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Development of Hydrogels in Tumor Immunotherapy

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Abstract. Immunotherapy is a fast-developing anti-cancer strategy which has shown great potential in help healing different cancer. For the moment, cytokine therapy, antibody therapy, tumor vaccine are methods that have been put into practice or very promising. With the enhancement of cognition to immune system and development of cell engineering techniques, a lot of new therapies are in different stages of clinical trials. We must admit that there still remain various challenges. In this article, some immunotherapies and challenges they face will be introduced.

Keywords: Hydrogel, Tumor Immunotherapy, cytokine, antibody, tumor vaccine

1. Introduction

When discussing the mechanisms behind tumor formation, it is important to first understand how tumors develop in the body. Tumors are the result of uncontrolled cell proliferation, where these cells not only invade normal tissues and organs, but also have the capability to spread within the body. Tumors are classified as benign or malignant, with only malignant tumors being referred to as cancer due to their aggressive and metastatic nature. Cancer can arise from different types of cells, leading to over a hundred different types of cancers. The most common types include carcinomas, sarcomas, and leukemia/lymphomas. The development of cancer is a multistep process, starting from abnormal cell proliferation and progressing through additional mutations and clonal selection to increase the cell growth and invasion capabilities.

Cancer is characterized by the uncontrolled proliferation of cancer cells, which invade normal tissues and organs and can spread throughout the body. Tumors can be benign or malignant, and only malignant tumors are called cancers because of their ability to invade and metastasize. Cancer can be produced by different cell types, resulting in more than a hundred different types of cancer. The most common types include cancer, sarcoma, and leukemia/lymphoma. Cancer development is a multi-step process that begins with abnormal cell proliferation and leads to tumor progression through additional mutations and clonal selection, increasing the cell's ability to grow and invade. The clonability of tumors, demonstrated by X chromosome inactivation studies, indicates the single-cell origin of many tumors, which in turn affects the functioning of other organs. Cancer usually develops later in life due to the accumulation of genetic abnormalities. Carcinogens, such as radiation, chemicals, and viruses, can contribute to cancer development by causing DNA damage,

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inducing mutations, or stimulating cell proliferation. Initiators, such as cancer-causing chemicals in solar radiation and tobacco smoke, can cause mutations in key target genes. Tumor promoters, such as phobolate, stimulate cell proliferation and are necessary for tumor cell growth. Hormones, especially estrogen, can act as tumor promoters in some cancers, while some viruses are known to induce cancer in animals and humans. Overall, cancer is a complex disease with multiple causes and types, but the underlying mechanism involves the uncontrolled proliferation of cancer cells due to accumulated genetic abnormalities [1].

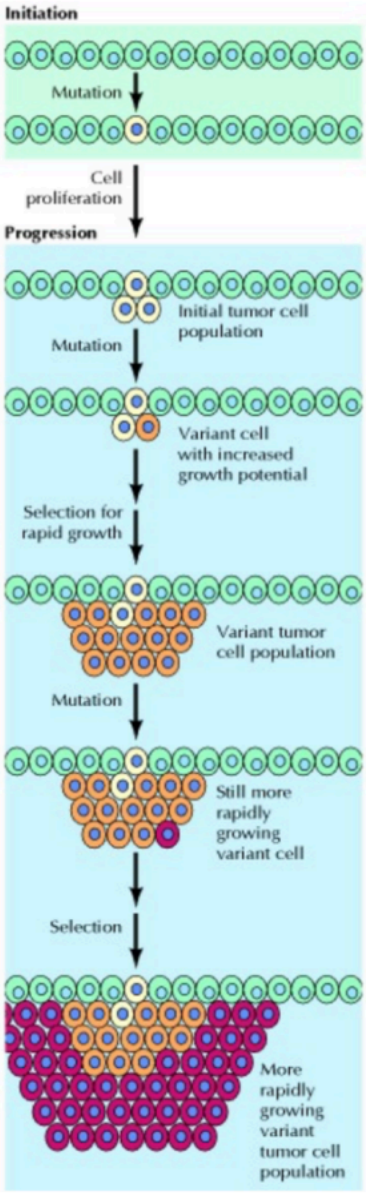

Figure 1. Stages of tumor development [1]

The body's defense mechanism generates a range of chemicals when it detects cancerous growths, and these substances significantly influence the success of the immune system's fight against cancer. A critical component of this immune response is the synthesis of pro-inflammatory cytokines, including interferon and tumor necrosis factor. These are vital for stimulating immune cells and enhancing the body's defense against cancer. The production of these cytokines is triggered

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once immune cells like T cells and dendritic cells identify antigens specific to tumors. Beyond pro-inflammatory cytokines, the immune system also secretes chemokines, which are essential for directing immune cells to the cancerous area. These chemokines are instrumental in establishing an inflammatory environment within the tumor, which is necessary for a robust immune reaction against cancer cells. By drawing immune cells to the tumor, chemokines reinforce the immune cells' ability to attack cancer and can lead to the reduction of the tumor. Furthermore, the immune system generates reactive oxygen species (ROS) and reactive nitrogen species (RNS) as a reaction to the presence of tumors. These substances have both direct and indirect impacts on cancer cells, contributing to their demise. They can cause oxidative stress and cellular damage in cancer cells, resulting in cell death. Moreover, they can affect the signaling pathways within cancer cells, which can disrupt the growth and survival of these cells. Indoleamine 2,3 dioxygenase (IDO) is an enzyme that the immune system produces in response to tumors. It is significant in immune tolerance by depleting tryptophan, a vital amino acid necessary for the multiplication and function of T cells. IDO can cause the programmed death of activated T cells due to tryptophan depletion, which promotes immune tolerance and suppresses the immune system's response to cancer. In summary, the immune system's response to tumors through chemical production is a multifaceted and dynamic process that involves intricate coordination among various signaling pathways and cell interactions. These chemicals are key in dictating the immune system's reaction to cancer and, consequently, the effectiveness of anti-tumor immunity. Gaining insights into how the immune system generates and uses these chemicals in response to tumors is essential for developing more potent immunotherapeutic strategies. By focusing on the immune system's chemical reactions to tumors, it is possible for medical professionals to enhance the immune system's cancer-fighting capabilities and improve treatment outcomes for patients with cancer [2].

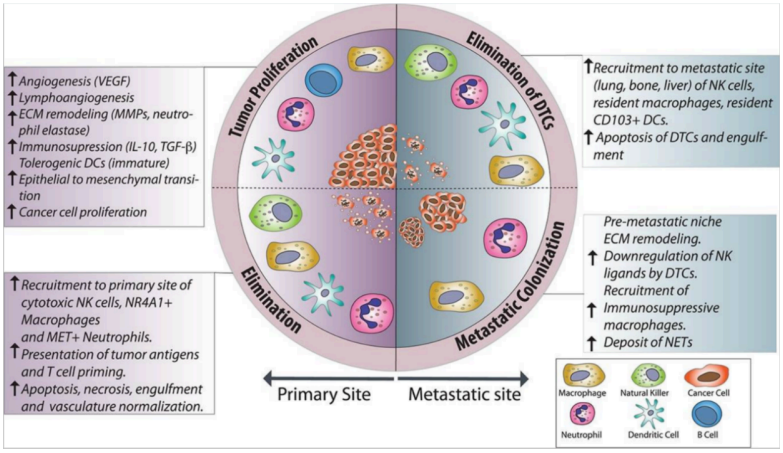

Figure 2. Roles of innate immune cells in metastatic cancers [2]

The immune system is instrumental in countering tumors, secreting a range of biological molecules that can either bolster anti-tumor activities or inadvertently support tumor growth. Among these molecules, chemokines—small proteins that facilitate communication between cells—play a pivotal role in guiding immune cells through the tumor microenvironment (TME). The interplay between anti-tumor and pro-tumor reactions is shaped by the phase of tumor development, the stimulation of immune cells, the influx of cells that either boost or suppress immunity, and the presence of chemokine receptors on various immune cells. Solid tumors are intricate structures, consisting not only of cancer cells but also of immune cells, blood vessel cells, connective tissue cells, and other non-cancerous elements. The immune cells within the TME are equipped with

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chemokine receptors that allow them to navigate the chemokine landscape, thus influencing cancer growth and spread. Chemokines are multifunctional in tumorigenesis, influencing cancer cell traits like stemness, proliferation, survival, and the processes of blood vessel formation and metastasis. The interplay between tumor cells and the TME, involving chemokines, can foster the expansion of the primary tumor and the emergence of secondary tumors elsewhere in the body. The diversity and variability of primary and metastatic tumors complicate the development of cancer therapies. Despite significant efforts to understand how these tumors sidestep the immune system's tumor-suppressing mechanisms, treating metastatic disease remains a formidable challenge. Chemokines are central to TME formation and the modulation of immune cell behavior, blood vessel growth, and tumor advancement. Gaining insights into the intricate interactions among TME cell types and their biological consequences is essential for crafting targeted cancer treatments. Given the complexity and variability of solid tumors, the pattern of immune cell infiltration into tumor tissues is inconsistent. Immune cells within the TME generate a spectrum of biological factors in response to tumors, including cytokines, growth factors, and chemokines. These molecules influence the movement, activation, and functionality of immune cells within the TME, which in turn can impact tumor development. There is optimism that fine-tuning chemokine networks within solid tumors could enhance treatment strategies. Approaches that zero in on specific chemokine signaling pathways, especially when paired with immunotherapy, show promise as novel cancer treatments, so the immune system's response to tumors involves the production of various biological factors, including chemokines, which are key to controlling immune cell movement and function within the TME. Elucidating the function of chemokines in solid tumors is vital for devising therapies that can address tumor diversity, metastasis, and resistance to treatment. Ongoing research is aimed at leveraging chemokine networks in tandem with other treatment methods to potentially enhance outcomes for individuals with cancer [3].

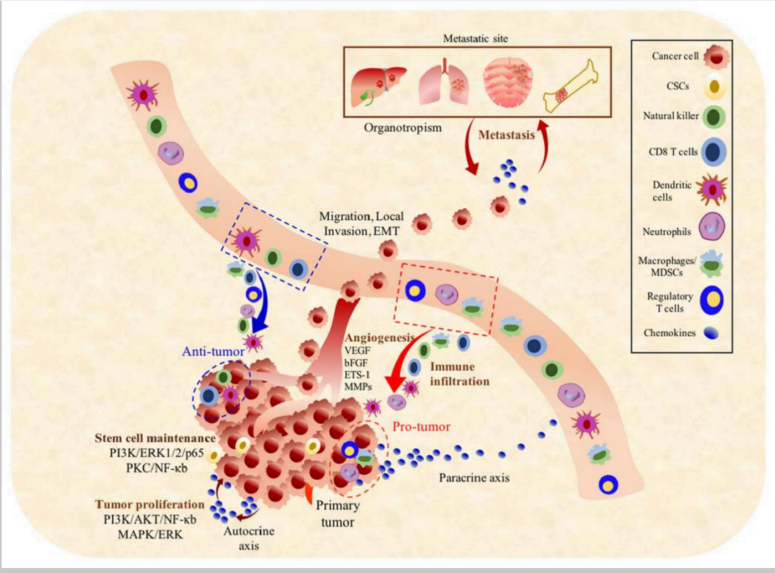

Figure 3. Role of chemokines in the progression of solid tumors [3]

The immune system is pivotal in combating tumors, secreting a variety of biological molecules that can either stimulate or suppress cancer development. These molecules are generated by immune cells in the presence of tumors and exert a range of influences on cancer cells. A significant class of these molecules is chemokines, which are small proteins that guide immune cells to the tumor location. They are essential in sculpting the tumor microenvironment by managing the arrival of

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various immune cells, including T cells, macrophages, dendritic cells, and neutrophils. The impact of chemokines on tumor growth can be either tumor-promoting or tumor-inhibiting, based on their interactions with the immune and cancer cells. Within the tumor microenvironment, chemokine/receptor interactions govern the penetration of immune cells and facilitate communication between cancer and immune cells. For instance, the CXCL8-CXCR1/2 axis has been observed to foster cancer growth, the development of new blood vessels, and the spread of cancer to other parts of the body. The CXCL12-CXCR4 axis also plays a significant role in the movement of cancer cells to other organs, enhancing their survival and reproduction. Chemokines are likewise involved in the regulation of cancer stem cells, which are capable of self-renewal and differentiation into diverse cell types. Beyond chemokines, the immune system responds to tumors by producing a spectrum of other biological factors such as cytokines, growth factors, and antibodies. Cytokines, which are signaling proteins, can influence immune cell activity in the tumor microenvironment. Interferons and interleukins, for example, have been shown to inhibit tumor growth by activating cytotoxic T cells and natural killer cells. Growth factors, such as vascular endothelial growth factor (VEGF), are also crucial for angiogenesis, the process of new blood vessel formation that nourishes tumors. This process is vital for tumor expansion and its spread to other parts of the body, and interventions targeting VEGF signaling are a prevalent strategy in cancer therapy. Antibodies generated by the immune system, especially by B cells, can target cancer cells and hinder their proliferation. Monoclonal antibodies designed to recognize specific antigens on cancer cells have been created as a form of targeted therapy for various cancers. In summary, the immune system's response to tumors involves the production of a wide range of biological factors that can significantly influence cancer cell growth, advancement, and spread. Gaining insights into the intricate relationship between the immune system and tumors is crucial for devising cancer treatments that can leverage the immune response to target and destroy cancer cells [4].

2. Immunotherapy that has been put into practice or has great potential

The immune system is a vital system in our body. When we are infected with bacteria or virus and so on, immune cells will help remove these harmful biological factors. But there is a premise, which is that our immune system is able to recognize them. In fact, some abnormal cells, including cancer cells, have a serious of ingenious escape mechanisms which allow them to hide from immune system. That’s why tumor immunotherapy is so important. It can activate, enhance or transform some of the key cells or chemicals to better recognize and attack tumors.

Immune system is very complex. When facing different types of pathogenic cells or virus, it will use different methods to solve the problems. In general, tumor immunotherapy can be divided into the following strategies: cytokine therapy, antibody therapy, tumor vaccine, adoptive cell therapy etc.

2.1. Cytokine therapy

Cytokine therapy is a form of immunomodulatory biological treatment that utilizes specific cytokines to enhance or regulate the immune system in order to fight against diseases. Cytokines are small protein or peptide molecules secreted by immune cells that, upon interacting with the receptors on the target cells’ surface, initiate a series of signaling pathways. These pathways influence the proliferation, differentiation, and function of immune cells, playing an important role in maintaining immune balance and defense responses within the body.

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In cancer treatment, cytokine therapy is used to stimulate the patient's immune system, enabling it to identify and eliminate tumor cells. For instance, interleukin-2 (IL-2) is one of the members of the IL-2 cytokine. Each of them owns a four alpha-helix bundle. IL-2 signals by the IL-2 receptor, which is a system made up of three chains called alpha (CD25), beta (CD122), and gamma (CD132) [5]. The interaction between IL-2 and CD25 does not improve signal transduction; however, it does increase the affinity of the IL-2 receptor by a hundredfold. T cell signaling is contingent upon the heterodimerization of the IL-2 receptor subunits. IL-2 can trigger signaling through either the intermediate-affinity dimeric IL-2 receptor (CD122/CD132) or the high-affinity trimeric IL-2 receptor (CD25/CD122/CD132). Therefore, IL-2 can promote the activation of T cells and natural killer (NK) cells, thereby enhancing their ability to kill virus or tumor cells. Interferons (such as interferon-α) are also used in the treatment of certain cancers, like melanoma. Ryan and Michael explore the use of cytokine therapy in melanoma [6]. In their essay, they highlight that interferon alpha simultaneously boosts dendritic cell (DC) activation and antigen expression while interacting with B- and T-lymphocytes, so a cytotoxic T-cell response appears. In some studies, it seems that IFN alpha has the ability to activate STAT1 and down-regulate activated STAT3. STAT stands for signal transducer and activator of transcription. STAT1 is created by a phosophorylation event, while STAT3 is a promoter of tumor growth and immunosuppression.

Beyond cancer treatment, cytokine therapy is applied in autoimmune and chronic inflammatory diseases. For example, anti-inflammatory cytokines like IL-10 can suppress an overactive immune system, thereby reducing inflammation and preventing tissue damage. Additionally, cytokines can be used in infectious diseases to boost the body's ability to fight pathogens. By adjusting the levels of specific cytokines, the immune response to viral or bacterial infections can be optimized for greater efficiency.

2.2. Antibody therapy

Antibody therapy is a biological treatment that uses antibody molecules to combat diseases. Antibodies are created by B cells and can specifically identify and bind to antigens, which are typically proteins or polysaccharides on the surface of pathogens or tumor cells. This binding triggers a series of immune responses. Modern medicine takes advantage of this specificity by using genetic engineering techniques to produce monoclonal antibodies, which target specific disease-related molecules for therapeutic purposes.

One of the most widespread applications of antibody therapy is in cancer treatment. Monoclonal antibodies can recognize and bind to antigens that are characteristic of cancer cells, either neutralizing them directly or tagging them for elimination by the immune system. For instance, trastuzumab (Herceptin) is a monoclonal antibody used to treat HER2-positive breast cancer. PierFranco Conte MD etc. made a study about trastuzumab emtansine adjuvant therapy [7]. They conducted a phase 3 KATHERINE trial. The QLQ-C30 is a 30-item questionnaire that measures overall QOL (global health status [GHS]), 5 functional dimensions (physical, emotional, role, cognitive, and social), and additional symptoms and single items. The QLQ-BR23 is a 23-item questionnaire designed to assess functioning across various domains and symptoms related to breast cancer and its treatment. For both tools, what is more desirable are higher scores on the functional and global health scales, as they reflect better functioning or quality of life (QOL). On the contrary, lower scores on the symptom or single-item scales are preferable, as they indicate fewer symptoms. The KATHERINE study allotted 743 participants in each group, and they successfully get a figure of the scores of the QLQ. The results are as Figure 4.

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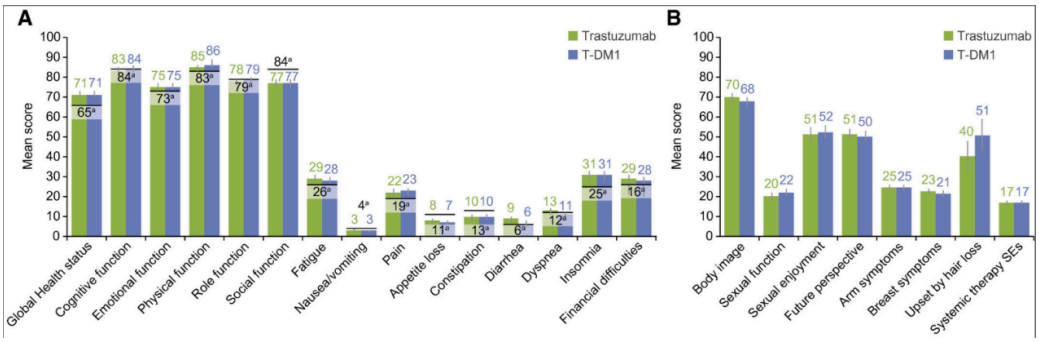

Figure 4. (A) Baseline QLQ-C30 and (B) QLQ-BR23 scale scores. The maximum possible score is 100

Figure 5 illustrates the proportions of patients reporting a clinically meaningful decline in the QLQ-C30 and QLQ-BR23 scales over time. By the 6-month follow-up, the proportion of patients experiencing such deterioration in symptoms and function was comparable between the two groups, except for role functioning. In this category, a higher percentage of patients in the T-DM1 group reported clinically meaningful deterioration compared to the trastuzumab group (23% vs. 16%, respectively), a trend that persisted at the 12-month assessment. It is important to note, however, that these data reflect only patients who remained enrolled in the study.

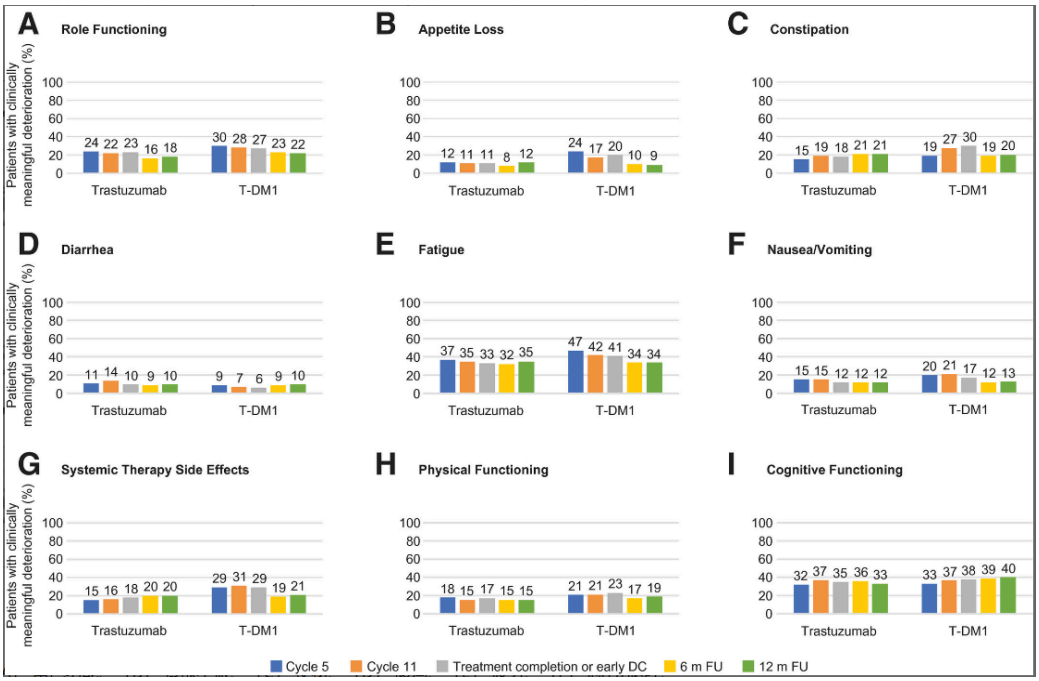

Figure 5. Proportion of patients reporting a clinically meaningful deterioration at each assessment point for (A) role functioning, (B) appetite loss, (C) constipation, (D) diarrhea, (E) fatigue, (F) nausea/vomiting, (G) systemic therapy side effects, (H) physical functioning, and (I) cognitive functioning

From the results we can make a rough conclusion, the randomized phase 3 KATHERINE trial revealed that adjuvant T-DM1 provided significantly better invasive disease–free survival compared to trastuzumab in patients with residual invasive disease after undergoing neoadjuvant chemotherapy and HER2-targeted therapy. But T-DM1 was associated with a higher occurrence of

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specific adverse events, such as fatigue, nausea, reduced platelet counts, and elevated liver enzyme levels, compared to trastuzumab.

Additionally, there are antibody-drug conjugates (ADCs), which link antibodies to chemotherapy drugs, allowing for the precise delivery of these drugs to cancer cells while minimizing damage to healthy cells.

Beyond cancer, antibody therapy plays a significant role in autoimmune diseases, inflammatory conditions, and infectious diseases. For example, in the treatment of rheumatoid arthritis, TNF-α inhibitors such as infliximab are used to neutralize excessive levels of tumor necrosis factor, reducing joint inflammation and damage. Antibody therapy also shows promise in treating viral infections, as seen in the use of neutralizing antibodies against COVID-19, which block the virus from entering cells and reduce the severity of the disease. In Bahman's study, it has been proved that antibody like infliximab (a chimeric monoclonal antibody targeting human tumor necrosis factor-α, used to treat conditions such as intestinal Behçet's disease and Crohn's disease) can reduce the mortality rate in COVID-19 [8]. The advantages of antibody therapy lie in its high specificity and relatively low side effects, as antibodies are designed to target only specific antigens.

2.3. Tumor vaccine

Tumor vaccines are one of the immunotherapies designed to activate patients' immune system to recognize and destroy tumor cells. Unlike traditional preventive vaccines, tumor vaccines are primarily used for patients already diagnosed with cancer, with the goal of helping the body fight existing tumors or preventing recurrence. The fundamental principle of tumor vaccines is to present tumor-associated antigens to the immune system, prompting it to generate a specific immune response that targets and destroys cancer cells.

Tumor vaccines can be classified into several types, including whole tumor cell vaccines, DNA/RNA vaccines, peptide vaccines, and dendritic cell vaccines. Whole tumor cell vaccines use inactivated or genetically modified cancer cells to trigger an immune response. Wang made a Newcastle disease virus-modified tumor whole-cell vaccine as a therapeutic vaccine to fight against lung cancer [9].Peptide vaccines utilize short peptide chains that mimic antigens on tumor cells' surface to stimulate the immune system. For example, Ibtihal Omer etc. designed an epitope-based peptide vaccine against Cryptococcus neoformans [10]. DNA/RNA vaccines work by introducing genetic fragments that encode tumor antigens, prompting the patient's own cells to produce these antigens and, in turn, initiate an immune response. Wang made a novel tuberculosis DNA vaccine which demonstrated a significant therapeutic effect on the mouse tuberculosis model through intramuscular injection combined with electroporation [11]. Dendritic cell vaccines involve using the patient's own dendritic cells, which are exposed to tumor antigens outside the body and then reintroduced into the patient to activate T cells against the tumor. Zhu made a dendritic cell vaccine loaded with MG-7 antigen, which can induce cytotoxic T lymphocyte responses against gastric cancer [12].

A well-known tumor vaccine is Provenge (sipuleucel-T), used to treat advanced prostate cancer. Provenge is created by collecting a patient's white blood cells, exposing them to a prostate cancer antigen in the lab, and then re-infusing the activated immune cells back into the patient to boost their immunological reaction against the cancer.

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3. The role that hydrogels can play in immunotherapy

As a new biomaterial, gel has shown great potential and broad application prospects in the field of tumor therapy. The advantages of hydrogel in tumor treatment mainly lie in: 1. Biocompatibility: hydrogel is similar to human tissue, which can reduce the rapid degradation of drugs in vivo and drug-related toxicity of brain tissue. 2. Degradability: hydrogel interacts with host tissue to regulate the degradation process. 3. Drug release control: some intelligent hydrogels can respond to a variety of external stimuli and accurately regulate drug release. 4. Easy to obtain: Hydrogels can be easily synthesized and mass produced by chemical methods.

3.1. Application of new composite materials in the treatment of lung cancer bone metastasis

Lung cancer is a common primary tumor with bone metastasis, leading to bone related events such as bone pain and pathological fractures. Traditional treatment methods such as radiotherapy and chemotherapy have problems such as significant side effects and susceptibility to drug resistance. Molecular targeted drug ANLO (anlotinib) is a third line drug used to treat bone metastases in lung cancer, but there is a risk of tumor recurrence after treatment. The sequential release of ANLO and TGF- β inhibitors through biomaterials can enhance the therapeutic effect. The researchers developed a new composite material, mPEG-PMet hydrogel PLGA microspheres, for molecular targeted immunotherapy to enhance bone metastasis of lung cancer. This material activates anti-tumor immune responses (such as increasing the proportion of CD8+ T cells and reducing the proportion of regulatory T cells) by sequentially releasing molecular targeted drugs ANLO and TGF-β inhibitor SB525334, improving therapeutic efficacy, significantly inhibiting tumor growth, and enhancing mouse survival [13].

3.2. Application of injectable hydrogel delivery system in tumor local immunotherapy

Immunotherapy has developed rapidly in tumor treatment, but some patients have a lower response to immunotherapy, which may be related to factors such as drug efficacy, drug retention time, and systemic adverse reactions. The injectable hydrogel system is easy to use, increases the local drug concentration, prolongs the drug retention time, and has good biocompatibility, so that it can enhance the anti-tumor treatment effect by increasing the local drug concentration and prolonging the drug retention time. Research progress includes the delivery of immune checkpoint inhibitors (ICI), immune cells, cytokines, and co delivery of chemotherapy and immunotherapy drugs (such as gemcitabine and PD-L1 inhibitors) [14-16].

3.3. Application of hydrogel in drug delivery system for local treatment of brain tumor

Brain tumors, especially glioblastoma, are highly invasive tumors, and the presence of the blood-brain barrier makes it difficult for some conventional tumor treatment drugs to reach the brain tumor tissue. As a drug delivery system, hydrogel can precisely control drug release through external stimulation. Researchers have developed a variety of intelligent hydrogel-based delivery vectors, such as temperature sensitive, pH responsive, light responsive and magnetic responsive hydrogels, for delivering chemotherapy drugs, immunomodulators and gene therapy vectors. These smart hydrogels can respond to external stimuli (such as temperature, pH, light and magnetic field) and release the wrapped bioactive substances. These hydrogels have shown the ability to effectively control drug release and reduce systemic adverse reactions in the treatment of brain tumors. These hydrogels can be divided into injectable hydrogels (injected into human tissues, such as colloidal

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water gel and polyvinyl alcohol (PEG) based hydrogels), spray hydrogels (can be directly sprayed onto specific surfaces or tissues, such as pectin containing drugs and polymer nanocrystals), and implantable hydrogels (can be implanted into the human body for local drug release, such as temperature sensitive hydrogels containing drugs) according to the way they enter the target tissues.

3.4. The role of self-assembled peptide hydrogel in tumor therapy

Short peptide is a small molecular peptide chain composed of amino acids, which can self-assemble into a nanofiber structure through various micro forces at high concentrations to form a three-dimensional gel with high water content. Self-assembled peptide hydrogels have become a powerful tool in tumor treatment because of their good biocompatibility, low immunogenicity and superior drug loading performance. Compared with other hydrogels, self-assembled peptide hydrogels have the advantages of reducing the frequency of drug use, improving the distribution of drugs in the body and slowing down drug degradation. The hydrogel can not only be used as a drug delivery carrier, but also be used as a natural anti-tumor peptide hydrogel to directly kill tumor cells. The following are some of the application achievements of the assembled peptide hydrogel as a sustained-release carrier in tumor treatment in recent years:

2019 Karavasili et al. first reported a self-assembled peptide hydrogel [ac-$(RADA)_4$-$CONH_2$] as a carrier of a drug combination (curcumin and doxorubicin) to jointly fight head and neck cancer cells. The results showed that the self-assembled peptide hydrogel [ac-$(RADA)_4$-$CONH_2$] can accurately control the encapsulated drug payload, and the drug combination hydrogel system plays the role of apoptotic cell response

2020 Dai et al. designed a series of hybrid peptide sequences of melittin-$(RADA)_n$ with different self-assembled RADA motifs, and screened melittin -$(RADA)_6$ with the best gel forming ability and in vitro anti-tumor activity, which can reshape the immunosuppressive tumor microenvironment and enhance the host's innate and adaptive anti-tumor immune response after targeted treatment of tumor cells

2021 Zhu et al. innovatively used bee venom peptide -$(RADA)_{16}$ loaded immunomodulatory agent metformin to induce sustainable CD8+ T cell responses, promote M1 macrophage polarization, and alleviate drug toxicity and side effects

The metabolic reprogramming of the tumor microenvironment and poor immunogenicity in 2022 are two challenges that cancer immunotherapy must overcome to enhance clinical benefits. For this reason, Wang et al proposed a local chemoimmunometabolic therapy for the first time, which can induce the death of immunogenic tumor cells by injecting supramolecular hydrogel and simultaneously releasing doxorubicin

2023 In order to address the issue of drug diffusion, Wu et al. reported the design and synthesis of a self-assembling peptide derived from lonidamine, which targets both integrin receptors and mitochondria in cancer cells [17].

3.5. Research on new self-adjuvant hydrogel vaccine

The research team has developed a spontaneously formed self-adjuvant hydrogel, which is formed by aldomannan (A-MA) and N, O-carboxymethyl chitosan (NOCC) through Schiff base reaction [18], without additional light source or crosslinking initiator. The hydrogel vaccine can continuously release antigen, trigger strong immune response, effectively promote the uptake, activation and maturation of dendritic cells, increase antigen accumulation in lymph nodes, and enhance specific

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humoral immune response. The hydrogel showed good biocompatibility in cytotoxicity tests on L929 and NIH-3T3 cells. The hydrogel vaccine showed strong immunogenicity and therapeutic effect in mouse models, significantly increased the production of antigen specific IgG in mice, and had potential for immunotherapy.

3.6. Application of alginate composite hydrogel in cancer treatment

Alginate is a polysaccharide biopolymer extracted from seaweed plants, which has good biocompatibility, biodegradability, and non-toxicity. Alginate can form hydrogels through a variety of ways, including ionic cross-linking, covalent cross-linking, free radical polymerization, phase change (thermal gel) and cell cross-linking, and can be used for the controlled release of bioactive molecules, tumor models and tumor localization. The hydrogel is used for drug-controlled release, tumor model and tumor localization, especially in breast cancer, lung cancer, prostate cancer, colorectal cancer and other fields. For example, the composite hydrogel stent made of dopamine modified alginate conjugate (Alg-DA) combined with 3D printing technology can be used for photothermal treatment and post repair of tumors, and this use has been verified on 4T1 mouse tumor models; A composite hydrogel composed of 50% alginate and 50% Matrigel developed by Cavo et al. successfully simulated the 3D microenvironment in vivo after embedding into fibroblasts and breast cancer cells, providing a new alternative model for cancer research. Alginate composite hydrogels have potential as drug delivery materials, but the current research is mostly at the basic stage, and further research is needed to improve its biodegradability and biocompatibility, and explore better composite materials [19].

3.7. New drug delivery system for the treatment of bladder cancer

The researchers developed a drug delivery system based on thermosensitive PLEL hydrogel for the collaborative treatment of bladder cancer. By combining chemotherapy and immunotherapy, the system uses thermosensitive hydrogel system to achieve local controlled release of drugs, improve the therapeutic effect and reduce side effects.

To sum up, hydrogel, as a multifunctional biomaterial, has shown extensive application potential in the field of tumor treatment. From molecular targeted therapy to immunotherapy, from drug delivery to vaccine development, the application range of hydrogels is expanding. In the future, with the further development of material science and biotechnology, hydrogels are expected to play a more important role in clinical tumor treatment.

4. Challenges

1. Biocompatibility and biodegradability: Although hydrogels usually have good biocompatibility, long-term implantation into the body may cause chronic inflammatory reaction or immune reaction. In addition, the biodegradability of hydrogel also needs to be optimized to ensure that its degradation products are harmless to the body.

2. Drug loading and drug release kinetics: The drug loading and drug release kinetics of hydrogel are the key factors affecting the therapeutic effect. How to improve the drug loading of hydrogels, achieve sustained and stable drug release, and adjust the release rate according to the changes of tumor microenvironment are the focus of current research.

3. Complexity of tumor microenvironment: tumor microenvironment is highly heterogeneous and dynamic, including hypoxia, acidity and high interstitial pressure. These factors may affect the

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stability of hydrogels and drug permeability.

4. Difficulties in clinical transformation: many hydrogel materials have performed well in laboratory research, but they face many challenges when transforming to clinical application, such as quality control of large-scale production, long-term safety evaluation, and validation of clinical trials.

5. Targeting and precise delivery: improving the tumor targeting of hydrogels, ensuring the effective aggregation of drugs in tumor tissues, and reducing the impact on normal tissues are the key to improving the therapeutic effect and reducing side effects.

6. Multi-functional integration: Tumor treatment often requires the integration of multiple functions, such as chemotherapy, immunotherapy, photothermal therapy, etc. How to design a hydrogel system that integrates multiple therapeutic functions to achieve synergy is the current research hotspot.

7. Cost benefit analysis: For clinical applications, treatment cost is also an important consideration. It is an important aspect to realize its clinical value to develop cost-effective hydrogel materials and make them widely used in areas with limited medical resources.

8. Regulatory and approval challenges: The development of new hydrogel materials and treatment strategies needs to pass a strict regulatory approval process, including safety, effectiveness assessment and possible environmental and health risk assessment [15,19].

5. Conclusions

In summary, we discussed the mechanism of how tumor forms. Tumors are results of cells' uncontrolled proliferation, which can be divided into benign tumor and malignant tumor. Generally, cancer is developed from malignant tumor. When immune system detects that tumor is growing, it will secrete various chemical substance such as proinflammatory factors, chemokines etc. By complex interaction, they are able to prevent tumors from germinating. For the present, useful or potential therapies include cytokine therapy, antibody therapy, tumor vaccine and so on. As new biological material, hydrogels possessed several advantages, including biocompatibility, degradability, controllable drug release, and ease of accessibility. It has already showed great treatment effects.

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Zhengting Chen, Jiahui Yang, and Jiani Jiang contributed equally to this work and should be considered co-first authors.

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