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Cancer Targeting using Nanoparticles

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Introduction

A tumor is a combination of many events ranging from abnormal cell formation, clonal proliferation, angiogenesis, immune response, and metastasis [1]. By tumor growth, the tumor microenvironment would be altered (Figure 1). Tumor cells became able to resist antitumor drugs, to fight tumor cell apoptosis, to gain reproducible tumor immortality, to trigger synthesis of neo-vessels, to invade and metastasize to other tissues/organs. Progressing tumors sluggishly infiltrate via lymphatic channels and localize tumor cells inside lymph nodes. In the same way, tumor cells invade blood vasculatures. Therefore, tumor cells travel via blood stream to other different tissues/organs e.g. liver and lungs in a phenomenon named metastasis. Since tumor undergoes many complicated heterotypic interactions like stroma's effect on growing, advancement, and metastasis, it has the ability to show important events like angiogenesis, inflammation, invasion, and Cancer Stem Cells (CSCs) maintenance [2,3].

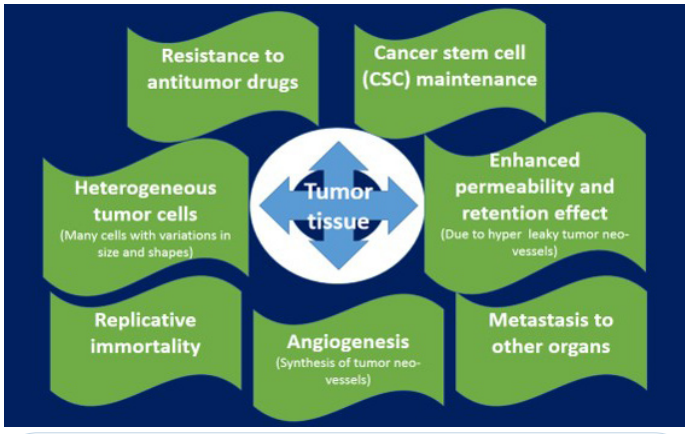


Figure 1: Tumor microenvironment.

The tumor microenvironment (seen in Figure 1) directed researchers to improve tumor therapeutic strategies and encouraged application of nanotechnology. Tumor neo-vessels are created in speed this make them immature, twisted, irregular, and more permeable with abnormal dynamics. These distinctive criteria make them distinguishable from normal blood vessels. Therefore, it is worthy for current and future cancer treatments to make use of these criteria in drug direction for tumor suppressing [4].

Cancerous expansion necessitates errors in cellular defense mechanisms. These defense mechanisms are controlled by cell cycle checkpoints that act to inhibit cells that have DNA damage from entering into the cell cycle before they were subjected to DNA repair (blocked at G1) and cells division (blocked at G2) [5]. The tumor suppressor proteins p53 and p21 have critical contributions in protecting cells. They stimulate cells blocking at G1. The p53 can interrupt the cell cycle at G1 and continue to repair DNA damage; if DNA repair was unsuccessful, p53 can induce apoptosis. A family of cysteine-aspartate proteases (named caspases) mediate cellular apoptosis initiation and execution. Caspases are activated by intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated) signaling pathways [6,7].

Disadvantages of standard methods for cancer treatment and what cancer targeting is suggested to do?

The present trend in cancer treatments comprises traditional triplet of surgery, radiation, and chemotherapy in addition to biological and targeted therapy in particular cancers. Surgery lead to loss of organ and function. Radiation is associated with many side complications. Chemotherapy is correlated with chemotherapeutics of high cost, and serious side effects on healthy tissues with the possibility for development of second malignancies and drug resistance. Sometimes, even using combination of both radiotherapy and chemotherapy remain unsuccessful. Lately, the great progress in human genomics and biotechnology allowed more understanding about pathogenesis of cancer and detection of new cancer markers as well as developing novel promising cancer therapies [4,8,9].

Cancer targeting is how anticancer drugs could deposited in a high-concentration inside the tumor or very near to the tumor-bearing site in the body. It is suggested to delay the need for surgery, reduce the need for radiotherapy and to reduce radiation-induced adverse effects via reduction of the needed radiation dose and duration of exposure, and to target the chemotherapeutic drug(s) more accurately with minimal adverse effects (Figure 2). Therefore, the overall goal of cancer targeting is to treat cancer more effectively with minimal side effects.

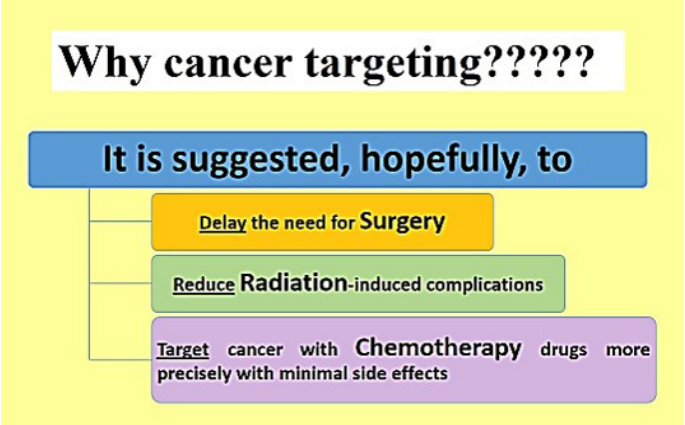


Figure 2: What cancer targeting is suggested to do?.

Nanotechnology

According to National Nanotechnology Initiative (https://www.nano.gov) nanotechnology is defined as "the application science, engineering, and technology conducted at the nanoscale using materials of size ranging from 1 to 100 nm". Medical nanotechnology era is a serious challenge. Latest few decades have seen great incredible advances and their application in oncology. Worldwide, several animal and human investigations have been conducted to search for the benefits of nanomedicine in cancer. Nanotechnology is hopeful to generate a big revolution in the field of cancer treatment through development of novel medications [4].

What are nanoparticles?

Nanoparticles (one to 100 nm in size) have a wide range of several shapes and structures. They involve spherical, tubular, irregular, fused, aggregated, agglomerated forms of organic, inorganic, crystalline or amorphous nanomaterials [10]. Nanoparticles are able to undergo interaction in a unique way with cellular molecules and could help in treating cancer. When drug particles are encapsulated in a nanocarrier, the drug(s) solubility and stability are increased. This opens the door to re-consider the therapeutic potency of anticancer drugs with poor pharmacokinetics [11].

Promise uses of nanoparticles in the field of cancer management

Recently, modern nanotechnology displays many promise applications in the field of cancer management. Some of the major possible promise uses are [4,12]:

1. More precise surgical elimination of tumor: Injection (topical/parenteral) of nanomaterials during surgical procedure help surgeons to eliminate tumor more precisely with useful surgical border.
2. Early detection of cancer: By nanoparticles attachment to cancer marker targeted antibodies cancer could be detected earlier at early stages.
3. Exact cancer imaging: Using nanoparticles with magnetic properties for imaging offers precise lesions mapping with higher resolution than using routine imaging materials.
4. Increasing radiation lethality with minimizing side effects: Injection (intra-tumor) of nanomaterials may trigger short-range electrons in the tumor tissue; make radiation more lethal with more protection to normal cells.
5. Minimizing anticancer drugs side effects: Nanocarriers loaded with lethal/cytotoxic anticancer agents can deliver these agents in or very near cancer tissue, avoid immune defense, and provide more protection to normal cells.
6. Optimizing the efficiency of the currently used chemotherapeutic drugs: Encapsulation of the currently used anticancer drugs in nanocarriers offers more localized delivery resulting in more efficiency in cancer cells killing.
7. Improving local cancer damaging: By injecting particular nanoparticles, like gold nanoparticles for example, in the tumor cells and stimulation of them to generate heat, the emitted heat leads to killing of cancer cells locally.

Clinically useful tumor markers for implication in cancer nanotechnology

There are many tumor markers for various types of cancers are clinically useful for implication in cancer nanotechnology. Examples: Thyroglobulin (Tg) for thyroid cancer, Carcino-embryonic Antigen (CEA) for colorectal cancer, Prostate Specific Antigen (PSA) for prostate cancer, Lactate Dehydrogenase (LDH) for bulky lymphoma, cancer antigen 19.9 (CA19.9) for pancreatic cancer, cancer antigen 125 (CA125) for ovarian cancer, Alpha-fetoprotein (AFP) for Hepatocellular Carcinoma (HCC), etc. [4].

Nanocarriers

Nanocarrier-based platforms are devoted systems for transmission and efficient delivery of effective chemotherapeutic drugs consisting of colloidal nanoparticles with usually size of < 500 nm into the diseased cells. Commonly, they have a great surface area to volume ratio. Their employment in drug delivery applications is supposed to improve the therapeutic outcomes; achieve effective disease treatment along with less adverse effects [13].

Types of nanocarriers

Application of some nanocarriers in treating many diseases and conditions including cancer have been approved. In spite of this, many others are still under clinical trials. In general, nanocarriers in practice include vesicles, liposomes, micelles, polymers, carbon nanotubes, etc. [13]. Nanocarriers can be divided into two broad groups' organic and inorganic nanocarriers as illustrated in Figure 3. As stated by Lombardo et al. [13] ''physiochemical characteristics of nanocarriers could be adjusted through changing:

(1) Their compositions: Organic, inorganic, or hybrid,

(2) Their dimensions: Small or large sizes,

(3) Their shapes: Sphere, rod, hyper branched, multilamellar, or multilayered structures, and

(4) Their surface properties: Functional groups, surface charge, PEGylation, coating, or substitution with targeting moieties.''

Common Organic nanocarriers	Carbon nanotube	Synthesized
	Solid lipid nanoparticle	Self-assembly have both hydrophilic and hydrophobic parts
	Vesicles (phospholipids bilayer)	Self-assembly have both hydrophilic and hydrophobic parts
	Dendrimer (Branched polymers e.g. Poly(amidoamine)	Synthesized
	Multilamelar liposome (Vesicles having at least one lipid bilayer)	Self-assembly have both hydrophilic and hydrophobic parts
	Micelles (closed lipid monolayers)	Self-assembly have both hydrophilic and hydrophobic parts
Common Inorganic nanocarriers	Gold nanoparticles (Au)	Hard nanoparticles
	Magnetite (Fe_3O_4)	Hard nanoparticles
	Quantum dot (Cd/Zn-Selenides)	Hard nanoparticles
	Mesoporous silica NPs	Hard nanoparticles

Figure 3: Examples of the most common employed organic and inorganic nanocarriers for application in drug delivery.

Advantages of nanocarriers utilization

Nanocarriers utilization is advantageous (Figure 4). It improves therapeutic outcomes and contributes to clinical success. It affects many effective factors. For example, it can increase the presently used drugs efficiency via improving their pharmacokinetics, prolong drug existence time in blood circulation, extend cellular uptake time, and prolong drug half-life time [14].

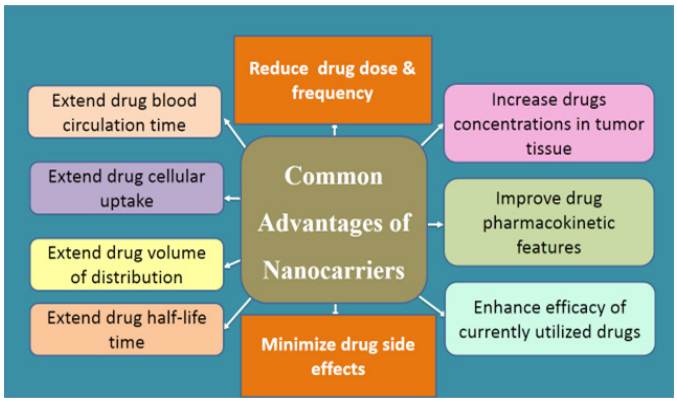


Figure 4: Common advantages of nanocarriers.

Synthetic and natural polymeric nanocarriers

Currently, various synthetic polymeric nanocarriers for example Polylactic Acid (PLA), Polyglycolic Acid (PGA), Polyethylene Glycol (PEG), and their copolymers have been created for employment as delivery systems for chemotherapeutic drugs. Also, many natural polymers like chitosan, dextran, heparin, hyaluronic acid, and gelatin have been used for the same purpose (Figure 5A). They can enhance the anticancer efficiency of chemotherapeutic drugs in a significant way [15] and successively increase patient satisfaction [16].

Commonly employed synthetic polymeric nanocarriers and why?

There are many biodegradable synthetic polymeric nanocarriers and there are many of them are commonly used. Between the commonly used group, the greatest recommended and utilized ones in drug delivery purposes are the saturated poly (α-hydroxy esters). These saturated biopolymers include PLA, PGA, and Poly(lactic-co-glycolic acid) (PLGA) copolymers. They have in vivo admirable criteria. They are excellent safe, and good biocompatible. They also have tunable biodegradation rate, and low immunogenicity and toxicity in the body. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved their use for drug delivery in man. By hydrolysis, polymeric nancarrier PLGA can be biodegraded (Figure 5B) to produce its monomeric constituents lactic and glycolic acids. By their turn, lactic and glycolic acids are continued to be metabolized via usual pathways like Krebs cycle [13].

Physicochemical and mechanical properties of PLA and PLGA can be adapted through copolymerization and functionalization. To produce an amphiphilic block copolymer from both PLA and PLGA (that have hydrophobic surface), PEG is the most commonly used. The hydrophobic PLGA core of poly(ethylene glycol)-poly(lactic-co-glycolic acid) (PEG-b-PLGA) diblock copolymer micelles can encapsulate several therapeutic agents and the hydrophilic PEG outer surface inhibits the adsorption of proteins and phagocytes resulting in extended blood circulation time [13,17]. Self-assembly character of PEG-PLGA diblock and PEG-PLGA-PEG triblock copolymers make them able to encapsulate hydrophilic/hydrophobic drug. These PLA and PLGA-based nanocarriers were tried on animals in treatment of several disorders such as diabetes, cancer, and cardiac disorder. They showed promise potential [13].

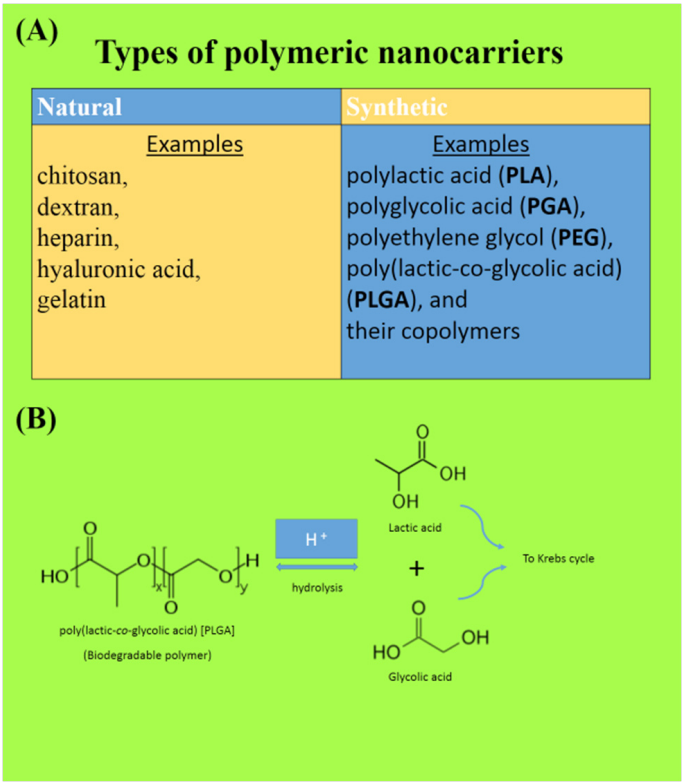


Figure 5: Types of polymeric nanocarriers (A) and Biodegradability of the PLGA polymer (B). Source for structures: https://en.wikipedia.org.

Cancer targeting using nanoparticles

Cancer targeting aims to concentrate anticancer drugs inside or near cancer-tissue. Nanoparticles can enhance permeability and retention of anticancer drugs at the tumor tissue (Figure 6). Nanoparticles of sizes 5 to < 200 nm are not able to go out the intravascular space in normal tissues, while they are capable to readily exit hyper-leaky tumor-neovessels. This ensures targeting tumor tissues and limits drug delivery to healthy tissues thus minimizes side effects. According to some studies, nanoparticles might be capable to influence the cancer stem cells (CSCs). This advance may really make future revolution in achieving cancer complete elimination, lowering relapse, and refine survival [4,15,18].

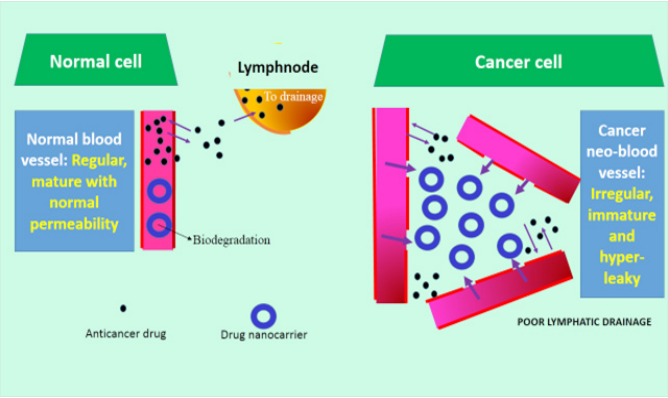


Figure 6: Tumor Enhanced Permeability and Retention (EPR) effect.

Suggested mechanism of action

As explained above, nanocarriers loaded with medications can target the tumor cells selectively and may possibly stimulate their programmed death (apoptosis) therein. A group of cysteine-aspartate proteases (named caspases) mediates initiating or ending of apoptosis process. Caspases are activated by two signaling pathways; intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated). The nanoparticles induce the two-apoptotic intrinsic pathways and one extrinsic. The nanoparticles produce too much Reactive Oxygen Species (ROS), leading to lipids, protein and DNA preoxidation. The resulting oxidative stress at that moment prompts mitochondrial- or Endoplasmic Reticulum (ER)-induced apoptotic pathways. In the intrinsic mitochondrial pathway, DNA oxidative-damage motivates p53 and lead to a rise in Bax levels. Disrupted mitochondrial membrane causes the cytochrome c and Apoptosis Inducing Factor (AIF) release to the cytoplasm. Together cytochrome c with caspase 9 and other factors form apoptosome and activated caspase 3 initiate cell apoptosis. Then, AIF is translocated to the nucleus and prompts DNA cracking. In the intrinsic ER pathway, accumulation of the stretched protein persuades caspase 12 activation. p38 MAPK, Chop and JNK are also included in this pathway. Regarding extrinsic pathway, Fas association with FasL employees FADD and pro-caspase8 creating Death Inducing Signaling Complex (DISC) and activated caspase 8. Caspase 8 by its turn activates caspase 3/or cuts Bid to truncated Bid (tBid). tBid move to mitochondria and encourages cytochrome c release [10].

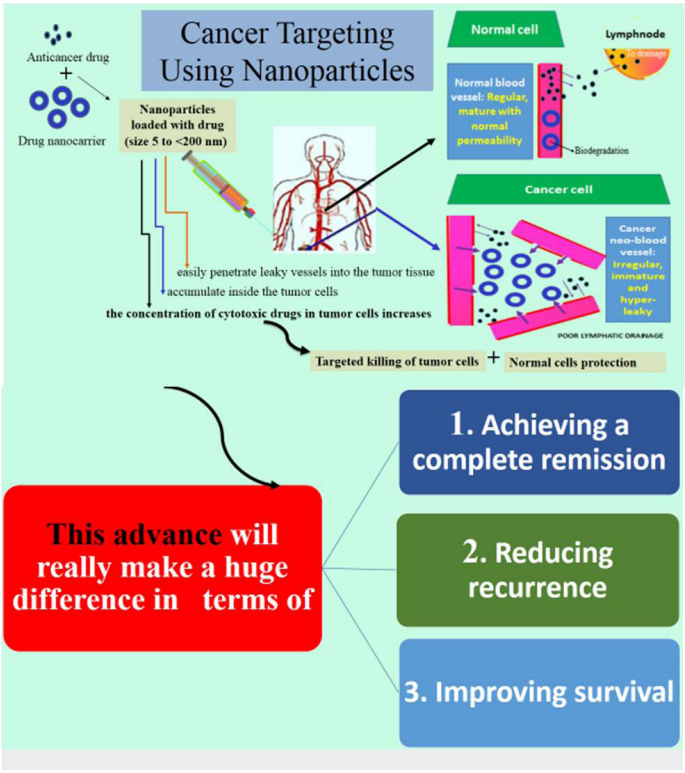
Cancer targeting using nanoparticles in literature

According to Mu et al. report (2018), there is an exponential increase in the number of published scientific studies that deal with drug delivery using nanoparticles. It ranged from < 300/year in 1999 to > 10,000/year in 2016. In the year 2016, the published in vivo study was approximately 40% from the total. Regarding clinical trial studies, the number was approximately 150/year for the last two decades. Among all diseases, cancer targeting published studies is in the top represented about 88% and about 66% from clinical trials. Mostly used nanomaterials in the published articles is polymeric nanoparticles (about 29% from publications and about 1.3% from clinical trials) followed by liposomes (about 16% from publications and about 72% from clinical trials) [19].

Where are we and to where we are going?

Nanotechnology is a big growing field still needs big continued efforts to be explored. It could possibly alter our knowledge about cancer treatment. Though, we still do not know (1) Consequences on the long-run, (2) The exact fate of all nanoparticle molecules in the human body, (3) How they will be excreted from body, and (4) Their accurate safety profile. Regardless, researchers' great efforts in nanotechnology field for more than a decade, only a little number of nanotechnology-based drugs are clinically applied, most of them use PEG micelle technology to cancel immune reactions [4].

As mentioned above, loaded nanoparticles with drug molecules as illustrated in (Scheme 1 below) can selectively target cancer cells and induce cancer cells apoptosis [10,15]. Selective targeting can considerably improve the anticancer potency of currently used/new chemotherapeutic medications and make patient more satisfied. Nanoparticles may have the chance and the ability to attack the CSCs. This progress is expected to make a big difference in cancer treatment and increases the chance to achieve cancer complete removal, to lower cancer relapse, and to refine patient survival. Therefore, the nanoparticles-induced cancer therapy may become a trend in the future. Finally, many more experimental and clinical research are required to join nanotechnology as an effective member in clinical cancer management in the future.



Scheme 1: Representative diagram of targeting cancer cells using nanoparticles

Looking to the future

It should be intended that:

(1) To design and characterize many biodegradable nanocarriers such as PLA, PGA, PEG, or their copolymers, or others in different nanoforms (nanoparticles or nanofibers, nanotubes, or other forms) loaded with a variety of current and new drugs.

(2) To investigate the potential anticancer activities of these newly designed loaded nanoforms against their free (non-nano; native) forms in vitro on different tumor cell lines and in vivo using different animals (mice, rat, or others) and different animal tumor models (solid or hematological tumors).

(3) To investigate the probable mechanisms of action.

(4) To try to investigate long-term consequences.

(5) To try to investigate metabolism of nanoparticles inside body.

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