Application of Nanoparticles in Modern Cancer Therapies

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Along with the extensive improvement in tumor biology research and different therapeutic developments, cancer remains a dominant and deadly disease. Tumor heterogeneity, systemic toxicities, and drug resistance are major hurdles in cancer therapy. Chemotherapy, radiotherapy, phototherapy, and surgical therapy are some prominent areas of cancer treatment. During chemotherapy for cancer, chemotherapeutic agents are distributed all over the body and also damage normal cells. With advancements in nanotechnology, nanoparticles utilized in all major areas of cancer therapy offer the probability to advance drug solubility, and stability, extend drug half-lives in plasma, reduce off-target effects, and quintessence drugs at a target site.

tumor heterogenicity chemotherapeutics microenvironment

1. Introduction

Despite numerous current developments in tumor biology and chemotherapy, cancer still endures as a widespread and deadly disease responsible for 10 million deaths in 2020 worldwide. Tumor heterogeneity, resistance to drugs, and systemic toxicities pose major hurdles in cancer therapy. Chemotherapy, phototherapy, radiation therapy, and surgery are the major therapeutic practices used to treat cancerous cells. Along with cancerous cells, these practices also cause damage to normal cells. The principal objective of scientists and physicians is to increase the safety and efficacy of cancer therapy. Drug targeting is the best approach for cancer treatments, which contains a harmonization of acts between the devastation of cancerous and healthy tissues, with impairment to the immune system and extremely replicating cells. Nowadays scientists are working to solve these side effects by using a new branch of biotechnology, i.e., nanotechnology. Newly established nano-technological approaches, such as vigorous targeting transporter, discriminatory targeting, and delivery of drugs in tumor tissues have increased the pharmacokinetics and diminished the systemic toxicities of chemotherapies. It selectively and directly helps to target chemotherapeutics to cancerous cells and neoplasms. Expansion of drug transfer in cancer, accelerated the growth of novel nanomaterials and nanocarriers to defend the drug from fast deprivation and permit it to reach the tumor site at the correct therapeutic concentrations, without delivery to normal sites to reduce adverse effects. Along with targeted delivery nanomaterials and nanocarriers, they have also improved the therapeutic efficacy of radiation treatment and in guidance of surgical removal of tumors.

2. Nanoparticles in Cancer Stem Cell (CSC) Therapy

The traditional way of tumor cell removal includes cellular damage, apoptosis, or necrosis by the use of chemotherapy or radiotherapy. They are targeted toward tumor cell removal but not towards the removal of cancer stem cells (CSC) [1]. The elementary source of cancer is Cancer Stem Cells (CSCs) which are a collection of dividing cells with a high power resistance to the drugs, residency in hypoxic tumor regions, often accountable for tumor development and re-occurrence. The use of nanotechnology in CSC-based therapies is an emerging field of biomedical sciences [2]. The use of nanomedicine for the treatment of CSCs resolves stability and solubility problems and increases their cellular uptake, prolongs systemic circulation, and improved biodistribution [3]. Abolishment of CSC will provide reduced metastasis and long-lasting treatment for remission. Several nanoparticles are designed to act as an antitumor drug [4]. Albumin nanoparticles entrapped in an all-trans-retinoic acid surface coated with hyaluronic acid attack the CD44 receptor present on CSC. Silica-based nanoparticles are used as nucleus-targeted drug delivery (NTDD) to reverse CSCs drug resistance and causality of apoptosis [1][5]. Pluronic F127 micelles expand the performance and improve the CSC effectiveness of citral in breast cancer [6]. In F9 teratocarcinoma stem cells, a model used for the evaluation of cytotoxicity- and differentiation-mediated cancer therapy shows the double role of silver nanoparticles [7].

3. Nanoparticles in Immunotherapy of Cancer

Immunotherapy has developed a potent clinical approach to cancer treatment. Autoimmunity and nonspecific inflammation are the commonly observed side effects of this therapeutics. Along with that the low insufficient immunogenicity of the tumor cells are the main hurdle in obtaining promising results through immunotherapy. The adaptability and tunability of nanoparticles mark them as an auspicious podium for attending to distinct challenges faced by numerous cancers [8]. Nanoparticles are engineered to transport chemotherapeutic, tumor antigens, phototherapeutic, or whole tumor cells in a fashion to efficiently and securely activate the host's immune organization in contradiction to tumor cells. Nanovaccines suggested a distinctive stage for the codelivery of modified tumor neoantigens and adjuvants for robust immune responses contrary to destructive tumors. Nanoparticles are engineered to elicit immunogenicity by inducing ferroptosis of the tumor cells. Ferroptosis is induced by ultrasmall iron oxide nanoparticles through the Beclin1/ATG5-dependent autophagy pathway [9]. The mixture of nanoparticle-induced ferroptosis and obstruction of programmed cell death proficiently obstruct the development of B16-F10 melanoma tumors and lung metastasis of 4T1 breast tumors, signifying the capability of ferroptosis initiation for endorsing cancer immunotherapy [10]. Immunomodulation of macrophages arose as a promising corrective approach against cancer. The attachment of signal regulatory protein alpha (SIRPα) on macrophages to CD47, a "don't eat me" signal on cancer cells and colony-stimulating factors, secreted by cancer cells, polarize tumor-associated macrophages (TAMs) to a tumorigenic M2 phenotype. Genetically engineered cell-membrane-coated magnetic nanoparticles (gCM-MNs) can disable both mechanisms [11]. Toll-like receptor (TLR-4) based Bacillus Calmette-Guérin (BCG) and monophosphoryl lipid A (MPLA) are active immunotherapeutics that have gained FDA agreement for their clinical use in cancer treatment [12].

4. Targeted Delivery of Therapeutics Using DNA and RNA in Tumor Cells

Nanoparticles used to deliver anticancer drugs grasp considerable capacity in cancer therapy, lacking specificity. Active targeting, by use of specific ligands to functionalize nanoparticles, is drawing ample consideration in recent years. The surface area of the nanoparticles can be coated with DNA, RNA, peptides, aptamers, or antibodies to use as targeted nanotherapeutics with drug delivery. The therapeutic and diagnostic properties of nanoparticles are commonly known as theranostic. DNA nanotherapeutics involve the delivery of plasmid DNA or specific DNA strands to treat malignant tumors. Guerrero-Cázares et al. [13] created biodegradable nanoparticles of poly β-amino esters (PBAEs) and loaded them with plasmid DNA. The transfection was done in Glioblastoma multiforme mouse models. The in vitro and in vivo experiments demonstrated safe and high transfection efficiency indicating nanoparticles as effective nano vehicles for the deployment of genetic medicines. In another study, DNAzymes nanoflowers were developed for doxorubicin (Dox) delivery. These DNAzymes catalytically cleave P-glycoprotein (P-gp) mRNA which aided in the release of chemo drugs for reversing multiple drug resistance in cancer therapy [14].

RNA molecules particularly siRNA, mRNA, and microRNA (miRNA) have enormous potential for nanotherapeutics and immunomodulation of cancer. They initiate a series of adaptive and innate responses of the immune system by silencing and upregulating immune-specific genes. Although RNA therapeutics is effective in gene knockouts or regulating the expression of proteins in the therapy of the targeted cancer cells, the RNAs instability, and many physiological barriers obstruct the effective transfection and delivery. Thus, it is a clinically important task to effectively deliver all RNAs to cancer tissues or cells. To make the transfection method more reliable, nanoparticle-based delivery of RNA molecules is used in many in vivo and in vitro [15][16][17].

The development of mRNA-based therapeutic vaccines is not only capable of delivering genetic information but also induces immunostimulatory activity [18]. Restoring the function of tumor-suppressing proteins is captivating therapy for cancer treatment. A study performed by Xiao et al. [19], showed that combinatorial therapy with the help of a CXCR4-targeted p53 mRNA nanoparticle platform and anti-PD-1 therapy induced the reprogramming of cellular and molecular components of immunosuppressive tumor microenvironment in p53 deficient hepatocellular carcinoma models. Another study demonstrated the restoration of functional tumor suppressor gene, phosphatase, and TENsin homolog deleted on chromosome 10 (PTEN) through the reintroduction of PTEN mRNA encapsulated in polymer–lipid hybrid nanoparticles coated with a polyethylene glycol shell, into the PTEN deficient prostate cancer cells. A significant reduction in tumor growth was observed in vivo in mouse models with prostate cancer [20].

In the progression of cancer, dysregulation of miRNA expression occurs. The restoration of proper expression of tumor suppressor miRNAs or inhibiting overexpressed oncogenic miRNAs is a suitable strategy for cancer therapy [21]. The first nanocarrier-formulated miRNA-based drug MRX34 encapsulated in a miR-34a mimic was terminated in phase Ist clinical trial due to toxicity induced by payload miR-34a. miR-34a affected the adjacent tissues causing toxicity and death. Another miR-16 mimic (Targomi R) showed encouraging results in malignant pleural mesothelioma or non-small cell lung cancer patients (NCT02369198 trial), in which 73% of patients have attained disease control. It was encapsulated in an EnGeneIC delivery vehicle (EDV), that consists of 400 nm nonliving bacterial minicells, coated with anti-EFGR bispecific antibody, a cancer cell-targeting moiety [22].

Specifically designed siRNA is used in targeting cancer-related genes, invasion, angiogenesis, and metastasis [23]. siRNA interacts and induces the silencing of targeted genes (mRNA) post-transcriptionally. Nine anticancer nanotherapeutics that involve siRNA-encapsulated nanocarriers reached clinical trials. However only, four siRNA nanotherapeutics reached the phase II trial; DCR-MYC was terminated by the sponsor, Atu027 and TKM-PLK1 have completed phase II, while siG12D LODER is currently recruiting. No nanotherapeutics have reached phase III trials. Many siRNA nanotherapeutics showed hematologic and electrolyte abnormalities. Thus, future nanotherapeutics must examine the optimization of siRNA formulation as well as the size of nanoparticle diameter for effective cellular uptake. Co-delivery of two or more siRNA will be more effective in antitumor efficacy. Standard nanoparticle vehicles replaced with biodegradable nanoparticles will ensure safety [24][25].

5. Cell Membrane Mediated Biomimetic Nanoparticles in Cancer Therapy

Traditional treatment methods for cancer lack precise drug delivery, induce toxicity, and non-specific targetability [26]. A biomimetics is a novel approach that employs biomaterials that mimic natural biological molecules to overcome immune barriers [27]. Biomimetic nanomaterials consist of extracellular vesicles, such as exosomes, microvesicles, and cell membrane-derived vesicles such as red blood cell membrane, white blood cell membrane, platelet membrane, the cancer cell membrane can provide efficient biocompatibility and biodegradability [28]. Combinatorial therapy using polymeric drugs and cell membranes improves drug delivery efficiency without causing high toxicity [29]. Zhang et al. [30] integrated poly (lactic-co-glycolic acid) (PLGA) with the red-blood-cell membrane (RBCm) and analyzed can GA-loaded RBCm nanoparticles to maintain and upgrade the GA-induced anti-tumor ability with reduced toxic effects in the treatment of colorectal cancer comparison to free GA. It was established through in vitro results that the biomimetic nanosystem provided biocompatibility and stability in comparison with bare nanoerythrosomes. Guo et al. [31] synthesized a biomimetic nanoplatform that utilizes dendritic large pore mesoporous silica nanoparticles (DLMSNs) for efficient delivery of oxygen as well as nano radiosensitizer. The external surface was coated with citric acid for the attachment of Cu-Se-Au alloy nanoparticles that have great photothermal conversion and radiosensitizing performances. The internal surface was coated with perfluorohexane for the delivery of oxygen. White blood cells were enclosed on the DLMNs surface to target tumors and lower abrasion to normal cells. The resultant nanosystem was effective against breast cancer. Lu et al. [32] have developed CRPC (Castration-resistant prostate cancer) cell membranes as biomimetic vectors for the coating of PEG−PLGA polymer consisting of the therapeutic drug docetaxel (DTX). In vivo studies confirmed target delivery in CRPC tumors in mice models. The therapeutic efficacy was also found to be improved. Jing et al. [33] demonstrated the potential use of extracellular vesicles as nanocarriers. They synthesized a nanoprobe system, 68 Ga-L-NETA-DBCO injected extracellular vesicles, obtained from adipose-derived stem cells. PET/CT and NIRF imaging results showed uptake of tracer in the orthotopic colon cancer model suggesting its potential role in image-guided surgery.

Exosomes and microvesicles are made up of bilayers that are released from the cell membranes for communication intercellularly. Therefore, nanoparticles based on both extracellular vesicles can carry therapeutic

RNAs and as well as perforate target cells to improve RNA-based cancer treatments [34]. In a study performed by Milán Rois et al. [35], gold nanoparticles are used as carriers to ensure the effective restoration of miRNA expression that was dysregulated in uveal melanoma. Yuan et al. [36] designed cancer cell membrane-camouflaged gelatin nanoparticles (CSG@B16F10) for delivery of CD73siRNA and oxygen-generating agent catalase (CAT) together thus, enhancing CD73-ADO pathway-mediated T cell immunosuppression and alleviation of tumor oxygenation. In vivo studies with mice showed PD-L1 checkpoint blockade and thus tumor suppression by ~83%. In another study, extracellular vesicles derived from hepatocellular carcinoma were utilized as a surface nanocarrier for consecutive nanocatalysts GOD-ESIONs@EVs (GE@EVs). Glucose consumption was catalyzed by glucose oxidase (GOD) and the generation of toxic free radicals catalyzed by ESIONs under an acidic tumor microenvironment.

6. Tumor Microenvironment (TME) Targeted by Nanotherapy

Numerous cell types that constitute the TME are fibroblasts, myofibroblasts, endothelial cells, stem cells, pericytes, immune cells, and inflammatory cells. Deficiency in the concentration of oxygen, resistance to drugs, low immunogenic antigens, acidic physiological conditions, and alteration in glucose metabolism are general features observed in many cancers causing obstructions in the efficacy of chemotherapeutic treatments [37]. Nanoparticle approaches are helpful in the delivery of drugs to the cellular as well as noncellular tumor microenvironment (physiological conditions).

6.1. Targeting Cellular Tumor Microenvironment

Normal cells contain fibroblasts that act as matrix support for normal epithelial cells. However, cancerous cells have prominent modified myofibroblasts (CAF; Cancer-associated fibroblasts) generally not found in normal cells. CAF in a stromal environment forms tumor-producing effects and prevents nanomedicine delivery by releasing pro-tumorigenic cytokines, enhancing solid tumor pressure and interstitial fluid pressure (IFP), and unspecific internalization [38]. A membrane-bound protease; Fibroblast Activation Protein (FAP), a cytoskeletal protein; α-SMA, ED-FN; a splice variant of fibronectin and vimentin are common overexpressed biological markers for inactivated CAFs [39].

A novel nanoparticle, albumin nanoparticle of paclitaxel (HSA-PTX) wrapped into the CAP-modified thermosensitive liposomes (CAP-TSL) with the incorporation of IR-780, a photothermal agent, into CAP-TSL, synthesized by Yu et al. [40]. The designed nanoparticle effectively increased the drug retention in tumors, simultaneously effluxion of HSA-PTX through FAP-α. Irradiation killed the tumor cells and fostered the penetration of HSA-PTX in its subterranean regions. The nanoparticle successfully showed an anti-tumor effect in Pan 02 subcutaneous and tumor mice. Another study done by Zhang et al. [41] demonstrated that the synergistic effect of gemcitabine-cisplatin nanoparticles on α -SMA-positive tumor-associated fibroblasts was synergically effective against tumor of bladder carcinoma. Wang et al. [42] developed a dual-target drug delivery system with the combination of paclitaxel (PTX)-loaded poly(ethylene glycol)-poly(lactic acid) nanoparticles (NPS) and a cyclic peptide (CNPs-PTX) inclining with platelet-derived growth factor/platelet-derived growth factor receptor (PDGFR-β)

overexpressed on both cancer-associated fibroblasts and myeloma cells. The cytotoxic analysis demonstrated toxicity in both CAF and myeloma cells led by cyclic peptide CNPs-PTX was more vigorous than PTX-loaded conventional NPs (NPs-PTX). Another study investigated the potential of P selection molecules involved in metastasis by localizing nanomedicines at tumor-affected endothelial cells. A fucosylated polysaccharide with nanomolar affinity to P-selectin; a drug delivery platform was created. The designed nanoparticle effectively localized in the tumor environment and targeted MEK (mitogen-activated protein kinase) inhibitor in tumor regions, causing antitumor effects [43]. Research led by Kuo et al. [44] demonstrated the downregulation of inhibitors of apoptosis proteins (XIAP and cIAP) and upregulation of caspase-3 expression by BV6- and GDC0152-encapsulated solid lipid nanoparticles (SLNs) with surface transferrin (Tf) and folic acid (FA) (BV6-GDC0152-Tf-FA-SLNs) in brain cancer stem cells of human.

6.2. Targeting Non-Cellular Tumor Microenvironment and Physiological Conditions

Hypoxia occurs due to the inability to meet the need for oxygen in cancer cells due to immature vasculature. Hypoxic regions in solid tumors are difficult to treat because of limited drug circulation and the absence of oxygen-free radicals in chemo- and radiation therapy, respectively [45]. In recent research, a hybrid sonosensitizer developed from a photosynthetic microorganism, cyanobacteria (Cyan) attached with ultrasmall oxygen-deficient bimetallic oxide $Mn_{1.4}WOx$ nanosonosensitizers (M@C), was developed to overcome resistance induced by hypoxic conditions in tumor [46]. With the assistance of nanosonosensitizers, the production of ROS was increased against cancer cells under ultrasound irradiation. Another MnO_2-based nanoparticle (HMIB NPs) was constructed to attain great phototherapeutic efficiency, by NIR light mediation, oxygen self-supply, and deep diffusion through tumor microenvironment response. The immunofluorescence analysis showed that HMIB NPs not only provide oxygen in the tumor microenvironment for lowering hypoxia but also decreased tumor microenvironment responsive size for the improvement of deep intratumoral diffusion [47].

The acidic microenvironment in cancer cells that arise due to increased glycolytic rate, has emerged as a multifaceted target for theranostic platforms [48]. Zhang et al. [49], developed a pH-sensitive system based on propylene glycol alginate sodium sulfate (PSS) that has anti-platelet aggregation ability. PSS@DC nanoparticles were designed in which chemotherapeutic drug doxorubicin (DOX) and celecoxib (CXB) compiled to form nanocores, hydrophobic in nature and PPS encapsulated these nanocores in conjunction with DOX via a benzoic-imine linker and treated in mice breast cancer model. The nanoparticles demonstrated distinct pH sensitivity and increased the efflux of DOX at the acidic pH mimicking the tumor microenvironment. Another study done by Chu et al. [50], showed biodegradable iron-doped ZIF-8 nanocrystals that can be degraded under an acidic tumor microenvironment, leading to the release of DOX (doxorubicin) and photothermal transforming agent, ICG (indocyanine green) at high speed. DOX and ICG demonstrated chemotherapeutic efficacy and NIR-triggered photothermal therapy. A fatality rate was 93.7% observed for cancer cells, which provides promising results in cancer treatments.

Alterations in metabolic pathways are one of the remarkable features of cancer. Liu et al. [51] developed an amorphous iron oxide nanoparticle (NP)-based RNAi system that modulated the glycolysis pathway by suppressing

MCT4 expression, induced acidosis in tumor cells, enhanced oxidative stress in tumor cells via the Fenton-like reaction, reducing tumor growth. Another research led by Yu et al. [52] showed inhibition of aerobic glycolysis by providing enough oxygen to facilitate anti-metastasis with the assistance of enzyme-powered nanomotor (NM-si).

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