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Research Article

Nanomaterials for cancer medication: from individual nanoparticles toward nanomachines and nanorobots

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Abstract

The nanomaterials for cancer medication are already reality providing a wide range of new tools and possibilities, from earlier diagnostics and improved imaging to better, more efficient, and more targeted anticancer therapies. The purpose of this critical review is to focus on the current use of clinically approved nanoparticles for cancer theranostic, nanovaccines and delivery platforms for gene therapy. These include inorganic, metal and polymer nanoparticles, nanocrystals and varieties of drug delivery nanosystems (micelles, liposomes, microcapsules and etc.). The recent progress in cancer nanomedicine enables to combine the benefits of individual nanoparticles with biomolecules into a multifunction nanomachines and even highly advanced nanorobots for targeted therapies. Nowadays clinical trials with advanced anticancer nanomachines provide potential for more accurately and effective identification and destruction of the cancer cells present in the human body.

Keywords

Drug delivery nanosystems, targeted nanotherapy, nanomachines, personalized nanomedicine

Introduction

The conventional approaches to combating cancer are limited to radiation, drug chemotherapy, and surgery, which are often not satisfactory treatments of patients with metastatic cancer. They simultaneously damage numerous healthy tissues and thus induce a lot of harmful side effects that accompanies these treatments. The nanoparticles have potential to be used as an alternative medication since they offer great benefits for targeted drug delivery directly to cancerous cells and neoplasms and enhance the therapeutic efficacy (Loukanov et al. 2018a). The nanomedicine advantages include enhanced solubility of hydrophobic drugs, prolonging circulation time, enhanced permeability and retention (EPR) effect in the leaky vasculature of tumor tissue, improved intracellular penetration, drug releases in controlled manner, minimizing nonspecific uptake, preventing undesirable off-target and side effects (Lou et al. 2019). The nanomaterials used for cancer medical application must meet the following general requirements. The nanoparticles should be long-circulating in the bloodstream (thus used in low doses), overcome the

several biological barriers involved in cancer, readily biodegradable or suitable for easy excretion from the patient (Dogra et al. 2019). Exceptions of this rule are some agents applied in cell cultures or used for microscopy of biopsy samples. If the nanoparticles are designed to degrade in body the process must occurred with minimal generation of toxic by-products, without aggregation or precipitation events in organs. A minimal risk has to exist during the controlled release of toxic compounds from encapsulated or embedded agents in the nanoparticles and thus reducing collateral toxicity to healthy cells and tissues. To date, a diverse variety of nanomaterials have been developed as nanocarrier platforms for tumor delivery applications, including inorganic (gold, iron oxide, silica), organic (polymer-base, lipid-based) and drug-conjugated nanoparticles (Fig. 1A). Remarkable progress in cancer nanomedicine have been made in the past decades and some nano-medications are already in clinical use (Fig. 1B).

Nanocrystals of drug molecules are approved for oral, local and intravenous administration because of their high drug-loading efficiency, great structural stability, long circulation time and steady dissolution (Miao et al. 2018). Numerous commercial hydrophobic or lipophilic drugs (e.g. paclitaxel, cyclosporine, busulfan, campto-

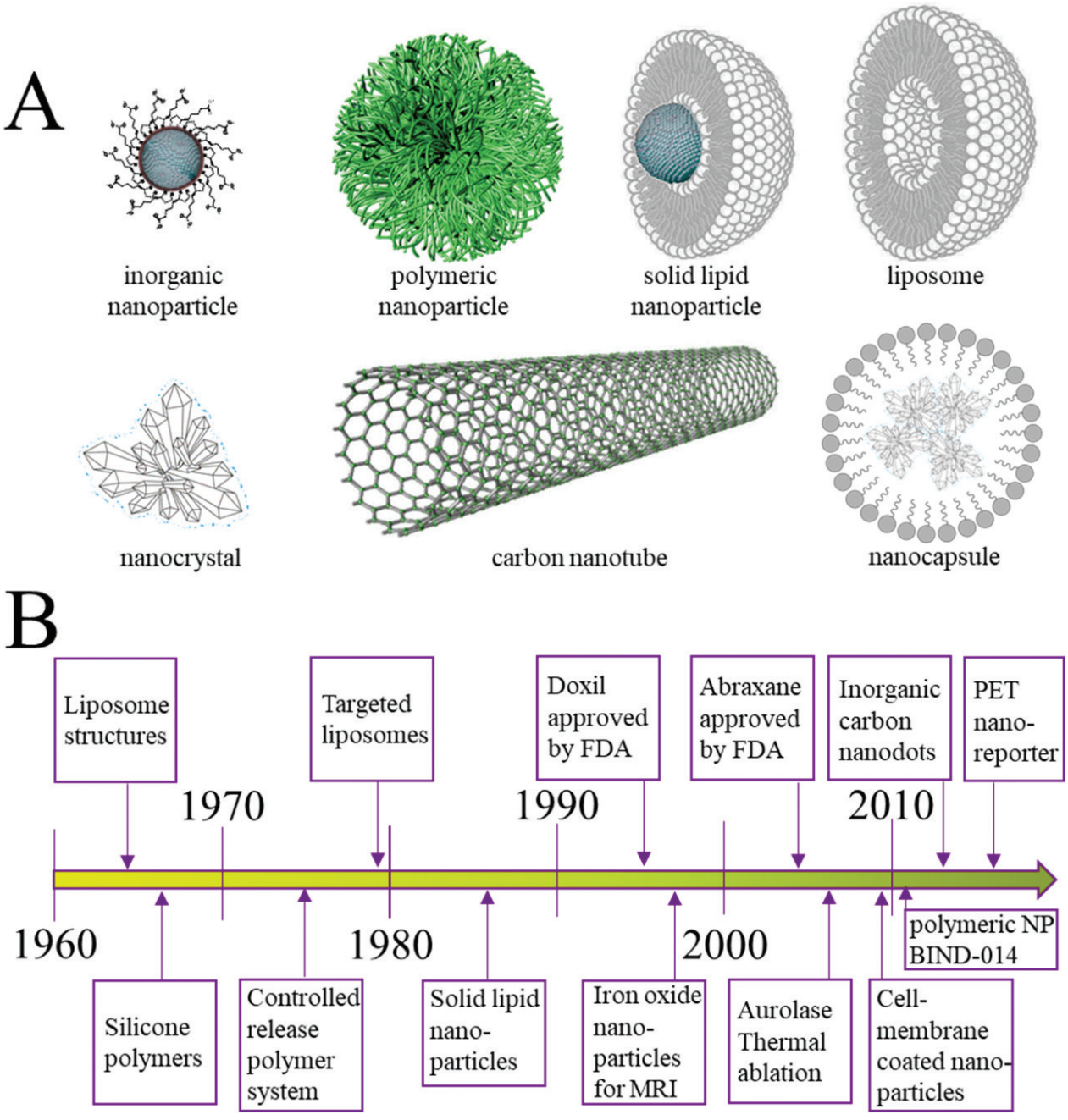

Figure 1. Overview of established nanoparticles for clinic use. (**A**) Various types nanoparticles used as nanocarrier platforms for cancer medication. (**B**) Timeline progress of the remarkable nano-medications in oncology.

thecin, etc.) stabilized by surfactants or polymeric steric substances might achieve almost 100 % drug-loading capacity (Lu et al. 2015). One of the key physicochemical properties of the anticancer nanocrystals is that their water solubility and dissolution rate are increasing at nano scale. Other advantages are their larger surface area, the ability for surface modification for improvement of duration time in blood circulation and systematic assessment of pharmacokinetics (Junghanns and Müller 2008).

Liposome systems for drugs encapsulating are used in some cancer therapies, because of the benefit to provide targeting of the anticancer substance, respectively in lower dose, which cause significantly reduced toxicity on the normal cells (Park 2002; Keck and Müller 2006; Suman et al. 2009). The liposomal treatments have better prolonged circulation as in the case of daunorubicin and pegylated liposomal doxorubicin, which is particularly useful for targeting extravasation from tumor vessels. Unilamellar (50~200 nm in size) or multilamellar (> 500 nm) structures (Fig. 2) can rapidly enter tumor sites from blood, but these are then kept in bloodstream by endothelial wall in healthy tissue. One of the greatest advantage is that the detection of drug-loaded liposomes can be avoided by the immune system (especially reticuloendothelial system). *The solid lipid nanoparticles* (SLN) possess numerous of advantageous as drug delivery systems to treat different types of tumors, while overcoming the biological barriers and resistance mechanisms in tumor microenvironment and cancer cells. SLN facilitate the cellular uptake of incorporated drugs (e.g. temozolomide, tamoxifen, resveratrol, erlotinib, etc.) through the modulation of passive, active, and cotransport mechanisms (Harris 1992; Gasco 1993; Barratt 2000; Allen et al. 2002; Baratt 2003; Cattel et al. 2003; Fang et al. 2006; Zucker et al. 2009; Mufamadi et al. 2011). As overall, SLN seem to be a promising strategy of oncologists in the fight against cancer diseases.

Lipid nanocapsules (LNC) with size distribution 25~110 nm have ability to encapsulate efficiently lipophilic drugs (etoposide, docetaxel, hydroxytamoxifen, paclitaxel, etc.), offering a pharmaceutical solution for their intravenous administration (Coon et al. 1991; Heurtault et al. 2002; Lamprecht et al. 2004; Sepre et al. 2004; Garcion et al. 2006; Khalid et al. 2006; Lamprecht and Benoit 2006; Lacoeuille et al. 2007; Anton et al. 2009; Huynh et al. 2009; Shegokar et al. 2011). They are all released according to a sustained pattern. LNC seem to inhibit the P-glycoprotein function, which is responsible for the pump of the drugs from the cell membrane. This effect might be harmonized with a stealth effect versus the complement system as well as mononuclear phagocyte system uptake. Thus, the defense system of cancer cell is blocked, it is not resistance anymore, and the active action of the anticancer agent is manifested. Currently, LNC are used in numerous therapeutic applications, including drug delivery, cancer diagnosis and therapy as well as gene and cell therapy.

Polymer nanoparticles provide sustained and time-dependent release of drugs (paclitaxel, gemcitabine, anthracycline, irinotecan, etc.), thereby controlled therapeutic approach (Tarcha 1990; Chiellini et al. 2001; Chaubal 2003; Tong and Cheng 2007; Masood 2016). When it is necessary to achieve long-term delivery (within weeks and months) the anticancer medication is incorporated into polymeric nanoparticles made by slowly biodegradable materials. They are usually long-term drug delivery sys-

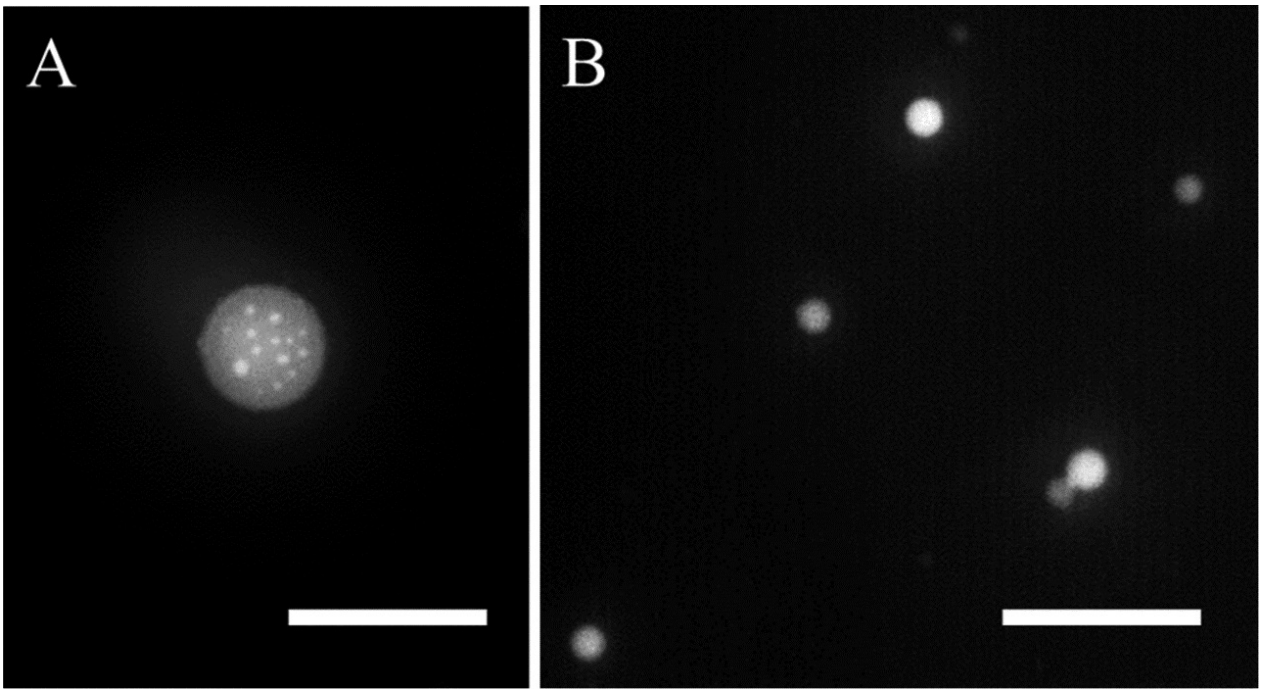

Figure 2. Multilamellar liposome (**A**) or vesicles as self-assembled nano-drug carriers (**B**) of photosensitizer drugs for photodynamic therapy application. Scale bars: 5 μm (**A, B**).

tems synthesized from suitable biocompatible materials for cancer therapy, as polyalkylcyanoacrylates, polyesters and polyorthoesters, polyphosphazenes, etc. The additional surface modifications with targeting molecule moieties (as folic acid or hyaluronic acid) is increasing their dose-efficacy due to the occurred specific ligand-receptor interactions. Some amphiphilic polymers with controllable properties cannot be detected by the biological defense mechanisms of the immune systems and are also suitable for clinical usage.

The presented above overview examined the various type nanomaterials for cancer medication. Below is discussed their clinical applications, which are already approved in the oncological practice.

Cancer nanotheranostics

The integration of diagnostic imaging and therapeutic functions in the same nanoparticles is highly beneficial for the personalized and precision nanomedicine. The gold nanoparticles (Au NPs) for cancer theranostics provide labeling, delivering, heating, sensing and detection (Loukanov et al. 2010; Loukanov and Gagov 2012). Au NPs have strong localized surface plasmon resonance that makes them suitable agents for imaging and enhanced photodynamic, photothermal and augmenting radiotherapy. Additional functionalization of Au NPs with antibody or aptamer (Fig. 3A, B), as well as organic ligands as folate, transferrin, dithiol-polyethylene glycol and doxorubicin enable their theranostic application for delivering chemotherapy and active tumor-targeting due to biorecognition reaction with the overexpressed receptors on the cancer cells (e.g. aurimune, auroshell for AuroLase therapy of refractory head and neck cancer).

The prostate cancer cells show enhanced inhibition if are simultaneously treated with glucose-bound gold nanoparticles and irradiation (Farokhzad et al. 2004). The nanoparticles effectively detect metastases of prostate and other cancers in lymph nodes (Harisinghani et al. 2003; Johannsen et al. 2005a, b; Johannsen et al. 2007). The limited expressed folic acid receptors in health cells

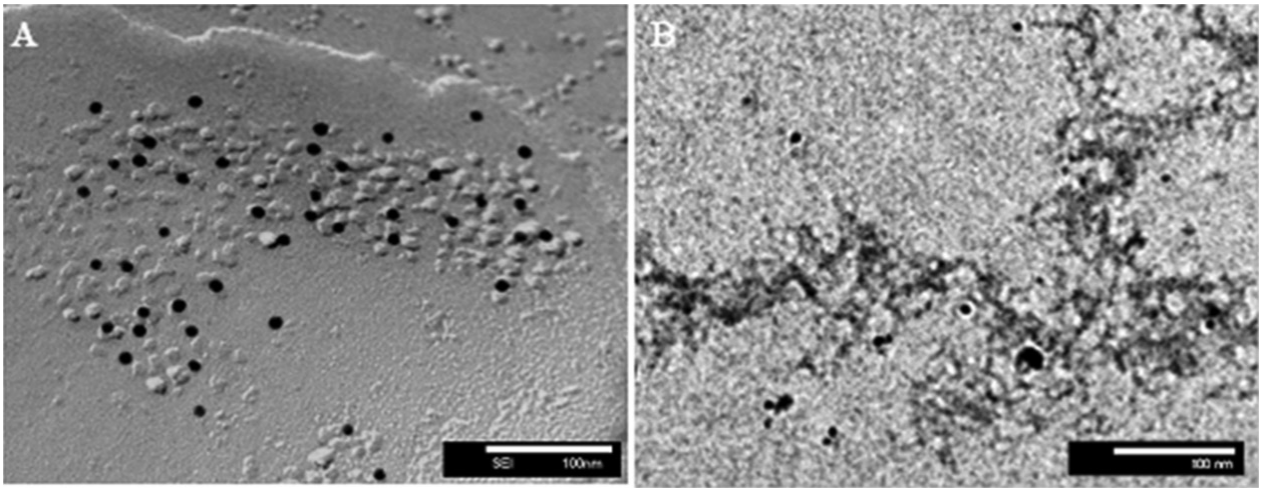

Figure 3. Electron microscopic images of gold nanoparticles with 5~10 nm diameter coated with (**A**) antibody IgG (Miao et al. 2018) and with (**B**) aptamer DNA (Loukanov et al. 2016a, b). Scale bar: 100 nm (**A, B**).

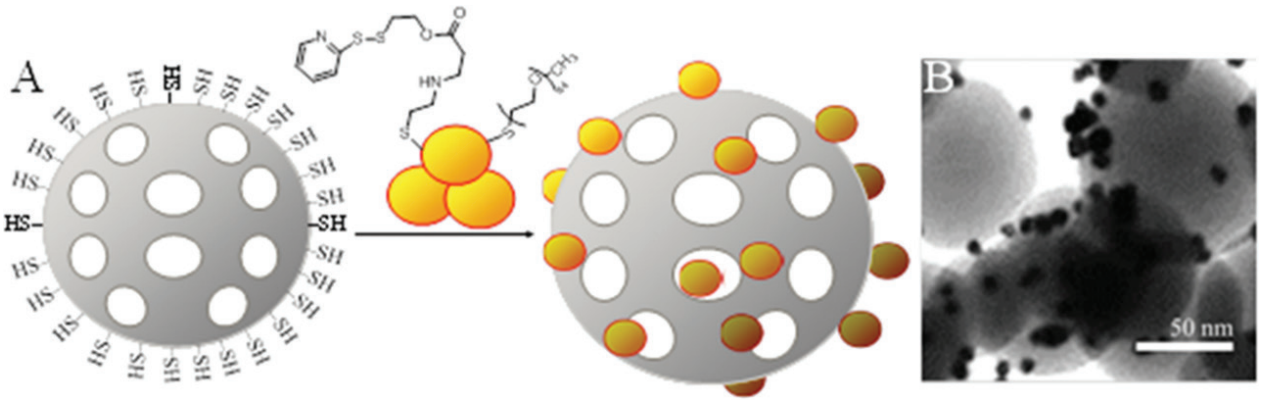

Figure 4. (**A**) Schematic illustration on the fabrication and (**B**) electron microscopic image of doxorubicin@gold/mesoporous silica nanoparticles. The nanoparticles are prepared in dual surfactant system using classic fast self-assembling method containing both cationic and non-ionic surfactants. Scale bar: 50 nm.

are often abundant in cancer cells. Attaching folic acid to various biodegradable nanoparticles is a successful strategy for their targeting. For example, folic acid-containing gold nanoparticles can recognize cancer cells for guided drug application and photothermal therapy (Bhattacharya et al. 2007).

The gold/mesoporous silica hybrid nanoparticles express the advantages of both mesoporous silica nanoparticle and conventional gold nanoparticles, namely great drug loading capacity, perfect photothermal converting ability and controllable drug release (Cheng et al. 2016). For example, the doxorubicin@gold/mesoporous silica nanoparticles (Fig. 4A ,B) when irradiated with NIR exhibit a synergetic anticancer effect of chemotherapy and photothermal therapy of hepatic, colorectal and breast cancer. In contrast to gold nanorod and other heat generating gold nanoparticles, the gold/mesoporous silica hybrid nanoparticles are photothermal stable and can be repetitive activated through near-infrared (NIR) irradiation. They can be conjugated with various ligands as folic acid, mannose, transferrin or monoclonal antibody to achieve active targeting therapy and nano-enabled immunotherapy.

The magnetic (iron oxide, Fe_2O_3 or Fe_3O_4) nanoparticles are used in cancer theranostics alone or loaded into polymer or liposomes as drug delivery platforms. They have prominent transverse relaxation time and are used successful as contrast materials for magnetic resonance imaging (MRI) or as hyperthermia agent, drug and gene delivery carriers (feridex, endorem, gastomark, sinerem). Iron oxide nanoparticles might produce reactive oxygen species by Fenton reaction and thus disturb the cellular homeostasis, alter the intracellular signaling and pathways of cancer functioning. The liposomes and micelles platforms can also encapsulate fluorescent dyes for optical detection or radionuclides for positron emission tomography (PET) imaging.

The nanoparticles of polyethylene glycol (PEG), poly($_{D,L}$-lactic acid), poly($_{D,L}$-glycolic acid) and poly(ε-caprolactone) have already been approved as polymer-based platforms for clinical usage (e.g. oncaspar, renegal, neulasta, etc.). In general, the polymer nanoparticles offers stabilization and biocompatibility, contain a therapeutic agents (siRNA or small-molecule drug) as well as imaging agents (radionuclide, photosensitizer or MRI contrast agent as gadolinium or superparamagnetic iron oxide). Chlorin e6 or porphyrins are commonly used as photosensitizer agents in the laser therapy. The nanoparticles might be conjugated with targeting ligands to enhance the delivery in tumor site (Namiki et al. 2004; Gao et al. 2006). Biodegradable polymeric nanoparticles that readily decompose in the body are co-administered with paclitaxel and ceramide as strong anticancer drugs that targeted drug resistant ovarian cancers. Microbubbles and nanobubbles resulting from mixture of sonicated doxorubicin-loaded micelles are commonly used as contrast agents in ultrasound for imaging of inflammation, angiogenesis and tumors. They can be accumulated in the breast cancer and thus are causing the tumor regression.

Cancer nanovaccines

The nanovaccines are designed to deliver antigens and/or adjuvants to tailor immune responses by specific targeting of immune cells (mostly dendritic cells or T cells). The cancer nanovaccination involves priming of the immune system with aim to induce a T-cell response against tumor-associated antigens. Nanoparticles-based cancer vaccines are already used to treat a wide array of cancers as melanoma (liposomes, carbon nanotubes), breast cancer (polymeric PEG nanoparticles functionalized with poly-lactic-co-glycolic acid or PLGA), prostate cancer (virus-like particles), etc. The polymeric nanoparticles are usually fabricated from biodegradable organics as PLGA, PEG, polycaprolactone, chitosan and dextran (Wen et al. 2018). PLGA nanoparticles demonstrate antitumor effect by CD40-targeting in dendritic cells when are codelivered with ovalbumin (OVA) antigen and poly(inosinic-polycytidylic acid) adjuvants. The vaccination showed higher $CD8^+$ T-cell proliferation and strong immunological response. Subcutaneous vaccinations of HER-2 derived peptide (p369–377) incorporated into PGLA nanoparticles with adjuvant sargramostim is successfully used in patients with stage III or IV HER-2 expressing cancer. Dextran nanoparticles (size about 200 nm) are able to deliver and release OVA antigen and stimulate enhanced immunological T-cell activation. Polymeric hybrid micelles (between PEG-phosphorethanolamine and polyethylenimine-stearic acid) enhance the immunological potency of cancer vaccines. They can coload melanoma antigen peptide Trp2 and CpG ODN with aim to improve the targeting efficiency in immune cells of popliteal draining lymph nodes and stronger cytotoxic T-lymphocytes responses. The nanoparticles composition or surface is often modified, for example conjugation with immunological adjuvant monophosphoryl lipid A or other antigen, to enhance delivery, cellular uptake and therapeutic efficiency. Peptide-dendrimer conjugates (from human papilomavirus E7 and E6) are proved as vaccine adjuvants for cervical cancer.

The vaccine liposomes are used as delivery systems for siRNA, DNA and hydrophilic or lipophilic antigens. The positively charged (cationic) liposomes induce strong immune response and are more efficiently taken by APCs-like macrophages and dendritic cells. For example, cationic DNA vaccine liposomes stimulate the long-lasting immune response for melanoma. OVA-loaded galactosylated liposomes demonstrated cytotoxic T lymphocytes (CTL) responses and remarkable antibody production against tumor growth (Jiang et al. 2015). The liposomes can be alternatives of polymeric nanoparticles in respect to encapsulation efficiency, limited solubility, phospholipid degradation, drug leakage and fusion in the body.

The inorganic particles (gold, quantum dots, aluminium-based nanoparticles, iron oxide, etc.) are also viable delivery systems for cancer vaccines. The peptide-conjugated gold nanoparticles (Fig. 5A, B) show more effective immune responses than free peptide. The commercial drug Sphere40-Es (based on Au NPs) induce strong im-

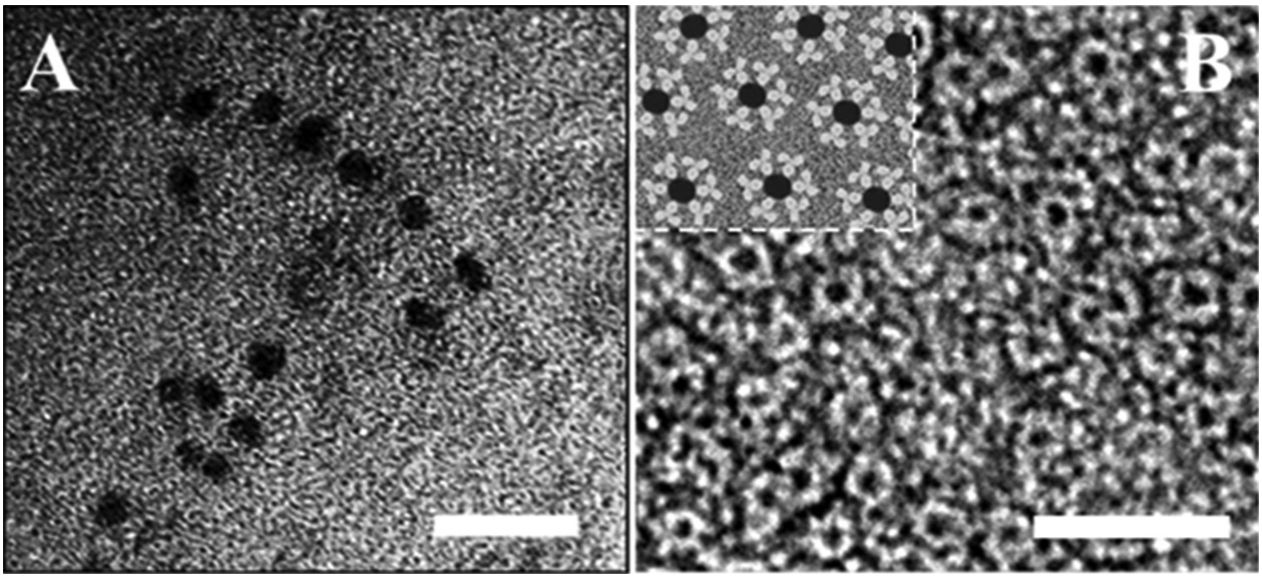

Figure 5. Transmission electron micrographs of nanoparticles chemically conjugated to peptides for cancer nanovaccination: (**A**) positive and (**B**) negative staining with uranyl acetate. Schematic illustration of the stained nanoparticles. Scale bar: 20 nm (**A**), 50 nm (**B**).

munological response and high level of cytokines (IL-6 and tumor necrosis factor-α), as well as granulocyte macrophage colony-stimulating factor.

The magnetic nanoparticles (iron oxide) are also desirable potential vaccine systems for cancer therapy. There is significant differences in the immune response and respective tumor inhibition in case of OVA formulated with iron oxide, in comparison with only soluble OVA alone. The iron oxide nanoparticles greatly promote the activation of immune cells and cytokine production. Combination therapy with iron oxide cause a higher accumulation in lymph node dendritic cells and increase the immune response.

Biomimetic nanoparticles as high-density lipoprotein (HDL) can be uptaken without causing immunogenicity and toxicity. HDL-like nanoparticles act as drug-delivery systems and can incorporate inorganic nanoparticles, such as gold, iron oxide and quantum dots in design enables long-term circulation in the blood system with potential ability to vaccines or/and antigens. Such nanoparticles, which consist the fusion peptide α-Ap efficiently target dendritic cells through scavenger receptor class B1 (SR-B1)-mediated pathway.

The presented nanoparticles can be tuned through modulating of their size, shape, composition and surface properties to enhance the immune response against cancer. In clinical usage the therapeutic effect is achieved by enhanced immune response activation due to the nanoparticle-mediated cancer vaccines, which provide insight for prognosis and serve as a proper reference for the future nanoparticle research development.

Nano-platforms for tumor gene therapy

Synthetic nanoparticles (polymers and lipids) have been developed as platforms for nucleic acid delivery in the gene therapy of tumors and alternatives to the toxic and potentially oncogenes viral vectors. Their design might avoid the stimulation of immune system. The simplest drug delivery platforms are formed as polyplexes, i.e. electrostatic complexation between cationic polymers (e.g. mix of polythyleneimine, PEI and PEG) and plasmid DNA. The stealth liposomes are providing stable and safe alternatives too for effective delivery of nucleic acids, including siRNA and miRNA. DNA-liposomes, known as lipoplexes can be easily modified with targeting ligands with aim to enhance the site-specific delivery function. Cationic lipids and polymers can be combined with either DNA or RNA to form a stable nanoparticles, which are capable to gene transfer into the target cells. Such commercial drug (named JVRS-100) is used for anti-tumor responses generated by the immune system, because it can enters the macrophages and dendritic cells and activates Toll receptors (Liu et al. 2016). It induces strong T lymphocyte response too, which has been evaluated in Phase 1 trial for treatment of leukemia. Another approach to deliver DNA vaccine is using polymeric of PLGA micro/nanospheres (as described in the previous section) for enhancing humoral and cellular immune response. The loading capacity and activity of these nanospheres can be improved by additional incorporation of PEI into PLGA.

The hyaluronic acid (HA) can form self-assembled organic nanoparticles for specifically delivery of siRNA (or other chemotherapeutic drugs) into malignant tumors. HA has negative charge which does not favor the complex formation with siRNA and due to this reason most nanocarriers include other cationic components (e.g. PEI), which influence the whole system's gene silencing efficiency. The overexpressed receptors in cancerous cells for hyaluronic acid are known as CD44. Another more effective strategy to target CD44 receptors is the association of siRNA with both HA polyanion and chitosan polycation. Such delivery system is decisive for the successful application of siRNA or

plasmid DNA-based death-induced gene therapy. Various challenges are still existing in the design of nano-platforms for perfect transfection vector, however the nanoparticles have been proved to be a suitable candidate.

Current development of anticancer nanomachines and nanorobots

Although numerous nanotherapies have received clinical approval, the most promising nanotechnology application for cancer medication still lie ahead. During the last decade the nanoparticles with anticancer activity and specificity were evolving in more complicate nanostructures, which mimic bioprocesses in the nature. Individual nanoparticles perform defined functions that may find application for some medical purposes, for example gold nanoparticles are utilized for treatment of the cancer of pancreas. However, a synergistic effect might be achieved if the benefits of various types' nanoparticles are combined as in the case of hybrid gold/mesoporous nanoparticles, which have higher drug loading capacity and better photothermal converting ability then the single nanoparticles. However, the human organism possesses defense mechanisms, biological barriers and multiple strategies to protect against foreign xenobiotics or biological agents as bacteria, viruses and even nanoparticles. This challenge can be overcome by design of complicated nanomachines, which are capable of independently performing numerous tasks. The engineering and fabrication of nanomachines is innovative and promising field in the modern nanomedicine. They are designed to store, deliver, and release payload in response to intentionally caused stimuli (Loukanov et al. 2019). The individual components (various nanoparticles, nucleic acids, etc.) in these tiny device are operating at nanoscale level as shown on Fig. 6. The electron microscopic image of a light-powered DNA nanomachine (Fig. 6A) show its internal structure, i.e. two nanoparticles (nanoconverters) linked with DNA aptamer. The aptamer are used for biorecognition reaction instead of antibody. This nanomachine reacts specifically with the overexpressed receptors on the cancer cell membrane and can enter in its cytoplasm through endocytosis uptake. Under illumination with near infrared irradiation the inorganic nanoparticles (iron oxide) induces apoptosis and programmed cell death (Fig. 6B). The reason is because the semiconductive iron oxide nanoparticles (hematite, Fe_2O_3) are conjugated with highly-fluorescent and non-toxic carbon nanodots (C-dots) (Loukanov et al. 2018a). C-dots are nitrogen-doped, i.e. they have high quantum yield and cooperate in synchronized photosensitized mechanism with the semiconductive iron oxide nanoparticles. The nanocomposite (C-dots@Fe_2O_3) is known as a nanoconverter (Loukanov et al. 2018b).

Another example for design of light-powered nanomachine is the so called "nanoimpeller". It is nanomechanical system that contains nano-sized mesoporous silica as a container to trap and release cargo molecules. The design allows of the nanoimpeller to be taken up by cancer cells in dark condition. The nanoimpeller releases its drug content from the tiny silica pores into the cancer cell interior when the specimen is irradiated (Lu et al. 2008). The nanomachine operation is regulated by variation of externally applied irradiation intensity, contact and excitation time. They could automate the tasks like drug delivery, identifying and destroying cancer cells more accurately, effective and etc.

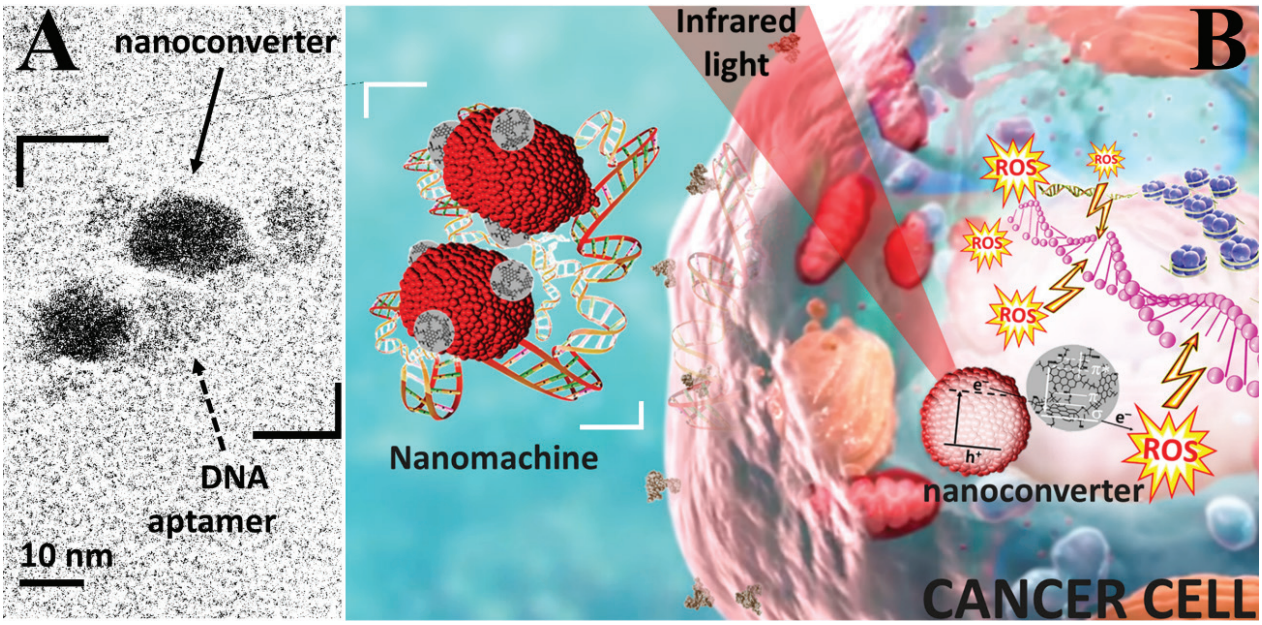

Figure 6. Light-powered nanomachine for inhibition of cancer cells. (**A**) TEM image and (**B**) schematic model of the nanomachine and principle of operation of the NIR-activated nanoconverter. The cancer cells are inhibited only in photodynamic regime of treatment. Scale bar: 10 nm.

In nanoscale design of nanorobots requires autonomous power supply, biosensors, nanomotors, etc. for overcoming of the low Reynolds number viscous drag and Brownian motion (Manjunath and Kishore 2014). Their substructures include payload, swimming tail and other nanoscale components as supramolecular structures, in which any self-assembled atoms may act as molecular mechanical parts, bearings, gears etc. The molecular nanomotor might be gas-powered pump with molecular weight of 88, 190 and 813 Da and it converts the gas pressure into rotary power. The medical nanorobots require also a molecular computing for synchronized operation of their components and properly monitor of the performance. The injected in the bloodstream nanorobots travel to the cancerous tumor and embed themselves within it delivering cell-destroying agents only to the cancer cells. This precise targeting allows the usage of lower doses of drugs and ensures that the medicine is delivered only to the cells that need to be destroyed. Another research direction for development of nanorobotics is the creation of artificial biological systems as therapeutic nanomachines – both engineered viruses and bacteria. These so called microbiological biorobots are able to implement the dozen or so important functions required for cancer medication. The engineered viruses are used in experimental genetic therapies as devices for transportation of anticancer drugs, salts, nucleic acids, other molecules, repairing damage and DNA replicating (Collins et al. 2001; Kodelka et al. 2015; Drexler and Merkle 2019). The oncolytic viruses that are highly specific against cancer cells open new medical approaches in antitumor therapies (Kaufman et al. 2015). The engineered bacteria are able to avoid potential immune response, to manufacture cellular biomolecules and to produce anticancer proteins that can shrink tumors. The nanorobotics bacteria is capable to navigate through the bloodstream and to target the tumor cells in the body (Felfoul et al. 2016).

Conclusion and future directions

The medical nanotechnology opens new opportunities to improve significantly the cancer therapy by novel generation nanomaterials and nanomachines. The rapid progress in the development of nanomachine and nanorobotics technology doubtless will create powerful tools for effective treatment of various malignant tumors. The nanorobots used in medicine are predicted to provide a wealth of promise. It is possible in the near further, these tiny nanodevices to contribute the progress of advanced nano-medication for personalized medical care, and for establishment a new era in the screening, treatment, and prevention of cancer diseases.

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