Cytokine Therapy with Nanomaterials Participates in Cancer Immunotherapy

Subjects: Others

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Immunotherapy has gradually become an emerging treatment modality for tumors after surgery, radiotherapy, and chemotherapy. Cytokine therapy is a promising treatment for cancer immunotherapy. There are many preclinical theoretical bases to support this treatment strategy and a variety of cytokines in clinical trials. When cytokines were applied to tumor immunotherapy, it was found that the efficacy was not satisfactory. As research on tumor immunity has deepened, the role of cytokines in the tumor microenvironment has been further explored.

immunotherapy drug delivery systems cytokine therapy nanomaterial combination therapy of cancer

1. Introduction

So far, cancer is still the most severe disease. The treatment methods usually include surgery, chemotherapy, and radiotherapy. Tumor immunotherapy, which inhibits tumor development by activating the immune system, has been considered the fourth most popular tumor therapy [1][2]. The immune escape strategy of tumor cells is regarded as a significant obstacle to immunotherapy for all cancers and provides favorable conditions for tumor progression and immune tolerance. In cancer immunotherapy, drugs activate the immune system against tumor progression and metastasis through enhanced immune responses [3][4].

The earliest records of immunotherapy for cancer can be traced back to ancient Egypt, when some tumors subsided naturally after inflammation [5]. The first to study cancer treatment through the immune system were two German doctors, Fehleisen and Busch, who found that the tumor disappeared after the patient was infected with erysipelas [6][7]. The subsequent considerable development comes from William Coley, who first attempted to use the immune system to treat tumors in 1891 [8][9]. He found some cases of natural remission in cancer patients after an erysipelas infection. He studied in depth the records left by his predecessors and found as many as 47 cases of cancer patients who could not be cured in theory and reported natural remission after acute bacterial infection [5][10]. However, because the proposed “Coley’s toxins” did not have a precise mechanism of action at that time and because of the risk of using highly pathogenic bacteria to infect cancer patients, the research results of Coley were shelved by academic circles until 1967, when Jacques Miller discovered the existence of T cells, he described their functions in *Nature*. People began to pay attention to the immune system [11].

Meanwhile, people also began to figure out how to use immunotherapy to treat cancer. IFN-α was approved for cancer immunotherapy in 1986 [12]. High-dose recombinant IL-2 was approved for metastatic renal cell carcinoma treatment in 1992 and then approved for metastatic melanoma in 1998.

In recent years, some cytokines have been used in various animal cancer models for research [13]. Cytokines are soluble proteins that respond to immune cells by transmitting inflammatory or anti-inflammatory signals, with dual and conflicting signals [14]. Once the cytokine meets the membrane receptor on the target cell, the intracellular signal pathway will be triggered, thus inducing different cells' survival, activation, and differentiation in the tumor microenvironment (TME). Various cytokines play their roles in the location of the tumor.

Most of the cytokines used in tumor therapy are "pro-inflammatory" factors that enhance the immune system response by stimulating immune cells to modulate the immune microenvironment of tumors. The immune system relies on APC cells to present antigens to immunological effector cells, which act as antitumor agents by secreting antibodies or by direct killing. Due to the immune escape mechanism, adding cytokines to therapy can enhance this antitumor pathway. For example, IL-2 can promote T cell responses, NK and CD4+ cell proliferation, and antibody production by B cells [15][16]; IFN-γ primarily regulates CD8+ and CD4+ T cell immune responses [17]. These properties allow the delivery of cytokines into the tumor microenvironment using drug delivery systems to enhance tumor immunotherapy.

On the one hand, some cytokines, such as IL-4 and IL-8, accelerate the progression of tumors and inhibit immunity. On the other hand, other cytokines have also played a vital role in enhancing the antitumor immune response. Cytokines used in cancer immunotherapy can be divided into the following categories: ① IL-2 Family: IL-2,7,15,21; ② IFN-α; ③ IFN-γ; ④ IL-12; ⑤ TNF; ⑥ colony-stimulating factor (CSF) Family: GM-CSF, Granulocyte (G)-CSF, erythropoietin (EPO), IL-3; ⑦ IL-1 Family: IL-1,18 [18].

In recent years, the involvement of various nanomaterials in tumor immunomodulation therapy has been shown to effectively target tumor tissues, which helps reduce the dose of administered drugs and mitigate adverse effects [19][20]. The application of nanomaterials can avoid degradation of the drug before reaching the tumor and achieve enrichment at the tumor site through enhanced permeability and retention (EPR) effects or active targeting [21].

2. Organic Nanomaterials

After years of exploration, researchers have discovered a variety of organic nanomaterials that can be used to deliver cytokines to target cells. Using these materials to transport cytokines is more efficient than using free drugs. At the same time, because organic materials are easier to modify and process, researchers can change the materials according to different needs to make the materials have other functions. These efforts make cytokines more and more important in cancer immunotherapy. This entry summarizes the existing organic nanomaterials into the following six categories: poly (lactic-co-glycolic acid)-based nanomaterials, poly-γ-glutamic acid-based nanomaterials, β-cyclodextrin-based nanomaterials, chitosan-based nanomaterials, polyethyleneimine-based nanomaterials, and liposome-based nanomaterials (**Table 1**).

Table 1. Classification of nanomaterials and cytokines involved in the regulation.

	Nanomaterials	Cytokines	References
Organic	PLGA-based nanomaterials	TNF-α, IL-6, IFN-α,GM-CSF	[22][23][24]
	Poly-γ-glutamic acid-based nanomaterials	IL-10, IL-12, IL-6,TNF-α, IFN-γ	[25][26]
	β-Cyclodextrin-based nanomaterials	VEGF, IL-10, IL-12	[27][28][29][30]
	Chitosan-based nanomaterials	IL-2, IL-12, IL-15, IL-21	[31][32]
	Polyethyleneimine-based nanomaterials	IL-6, TNF-α, IL-12, IFN-γ	[33][34]
	Liposomes-based nanomaterials	IL-2, TGF-β	[35][36]
	Silica nanoparticles	IL-2, IFN-γ, IL-12	[37][38]
Inorganic	Magnetic nanoparticles	IFN-γ, TNF-α, IFN-α	[39][40][41]
	Gold nanoparticles	TNF-α, IFN-γ	[39][42][43]
	Calcium carbonate/Calcium phosphate nanoparticles	IL-2, IL-4, M-CSF	[42][44][45]

3. Inorganic Nanomaterials

With the rapid development of organic nanomaterials, researchers have found that several inorganic nanomaterials can carry drugs to transfer or induce cytokines. Furthermore, inorganic nanomaterials' physical and chemical properties can synergize in cancer immunotherapy. For example, the magnetic properties of Fe_3O_4 nanoparticles

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can be used to enhance immunotherapy. This entry mainly introduces silica nanoparticles, magnetic nanoparticles, and gold nanoparticles. (**Table 1**)

3.1. Silica Nanoparticles

In the past decade or so, mesoporous silica nanoparticles have been widely studied. Mesoporous silica nanoparticles (MSNPs), with the advantages of a larger contact area, a higher drug loading rate, and better modifiability than other nanoparticles. These advantages have led to its importance in the biomedical field. Some drug-loading systems can enhance biocompatibility when combined with silica [46][47][48]. Mesoporous silica nanoparticles can easily adjust the pore size, thus changing the mode of drug delivery. Modified MSNPs are a safe and efficient nanomaterial for targeted tumor therapy [49][50][51].

Liu et al. reported that silica nanoparticles could have a role in promoting humoral immunity [52]. Choi, E.W. et al. investigated the effect of silica NPs loaded with GM-CSF mRNA on dog leukocytes [53]. Kong, M. et al. embedded ATRA, DOX, and IL-2 in hollow MSNPs for immunotherapy of the B16F10 melanoma model [37]. The nanoparticle-mediated combination treatment plays a regulatory role in the tumor microenvironment by activating TILs, promoting the secretion of cytokines, and down-regulating MDSCs. Wan, Y.F. et al. prepared tumor-targeted, microenvironment-responsive mesoporous silica nanoparticles used to wrap IL-12 [38]. Studies have shown that the nanoparticles can effectively target tumor tissue, be swallowed by macrophages, release IL-12 locally, and repolarize TAM to an M1 phenotype that can kill the tumor with fewer side effects.

3.2. Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) are mainly based on Fe_2O_3 and Fe_3O_4. Because of the biocompatibility and modifiability they possess, these nanoparticles are well-suited as drug delivery platforms for drug delivery. In addition, the magnetism of MNPs provides an essential ability to transmit heat [54]. The magnetic properties of MNPs make them uniquely suited to receive magnetic field stimulation in vitro, a property that can be used for immune enhancement.

Mejías, R. et al. used dimercaptosuccinic acid (DMSA) for surface modification of Fe_2O_3 NPs. They studied the inhibitory effect on tumors after adsorption of IFN-γ in a mouse pancreatic ductal adenocarcinoma model [39]. The nanoparticles enabled efficient drug delivery and tumor enrichment with a substantial increase in T cells and macrophages for effective tumor suppression. Hu, B. et al. prepared anti-cancer magnetic polymer microspheres T9-TNF-PC-M containing human transferrin receptor monoclonal antibody (T9), TNF, and Fe_3O_4 ultrafine magnetic powder (M) by solvent evaporation method [40]. The T9-TNF-PC-M has a stable release rate of tumor necrosis factor, a solid magnetic response, and high drug loading in phosphate-buffered saline solution. The cytotoxicity test in vitro showed that T9-TNF-PC-M and their conjugates strongly inhibited human hepatocellular carcinoma cells. The in vivo targeted therapy showed that the antitumor activity of microsphere T9-TNF-PC-M and T9-TNF against Bel-7402 was significantly higher than that of free tumor necrosis factor. Yu et al. synthesized magnetic liposomes containing recombinant human interleukin-2 (rhIL-2) by combining the magnetic material Fe_3O_4

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with liposomes and evaluated the safety and therapeutic effect of this combination on cells and hepatocellular carcinoma in mice [41]. The results show that MIL can neither dissolve red blood cells nor affect the platelet aggregation rate in blood. The nanoparticles effectively prolonged the drug action time by applying a magnetic field externally. MIL significantly inhibits the development of hepatocellular carcinoma cells. The targeting experiment of MIL showed that MIL could considerably reduce the tumor volume of nude mice, which was 38% of that of the control group.

3.3. Gold Nanoparticles

Gold nanoparticles (GNPs) are widely explored because of their excellent prospects in nanotechnology, especially in biological nanotechnology for detection, imaging, and therapy [55]. Colloidal gold was commonly used in treating various diseases, primarily because of its optical properties and magnetism. GNPs have low toxicity and good biocompatibility, which benefits their interaction with other biomolecules [56]. GNPs are increasingly used in clinical research because they are easy to synthesize and process [57]. Gold is usually designed as nanoparticles, nanocages, nanoshells, nanostars, nanorods, and so on [58].

A team from Milan, Italy, has developed a drug delivery platform that enhances tumor targeting by modifying gold nanoparticles to deliver cytokines to tumor cells [42][59][60]. One of the gold nanoparticles labeled with a novel tumor-homing peptide containing the CD13 ligand ASN-Gly-Arg (NGR) expressed in tumor neovascularization can be used as a carrier for the delivery of cytokines to tumors [42]. In mice with fibrosarcoma, NGR-labeled nanoparticles can deliver very low but pharmacologically active levels of TNF to cancer. This experiment shows that NGR-labeled gold nanoparticles can be treated as a new platform, enhancing drug delivery targeting.

Mohsen N. et al. developed a gold nanorod coupled with interferon-γ and methionine combined with near-infrared laser hyperthermia, which can be used to treat tumors [43]. Different concentrations of GNPs were added to cultured breast cancer cells and irradiated with NIR light. In the process of NIR light irradiation, the number of tumor cell deaths in the presence of GNPs was significantly higher.

3.4. Calcium Carbonate/Calcium Phosphate Nanoparticles

$CaCO_3$ and $Ca_3(PO_4)_2$ nanoparticles are suitable drug carriers with good biosafety and degradability and have already been used in tissue engineering and drug delivery [61]. Because of their responsiveness to the acidic tumor microenvironment, $CaCO_3$ and $Ca_3(PO_4)_2$ nanoparticles are well-suited drug delivery systems for tumor immunotherapy [62].

Liu et al. prepared calcium carbonate nanoparticles loaded with shiitake mushroom polysaccharides, which could be treated as immune adjuvants to strengthen cellular and humoral immune responses. In a tumor model, the NPs induced the secretion of IL-2 and IL-4 [44]. Mao et al. prepared M-CSF-loaded $CaCO_3$ nano micelles that were pH-responsive to the tumor microenvironment and could effectively target C57BL/6 mouse melanoma tissue and release M-CSF to enhance the antitumor effects of macrophages and T cells [45]. Chen et al. used $CaCO_3$

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nanogels with anti-CD47 antibodies to prevent local tumor recurrence and to improve macrophage phagocytosis and antigen presentation by postoperative in situ spraying [63].

4. Novel Nano Delivery Systems

With the development of nanomaterials and cytokine therapies, a series of novel nano-delivery systems have emerged in recent years. Hybridized nanoparticles have come into the limelight due to their ability to combine various types of nanoparticles. By combining two or more nanomaterials, the nanoparticles can synergize with cytokines to enhance tumor immunotherapy. Zhang et al. prepared lipid-polymer nanoparticles synthesized by PCL-PEG-PCL and DOTAP (IMNPs). The nanoparticles loaded with TLR 7/8 agonist and TLR4 agonist monophosphoryl lipid A (MPLA) could effectively target DC cells to suppress tumors and prolong survival in mice [64]. Gao et al. developed a Gd-Au DENP-PS nanoplatform for encapsulating PD-1 siRNA. The nanoparticles are dendritic molecules that activate T cells and bind to IDO to enhance tumor immunotherapy [65]. A manganese-based hybrid nanoparticle was also reported. Using amorphous porous manganese phosphate (APMP) loaded with DOX and phospholipids (PL), Hou et al. The drug enhanced cellular immune response and tumor-killer cell recruitment while increasing the secretion of cytokines, acting as an antitumor agent [66].

Membrane camouflage nanoparticles (MCNPs), usually derived from erythrocytes, cancer cells, neutrophils, and platelets, are potential drug delivery platforms because of their immune advantages. These materials can often avoid drug clearance in vivo and target tumor cells more effectively, and they have a high affinity for cells of the exact origin [67][68]. Erythrocyte membrane is the most common source of MCNPs due to its ease of obtaining, excellent biocompatibility, and strong protection for loaded drugs [69]. Cancer cell membrane nanoparticles have the following distinctive characteristics: they cannot be easily removed; adhesion molecules on the membranes can promote the homologous targeting of cancer cells; and CD47 on the membrane of cancer cells prevents phagocytes from engulfing nanoparticles [70][71]. Platelet membrane is rich in CD47, which has potential camouflage to evade immune surveillance, and avoids the circulatory release of drugs, which can be an ideal material for biomedical carriers. Therefore, developing nanoparticles camouflaged by platelet membranes is a promising research direction [72]. Neutrophil membranes are also unique because they have a variety of cytokine receptors on their surface [73]. In summary, the excellent camouflage and good biocompatibility provided by cell membranes will have significant advantages in competing with other immunomodulator delivery technologies.

Similarly, because of its outstanding biocompatibility, the cell-based nano-drug delivery system is also a new way of drug delivery, such as nanosystems based on red blood cells (RBC) [74], nanosystems based on immune cells [73], nanosystems based on stem cells [73], and nanosystems based on platelets [75]. This kind of system will deliver cytokines to tumor cells more efficiently. Therefore, more attention should be paid to applying cytokine drugs to cell-based nanosystems.

NPs based on phototherapy have the advantages of a solid curative effect, low invasion, and few adverse reactions in tumor therapy. Photothermal therapy (PTT) and photodynamic therapy (PDT) are the two primary treatment modalities of phototherapy. PTT and PDT based on nanoparticles can kill tumors directly and induce

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contribute to antitumor immune effects. PTT uses heat to kill tumors, while PDT kills tumors by producing large amounts of ROS in tumor cells. In particular, the death of many tumor cells after PTT and PDT results in a more intense immune response, including reprogramming and activation of the immune microenvironment, modulation of cytokines, and mediation of a more intense T-cell immune response [76][77][78][79][80]. If phototherapy can be combined with existing cytokine immunotherapy, it will become a more efficient method for tumor treatment.

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