Chapter 6
Harnessing Biomaterials to Overcome Challenges in Cancer Immunotherapy

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ABSTRACT

The intrinsic immune system activity awakens and trains the patient's immune system to destroy tumor cells. Immunotherapy has become a standard method for treating cancer since it is a more potent and secure option than conventional therapies like surgery, radiotherapy, and chemotherapy. Chimeric antigen receptor-modified T cells, immune checkpoint blockades, and cancer vaccines are the three primary forms of cancer immunotherapy that have been developed recently. Chemotherapy, radiation therapy, and surgery continue to be the mainstays of cancer treatment de-

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spite decades of advancements. Lung cancer, melanoma, advanced bladder, kidney, and other advanced tumors have all been successfully treated with immunotherapy. Immunotherapy is used to cure illnesses by regulating an overactive or underactive immune system. Biomaterials efficiency will be increased with the help of immune system engineering and targeted drug delivery. Chapter highlights the recent advancement in tailored biomaterials for cancer immunotherapy.

1. INTRODUCTION

Globally, cancer is one of the leading causes of death. Every year, there are over 10 million new cases, and over 6 million people will pass away from the illness. There are numerous reasons for the recent rise in cancer cases. Another important factor is changing one's lifestyle, particularly with relation to diet, alcohol consumption, and tobacco use, (Yoo & Shin, 2003). Cancer is a disorder when body tissue is destroyed by uncontrollably dividing aberrant cells which spreads to other parts of the body. It is a major global health challenge as it affects millions of people each year. The most prevalent cancers in men are bladder, colon and rectum, lung and bronchus, and prostate, in that order. The breast, lung and bronchus, colon and rectum, uterine corpus, and thyroid are the areas in women where cancer is most common. This demonstrates that breast cancer in women and prostate cancer in males make up a sizable percentage of all cancer cases, (Siegel, Miller, & Jemal, 2019). An abnormal mass of tissue called a neoplasm, neo means new and plasia means tissue or cells. neoplasm, which in Greek literally translates to "new tissue." This suggests that tumors are essentially newly formed cell growths, develops when cells divide and expand more than they should or do not die when they should. There are two types of neoplasms known as malignant (cancerous) and benign (non- cancerous), (Sirica, 1989).

In order to stop cancer and tumor growth, the immune system is crucial. Immunotherapy has showed considerable promise in treating a variety of cancer types, with many cases showing promise for a cure. The body's immune system is used in this method to identify and combat cancer cells, (Zhang & Zhang, 2020). Immunotherapy has become a viable substitute for conventional cancer therapies such as radiation and chemotherapy because of a number of important benefits such as Focused strategy More accurately than with conventional treatments, immunotherapy enables physicians to target cancer cells. These treatments can kill cancer cells only while leaving healthy tissue intact by boosting the immune system, (Tan, Li, & Zhu, 2020). In order to treat illnesses, immunotherapy is utilized to regulate an overactive or underactive immune system. Biomaterials can help with immune system engineering and targeted medicine delivery, which can increase its effec-

tiveness. However, we also need to take into account how these substances impact the immune system, (Dai, Fan, & Wang, 2022).

Biomaterials are substances created with the intention of interacting with biological systems. These substances are bioactive and readily assimilated into human tissue. The extent of their biodegradability can be considered quite significant and effective. They are frequently employed in the production of human body parts, tissue engineering, medications, and other manufacturing processes. Biomaterials and sustainability work together to assist the creation of new sustainable materials through the use of cutting-edge technical methods. Biomaterials are environmentally friendly and it is produced from various biological resources, (Biswal, BadJena, & Pradhan, 2020).

Since ancient Egypt, anecdotal evidence of spontaneous tumor regressions following infections has supported the idea that the immune system can be used to combat cancer. William Coley created one of the earliest immune-based cancer treatments in the late 1800s by injecting bacterial toxins to trigger the body's defenses against malignancies, (Dobosz & Dzieciatkowski, 2019). Significant advancements were made in the 1990s and 2000s with the identification of immunological checkpoints and the creation of checkpoint inhibitors. Another effective immunotherapy strategy that surfaced in the 2010s was CAR T-cell treatment, (Decker et al., 2017). Interest in employing biomaterials to improve immunotherapy has grown in recent years. The use of biomaterials such as hydrogels, micelles, and nanoparticles to more efficiently administer immunotherapeutic is being investigated. Utilizing biomaterials customized for each patient's biopsies, individualized immunotherapy techniques may be possible. The best biomaterial systems for various tumor types are still difficult to build, (Yang et al., 2020).

Different immunotherapy techniques have different mechanisms of action and aim to improve the recipient's immune function. Based on their capacity to induce memory immunological responses, immunotherapies are sometimes divided into two categories: passive (adoptive) and active immunotheapies, (Dahri et al., 2023). Active immunotherapy produces immunological memory and a long-lasting response by actively stimulating an immune response. The reactions might be specific, which refers to generating immune responses against particular antigens, or non-specific, which is referred to as a general immune system response via cell signalling molecules, (Beheshtizadeh et al., 2021). Direct antibody delivery is known as passive immunotherapy since it does not stimulate the immune system and instead promotes the development of immunological memory, (Tostanoski, Gosselin, & Jewell, 2016).

2. BIOMATERIALS IN CANCER IMMUNOTHERAPY

The term "cancer immunotherapy" refers to methods of treating cancer that alter the host immune system or use immune system components. Regulatory agencies have approved 17 immunologic products due to their anticancer properties. These consist of the cytokines, interleukin-2 and interferon-α, the nonspecific immune stimulants levamisole and BCG, monoclonal antibodies, radiolabeled antibodies, immunotoxins, nonmyeloablative allogeneic transplants with donor lymphocyte infusions, and the anti-prostate cancer cell-based treatment sipuleucel-T, (Dillman, 2011).

In terms of survival and quality of life, cancer immunotherapy has significantly improved patient outcomes when compared to earlier standards of care such as chemotherapy, radiation, and surgery. With many cancer types, immunotherapy has now solidly established itself as a novel pillar of cancer care, from the metastatic stage to the adjuvant and neoadjuvant settings, (Esfahani et al., 2020). The goal of cancer immunotherapy is to reorient the target from the tumor cells to the patient's immune system in order to facilitate its mobilization and improve the antitumor immune response's activation. This aids the immune system in identifying, attacking, and ultimately getting rid of the tumor cells, (Miller & Sadelain, 2015). Melanoma, lung cancer, kidney cancer, bladder cancer, head and neck cancer, liver cancer, Hodgkin lymphoma, and Merkel cell carcinoma are among the types of cancer for which immune checkpoint inhibitors have been authorized for use in treating select patients. The development of genetically modified immune cells, the identification of various cancer immune checkpoints, the growing knowledge of the function of cytokines in triggering the antitumor response, and advancements in genetic engineering technology have all altered the field of cancer treatment and brought the possibility of a definitive cure closer than ever, (Kciuk & Yahya, 2023). In order to be eligible for immunotherapy therapies, patients usually need to fulfill certain requirements. Surgery, chemotherapy, radiation, and hormone therapy are examples of conventional therapies that are either unavailable or extremely harmful to patients, (Padmanabhan, Meskin, & Al Moustagfa, 2021). The list of tumors that immunotherapy can treat is always changing as more treatments are assessed in clinical trials. Frequently, immunotherapy is used in conjunction with targeted medicines or chemotherapy, (Cook et al., 2016). The use of immunotherapy in cancer in its early stages, either before to or following surgery, is growing. In certain instances, immunotherapy is currently being utilized to treat brain metastases, (Sampson et al., 2020).

The complex ecology that surrounds a tumor and is made up of different cells and non-cellular elements is known as the tumor microenvironment. These cells are essential for tumor development, invasion, and treatment response, (Arneth, 2019). The efficacy of traditional treatments like surgery, radiation, and chemotherapy may

be surpassed by cancer immunotherapy, which has been referred to as the fourth pillar of tumor therapy, (Shi et al., 2018). There are five main types of cancer immunotherapies such as the regulation of immune checkpoints, oncolytic virus therapies, cancer vaccines, cytokine therapies, and adoptive cell transfer.

2.1 Immune Checkpoints Inhibitors

In the field of cancer immunotherapy, the identification of immune checkpoint proteins like PD-1/PDL-1 and CTLA-4 marks a major advancement. Humanized monoclonal antibodies that target these immune checkpoint proteins have therefore been used with efficacy in treating patients with non-small lung cancer, head and neck malignancies, renal cell carcinoma, and metastatic melanoma, (Shiravand et al., 2022). ICIs are cancer immunotherapies that work by focusing on immunologic receptors on the surface of T-lymphocytes to increase anti-cancer immune responses. Therefore, in 2011, when ipilimumab was approved, ICIs were seen as a revolutionary treatment option that revolutionized the treatment of cancer, (Robert, 2020) (Ledford, 2011). ICIs function differently from conventional therapeutic approaches by boosting the host immune system's ability to combat tumor cells, (Cai et al., 2021). These immunological checkpoints are a collection of pathways that affect immune cell activity, both stimulatory and inhibitory, (Pardoll, 2012). The most popular immunotherapeutic medicines in the past ten years have been antibodies that target immunological inhibitory receptors, including CTLA-4, PD-1, and PD-L. There are a number of antibodies and small molecules in clinical development that target different immune checkpoint proteins, such as CD39, CD73, B7H3, the adenosine A2A receptor, and CD47, (Chrétien et al., 2019).

2.2 Oncolytic Virus Therapies

Interest in oncolytic virus immunotherapy is growing quickly in the field of cancer immunotherapy. Therapy with oncolytic viruses (OVs) is an intriguing treatment option because of the low toxicity at the end of treatment and the simultaneous action of direct oncolysis and immune activation. Several OVs have undergone clinical trials to evaluate their safety and effectiveness, yet the FDA has only approved one OV to date, (De Graaf et al., 2020). Using genetically modified viruses, viro immunotherapy is also referred to as oncolytic virotherapy is a type of cancer immunotherapy that targets and kills cancer cells while triggering the immune system to target tumor cells, (Volovat et al., 2024) (Zeng et al., 2021). The examples of oncolytic viruses used in viro immunotherapy include vaccine virus (VV) is a naturally occurring member of the Poxviridae family that targets cancer. It has been designed to take many different forms, such as: (JX-594) Pexa-Vec: In phase I and

II clinical trials, an oncolytic VV equipped with GM-CSF and TK gene disruption is being studied for the treatment of soft-tissue sarcoma, advanced breast cancer, and renal cell carcinoma. Another oncolytic viruses is the herpes simplex virus (HSV). Newcastle disease virus (NDV) is an oncolytic virus that is a paramyxovirus. Reovirus is a double-stranded RNA virus that takes advantage of cancer cells' weakened antiviral defenses to multiply in those cells. Seneca Valley virus (SVV) is an Oncolytic virotherapy employs this picornavirus. The measles virus (MV) is a paramyxovirus that has been modified to act as an oncolytic. Poliovirus is another example of Oncolytic virotherapy employs this picornavirus. An encapsulated RNA virus that functions as an oncolytic platform is the Vesicular Stomatitis Virus (VSV), (Jafari et al., 2022). Adenoviruses, especially serotype 5 (group C) adenovirus, are the most often utilized backbone for oncolytic viral creation. Some examples are as follows such as in clinical trials, Ad5:0, an attenuated adenovirus with neither E1 or E4 genes, has demonstrated encouraging outcomes. A modified adenovirus called Delta24-RGD replicates specifically in glioma cells because E1A no longer binds to the Rb protein. Adenoviruses: Widely used in oncolytic virotherapy because of their capacity to infect cells regardless of the state of cell division, (Hemminki, Dos Santos, & Hemminki, 2020). These viruses, which can be naturally occurring or manufactured, proliferate only in cancer cells while avoiding normal tissues. Directly destroying cancer cells and triggering anti-tumor immune responses are two of the ways they function. Numerous of these viruses are being studied in clinical trials for different kinds of cancer.

2.3 Cancer Vaccine

The goal of cancer vaccines is to stimulate the immune system to identify and fight cancer cells. Preventing tumor growth, recurrence, or metastasis while improving the immune system's ability to recognize and eradicate cancer cells are their main goals. In order to target particular tumor-associated antigens (TAAs), cancer vaccines trigger an immune response. Cancer cells are destroyed as a result of this immunological response, which includes the activation of T cells, B cells, and other immune cells, (Kaczmarek et al., 2023). Traditionally, vaccinations based on cells are made from isolated tumor antigens or complete, dead cancer cells. Microbial vector vaccines are the vaccinations that deliver tumor antigens using bacteria or viruses as vectors. Peptide vaccines: Made up of brief tumor antigen sequences. Genes that encode tumor antigens are the basis for genetic vaccinations, (Verma et al., 2023).

2.4 Cytokine Therapies

Cytokines are molecular messengers that facilitate communication between immune system cells, resulting in a coordinated, strong, yet self-limited response to a target antigen. Over the past 20 years, there has been an increase in efforts to describe cytokines and take advantage of their extensive signaling networks in order to develop cancer treatments, in tandem with the growing interest in using the immune system to destroy cancer, (Lee & Margolin, 2011). Cytokines are polypeptides or glycoproteins that have a molecular weight of less than 30 kDa and give various cell types signals for growth, differentiation, and inflammation or anti-inflammation, (Berraondo et al., 2019). Interferon-α is family of cytokines has been utilized to treat solid tumors and a number of hematological malignancies at high dosages to take advantage of their direct pro-apoptotic/anti-proliferative action on tumor cells since IFN-α was originally approved in 1986 for the treatment of hairy cell leukemia. These elevated levels of IFN-α also have anti-tumor effects because they have a strong antiangiogenic effect on the tumor vasculature, (Spaapen et al., 2014). Additionally approved for use as an adjuvant therapy for melanoma was PEGylated IFN-α, (Herndon et al., 2012). Current clinical trials are investigating a number of cytokines, such as GM-CSF IFN gamma (IFNγ), IL-7, IL-12, IL-15, and IL-21.Recently, IL-15 finished its first clinical trials as a single drug.The difficulties associated with cytokine monotherapy are being addressed by ongoing trials that examine cytokines in conjunction with other biological agents, (Conlon, Miljkovic, & Waldmann, 2019). Targeting cytokine pathways has recently demonstrated encouraging therapeutic potential, providing novel approaches to immune system modulation, tumor development inhibition, and treatment resistance. Our knowledge and use of cytokine- and chemokine-targeted treatments for cancer patients are greatly enhanced by ongoing clinical trials, (Yi et al., 2024).

2.5 Adoptive Cell Transfer

The treatment known as adoptive cell therapy (ACT) uses the anti-tumor-active T cells that cancer patients have naturally, which are then grown in vitro and reinfused into the patient. It entails finding ex vivo autologous or allogeneic lymphocytes that exhibit anticancer activity and administering them to cancer patients.Just a handful of anti-tumor cells with suitable characteristics need to be found and grown. Tests conducted in vitro can pinpoint the precise populations and effector roles needed for cancer regression. In the lab, cells can be stimulated without the presence of endogenous inhibitory molecules. Before cell transfer, the host environment can be changed to create the best possible conditions, (Rosenberg et al., 2008). Recently, ACT has been linked to a steady rate of long-lasting regressions in patients with

renal cell carcinoma and melanoma. It also has significant potential in a number of other oncological contexts, (Galluzzi et al., 2012).

Since biomaterials allow for the local delivery of immunomodulatory drugs, they are becoming more and more significant in the advancement of cancer immunotherapy. Novel delivery methods for cancer immunotherapies are being developed using engineered biomaterials, such as implantable, injectable, and transdermal materials, (Cai et al., 2020). For the delivery of localized immunotherapy, a variety of tailored biomaterials are being investigated. Materials like as PLG, alginate, and hyaluronic acid are used to create implantable scaffolds. Systems of injectable hydrogels Transdermal arrays of microneedles These can be engineered to recruit immune cells, regulate release kinetics, and establish advantageous tumor microenvironments, (Chao, Chen, & Liu, 2020). Instances of biomaterial-based strategies examples are Dendritic cells are recruited using PLG scaffolds loaded with GM-CSF. Anti-PD-L1 and chemotherapeutics in hydrogel systems Microneedle patches that administer tumor lysate and checkpoint inhibitors. In preclinical models, these methods have demonstrated potential by improving local immune responses in contrast to conventional systemic injections. In conclusion, biomaterials are making it possible for immunotherapies to be delivered more precisely and efficiently, resolving major issues in the treatment of cancer by enhancing localization and lowering systemic adverse effects. In order to fully grasp the potential of biomaterials in immunotherapy, ongoing research endeavors to enhance their characteristics and delivery methods, (Cunningham, Lapointe, & Lerouge, 2022) (Zhang, Billingsley, & Mitchell, 2018).

2.6 Benefits

It aims in Targeted delivery that Biomaterials can enhance targeting by conjugating ligands or antibodies to receptors expressed on target tissues or cells, (Leach, Young, & Hartgerink, 2019). Biomaterials can improve pharmacokinetics and reduce toxicity through controlled release profiles. Biologic cargo can be protected by biomaterials from enzymatic degradation and extreme pH levels, (Chen, Chen, & Liu, 2019). Better tumor targeting, The EPR effect allows materials to collect at tumors preferentially. The medicine can be released gradually over time or when it reaches target tissues, including tumors, to reduce systemic toxicity. Combination therapy is the use of biomaterials to produce multiple therapeutic molecules. It helps in Reprogramming immune cells as some biomaterials are naturally immunogenic, they may be exploited to polarize immunity. Many immunological signals can be constructed via self-assembly techniques, which eliminate the requirement for artificial carriers, (Gammon, Dold, & Jewell, 2016).

2.7 Innovations and Ongoing Clinical Trials

There are several cancer vaccines based on biomaterials undergoing clinical testing. For instance, the FDA authorized sipuleucel-T (Provenge), an autologous dendritic cell vaccine that encapsulates GM-CSF linked to prostate cancer antigen PAP, in 2010. CTLA-4 inhibition is currently being investigated in conjunction with this vaccine in phase II trials, (Pardoll, 2012) (Sharma & Allison, 2015). A phase II clinical trial is under underway to examine GVAX, a whole cell pancreatic cancer vaccine that uses tumor cells that express GM-CSF, in conjunction with nivolumab, a PD-1 checkpoint inhibitor, (Wrzeskinski, Wan, & Flavell, 2007).

DNA vaccines are now undergoing phase I and II clinical studies for a number of malignancies, including cervical, prostate, lymphoma, and melanoma. Although several have so far demonstrated very modest effectiveness, advancements in delivery techniques such as electroporation and gene gunning are being investigated further, (Tiptiri-Kourpeti et al., 2016). Additionally, clinical trials for mRNA-based cancer vaccines are beginning. In order to increase the effectiveness of DNA vaccines, attempts are being made to optimize their delivery through the use of biomaterial-based vehicles, (Pardi et al., 2018). Research on advanced biomaterials to enhance cancer modeling is being funded by the NIH/NCI through SBIR grants. This implies that new biomaterials are still being developed for use in cancer applications. Although numerous preclinical trials of early-stage biomaterial-based immunotherapy techniques have demonstrated promise, it is still difficult to translate these into clinical success. Which biomaterial-based strategies provide patients with long-term advantages will be determined in part by ongoing research. The sector is still developing quickly, with new materials and delivery systems being created to solve lingering issues, (Peer et al., 2020) (Avula & Grodzinski, 2024).

3. DRUG DELIVERY SYSTEMS (DDS)

3.1 Implantable Biomaterials

Implantable biomaterial scaffolds that are preloaded with cells, bioactive substances, or immunological agents can be placed subcutaneously or into resected tissue space by a minor surgical operation. It is possible to recruit immune cells

into scaffolds and activate them for additional biological programming by releasing immunoregulatory agents gradually, (Li et al., 2020)

Some of the examples of engineered polymeric biomaterials which is used as scaffolds in implantable delivery systems include poly(lactide-co glycolide) (PLG), alginate (ALG), polyglyconate and porcine gelatin, collagen, and hyaluronic acid (HA), (Cai et al., 2020).

3.2 Injectable Biomaterials

Transformable gel-like biomaterials known as injectable biomaterial scaffolds can be injected into the site of a tumor or resection to generate a potent local or systemic immune response against the tumor, (Villard et al., 2019). The degradable hydrogel which is injectable and forms in-situ (via a Michael-type addition reaction) was created that may simultaneously deliver microparticles co-loaded with DNA and siRNA and DC-attracting chemokines. At the injection location, such as muscle, the released chemokines draw in naïve immature DCs, which phagocytose the DNA/siRNA-loaded microparticles extracted from the disintegrating gel and become activated, (Singh et al., 2011).

3.3 Transdermal Delivery System

The physicochemical characteristics of medicinal substances plays a crucial role for transdermal immunotherapy, because the way that medicinal drugs are administered has a significant impact on their bioavailability. One accessible, painless, and non-invasive method of administering medications is transdermal administration. Because it avoids the gastrointestinal tract and shields medications from first-pass metabolism, it is an effective method for systemic delivery, (Dahri et al., 2023) Additionally, this removes the need for intrusive, uncomfortable needles that produce medical waste, increase the risk of infection, and require medically trained personnel to administer, (Bird & Ravindra, 2020).

4. TYPES OF BIOMATERIALS IN IMMUNOTHERAPY

Architecture, aerodynamics, mechanical engineering, materials science, and other technical fields are constantly inspired by biological structures to solve their problems. The comparatively small number of basic elements found in natural materials are utilized to create a wide range of minerals and polymers, (Fratzl, 2007). Classification of biomaterial is illustrated in table 1. The four main classification of materials that comprise biomaterials are metals, polymers, ceramics (including

carbons, glass-ceramics, and glasses), and natural materials (including those derived from plants and animals), (Ige, Umoru, & Aribo, 2012) The biomedical industry makes extensive use of polymeric materials. Natural polymers are also necessary because of their biocompatibility and biodegradability, even though synthetic polymers are far simpler to employ in the biomedical area. Blending synthetic and natural polymers is another way to generate polymeric materials for biomedical uses. In comparison to a number of naturally occurring polymers, synthetic polymers exhibit superior mechanical and thermal stability. The primary biopolymers utilized in the production of materials for biomedical purposes are elastin, collagen, chitin, chitosan, keratin and silk —all naturally occurring polymers obtained from animal tissues. Additionally, there is a class of natural polymers that come from plants, including pectinc, cellulose, and starch, (Bhatia & Bhatia, 2016).

Table 1. Classification of biomaterials

Types of polymers	Examples
Natural polymers	Collagen, chitin
Synthetic polymers	Plga, carbon quantum dots

4.1 Collagen

Collagen is a natural protein present in the skin, connective tissues, and bone. It is widely utilized as a cosmetic ingredient. collagen-based biomaterials is considered to be both adaptable and compatible with human tissues have attracted a lot of attention for the replacement and repair of bodily tissues such bones, tendons, skin, vascular grafts, heart valves, and teeth, (Sionkowska, 2011). Recent research has demonstrated that collagen can influence the activity and phenotype of many types of tumor-infiltrating immune cells, including tumor-associated macrophages (TAMs) and T cells, (Radhakrishnan et al., 2020). Collagen is an intriguing biomaterial due to its many general characteristics, including its low antigenicity, strong mechanical strength of the fibers, suitability as a cell growth substrate, and adjustable stability through chemical or physical cross-linking, (Goh & Holmes, 2017).

4.2 Chitin

Found in the walls of fungi and the shells of crustaceans, chitosan is a partially deacetylated derivative of chitin, one of the most prevalent polymers in nature. It is made up of widely dispersed β-(1-4)-linked D-glucosamine (glucosamine) and N-acetyl-d-glucosamine (N-acetylglucosamine) structural units that resemble gly-

cosaminoglycan, a crucial component of the cell surface and bone matrix, (Liang et al., 2022). Chitosan has been employed as an immunotherapeutic agent carrier to increase antitumor response, control the immune system, and improve bioavailability. Because of its readily adaptable structure, chitosan can be used to create a wide variety of delivery vectors for improved immunotherapy, (Cao & Wang, 2009). Biomaterials are also biologically derived materials employed for their structural rather than biological qualities. The food sector also uses biotechnologically modified carbohydrates as bulking agents and as lubricants for biomedical applications. Biomaterials generated from natural sources have only recently been investigated as potential promoters and facilitators of healing and regeneration. Everything from tendon and ligament restoration to wound dressings is being done now with biomaterials of all kinds, (Huang & Zeng, 2020).The materials that have been utilized for artificial antigen presenting cells (aAPCs) include biological or biomimetic materials like cell membranes or liposomes, inorganic materials like carbon nanotubes or iron oxide, and polymeric materials like polystyrene or poly(lactic-co-glycolic acid) (PLGA). Material choice plays a crucial role in determining the function of artificial antigen presenting cells(aAPC) because material choice creates significant impact on properties of the particle such as membrane fluidity, nanoscale organization of ligands, stability, stiffness, degradability, surface area, ease of encapsulation of soluble factors and response to magnetic field. dendritic cells which is also known as the most potent professional APCs (Antigen presenting cells) are capable of combining both adaptive and innate immunity. Antigen Presenting Cells in particular dendritic cells must seize the antigens inorder to induce the cytotoxic CD8+T – cells (CTC) immune response which is directed against cancerous cells.

4.3 Lipid Based Materials

Lipid- based nanomaterials like liposomes have been discovered to distribute antigens and adjuvants directly to dendritic cells in vivo, (Karanth & Murthy, 2007). Liposomes, which are commonly known as lipid-based vesicles, are seen as one of the most adaptable and flexible drug delivery vehicles, (De Leo et al., 2021). A phospholipid bilayer forms the nanosized bubbles known as liposomes, which is also known as the primary lipid- based nanobiomaterials. The surface of liposomes was altered to include extremely pH-sensitive polymers, which increased the tumor's therapeutic effects and encouraged the release of Th1 cytokines from dendritic cells, (Chelu & Musuc, 2023) (Makadia & Siegel, 2011). These pH-sensitive liposomes is used to double-stimulate Dendritic Cells and enhance antitumor immunity when combined with adjuvants that target Dendritic Cells, (Xiong et al., 2021).They have proven to be more effective than synthetic polymers due to their high biocompatibility,

ready biodegradability, excellent drug loading capacity and rapid absorption which helps them in site specific drug targeting and delivery, (Ginjupalli et al., 2017).

4.4 Polymer Based Biomaterials

The most widely used multifunctional materials in biomedicine are polymers. Using micellar structures or polymer-drug conjugates, they have been utilized to provide a range of treatments. Some polymers have special photochemical characteristics that make them useful for cancer treatment. To improve antitumor immunity, several polymer-based substances have been employed as adjuvants or neoantigen carriers, such as poly(lactic-co-glycolic) acid (PLGA), and polyethyleneimine, (Patil et al., 2024).

4.5 PLGA Poly(Lactic-Co-Glycolic)

Saturated aliphatic polyesters, such as poly(glycolic acid) (PGA), polylactic acid (PLA), and the copolymer poly(lactic-co - glycolic acid) (PLGA), are widely employed to create 3D scaffolds used in tissue engineering because of their biocompatibility and biodegradability, (Brugnera et al., 2022). As a highly crystalline, hydrophilic polymer that degrades relatively quickly in aqueous solutions or in vivo, PGA is widely used in injectable microspheres, biological adhesives and glues, oral surgery, and medication delivery, (Davis et al., 2022). Using polymer-based materials, medicines with different hydrophilic and hydrophobic qualities can be delivered simultaneously to enhance conventional treatments like gene editing, photodynamic therapy (PDT), chemotherapy, and radiotherapy. This shows how the substances have the ability to produce antitumor immunity and immunogenic cell death, (Yuan et al., 2024).

4.6 Synthetic Biomaterials

One interesting method for locally delivering immunotherapeutic drugs is the use of synthetic scaffolds. Scaffolds, when positioned strategically throughout the body, can increase the concentration of the substance at the place of interest while decreasing adverse effects, (Cai, Zhu, & Qi, 2020). Synthetic biomaterials are biomaterials which is created in labs which offer more durability and strength than natural biomaterials, (Li et al., 2024).

4.7 Metals

The main purpose of metallic biomaterials is to replace damaged hard tissues. Numerous biomedical applications use different kinds of high-strength alloys that contain harmless components. The remarkable shape of memory and super elastic capabilities of NiTi (Nitinol) alloys have led to the development of functional devices based on these materials. In addition to super elastic bone staples for orthopaedics and super elastic orthodontic wires for dentistry, the alloy is utilized in the production of self-expandable stents for cardiovascular surgery, (Jana & Dev, 2022). The required biocompatibility, bioactivity, surface integrity, and wear resistance are made into patient-specific medical implants, such as bone plates, screws, cranial, or dental devices, (Escriche-Navarro *et al*., 2022). Among metal-based materials utilized in immunotherapy, the most commonly adopted strategy involves delivery of immunomodulators, including adjuvants, cytokines, neoantigens, and checkpoint inhibitors, (Yan et al., 2020). According to recent research, the main obstacles to immunotherapy include the tumor immunosuppressive microenvironment, poor response rates to current therapies, and severe side effects. Through Tumor Microenvironment reversal, immune adjuvant activity, and the induction of novel models of programmed cell death, metal-based biomaterials can improve the effectiveness of immunotherapy, (Pei, Lei, & Cheng, 2023).

4.8 Inorganic Biomaterials

The efficient delivery of drugs with improved bioavailability and fewer side effects is being studied extensively using biodegradable inorganic drug nanocarriers. High biosafety for in vivo applications requires a drug nanocarrier with both high biocompatibility and good biodegradability. Examples of several inorganic drug carriers include silica, metal oxides, and carbon-based compounds, (Hess, Medintz, & Jewell, 2019).

4.9 Carbon Quantum Dots

Typically spherical in shape and less than 10 nm in size, carbon quantum dots (CQDs) are carbon-based nanoparticles that exhibit photoluminescence. Distinct physicochemical characteristics, remarkable biocompatibility, environmental friendliness, and simplicity of surface functionalization are all displayed by these nanoparticles. Due to their small size, CQDs can approximate the glomerular filtration barrier, which makes them appropriate as mediators of reactive oxygen species (ROS) production and carriers for the transport of drugs, (Mowery & Chen, 2024). Hence researchers have been using Carbon Quantum Dots extensively in cancer

cell imaging, cancer targeted drug delivery and in immunotherapies in recent years, (Pérez-Herrero et al., 2024).

4.10 Mesoporous Silica-Based Materials

It has been reported in recent years that mesoporous silica-based nanomaterials can function as adjuvants, an immunological substance that can activate APC and trigger an immune response. These nanoparticles can trigger both tumoral and cell-mediated immune responses, which sets them apart from conventional adjuvants. They can also be used as nanocarriers to deliver antigens in cancer vaccines, (Uhrich et al., 1999).

5. APPLICATIONS OF BIOMATERIALS IN CANCER IMMUNOTHERAPY

5.1 Drug Delivery Systems

The FDA has approved many immunotherapy-based medications to treat primary and metastatic tumors, however due to primary and acquired resistances, only a tiny percentage of the population can benefit from these medications. Additionally, the short half-lives of the molecules involved, the challenges of delivering them to the target sites, and some serious side effects linked to these approaches make it difficult to translate immunotherapy from the bench to clinical practice, (Ribas & Wolchok, 2018). Drug delivery methods may be able to directly target cancer cells, which would lessen acquired resistance and off-target side effects. Additionally, they lower the necessary dosage, which lowers toxicity, and they can increase effectiveness and enable immune response tunability. Drug delivery systems can extend the shelf life of pharmaceuticals, resulting in scalable products, and, if required, can protect the therapy from immune system identification or degradation. Additionally, they have the ability to modify drug release rates, which can benefit patients in a variety of ways, (Choi et al., 2024).

5.2 Immune Checkpoint Blockade Therapy

Long-lasting tumor responses in cancer patients have been caused by immune checkpoints, which restrict antitumor responses. By inhibiting the PD-1 or CTLA-4 pathway, this is accomplished. Even when the condition is under control, one-third of individuals experience relapses. Although the mechanisms of acquired resistance are not well understood, they may be addressed by changes in interferon-γ signaling

pathways and antigen presentation, (Yu et al., 2024). The development of immune checkpoint blockade (ICB) treatments has accelerated the expansion of cancer immunotherapy, especially after cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors such as ipilimumab were initially approved. The therapy options for a variety of cancers have expanded as a result of the thorough investigations into numerous immune checkpoint antibodies. With fewer than 15% responsiveness and significant side effects in certain individuals, the clinical response to these antibody-based ICB treatments is still quite small, (Lin et al., 2024).

5.3 CAR-T Cell Therapy

The process of CAR-T treatment involves altering the patient's own T cells to express particular receptors that can identify and eliminate cancerous tumor cells, (De Graaf et al., 2020). Recent years have seen a tremendous advancement in the study of using biomaterials to improve the effectiveness of cell immunotherapy, (Chao & Liu, 2023). In order to address abnormal vascular distribution, hypoxia, acidity, and heterogeneity, biomaterial-based delivery systems have been created to alter and enhance TME (Tumor Microenvironment). Additionally, they encourage the infiltration of different immune cells and boost the activity of immune cells that fight tumors, which improves the effectiveness of immunotherapies, (Roma-Rodrigues et al., 2019). CAR-T cells bind to several types of biomaterials loaded with various functional biomolecules to enhance synergistic immunotherapy in solid tumors, (Lai et al., 2021).

5.4 Modulating Tumor Microenvironment

Immunotherapy response is significantly influenced by the immunosuppressive tumor microenvironment (TME). The tumor microenvironment (TME) of solid tumors can inhibit immune cell function and stop infiltration. Through the use of biomaterials-based techniques that target, react to, and modify the TME's physico-chemical characteristics—such as hypoxia, acidity, elevated reactive oxygen species, a dense extracellular matrix, and aberrant vasculature—the immunosuppressive aspects of the TME can be altered, (Emens et al., 2024). Biomaterials are essential for improving cancer treatment by focusing on the TME. Mesoporous silica NPs and metal oxide NPs are examples of inorganic NPs that allow for precise drug administration and immunomodulation in the TME. Natural and manufactured biopolymers are examples of organic biomaterials that provide flexible platforms for immune cell targeting. These techniques consist of Treg cell modulation, Tumor Associated Macrophages (TAM), DC, and NK, (Chu et al., 2024).

6. CHALLENGES AND OPPORTUNITIES

6.1 Challenges

Methods of antitumor action are the processes driving the toxicity and effectiveness of anticancer drugs in human versus animal models are not well understood. Better biomarkers are needed to predict toxicity and response. Resistance to therapy Tumors that are resistant to treatment acquire immune system escape mechanisms. Understanding the mechanisms of resistance is still challenging. Targeting and delivering are the challenges of efficiently transporting pharmaceuticals to their designated places. Single-target techniques are not very effective or specific. The toxicity Serious adverse events (irAEs) connected to the immune system could occur. Reducing toxicity is necessary to optimize anticancer efficacy. Modeling before clinical use of Current animal models only partially mirror human immune systems and malignancies. We need more pre-clinical models that are therapeutically useful. Standards and data exchange of the sector's progress is hampered by a lack of data exchange. We need standard concepts and frameworks to study ir-toxicity, (Whiteside et al., 2016) (Peterson, Denlinger, & Yang, 2022).

6.2 Opportunities

Synergistic effects when combining several immunotherapy treatments are the possibility of increased efficacy through logical combinations. Personalized immunotherapy based on individual profile is possible with the discovery of new immunologic biomarkers for response monitoring. Discovery of tumor antigens that is the Recognition of neoantigens from cancer mutations where the better creation of vaccines based on antigens specific to tumors. Advances in cellular therapy are the ability to produce, transport, and distribute therapeutic cells more efficiently. The possibility of cellular medicines becoming more widely available. In addition to other therapies, Synergy between immunotherapy and traditional treatments, such as radiation Potentiation of immunotherapy may have abscopal consequences. Focusing on immune-suppressive processes leads to the discovery of new checkpoints and inhibitory pathways are found, and inhibitors that target these pathways are developed, (Remesh, 2012) (Uranga, Nurgali, & Abalo, 2023).

6.3 Safety and Long-Term Effects

Most pharmacological anticancer drugs affect the cell growth process. The rapid proliferation of certain normal cells, including bone marrow cells, oral mucosal cells, and hair follicles, must be mentioned in addition to cancer cells, (Trill, 2013). This

explains the serious adverse effects of cancer chemotherapy, (Berger et al., 2010) (Lewandowska et al., 2020). Anticancer medications harm the epithelium protecting the gastrointestinal system, resulting in the most frequent adverse effects, nausea and vomiting, (Chen, Yu, & Yang, 2008). As a result of intestinal epithelium damage, diarrhea is another common adverse effect, (Gammon, Dold, & Jewell, 2016). Alopecia and hair loss are common side effects of chemotherapy, but thankfully, they are treatable, (Aguado et al., 2018). Cancer chemotherapy also frequently causes anxiety, sleep issues, sexual dysfunction, and exhaustion, (Maciejko, Smalley, & Goldman, 2017). These problems can be solved by using biomaterials for cancer immunotherapy.

6.4 Advances in Personalized Medicines

As the need for precision medicine grows, the "one-size-fits-all" method of creating medical treatments and equipment is becoming less and less effective. Although biomaterials offer a lot of potential to revolutionize precision medicine, the intricacy of each patient frequently means that combining several uses into one device is necessary to effectively customize individualized treatments, (Song, Musetti, & Huang, 2017). The field of personalized medicine has changed to adapt to the new cancer immunotherapy to overcome the constraints of individualized cancer treatment, new platform technologies have been developed by reprogramming patient-autologous T-cells, novel approaches are being employed to customize immunotherapy. Immunotherapeutics are being delivered locally via engineered biomaterials such as transdermal, injectable, and implantable. The goal of these biomaterial-based strategies is to increase safety and effectiveness by triggering anticancer immunity only when necessary. Biomaterials enable spatially regulated release of immunomodulators and enhanced drug accumulation at target sites, (Goldberg, 2019).

7. EMERGING TRENDS IN NANOTECHNOLOGY AND BIOMATERIALS IN CANCER IMMUNOTHERAPY

Materials that have at least one dimension between 1 and 1000 nm are called nanomaterials, while in practice they could be anywhere between 1 and 200 nm. Over the last three decades, there has been significant progress in the use of different nanomaterials for cancer treatment and diagnosis, (Chen et al., 2020). Pioneers in the field of cancer immunotherapy were granted the 2018 Nobel Prize in Physiology or Medicine because it has been clinically proven that using a patient's coordinated and adaptive immune system to combat their particular tumor is effective. Because

tumors can evade the immune system in a number of ways, the percentage of patients who react to immunotherapy is still limited around 15% objective response rate across indications, (Dong et al., 2020).

Administration systems based on nanoparticles that is Nanoparticles are being investigated extensively for the regulated and targeted administration of immunotherapeutic drugs straight to malignancies. Researchers are taking advantage of the capacity to alter the surface of nanoparticles in order to enhance their targeting and interaction with molecular and cellular targets. Self-assembled nanostructures are Novel strategies which are being investigated for photodynamic therapy, such as the self-assembly of pyro pheophorbide derivatives, (Kandasamy, Karuppasamy, & Krishnan, 2023). Optogenetic approaches like light-sensitive immunomodulator-loaded hydrogel implants are being studied for perioperative immunotherapy. In DNA nanocarriers, Research is being conducted on loading exosomes with therapeutic agents and altering their surfaces for improved targeting. The development of novel DNA-based carriers that co-encapsulates many treatments (such as doxorubicin and CpG) for chemoimmunotherapy is underway, (Xiao et al., 2023). Targeting the tumor microenvironment that is Targeting primary and metastatic cancers by taking advantage of physical characteristics like stiffness is becoming more and more popular. Optogenetic up conversion systems are being investigated for the regulated release of cells with immunomodulatory engineering. In Phage-based vaccination platforms, new vaccine strategies are being developed using M13 bacteriophage-based systems, (Yan et al., 2019).

Combination therapies are equipped by Many as people are interested in using nanocarriers to combine immunotherapy with other treatments like radiation therapy, photothermal therapy (PTT), and chemotherapy. Before clinical translation, there is an increasing need to evaluate these biomaterial-based techniques' safety and effectiveness in more detail. The continuous attempts to overcome obstacles in cancer immunotherapy by using novel biomaterials and nanotechnology techniques are reflected in these trends. Discipline is still developing quickly as scientists look at novel substances, ways to distribute them, and ways to combine them to enhance therapy results, (Shams et al., 2022).

7.1 Nanomaterials for Antigen Delivery

Antigen-presenting cells such as dendritic cells are receiving tumor antigens via nanoparticles (NPs) such as polymeric NPs, liposomes, exosomes, metal NPs, mesoporous silica NPs, carbon nanotubes, and virus-like particles. Targeting DCs in lymph nodes, NPs can alter the tumor microenvironment and trigger downstream effector T cells. Various NP types have special qualities that make them ideal for

delivering antigens, including vast surface areas, controlled release, and targeting abilities, (Fan et al., 2018).

7.2 Nanomaterials for Vaccine Carriers

As vaccine carriers, PLGA NPs, dendrimers, micelles, liposomes, exosomes, metal NPs, MSNs, CNTs, and VLPs are being investigated to improve immunogenicity. Nano vaccines offer prolonged antigen release and are more efficient than standard vaccines at targeting immune cells. Numerous Nano vaccines have demonstrated potential treating a range of cancer types in preclinical investigations, (Kaur et al., 2024).

7.3 Nanomaterials for Checkpoint Inhibitors

To increase efficacy while lowering toxicity, checkpoint inhibitors like anti-CTLA-4 and anti-PD-1 antibodies are being coupled with nanoparticles. NPs coupled with anti-CTLA-4 and anti-PD-1/PD-L1 antibodies are two examples. Compared to free antibodies, certain nano combinations exhibit better tumor targeting and immune activation, (Parhi, Mohanty, & Sahoo, 2012).

7.4 Targeting Immune Cells

Targeting different immune cells, such as dendritic cells, T cells, regulatory T cells, and myeloid-derived suppressor cells, is done with nanoparticles in cancer immunotherapy. For instance, macrophages linked to ovarian tumors have been targeted by large anionic liposomes. Immuno-checkpoint blockade in conjunction with hybrid nanoparticles has demonstrated potential in regulating T cells.

7.5 Combination Therapies

Combining several therapeutic modalities, including immunotherapy, photodynamic therapy, and chemotherapy, is being investigated in nanoparticle-based combination therapies. To treat ovarian cancer, for example, biodegradable photo responsive nanoparticles have been developed for photothermal, photodynamic, and chemotherapy treatments.

8. CONCLUSION

It is true that biomaterial-based immunotherapeutic approaches have demonstrated significant promise in cancer immunotherapy treatments, further research is required to improve the biomaterials design in order to provide more individualized treatment plans for cancer patients with distinct characteristics. In this chapter various immunotherapy approaches and its cutting-edge biomaterials that could be used to increase therapeutic efficacy and lessen side effects. Despite the rapid advancements in cancer immunotherapy, the use of biomaterials to create the best systems for different tumor types is still in its infancy. Biomaterials are hoped to be more broadly and creatively developed for cancer immunotherapy, increasing its effectiveness and lowering immune-related side effects. Biomaterials are essential in CAR T-cell treatment, cancer immunotherapy, vaccines, and tumor regulation associated with checkpoint blockade. A wide variety of biomaterials, including macroscale particles, viruses, bacteria, tiny chemicals, and nanosized organic and inorganic particles, have been developed to improve antitumor immune responses. Utilizing these formulations enhances treatment efficacy of tumor and offers many benefits and functions to increase antitumor immunity. Biomaterials adaptability in creating individualized therapies has enormous potential for more focused and efficient cancer treatments.

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