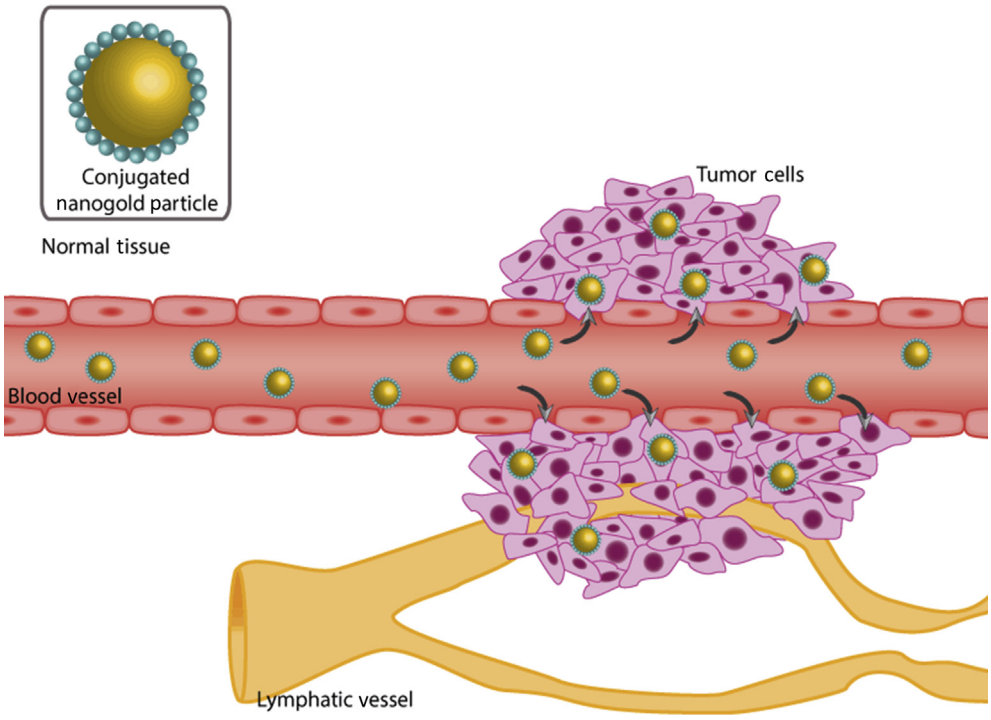

Figure 1 Graphic illustrating the accumulation of circulating gold nanoparticle conjugates at tumor sites by the enhanced permeability and retention effect. Because of disordered endothelial cells, gold nanoparticles can penetrate through blood vessels at the tumor site. The tumor site has diminished lymphatic vessels that reduce the gold nanoparticle clearance from the tumor.