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Understanding the Relationships between Cancer Immunotherapy and Drug Delivery System: A Comprehensive Review

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ABSTRACT:

Immunotherapy and drug delivery systems are revolutionizing medicine by boosting the immune system's ability to combat cancer, autoimmune disorders, and infections. These advancements enable more personalized patient care. Key developments in immunotherapy include cancer vaccines, CAR T-cell therapies, and immune checkpoint inhibitors. However, challenges such as immune-related adverse effects, limited efficacy in certain patient populations, and resistance within the tumor microenvironment need to be addressed. Researchers are working on innovative immunotherapeutic drug delivery methods that specifically target particular cells or areas to overcome these obstacles. Techniques such as microneedles, nanoparticles, liposomes, and hydrogels are being employed. Nanoparticle platforms can deliver both antigens and adjuvants simultaneously to enhance immune responses, while controlled-release systems offer long-lasting benefits. Additionally, stimuli-responsive delivery devices can release drugs selectively in response to changes in temperature, pH, or enzyme activity within the tumor microenvironment. Advancements in biomaterials, nanotechnology, and molecular engineering have enabled the creation of multifunctional delivery strategies. These systems can diagnose and treat health issues concurrently. Theranostic nanoparticles possess imaging and therapeutic capabilities that allow for ongoing assessment of treatment effectiveness. To overcome the limitations of traditional immunotherapy, researchers are investigating tailored neoantigen vaccines, gene editing, and RNA-based therapeutics. Challenges such as high treatment costs, regulatory approvals, and large-scale manufacturing must be tackled. Improving pharmaceutical distribution methods and leveraging artificial intelligence (AI) and machine learning (ML) in drug development requires interdisciplinary research. Overall, immunotherapy and modern drug delivery systems enhance healthcare outcomes and improve patients' quality of life.

INTRODUCTION

A serious threat to human health, cancer is a huge global public health issue that is becoming more common and deadly (1). Immunotherapy increases or restores the body's capacity to fight cancers by exogenously interfering with the immune system, preventing, controlling, and curing cancer. With impressive clinical findings, immunotherapy has emerged as a possible alternative therapy for a variety of malignant tumors when compared to standard therapy. Examples of this include cancer vaccines, cytokine immune checkpoint inhibitors (ICIs), and more (1–4). Even with immunotherapy's obvious advantages, there are still a number of problems that must be resolved immediately for clinical use. Systemic injection of immunological medications, such as monoclonal antibodies, is the foundation of immunotherapy. However, this method fails to precisely target the lesions and instead distributes the medications to other tissues and organs throughout the body, which can lead to a number of adverse effects associated to the immune system (4–6). Effective anti-tumor immunological drug development should focus on issues that can maximize the therapeutic effects, such as how to improve the drugs' pharmacokinetics and in vivo distribution, increase the targeted cells' specificity and intracellular

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drug accumulation, and lessen the systemic severe side effects that result from the drugs' non-specific reactions. As a result, there is a growing emphasis on drug delivery system (DDS) research and development (7–9). DDS offers the benefits of regulating drug release, enhancing drug solubility, enhancing pharmacokinetics, and enhancing drug distribution. It is based on different chemical or biomaterials as drug delivery vehicles or by combining pharmaceuticals with ligands targeted to certain cells (9–11). Furthermore, drug carriers (such nanoparticles) can be surface modified with specific ligands to precisely transport medications to the intended location, increasing treatment effectiveness and lowering adverse responses (12). Therefore, the combination of DDS with tumor immunotherapy can effectively and accurately deliver immunological medicines to targeted locations, resulting in useful anti-tumor effects (13). The notion of "magic bullets," which included mounting cytotoxic medicines on certain monoclonal antibodies to target tumor cells, was created by Professor Paul Ehrlich at the beginning of the 20th century and gave rise to DDS (14). Antibody-drug conjugates (ADCs) were introduced decades later (14). Nanoparticles including liposomes, polymer nanoparticles, extracellular vesicles, and different coupling medicines have been employed in clinics in recent decades as pharmaceutical technology has matured. Numerous coupling medications and nanoparticles have been authorized thus far for the treatment of cancer (14, 15). However, the majority of them are employed to provide cytotoxic medications during chemotherapy. The use of poorly stabilized and patterned drugs (e.g., proteins, peptides, antibodies, and nucleic acids) for tumor immunotherapy is increasingly being studied due to the ongoing development of novel delivery platforms, such as extracellular vesicles (EVs), biomimetic nanoparticles, virus-like particles (VLPs), hydrogels, etc. (13, 16–19). In addition to making it safer and easier to target immunomodulators to the targeted tumor or immune cells, continuously enhanced delivery technology also offers a platform for multi-drug combinations. In this work, we present DDS from the viewpoints of coupling technology and drug delivery systems based on nanoparticles, and we examine the most recent studies on their use in tumor immunotherapy.

NANOPARTICLE BASED DRUG DELIVERY SYSTEM (DDS) FOR CANCER IMMUNOTHERAPY

Lipid-based, polymer-based, and inorganic nanoparticles are the most prevalent types of nanocarriers, a novel class of minuscule carriers that typically have a diameter of less than 200 nm (9). By technological methods including physical encapsulation, electrostatic adsorption, and encapsulation, nanoparticles load anticancer chemicals. They subsequently attach to certain receptors to enter target cells by cellular endocytosis (20, 21). As a result, the loaded medication is effectively released into the target cells. Furthermore, EVs may also be regarded as nanocarriers as they are nanoscale media with a bilayer membrane structure that are released from cell membranes or produced by cells. Because of their varying origins and diameters, EVs are categorized as exosomes, apoptotic vesicles, and microvesicles (22). Drug loading techniques for EVs, however, are different from those for other nanoparticles. These techniques include chemically treating the cells, physically incorporating exogenous RNA or protein medicines using electroporation, or manipulating primordial cells to overexpress certain chemicals (23, 24). EVs can fuse with the target cell's plasma membrane directly and release the loaded medication, in addition to entering the target cell through ligand-receptor interaction or endocytosis (25). Nanoparticles have been extensively created for the delivery of chemotherapeutic medications to tumors, but there is less for tumor immunotherapy, according to preliminary studies. Eleven nanocarrier medications have been authorized and put on the market thus far to treat solid tumors, such as liver, lung, ovarian, and breast cancers (15, 26). With the exception of Mepact, which is derived from liposome-encapsulated mifamurtide and is used for immunotherapy of osteosarcoma, the most of these medications are chemotherapy-based. Over the past 20 years, there have been new opportunities for the development of nanocarriers for tumor immunotherapy applications due to ongoing advancements in nanoengineering technologies and a better understanding of the significance of nanoparticle properties (such as size, shape, and surface properties) on biological interactions. Notably, by addressing physiological barriers to drug delivery, improving drug solubility, targeting drug delivery, and offering a multifunctional drug delivery platform, ongoing advancements in nanodrug delivery systems can increase the effectiveness of antitumor

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immunotherapy (27). The most recent studies on the application of DDS based on nanoparticles for cancer immunotherapy under various immune systems will be the main topic of the sections that follow.

The body's most powerful antigen-presenting cells (APCs) are dendritic cells (DCs), which recognize, process, and present antigens. They also efficiently stimulate T cell responses and trigger the production of particular cytotoxic T lymphocytes, which starts, sustains, and controls the immune response (28). Research indicates that ineffective antigen presentation and compromised DC maturation are crucial for the initiation and spread of tumors (28). Consequently, a number of nanoparticles have been created to encourage DC activation in order to start and strengthen the immune response against tumors.

The body's anti-tumor and anti-infection mechanisms heavily rely on the cGAMP-STING immunological signaling pathway (29). The second messenger, 2', 3'-cyclic guanosine monophosphate adenosine monophosphate (cGAMP), is produced in the mammalian natural immune system when cytoplasmic DNA from tumors or microbes activates cyclic GMP-AMP synthase (cGAS). When cGAMP attaches itself to the stimulator of interferon genes (STING), it forms a dimer that attracts TANK-binding kinase 1 (TBK1), phosphorylates and activates IRF3, and causes DCs to release type I interferon (IFN) and other cytokines (29). By stimulating tumor antigen-specific CD8+ T lymphocytes in lymph nodes, matured and activated DCs subsequently support anticancer immunity (30–32). This suggests that the field of anti-tumor immunotherapy holds a lot of promise for STING agonists.

The researchers advise intra-tumor injection as a delivery method because cyclic dinucleotides (CDNs), the natural ligands of STING, are small hydrophilic molecules that are impermeable to membranes and prone to quick nuclease degradation, making them unsuitable as reagents for systemic administration (32). Local T cell activation is induced by intratumoral injection of STING agonists, which significantly inhibits proximal tumors but not distant ones (32). Therefore, relying exclusively on intratumoral injection as a mechanism is insufficient for the translation of STING agonists into therapeutic application. Researchers have created a number of liposomes and polymer-based nanocarriers for the systemic administration of STING agonists in an effort to increase tumor control rates (33–36). For instance, Mohamed Wehbe et al. used endosome-destabilizing polymer vesicles to encapsulate CDNs, whereas Ning Cheng et al. created liposome-based nanoparticles. The elimination of CDN half-life was further prolonged by the use of these nanoparticals, which enhanced tumor accumulation and, in turn, STING activation in the tumor microenvironment (TME) (35, 36). However, only a small percentage of cancer cells or tumor-infiltrating immune cells take up CDNs as a result of these techniques because of their limited capacity to penetrate through the thick extracellular matrix of tumors (35, 36). Following years of investigation, scientists now think that the shape of the nanoparticle has a crucial role in drug cycle duration, biodistribution, and cellular absorption to produce more efficient drug administration, in addition to the size and surface property selection (37, 38). Liposomes, gold nanoparticles, mesoporous silica, and other sphere-shaped nanoparticles are among the majority of those authorized for commercialization and now under development (15, 26). In contrast to spherical nanoparticles with the same surface characteristics, rod-shaped nanoparticles demonstrated decreased clearance and extended circulation durations in mice, according to Discher and Arnida et al. (39, 40). This implies that altering the form of nanoparticles may be able to increase their delivery efficiency. A non-spherical lipid nanoparticle was demonstrated by Eric L. Dane et al. (41). The researchers used cleavable linkers to bind the CDNs pre-drugs to polyethene glycolized lipids, following the design principle of antibody-coupled pharmaceuticals. They created LND-CDNs (later known as LNDs) by doping them into lipid nanodiscs. Lipid nanodiscs are disc-shaped nanoparticles that develop by self-assembly, as opposed to liposomes, which have a homogeneous spherical vesicle shape. They discovered that because LNDs could deform and completely enter holes smaller than their equilibrium diameter, they were more easily absorbed by cells or entered tumor spheres while releasing more parental CDNs. After intravenous injection, the MC38 tumor-bearing mice confirmed this outcome. In addition, LNDs' circulation half-life was 0.6 times longer than liposomes'. In conclusion, when it comes to delivering STING agonists deep into the tumor, LNDs clearly outperform traditional liposomes. After LNDs and conventional liposomes were administered intravenously to MC38 tumor-bearing mice, LNDs were taken up by more tumor cells, produced substantial tumor cell death, and showed

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greater levels of IFN-β in tumor tissue. They also accumulated twice as much in CD11c+ DCs as conventional liposomes. To sum up, our findings highlight the significance of nanoparticle form in enhancing delivery effectiveness.

In addition to altering the carrier's physical characteristics, researchers have created active targeting techniques to increase the effectiveness of STING agonist delivery (42). Type I IFN has been shown to stimulate CD103+ DCs to release the chemokines CXCL9 and CXCL10 following STING pathway activation, which attracts T lymphocytes to the tumor (30, 43). The C-type lectin receptor Clec9a is not found in any other hematological cells but is strongly expressed in CD8 α + and CD103+ dendritic cells (44, 45). Aatman S. Doshi et al. modified liposome agents encapsulated with CDN (Adu-S100) using Clec9a peptides that target CD103+ DCs (42). In the meanwhile, they manufactured non-targeted liposomes using the same technique. Both liposomes containing STING agonists may encourage CD103+DCs to take up the agonists, activate APCs, and greatly increase CD8+T cell infiltration in tumors in MC38 tumor-bearing mice. On the other hand, the targeted group elicited greater levels of IL-6 and type I IFNs than the non-targeted group. This demonstrates the benefits of focusing on Clec9a tactics. Furthermore, they discovered that even after intravenous injection of a modest dosage of 0.1 mg/kg, the tumor-bearing mice had a strong immune response. Apart from its use as a monotherapy, the chemical demonstrated noteworthy anti-tumor effect when paired with PD-L1 antibody. Surprisingly, systemic delivery of targeted liposome medicines might also result in effective immune activation in tumors like B16F10 that have relatively little cytotoxic immune cell infiltration. VLPs have been created as vehicles for the delivery of STING agonists in addition to lipid nanoparticles (46). Viral capsid proteins, core proteins, or envelope proteins self-assemble to generate VLPs, which are particles that resemble the original virus in size, shape, and symmetry but lack the genome and replication enzymes, making them incapable of self-replication (47). Prophylactic and therapeutic vaccines for a variety of illnesses, including solid tumors, are frequently developed using VLPs (48–50). Eric L. Dane et al. recently described delivering the STING agonist 2′3′-cGAMP via virus-like particles (VLPs) (46). By being encapsulated in enveloped virus particles, 2'3'-cGAMP, a naturally occurring mammalian STING agonist, has been shown to activate STING in DCs just after fusion (51, 52). The HIV-1 structural protein and the vesicular stomatitis virus glycoprotein envelope glycoprotein make up the VLPs that Eric L. Dane et al. produced to encapsulate cGAMP. According to this study, cGAMP-VLPs delivered cGAMP into cells around fifty times more effectively than traditional liposomes. The researchers concentrated on the impact of intratumoral injection on tumors in mice, which was different from the previously published investigations. The MB49 tumor-bearing mice's subcutaneous tumors disappeared following an intratumoral injection of cGAMP-VLP. Additionally, some mice treated with cGAMP-VLP showed a substantial rise in CD4+T cells in their blood, whereas other animals showed a significant increase in CD8+T cells. On the side of the tumor that received an intratumoral injection of cGAMP-VLP, CD8+ T cells increased while Tregs and NK cells decreased in the B16-OVA double tumor mice. In distant tumors, CD8+T cells grew concurrently, whereas Tregs and NK cells remained mostly unchanged. Crucially, cGAMP-VLP works in concert with anti-PD1 to effectively suppress both local and distant tumor development. The lack of local injection of free STING agonist can be adequately compensated for by the combination with VLPs. To sum up, this vector-based method of targeted STING agonist administration provides a promising treatment option for enhancing patients' anti-tumor immune responses. Antigen stimulation to trigger the production of antibodies is known as active immunity. Vaccination is a type of active immunotherapy used in cancer immunotherapy. Using therapeutic DC vaccines to increase active immunity and in conjunction with ICIs, a number of clinical trials have been started in recent years (53, 54). This has led to the development and creation of targeted DCs using a variety of novel nano-delivery technologies, including as lipid-based, polymeric, inorganic, EVs, and other nanoparticles (55–58). Of these, liposome-based tumor vaccines have been investigated in clinical studies (59–61). In contrast to other nano-delivery technologies, EVs are highly biocompatible, effectively evade the mononuclear phagocyte system, and are comparatively harmless following lysosome destruction in recipient cells at the end of the delivery task (62). The most recent studies on EV usage for DC vaccine production are reviewed in this section.

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Exosomes are extracellular vesicles that range in diameter from around 30 to 150 nm. They are created when the limiting membrane of the inner body sprouts inward (63, 64). Exosomes are crucial intercellular messengers, and their capacity to carry biomolecules to destination cells makes them very desirable for drug delivery (65). Tumor-derived exosomes, or Tex for short in this work, are thought to be attractive candidates for tumor vaccines because they include a variety of immunomodulatory proteins, co-stimulatory molecules, and adhesion molecules (66). But there are drawbacks as well, such low immunogenicity and the potential to encourage the growth of tumors (67). To address these issues, ongoing research has altered Tex, for instance by designing surface changes or encapsulating immune agonists or adjuvants (67, 68). For example, Lanxiang Huang and colleagues created a Tex vaccine using a breast cancer cell line that overexpresses α-lactalbumin (α-LA). As an in-situ DC vaccination for breast cancer therapy, they encapsulated human neutrophil elastase (ELANE, an immunogenic cell death inducer) and Hiltonol (toll-like receptor 3 agonist, a common immunological adjuvant) within the Tex, which they called Hiltonol-ELANE-α-LA-engineered exosomes (HELA-Exos) (68). According to reports, the majority of human breast tumors express α-LA specifically. An important method of stimulating the immune system to fight cancer is immunogenic cell death (ICD) (69). The process via which tumor cells transform from non-immunogenic to immunogenic and produce a number of signal molecules to orchestrate the anti-tumor immune response when they die in response to external stimulation is known as immune cell death (ICD) (70). After intravenous treatment, it demonstrated strong anticancer efficacy in human breast cancer-like tissues and in situ triple-negative breast cancer (TNBC) mice models. By promoting tumor antigen exposure and immunostimulant release, HELA-Exos contains an ICD inducer that favors DCs' increased absorption of dying tumor cells (71, 72). Because DCs have a high level of toll-like receptor (TLR) 3 expression, HELA-Exos was able to induce DCs to mature more successfully and had a greater triggering impact on CD8+T cells when TLR3 agonist and ICD induction were coupled. Conventional medications have trouble overcoming barriers in tumors with thick fibrotic stroma, including pancreatic ductal adenocarcinoma (PDAC) (73). Wenxi Zhou et al. created spMEXO, an exosomal vaccine that targets DCs with CCL22 siRNA generated from mitoxantrone (MTX)-treated PDAC cells, to efficiently accelerate the maturation of DCs in PDAC (74). Exosomal membranes from MTX-treated PDAC cells can generate immunostimulatory signals that encourage DC maturation, and MTX can cause ICD in tumor cells (75). Melanoma antigen recognized by T-cells 1 (MART-1) peptide was added to the surface of exosomes in order to increase the generation of tumor-specific T cells. According to reports, the MART-1 peptide is a very prevalent immunogenic epitope of tumor-infiltrating lymphocytes unique to HLA-A2-restricted melanoma that can proliferate CD8+ T cells (76). By encouraging DC maturation, activating CTLs, secreting anti-tumor cytokines, and preventing DC recruitment of Tregs via the CCR4/CCL22 axis, spMEXO may have therapeutic benefits in in situ PDAC mice models and effectively suppress tumor development. They also came to the conclusion that administering the medication intramuscularly to move it into the lymphatic circulation was a preferable alternative because of the hypovascularization and hypoperfused vessels in PDAC. They demonstrated that spMEXO accumulated at the tumor location 2.8 times higher following intramuscular treatment than intravenous administration, comparing the effectiveness of intravenous and intramuscular administration in targeting tumors. This implies that the best administration method should be selected based on the tumor's vascular distinction. Currently, the majority of clinical studies employ either an intramuscular or subcutaneous injection of the tumor vaccine (77, 78). Oral vaccinations have the ability to stimulate mucosal immunity and make immunization easier than injectable vaccines (77, 79). Due to the complex environment of the gastrointestinal tract and the presence of intestinal epithelial barriers, the anti-tumor effects of several oral vaccines based on carriers like liposomes, polymeric nanoparticles, and oil droplets have not been satisfactory over the past 20 years (77, 80, 81). The National Nano Centre of China team led by Professor Guangjun Nie suggested employing genetically modified outer membrane vesicles (OMVs) generated from E. coli as delivery systems for oral tumor vaccines that target DCs (82). OMVs are a promising vehicle for oral tumor vaccines because they can cross the intestinal epithelial barrier and interact with immune cells in the intestinal lamina propria, which DCs specifically identify to trigger immune responses (83). The group fused the tumor antigen and the mouse immunoglobulin G Fc fragment to the C-

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terminus of ClyA, the OMV surface protein (ClyA-Ag-mFC), via fusion protein binding (82). They modified E. coli to regulate the production of the fusion protein on its secreted OMVs by introducing an arabinose (Ara) inducible promoter, taking into account that prolonged antigenic stimulation results in immunological tolerance of the organism. The regulated in situ creation of a tumor vaccine, OMV-Ag-mFC, in the gut was made possible by the concurrent oral administration of Ara and the modified OMVs. The tumor-suppressing microenvironment in MC38 tumor-bearing mice was markedly enhanced by oral administration of OMV-Ag-mFC: immunosuppressive CD3+CD4+CD25+ Tregs were greatly reduced, and tumor-infiltrating CD3+ T cells, CD3+CD8+ T cells, CD3+CD4+ T cells, and CD11c+ DCs were increased. More significantly, healthy mice that received the oral ClyA-OVA-mFc vaccination developed a sufficient immunological memory over the long term. The team has been working for a long time to create and analyze nano-tumor vaccines based on bacterial membrane materials using the concept of vector and adjuvant integration, and they have produced a number of ground-breaking discoveries. The team released a review in 2022 that includes related studies (84). The primary drivers of the tumor microenvironment, tumor-associated macrophages (TAMs) make up up to 50% of all cells in some solid tumors, making them one of the biggest populations of immune cells that infiltrate tumors (85). Different stimulatory stimuli often repolarize TAMs with great plasticity and heterogeneity into two opposing phenotypes: M2-like TAMs that decrease T-cell function and M1-like TAMs with anti-tumor activity (86). Consequently, a possible method to enhance the immunosuppressive tumor microenvironment is the efficient targeted administration of medications that alter polarization to TAMs. By blocking cyclooxygenase-2 (COX-2) and its downstream product prostaglandin E2 (PGE2), salicylic acid and its derivatives, a conventionally authorized anti-inflammatory medication, rewire TAMs from M2 to M1 type (87,88). For the first time, Kai Sun et al. reported hypoxia-stimuli-responsive iron-5, 5’-azosalicylic acid nanoscale coordination polymer nanodrugs (FeNCPs) to better substantiate the unique function of salicylic acid in anticancer treatment (89). They next attached polyethylene glycol (PEG) to the FeNCPs' surface. Longer half-life, decreased or eliminated immunogenicity, and less harmful side effects were all cited as benefits of the PEG alteration (90). One common tactic in the pharmaceutical industry is PEGylation of nanoparticle surfaces (90). Solid tumors often have hypoxia, which can encourage azo reductase overexpression (91). When PEG-FeNCPs are injected intravenously into 4T1 tumor-bearing mice models, azo reductase may break them down in hypoxic environments, releasing 5-aminosalicylic acid. By rerouting TAMs to the M1 phenotype, 5-aminosalicylic acid was able to improve the immune response and relieve the immunosuppressive tumor microenvironment. Interestingly, TAMs have also been shown to change into the M1 phenotype when exposed to iron-based nanomaterials (92). The study's findings demonstrated that the proportion of CD80+ M1-like TAMs, the infiltration of CD8+ cytotoxic T cells, and the maturity of DCs in tumor-draining lymph nodes were all markedly elevated, but CD206+ M2-like TAMs were the opposite. Furthermore, PEG-FeNCPs dramatically slowed the development of tumors in mice.

One well-known medication used to treat diabetes mellitus is metformin (Met). Recently, Met has been a hot topic in "new uses of old drugs" due to its recently revealed anti-tumor capabilities. Met has been demonstrated in several studies to control tumor metabolism, prevent tumor cell invasion, migration, and proliferation, and trigger apoptosis (93,94). More significantly, Met can improve the immunosuppressive microenvironment, hypoxia, and chronic inflammation to have anti-tumor effects (95). According to recent research, met inhibits the pro-tumor actions of M2 TAMs by drastically downregulating M2 TAM markers and changing the polarization of TAMs from M2 to M1 (96,97). Met@Man-MPs are mannose-modified murine macrophage-derived microparticles (Man-MPs) loaded with Met, as created by Zhaohan Wei et al. (98). Cells respond to a variety of endogenous or exogenous stimuli by releasing cell microparticles (MPs), which are extracellular vesicles with a diameter of 100–1000 nm (22, 99). MPs are a promising drug carrier that shares traits with exosomes, including the ability to transport messenger molecules, enzymes, and nucleic acids across cells (100). MPs produced from macrophages are naturally able to target tumors (101). Since the mannose receptor is strongly expressed on M2 TAMs, mannose modification allows Met@Man-MPS to target M2 TAMs. Met@MPs dramatically reduced the mRNA expression of Arg1, Mrc1, and Mgl1, as well as the protein expression of CD206 (M2-related markers), while increasing the protein expression of CD80 and CD86 (M1-

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related markers) in H22 tumor-bearing mice. By decreasing the quantity of Tregs and MDSCs in tumor tissue and boosting the recruitment of CD8+ T cells, the targeted macrophages successfully restored the anti-tumor immune milieu. Furthermore, Met@Man-MPs significantly slowed the formation of tumors and extended the mice's life period. Remarkably, Met@Man-MPs efficiently caused the breakdown of tumor-associated extracellular matrix type I collagen when paired with anti-PD-1 antibodies. This improved the concentration of anti-PD-1 antibodies in tumors and their anti-cancer properties.

Tumors are classified into three primary immunophenotypes based on the spatial distribution of cytotoxic immune cells in the tumor microenvironment: immunological-inflamed, immune-excluded, and immune-desert phenotype (102). Because of their strong T cell infiltration, elevated IFN-γ signal transduction, PD-L1 expression, and other factors, immuno-inflammatory phenotypic cancers are referred to as "hot tumors" (103). Additionally, immunotherapy frequently works better on certain types of cancers (104, 105). Tumors with immune-excluded and immune-desert phenotypes are referred to as "cold tumors" (106). Poor T cell infiltration, a low mutation burden, and low PD-L1 expression are characteristics of cold tumors (106). Researchers usually induce ICD to boost the recruitment and activation of tumor-specific T cells to "ignite" the tumor and improve the efficacy of immunotherapy since inadequate T-cell infiltration in "cold" tumors is a key cause of poor immune response (107). The traditional ICD inducer doxorubicin (DOX) must be used in conjunction with other immunotherapies since it is insufficient to trigger a robust immune response that would ignite cold tumors. FD/FM@siTOX NPs are new carrier-free fluorinated polymer nanoparticles based on DOX, siTOX, and melittin that were created by Pengkai Wu et al. (108). One important regulator of T cell failure is the protein known as Thymocyte Selection-Associated High Mobility Group Box (TOX) (109). In order to decrease T-cell depletion and increase T-cell invasion by inducing ICD, they paired DOX with siRNAs that block TOX expression. Interestingly, melittin has the ability to specifically kill tumor cells, and its ability to dissolve membranes makes siRNA transfection safe and efficient (110, 111). It was established that FD/FM@siTOXNPs considerably improved the impact of ICD in the 4T1 tumor-bearing animal models, inhibited CD8+T cell depletion, and markedly increased the production of the cytokines perforin (PRF), IFN-γ, and granzyme-B in CD8+T cells. Mice's life duration may be increased and tumor development and liver metastasis can be considerably inhibited by intravenous injection of FD/FM@siTOXNPs. In summary, this combo approach is a potential DDS to turn "cold" tumors into "hot" ones and can improve the overall anti-tumor immune response of FD/FM@siTOX NPs. By releasing PRF to puncture the cell membrane, activated CD8+ T lymphocytes can promote tumor cell death during immunotherapy (112). Nonetheless, immunotherapy failure may be mostly due to the membrane repair process, particularly in cold tumors where there are not enough infiltrating CD8+ T cells (113,114). According to Zhanwei Zhou et al., CD8+ T cell-mediated tumor cell death may be improved by supplementing with exogenous cytotoxic proteins before pore closure (114). For in situ gelling, which involves administering a drug in solution form with an instantaneous phase transition at the site of administration from a liquid state to a non-chemically cross-linked semi-solid formulation of the gel, they injected human serum albumin nanoparticles containing the photothermal agent IR780 (HIR780), ribonuclease A (RNase A), poloxamer 407, and α-cyclodextrin (the main ingredient for hydrogel formation) into the tumor. A slight photothermal effect at 45°C can cause ICD in 4T1 tumor-bearing mice and trigger an immune response. This triggers CD8+ T cells to release PFR, which pierces the tumor cells' plasma membrane. It also encourages RNase A to enter tumor cells and triggers the caspase-3 and gasdermin-E pathways, which cause apoptosis and scorch death to further stimulate immunity. IFN-γ expression was significantly up-regulated as a result of CD8+T cells' effective infiltration into the tumor tissue. The mouse tumor was greatly inhibited without any suspense. Nonetheless, prior research indicates that moderate photothermal treatment (PTT) can shield tumor cells from CD8+ T cell assault and cause PD-L1 to be upregulated on tumor cells (115). As a result, a PD-L1 antibody must be added to the medication combination mentioned above. This group of researchers investigated the simultaneous administration of PD-L1, RNase A, and HIR780 antibodies. It demonstrated that the anti-tumor effects of this hydrogel formulation with PD-L1 antibodies were noticeably greater than those of the formulation without PD-L1 antibodies (114). Another type of immunotherapy that increases the anti-tumor impact by triggering ICD is

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photodynamic treatment (PDT) (116). PDT is the process by which an excited light source irradiates the photosensitizer with the help of oxygen molecules to create cytotoxic reactive oxygen species (ROS), which causes ICD and kills a significant proportion of tumor cells (117). However, because of their limited solubility in the biological milieu, the majority of photosensitizers are prone to aggregating, and the quenching effect caused by molecular assembly further diminishes the photosensitizers' capacity to produce ROS and emit fluorescence (118). Hongmei Cao et al. created MBPN-TCyP, a mitochondria-targeted photosensitizer with aggregation-induced emission (AIE) capabilities, to solve this problem (119). According to their earlier research, encasing AIE photosensitizers in amphiphilic polymers not only causes inadequate loading but also restricts the photosensitizer's intramolecular mobility, which results in ineffective mitochondrial targeting (120). As a result, DCs-derived EVs (DEVs) were employed as delivery vehicles in the current study. The bionic packaging of the AIE photosensitizer produced excellent biocompatibility and successfully evaded clearance by the mononuclear phagocyte system, thereby generating a significant amount of ROS and specifically targeting the mitochondria of tumor cells (119). DEV-AIE's capacity to target mitochondria enabled it to improve the ICD response in 4T1, CT26 tumor-bearing mice. Furthermore, natural ligands (CD80/86, MHC I/II) on the DEV membrane might be used by DEV-AIE to directly activate T cells. In tumor tissues treated with DEV-AIE, the proportion of activated CD4+ and CD8+ T lymphocytes was markedly elevated. Likewise, there was a considerable inhibition of the tumors in mice. In summary, when compared to traditional medications, nanocarrier-based DDS offer several benefits, including: specific targeting of drug delivery following processing and modification; delayed drug release time, extending its duration of action; protection of drug molecules and notable improvement of drug stability; and, to a lesser extent, enhanced drug absorption and utilization. Unfortunately, practically all of these successful examples were rarely employed in clinical studies and were only accomplished in animals. Clinical translation of nanodrug delivery technologies is still fraught with difficulties (121, 122). We separated the nanoparticles into many subcategories to illustrate their own benefits and drawbacks because of the variety of materials. However, because of their limits in biology, technology, and medicine, nanoparticles also confront particular difficulties. The distinction between preclinical research in animal models and clinical research in humans is one of the primary issues with the clinical transformation of nanoparticles (123, 124). As an illustration, consider the enhanced permeability and retention (EPR) effect, which describes the fact that certain macromolecular materials of a particular size, like nanoparticles and some macromolecular medications, are more easily absorbed by tumor tissue and stay there for a longer period of time than normal tissues (123). Although there is a dearth of trustworthy data in people, this has been confirmed in animal models (123). Another significant obstacle to the clinical development of nanodrugs is the issue of illness heterogeneity in many individuals at different times. Before going into clinical use, a consistent and highly reproducible drug synthesis formula is required in terms of technical synthesis. It is uncertain if the same outcomes can be achieved following large-scale synthesis, nevertheless, as the majority of preclinical studies employ modest amounts of manufactured nanoparticles (125, 126). Since EVs are distinct natural nanoparticles, little is known about the intricate transport therapeutic method they use in the human body (64, 127). Will EVs' tumor propensity be influenced by their membrane structure and other physical and chemical configurations, for instance? How well do various cargo loading techniques work for packaging various antineoplastic compounds? Will exosomes generated from tumors accelerate the growth of tumors in some way? Therefore, closing our knowledge gap is essential to enhancing the production of EVs. Furthermore, the large-scale manufacture of EVs is an important issue due to the absence of a standardized separation and purification scheme (128). The primary obstacle to its use in targeted therapy is also the low load of therapeutic goods in EVs (129). This might be as a result of EVs containing some of the mother cell's contents during creation (129). In summary, nanoparticle-based drug delivery systems exhibit significant promise for enhanced drug delivery and therapy in the field of biomedicine, despite significant obstacles and problems in their implementation.

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DRUG DELIVERY SYSTEM (DDS) BASED ON COUPLING TECHNOLOGY FOR CANCER IMMUNOTHERAPY

Coupling technology has made it possible to administer chemotherapeutic medications precisely, which has successfully decreased their systemic toxicity, which has been a problem (10, 130, 131). The two most popular linked drug delivery technologies at the moment are peptide-drug conjugates (PDCs) and ADCs. They are molecular drug delivery technologies that do not rely on carriers. In contrast to the above-discussed nanocarrier-based drug delivery systems, they combine the antitumor characteristics of cytotoxic molecules with the specific targeting capabilities of monoclonal antibodies (mAbs) or peptides to deliver chemotherapeutic drugs to tumor tissue in a way that reduces systemic toxicity. Scientists have continued to create novel delivery ideas, such as targeted protein degradation (TPD), which includes lysosome targeting chimaeras (LYTACs), proteolysis targeting chimaeras (PROTACs), and others, in addition to technologically upgrading the original delivery methods (132–134). The features of ADC, PDC, and TPD technologies as well as the most recent studies on their use in cancer immunotherapy will be the main topics of discussion in the sections that follow.

The German scientist who invented chemotherapy, Paul Ehrlich, initially proposed the idea that it could be feasible to selectively destroy cancer cells without endangering healthy cells if hazardous medicines were mounted on carriers that target tumor cells (135). Gradually, studies have demonstrated that some antibodies can target tumor cells by recognizing tumor cell-surface antigens (tumor specific antigen, or TSA; tumor-associated antigen, or TAA) (136). Although the idea of ADCs was initially put out in 1967, technological constraints kept development at a theoretical level. Since 1975, monoclonal antibodies (mAbs) have been produced in large quantities thanks to the advancement of hybridoma technology. Many monoclonal antibodies (mAbs), including trastuzumab, rituximab, and cetuximab, have been authorized in recent decades to treat a variety of solid malignancies (137-140). Nevertheless, mAbs do not kill cancer cells as well as chemotherapeutic drugs when taken alone (141). ADCs have thus been extensively studied as innovative agents that can make up for the shortcomings of cytotoxic medications and mAbs.

ADCs are composed of three primary parts: cytotoxic drug payloads, mAbs that target tumor cell surface antigens, and linkers that connect the two. One essential element that keeps ADCs from dissociating in the bloodstream is the linker. Drug release may be classified into two categories based on whether the linker is cleavable, and the majority of ADCs are internalizable (130, 142). To release their ADC carrier payload, cleavable linkers rely on the physiological conditions inside the tumor cell, such as low pH, hydrolysis of proteases, or elevated intracellular glutathione levels. The linker remains connected to the cytotoxic medication for release into the cytoplasm if the linker cannot be broken down by the lysosome. This non-cleavable linker exhibits comparatively minimal off-target toxicity and is more stable in the circulation (143). Some ADCs have an anticancer impact that includes the function of the Fc fragment in the mAb molecule in addition to delivering cytotoxic medicines to the tumor site (144,145). These ADCs have the ability to use the Fc fragment to carry out their immune effect function in addition to precisely identifying the target through their Fab domain. The three most significant effector modalities in the Fc fragments are complement-dependent cytotoxicity (CDC), antibody-dependent cell phagocytosis (ADPC), and antibody-dependent cell-mediated cytotoxicity (ADCC) (145). ADCs can destroy tumor cells directly when Fc fragments attach to the FcR on the surface of killer cells, such as macrophages and NK cells. Additionally, we direct readers who are curious about this topic to published works that particularly address the mechanism of effects in Fc fragments (145). Additionally, the antibody component of ADCs has the ability to selectively attach to cancer cell epitope antigens and block antigen receptor downstream signaling, which in turn stops cancer cell development. Eight ADCs have been used therapeutically to treat solid tumors since the Food and Drug Administration (FDA) authorized Mylotarg, the first ADC medication, in 2000 (146). These ADCs are loaded with cytotoxic medicines, such as DNA-damaging agents and antitubulin, as are the majority of those now undergoing clinical trials (14). Anthracyclines, platinum, and ruthenium are a few examples of these cytotoxic medications that might cause ICD, which activates DCs and triggers T-cell-mediated anti-tumor immune responses (144). Additionally, several ADCs have been shown to enhance PD-L1 expression in tumor cells, and they have been shown to work in concert with immune checkpoint inhibitors (115, 147–149). TLR agonists and STING agonists, often referred to as

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immunostimulating antibody conjugates (ISACs), are two small molecule immunomodulators that have been employed in the creation of new ADCs in addition to conventional cytotoxins (150–152). Known as ISACs, BDC-1001 is a new ADC that is presently undergoing clinical development (Phase I/II, NCT04278144) (153). It is used to treat patients with HER2-positive solid tumors and is made up of a TLR 7/8 agonist and a HER2-targeting antibody with a non-cleavable linker. SBT6050 (Phase I, NCT04460456) and SBT6290 (Phase I/II, NCT05234606) are other ISACs that target solid tumors (154, 155). While SBT6050 targets HER2, SBT6290 targets Nectin4 (Nectin cell adhesion molecule 4, a type I membrane protein that is overexpressed in a variety of tumor cells). Both medications employ TLR8 agonists as payloads. It's worth waiting for their clinical results. Technological advancements like the creation of antigen-binding fragments that are more stable in circulation, the improvement of linkers for better plasma stability, and the optimization of the interactions between antibodies and FcγRs have all contributed to the recent increase in the number of ADCs entering clinical trials (156). Regretfully, a number of ADCs that had great promise in preclinical research have underperformed in clinical trials. One major factor contributing to the inadequate clinical use of ADCs is incomplete internalization. As previously mentioned, internalization mechanisms are frequently used in the construction of ADCs. This is mostly dependent on internalizing antigen overexpression, which is uncommon in malignancies. Furthermore, antibodies are big molecular proteins that continuously attach to cancer cells near blood arteries on the tumor's perimeter, preventing them from penetrating further into the tumor. They also disperse slowly and have limited tumor penetration (157). Consequently, the creation of non-internalizing ADCs with extracellular payload release mechanisms has been the subject of increased study during the past ten years (142, 158). Non-internalizing ADCs are designed and developed to target non-internalizing antigens on the surface of tumor cells, allowing for targeted drug administration and release rather than relying on the internalization process of tumor cells. In order to release the payload outside of the tumor cells and spread to nearby cancer cells to exert their cytotoxic effects, the linkers of non-internalizing ADCs are made to be unstable in the extracellular tumor microenvironment and take advantage of the distinct chemical or enzymatic environment of tumors in comparison to healthy tissue (142). As of right now, the tumor microenvironment and tumor cell membrane proteins are the primary targets of non-internalizing ADC. We won't go into great depth on the goals in this post due to space limitations. In other words, because non-internalizing ADC does not rely on the production of highly similar antigens, it clearly broadens the spectrum of tumor targets when compared to the conventional internalizing ADC (142). Aside from that, non-internalizing ADC might lessen toxicity and adverse effects by utilizing the distinct chemical or enzymatic environment of tumors and avoiding cracking in healthy tissues (142). Another significant factor contributing to ADCs' poor performance in clinical settings is their potential for off-target effects, whether absorbed or not (169). In order to guarantee that the antibody binding properties are preferentially activated in the tumor site, researchers primarily conceal the antibody's antigen binding fragments in order to prevent the miss effect (170). However, the antibody's Fc domain's function is disregarded. On the basis of this, Adrian Elter et al. postulated that the antibody's Fc domain stays passive while in circulation and, when reaching the malignant tumor, recovers the effector's functional characteristics (171). They employed a matrix metallopeptidase 9 (MMP-9) cleavable linker to fuse the single-stranded variable fragment (scFv) onto the C-terminal of the trastuzumab light chain. The FcγRs interaction location on Fc is particularly bound by ScFv. The antibody triggered by the Fc segment demonstrated complete recovery of binding to FcγRs and C1q following MMP-9-mediated splicing cleavage and scFv separation, as well as restored ADCC and CDC effects. Trastuzumab of Fc-masked arrived in the tumor tissue later. More significantly, the effector-enhanced engineered antibody and the Fc-masked antibody form can work in concert. Combining the two can lessen the possibility of systemic toxicity while simultaneously increasing the anti-tumor efficacy.

Linkers, cytotoxic drug payloads, and homing peptides are the primary constituents of PDCs. As seen in Figure 2, PDCs and ADCs have a similar structure, with the exception that PDCs target using peptides (131). Cell-penetrating peptides (CPPs) and cell-targeting peptides (CTPs) are the two categories into which homing peptides fall (172). Through a variety of methods, CPPs can enter cells directly and transport cargo within them (173). CTPs can potentially deliver payloads selectively because of their strong ability to target particular targets (172). There

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are several benefits to using peptides as targeting agents in drug conjugates as opposed to ADCs. PDCs are easier to produce, less costly, and have a smaller molecular weight, higher tissue penetration, and extremely low inherent immunogenicity. They also make it easier to increase the stability of the medication by structural alterations (174–176). For the treatment of solid tumors, only one PDC medication, 177Lu-DOTA-[Tyr3]-octreotate (Pepaxto), has received approval (133). In 2018, the FDA authorized its use for the treatment of gastrointestinal pancreatic neuroendocrine tumors that were positive for growth inhibitor receptors. Many PDCs are undergoing preclinical or clinical studies, and we've included a list of some of the most popular medications being developed worldwide for PDCs.

PDCs have received less research attention as immunomodulators than ADCs. The PDCs from Bicycle Therapeutics are more noticeable in this regard. Bicycle Therapeutics has created a unique peptide coupling as a tumor-targeted immune cell agonist™ (BicycleTICA™) based on a completely synthetic limited bicyclic peptide technology (177). They use a three-armed branching polyethene glycol junction to connect peptides that target tumor-specific receptors and CD137, respectively. There are no immunomodulatory or cytotoxic medications in this combination. The first BicycleTICATM of this class to be used in clinical studies for advanced solid tumors is BT7480 (Phase I/II, NCT05163041). Kristen Hurov et al. employed spatial proteomics imaging in preclinical trials with BT7480 to detect nectin-4+ tumor cells in bladder cancer, head and neck squamous cell carcinoma, and non-small cell lung cancer that were encircled by CD137+ immune cell infiltration and situated inside the tumor core. Thus, they created PDCs that can target both CD137 and Nectin-4, specifically BT7480. Because of its high affinity for both CD137 and Nectin-4, it can activate immune cells to have anti-tumor effects by bringing CD137-positive immune cells into contact with Nectin-4-positive tumor cells at the same time. Intravenous BT7480 injection enhanced CD8+ T cell tumor infiltration and caused total tumor regression in MC38 tumor-bearing mice that expressed nectin-4. In rodents and non-human primates, the chemical exhibited excellent anti-tumor effectiveness and tolerability. Additionally, BCY12491, the company's BicycleTICATM, which targets both CD137 and EphA2, has demonstrated strong anti-tumor and immunomodulatory properties (178). Some of the drawbacks of ADCs are offset by PDCs. However, the efficacy of payload delivery to tumor cells is limited due to the limited dispersion and targeting time of PDCs in vivo caused by the short biological half-life of peptides (131, 179). Due to this limitation, PDC development has been more sluggish, and fewer potential medications have been created than ADCs. Despite some first attempts to increase the half-life by chemical modification, the outcomes were unsatisfactory (180–183). Because the neonatal Fc receptor circulatory route prevents the Fc domain of IgG or albumin in the organism from being broken down by lysosomes (184–186). In recent years, several researchers have suggested covalently binding the peptide with albumin or connecting the Fc domain at the peptide's C-terminal, followed by recombinant production (184, 185). As a result, it can prolong the polypeptide's circulatory circulation and protect it. In summary, safer and more efficient PDCs for tumor immunotherapy are anticipated as more creative and enhanced approaches are researched.

TPD is a significant technique that has advanced quickly in the past ten years to disrupt target protein function in cancer treatment. PROTAC technology is now the most advanced advancement in this sector (187). By delivering E3 ubiquitin ligase ligands to target proteins of interest (POIs), PROTACs—novel protein "degraders"—promote ubiquitination and breakdown. The POI and E3 ubiquitin ligases are recruited and bound by ligands, respectively, and a linker joins the two ligands to form PROTACs. By destroying the entire POI and removing its entire function, PROTACs can overcome some possible drug resistance of standard medications, in contrast to conventional treatment techniques (187). More significantly, PROTACs have the ability to target a wider range of targets, including proteins that conventional drugs are unable to address (188). The first small molecule PROTACs that successfully targeted the androgen receptor were reported by Professor Craig Crew's team at Yale University in 2001 (189). The first PROTACs drugs to enter human trials were ARV-110 (Phase I/II, NCT03888612), which targeted the androgen receptor (AR), for metastatic prostate cancer (128) and ARV-471 (Phase I/II, NCT04072952), which targeted the estrogen receptor (ER), for ER+/HER2-metastasized breast cancer (191). ARV-110 allegedly showed encouraging first-line effect in patients with metastatic desmoplasia-resistant prostate cancer (mCRPC) in phase I clinical studies, reducing prostate specific antigen (PSA) by more than 50% at dosages exceeding 280 mg (192).

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Additionally, 80% tumor size decrease and partial remission were demonstrated in 1 out of 5 patients (192). ARV-471 had a clinical benefit rate in 42% of patients and dramatically decreased ER expression levels in tumor tissues by a mean of 62% and a maximum of 90% (192). Additionally, both had a good safety record at all tested dosage levels (192). This suggests that the use of PROTAC technology in anti-tumor therapy has a promising future. PROTACs are particularly interested in immune checkpoint proteins in cancer immunotherapy. The first PROTAC compound to efficiently degrade IDO1 was reported by Mingxing Hu et al. in 2020 (193). After creating seven IDO1 PROTACs degraders, they discovered that 2C, a PROTACs molecule, could significantly degrade IDO1, with a maximum degradation rate of 93% in Hela cells. A PROTACs molecule 21a was created by Yubo Wang and colleagues in 2021, and it has the ability to cause intracellular PD-L1 protein degradation in a variety of tumor cells in vitro (194). When 21a was administered to MC38 tumor-bearing animal models, the tumor development was suppressed, the toxic effects of CD8+ T cells were increased, and the PD-L1 protein levels were dramatically decreased. Because PD-L1 is constantly self-renewing from the cytoplasm to the cell membrane, 21a dramatically decreased both the total and cell membrane levels of PD-L1 protein. Because of the constraints of the ubiquitin-proteasome system (UPS), traditional PROTACs are limited to membrane proteins, function primarily on intracellular proteins, and cannot break down extracellular proteins (187, 195–197). Furthermore, only around 10 of the 600 E3 ligases found in the human body, like CRBN, VHL, IAP, MDM2, DCAF15, DCAF16, RNF114, etc have been evolved for PROTACs (198, 199). In order to address these issues, LYTACs and other PROTAC-derived technologies have been developed at a rapid pace (133, 200–202). The endocytosis-lysosome route is used by the LYTAC idea, which was initially proposed by Dr. Carolyn Bertozzi in Nature in 2020, to specifically degrade extracellular and membrane proteins (203). A linker connects the two primary parts of LYTACs, one of which targets the target protein (antibody, peptide, or other small molecule) and the other the lysosome-targeting receptor (LTR) on the cell surface. LTRs are necessary for the transport of proteins to the lysosome. The target protein is broken down by the lysosome after the LYTACs molecule combines with it and the LTR to create a complex. The complex enters the cell by endocytosis. The dissociated LTR, on the other hand, is uncontaminated and capable of carrying the target protein through the endosomal cycle (204). The mannose 6-phosphate/IGF-II receptor (M6P/IGF-IIR) and the related sialic acid glycoprotein receptor (ASGPR) are the most prevalent and extensively researched LTRs. It has been demonstrated that these receptors mediate the entrance of substrates into the lysosome for breakdown as lysosomal transport proteins (205–208). There are still several obstacles to practical use, despite the fact that drug research employing PROTACs and their related technologies is extremely promising and offers new therapeutic options for tumor immunotherapy (209). In addition to the difficulties in creating small molecule E3 ligase ligands, the molecules of produced PROTACs have a large molecular weight, low cell permeability, poor cell and tissue selectivity, off-targeting, and poor stability (210–213). Furthermore, it is yet unknown where oligosaccharide structures in LYTAC molecules bind best to antibodies, and this artificial sugar structure may be quite immunogenic to people (210). More significantly, since LTRs are extensively expressed on the surface of the majority of cells, it is imperative to figure out how to make LYTACs safer and prevent them from targeting cells that do not display the target proteins (210).

OTHER DEVELOPABLE AREAS ON DRUG DELIVERY SYSTEM (DDS) FOR CANCER IMMUNOTHERAPY

Cell-based DDS has been evolving quickly in recent years and has proven to be more effective than conventional delivery methods. Red blood cells, platelets, stem cells, immune cells, and other cell types are among the numerous that can be utilized for cellular delivery (214, 215). When it comes to tumor immunotherapy, traditional cell therapies like T-cell receptor engineered T (TCR-T) cells, chimeric antigen receptor T (CAR-T) cells, and chimeric antigen receptor natural killer (CAR-NK) cells all function by obtaining the body's own immune cells, modifying them in vitro, and then reintroducing them into the body to target and eliminate tumor cells (216, 217). In order to cure disorders, CAR-T cell therapy involves transferring autologous T cells into patients after they have been genetically altered in vitro (216). As of right present, hematological cancers may be treated with nine different types of CAR-T cells (216). Bispecific T cell engagers (BiTEs), another well-known medication, are used to

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reroute cytotoxic T cells to their targeted tumors, similar to CAR-T cells (218). Two distinct single-stranded variable segments of the antigen binding domain of anti-CD3 and anti-TAA antibodies are covalently joined by short junction peptides to form BiTEs, a novel kind of bispecific T cell-redirecting antibody (218). BiTE-based T cell immunotherapy has shown promise in a number of preclinical and clinical trials targeting hematological cancers, including one that the FDA has authorized for the treatment of leukemia (218). However, the therapeutic impact of CAR-T or BiTEs alone in solid tumors is not optimal because to the immunosuppressive microenvironment restriction and significant miss effect (219, 220). Studies on the creation of nano-drug carrier platforms for these two treatments have been published recently; the majority of these studies combine modified nanoparticles on the surface of CAR-T cells or nano-antibodies with BiTEs to play a probe-like targeting effect, and preclinical experiments have shown promising results (221, 222). The specificity and safety of medications will be significantly increased by this possible immunotherapy and DDS combination, which will also provide solid tumor immunotherapy more hope.

Oncolytic viral treatment (OVT) has recently generated a lot of interest as a novel tumor immunotherapy. One type of live attenuated virus that may selectively infect and lyse tumor cells without harming healthy cells is called an oncolytic virus (OV) (223). To improve anti-tumor activity or immune response, OVs can be further altered as a vector to deliver therapeutic transgenes to TME in a targeted manner (223). Costimulatory molecular genes, chemokine genes, cytokine genes, and ICI gene sequences are examples of these therapeutic transgenes (224, 225). Four oncolytic viruses have received commercial approval thus far. In 2015, the FDA authorized T-VEC as the first oncolytic virus to treat metastatic melanoma that was incurable (226). It has coding sequences for granulocyte-macrophage colony-stimulating factor (GM-CSF), which boosts immunity. The fact that 45.9% of patients in a phase II clinical study of preoperative T-VEC with neoadjuvant chemotherapy experienced complete remission following treatment is promising. Additionally, 89% of patients saw no recurrence two years following therapy. Furthermore, OVs are a possible immune adjuvant that can improve the effectiveness of other tumor immunotherapies including cell therapy and ICIs due to the selectivity of tumor cells and their capacity to trigger a systemic anti-tumor immune response (225). More than 40 early clinical trials investigating the combined treatment of Ovs, PD-L1 monoclonal antibody, and CAR-T are now underway, and they are demonstrating good curative effects (225, 226).

FUTURE PERSPECTIVE

DDS are frequently employed in tumor immunotherapy to administer nucleic acid medications, tumor vaccines, and immune modulators. They also offer a great platform for integrating immunotherapy with chemotherapy, PTT, PDT, and other treatments. The numerous drug delivery systems examined in this research have distinct properties since they are based on different materials and synthetic techniques. Furthermore, given the variety of DDS, it is crucial to select the best delivery method based on the target's properties, distribution, and biological function (e.g., internalization potential). To increase the effectiveness of drug delivery and improve its penetration into the tumor, we should take into account various delivery strategies and modes of administration, depending on the intracellular localization of target proteins and the features of various cancer types, such as dense tumor stroma and hypervascularized PDAC, as previously mentioned. The existence of a physiological barrier is another significant problem that has to be addressed in DDS research (227). In the realm of pharmacology, laser-assisted drug penetration has drawn a lot of interest among penetration-enhancing techniques (228). In addition to destroying tumor cells by triggering photosensitizers in PDT, lasers can damage the blood-brain barrier and kill tumor cells by applying heat. According to reports, laser interstitial thermal therapy (LITT) has been a common treatment for gliomas in recent years. It can increase drug permeability, directly trigger the anti-tumor immune response, and work in concert with systemic immunotherapy (228, 229).

Furthermore, scientists are always looking for better ways to combine DDS, and they have looked into the possibility of creating even more remarkable "chemical reactions" by merging nanotechnology with TPD. For instance, GlueTACs, a covalent nanobody-based PROTAC technique, was described by Heng Zhang et al. to target membrane protein degradation (204). With the aid of cell-penetrating peptides and lysosomal sorting sequences, they employed extremely stable and permeable nanoantibodies that covalently bind to antigens to create complexes that are then internalized into cells and broken down by

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lysosomes. Additionally, it was shown that in the melanoma mice models, PD-L1-targeted GlueTACs exhibited a more robust and prolonged PD-L1 degradation impact than PD-L1 blocking. In addition to targeting nanobodies, Ji Qi et al.'s new photosensitive nanoparticle was able to create multivalent cross-links by binding to PD-L1 on tumor cell surfaces, delivering endocytosed cross-linking complexes to the lysosome, and serving as a platform for LYTACs to facilitate PD-L1 internalization and degradation in the lysosome (230). Researchers are always looking for reliable new vectors to transport medications to the right cells in addition to the DDS that is now in use. The "syringe" for delivering therapeutic proteins into human cells may be bacterial contractile injection systems (CISs), according to a recent study by Feng Zhang and his colleagues (231). CISs are strikingly similar to the contractile tail of the T4 phage in that the rigid inner tube containing the therapeutic protein is punctured into the recipient cell by a contractile rotational action to complete protein release, while the contractile outer tube forms an adhesion point using a substrate complex. Furthermore, CISs can target particular tumor cells by altering the tail fibronectin. To put it briefly, more effective delivery methods or innovative drug delivery systems, such as CISs, will be progressively investigated. Effective and improved immune responses and improved therapeutic results can be achieved by accurately delivering immunomodulators to target tissues or particular immune cells via DDS. However, there are still a number of unresolved problems that must be resolved in order to increase tumor immunotherapy's effectiveness.

i. In order to reduce the toxicity or off-target effects of the carriers, the synthesis of complex carriers necessitates the use of multiple raw materials, making carrier design more complex. Additionally, interactions between complex carrier structures and organisms can result in even more unpredictable biological effects and safety in real-world applications.
ii. The co-delivery method of DDS typically makes it difficult to accomplish precision distribution to several cells in the tumor tissue at the same time, which may enhance the off-target effect of medications. Cytotoxic agents and immunomodulators typically target distinct cells. Thus, a new avenue for combination treatment research is the logical design of DDS with scheduled and quantified drug release to accomplish precise targeting of several medications to different cells.
iii. Polyethylene glycol (PEG) modification of nanoparticles is generally regarded as an efficient way to avoid reticuloendothelial system clearance and extend circulation duration (232). However, PEGylation is also controversial since it might cause allergic responses, interfere with cellular connections, and increase the production of IgM after repeated administration (233).
iv. Researchers must create individualized treatment plans at the molecular level since the tumor microenvironment might vary greatly across patients or throughout different times in a patient's life. Therefore, a difficult task that remains unfinished in the current tumor immunotherapy research is the design of DDS with a straightforward structure, easy industrial manufacturing, good biocompatibility, selective targeting, and high delivery efficiency under the presumption of guaranteeing biosafety.

DISCUSSION AND CONCLUSION

In conclusion, the present approach of combining DDS with immunotherapy has great promise for use and can greatly increase the effectiveness of tumor treatment while lowering systemic harmful side effects. Researchers have investigated many kinds of delivery carriers by utilizing the benefits of different kinds of materials. Our goal is to inspire doctors who are interested in a certain drug carrier by giving them as complete a picture of the available DDS as feasible. It is anticipated that safe and effective immunological drug delivery techniques will soon be used in clinical settings, despite the fact that several problems remain unresolved. This is due to the advancement of DDS research, growing knowledge of materials, and material development. Immunotherapy will assist more people with cancer.

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