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Review

Nanoparticles and targeted drug delivery in cancer therapy

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ABSTRACT

Surgery, chemotherapy, radiotherapy, and hormone therapy are the main common anti-tumor therapeutic approaches. However, the non-specific targeting of cancer cells has made these approaches non-effective in the significant number of patients. Non-specific targeting of malignant cells also makes indispensable the application of the higher doses of drugs to reach the tumor region. Therefore, there are two main barriers in the way to reach the tumor area with maximum efficacy. The first, inhibition of drug delivery to healthy non-cancer cells and the second, the direct conduction of drugs into tumor site. Nanoparticles (NPs) are the new identified tools by which we can deliver drugs into tumor cells with minimum drug leakage into normal cells. Conjugation of NPs with ligands of cancer specific tumor biomarkers is a potent therapeutic approach to treat cancer diseases with the high efficacy. It has been shown that conjugation of nanocarriers with molecules such as antibodies and their variable fragments, peptides, nucleic aptamers, vitamins, and carbohydrates can lead to effective targeted drug delivery to cancer cells and thereby cancer attenuation. In this review, we will discuss on the efficacy of the different targeting approaches used for targeted drug delivery to malignant cells by NPs.

1. Introduction

Targeted cancer therapy can discriminate the small differences between normal and cancer cells. Targeted therapies are usually more effective than other conventional treatments and exhibit lesser unwanted adverse effects. Since the non-specific and systemic drug delivery leads to rapid elimination of drug, administration of the highest tolerable dose of the drug is needed which is not economical and usually exhibits high toxicity.

In recent years, accumulating studies have been shown the efficacy of nanosized materials for tumor targeting, diagnosis (imaging) and therapy [1]. Nanoparticles (NPs) are nanosized materials that can embed drugs, imaging agents, and genes [2]. NPs can deliver the high doses of therapeutic factors into tumor cells while bypass normal cells. While the scaffold structure of NPs enables the attachment of drugs and contrast agents, their surface facilitates biodistribution and specific delivery through conjugation with ligands that bind to tumor biomarkers [3]. NPs have solved the problems of conventional chemotherapy, including non-specific biodistribution, drug resistance, and unwanted adverse effects.

Interesting features of NPs have been led to the entrance of several NP-based therapeutics into the clinical trial stage during the last two decades [4]. Possibility of modulation of various features of NPs has made them as potent therapeutic vectors for cancer therapy. Nanocarriers increase the circulation half-life of therapeutics in body and enhance their accumulation in tumors site, which is in part related to the small size of NPs and deregulated vascular structure and enhanced permeability and retention (EPR) effects [5].

The physicochemical features of nanocarriers significantly affect the half-life and biodistribution of NPs [6,7]. Size of NPs is an important

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factor in the fate of particles. While NPs smaller than 7 nm in hydrodynamic diameter fall into renal filtration and urinary excretion [8,9], nanomaterials larger than 100 nm are usually cleared from the circulation by phagocytic cells [10,11]. Moreover, the surface positive charge of particles facilitates internalization into the cancer cells. Surface addition of some polymers such as polyethylene glycol (PEGylation) to NPs can also enhance the circulation half-life of particles in part through prevention of clearing by reticuloendothelial system and enhancing the accumulation of particles in tumor site [12]. Although, surface modification of NPs may improve their circulation time, however, it can affect their internalization into cancer cells. Therefore, addition of some tumor-specific ligands to the surface of NPs (active targeting) which facilitates internalization of NPs into cancer cells may lead to overcome this problem [13].

2. Therapeutic NPs

Several NPs have been used in the wide variety of pathologic conditions during the last two decades [14].

Liposomes with a lipid scaffold structure were discovered 40 years ago by Bangham [15]. Liposomes are composed of self-assembled phospholipids into bilayers with spherical shape [16]. Size of these nanomaterials is varied from the 30 nm to microns [17]. Liposomes can encapsulate both the hydrophilic and hydrophobic therapeutic factors within the vesicles and lipid bilayer, respectively. These nanocarriers are highly biocompatible and can easily modified for exhibition of better properties, such as increased circulation time and active targeting [18]. Currently, multiple liposome-based anti-cancer therapeutic compounds such as DaunoXome®, Myocet®, VincaXome®, DepoCyt®, Doxil®, Caelyx® are available in the market for clinical use [19].

Nanostructured lipid carriers (NLC), which were identified in the late 1990s are composed of a mixture of a solid and liquid lipid [20]. These nanocarriers can potently internalized by tumor cells and exhibit several advantages, including high drug loading potential, controlled drug release, increasing drug stability, and the ease of large-scale generation [21,22].

Solid Lipid NPs (SLNs) are non-toxic nanocarriers generated with natural lipids or synthetic lipids [23]. Production of SLNs does not need to use of toxic organic solvents, which help to intact maintenance of the drug composition. These nanomaterials can carry both the lipophilic or hydrophilic drugs. SLNs are versatile nanocarriers since they are capable to controlled release and protection of drugs which lead to possibility of administration through both the parenteral and non-parenteral routes [24].

Poly (lactic-co-glycolic acid) (PLGA) is a biodegradable polymeric NP composed of co-polymerization of the glycolic acid and lactic acid, and approved by the Food and Drug Administration (FDA) for drug delivery [25]. Due to hydrolysis of PLGA in the body to its original components, it is considered as a very useful nanovector. Lupron Depot® which is PLGA-based commercial nanocarrier is used for the attenuation of advanced prostate cancer.

Dendrimers are composed of the repeatedly highly branched polymeric star-like molecules with a 3D geometric shape. Dendrimers exhibit three different parts including a central core, the branches, and an exterior surface with various surface functional groups [26]. There are two main strategies for production of these dendrimers including divergent (outward from the core) and convergent (inward towards the core) strategies [27]. Presence of tertiary amines in the structure of dendrimers let us to add various molecules for active targeting [28]. Dendrimers are characterized through the generation of monomers (G) added to a main core. Dendrimers are the smallest nanocarriers generated with size of 1.9 nm for G1 and 4.4 nm for G4 which facilitates their application in the some specific conditions [29]. They are used for both the diagnostic (imaging) and therapeutic purposes [30]. Vivagel® is the first dendrimer-based compound which is considered as the Fast Track Status by the FDA [31].

Iron oxide NPs are of important types of inorganic NPs with size of 1–100 nm in diameter. Since these particles can be visualized by Magnetic Resonance imaging (MRI), they have been used for imaging purposes in various tumors [32]. Regarding the magnetic feature of these nanomaterials, they can be used for therapeutic goals via hypethermia through conduction by external magnetic field into tumor site [33]. These NPs can also be used for *in vivo* investigations, because they are biodegradable and degraded iron can be absorbed by hemoglobin in body [34]. A superparamagnetic iron oxide NPs (SPIONs) are potent useful nanomaterials that can be applied for both the imaging and therapeutic applications [35]. There are multiple iron oxide based NPs in market which can be used for therapeutic or imaging applications such as Ferridex I.V.®, Ferumoxytol®, and Combidex® [35].

Gold NPs were identified by Michael Faraday for the first time [36]. The surface of gold NPs can be easily modified by amine and thiol groups for tumor specific targeting. Moreover, gold NPs show surface plasmon resonance [37]. Regarding the small size of these nanocarriers, they can enter to tumor cells through EPR effect. Gold NPs-based therapeutics have also experienced the early-phase clinical trials which were associated with hopeful outcome [38]. Due to the high atomic number of gold NPs, they can also be used as imaging vectors and tumor-selective photothermal therapy [39].

3. The mechanisms of nanoparticle internalization in cancer cells

Endocytosis which is the main mechanism of NP internalization in target cells can be categorized into phagocytosis and pinocytosis. The phagocytosis is the main mechanism of capture by phagocytic cells including neutrophils, dendritic cells, and macrophages, whereas the pinocytosis is observed in all cells and may be classified into clathrin- or caveolae-mediated endocytosis, clathrin/caveolae-independent endocytosis, and micropinocytosis [40–42].

Large particles are usually captured by phagocytosis pathway. For phagocytosis, NPs should be covered with the opsonins which facilitate their adherence to phagocytic cells through opsonin receptors such as mannose and scavenger receptors. The interaction of receptor–ligand results in actin rearrangement and phagosome formation, leading to the induction of cup-like membrane extension, which capture and internalize the NPs [41].

Pinocytosis is usually effective in the enclosing fluids and suspensions containing small particles. Based on the type of proteins involved, it can be divided to clathrin-dependent and caveolae-dependent endocytosis, macropinocytosis and clathrin- and caveolae-independent endocytosis.

Clathrin-dependent endocytosis is observed in all mammalian cells and is involved in the capture of essential nutrients such as cholesterol (LDL) through the LDL receptor, or iron through the Tf receptor [43]. Ligated receptors bind to cytoplasmic adaptor proteins to form a clathrin lattice [44]. The GTPase activity of dynamin detaches the vesicle from the plasma membrane which leads to generation of a clathrin coated vesicles [45]. Poly(ethylene glycol)-polylactide [46], Poly (lactic-co-glycolic acid) (PLGA) [47], Silica-based nanomaterials [48], chitosan [49], surface-modified NPs that target Clathrin-dependent endocytosis (modified with Tf) [50] are some examples of NPs which use Clathrin-dependent endocytosis mechanism for the cellular entry.

Caveolae are a type of lipid rafts at cholesterol-rich area of membrane enriched with caveolin-1 [51]. As this internalization mechanism bypass lysosomes, several pathogens use caveolae-mediated transport to enter target cells [51]. The caveosome has a neutral pH and use actin to move within the cell [52]. NPs which use this internalization mechanism bypass a degradation and increase the drug delivery to an ER or nucleus. It has been shown that the anionic NPs usually apply caveolae-dependent endocytosis [53].

Macropinocytosis is a growth factor-induced, actin-promoted endocytosis that encloses a large content of fluid-phase [54] and is observed in almost all cells. This route is usually started following