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Mini-review

Development of highly efficient nanocarrier-mediated delivery approaches for cancer therapy

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ABSTRACT

Nanocarriers (NCs) are a group of nano-sized vehicles devised to deliver drugs to targeted malignant tissues or organs that provide remarkably improved targeting efficiency and therapeutic efficacy for cancer therapy. A variety of NCs have been developed to accommodate appropriate loading and release of drugs with a wide spectrum of chemical and physical characteristics. In addition, physicochemical modifications to the surface or interior of NCs allow for modulation of pharmacokinetic features reflecting clinical demands. However, cancer-related mortality is still high and drug-mediated cancer treatment remains a challenging research field despite the remarkable advances in targeting efficiency and therapeutic efficacy resulting from NCs. In this review, we focus on typical approaches and recent trends in NC-mediated drug delivery systems and their potential for targeted cancer therapy.

Introduction

Cancer is one of the most devastating diseases against human health. Various diagnostic and therapeutic tools that target cancer have been developed over the past decades [1]. In spite of the great advances in medical technology for cancer treatment, mortality rates still exceed expectations and cancer treatment remains a challenging field. The purpose of basic drug mediated cancer therapy, i.e. chemo, gene, immune, and photothermal (or photodynamic) therapy, is to reduce tumor volume before surgical removal of the solid tumor or eliminate minute residual tumors after surgery and radiotherapy [2–5]. For these drug-mediated treatments, tumor selectivity of the drug and drug stability are key governing factors for therapeutic efficacy. However, most cancer drugs exhibit poor stability and tumor-targeting efficiency under physiological conditions, resulting in low therapeutic efficacy and toxic side effects to normal tissues or organs [6]. Consequently, development of targeted drug delivery systems that are highly stable, with suitable pharmacokinetic profiles is of great importance for efficient cancer treatment.

Among efforts to improve drug pharmacokinetics, nanocarriers (NCs) have emerged as nano-sized drug carriers promising targeted drug delivery for cancer therapy [6] (Fig. 1). NCs are classified into subgroups such as polymeric nanoparticles, micelles, liposomes, dendrimers, nanogels, and inorganic nanomaterials [6,7]. One attractive feature of NCs is their excellent drug loading capability, attributable to large surface areas or inner volumes into which a considerable amount of drug can be incorporated [7]. The physicochemical features of NCs are easily modified on the surface or interior – allowing for additional improvements in pharmacokinetic features for practical uses. For example, surface modifications or modulation of NC size may allow it to circulate within the blood plasma with minimal opsonization or filtration by reticuloendothelial system (RES), resulting in enhanced tumor selectivity and therapeutic efficacy. Moreover, tumor selectivity of NCs can be enhanced by conjugation of targeting moieties or anti-fouling molecules on the surface [8,9]. More recent approaches include the addition of new functional types with unprecedented features such as the ability to co-deliver multiple drugs with different physicochemical characteristics or for internal/external stimuli-activated drug delivery to target sites. These new approaches have further enhanced the targeting efficiency and therapeutic efficacy of cancer drugs [10,11]. Since a wide variety of NCs and their beneficial features have been well demonstrated in the field of cancer therapy, it is anticipated that NCs will serve as an alternative to traditional drug formulations.

In spite of the advances in NC technology, most therapeutic nanoformulations in clinical trial have been designed with basic and simple formulations and no specificity [7]. However, NCs having unique specificity and unprecedented multi-functionality with beneficial pharmacokinetic features are gaining recognition for clinical applications. NC-related therapeutic approaches for cancer treatment are remarkably challenging fields of study, but hold great potential for clinical use. In this review, we focus on recent advances and potential for NCs as novel cancer therapeutics by

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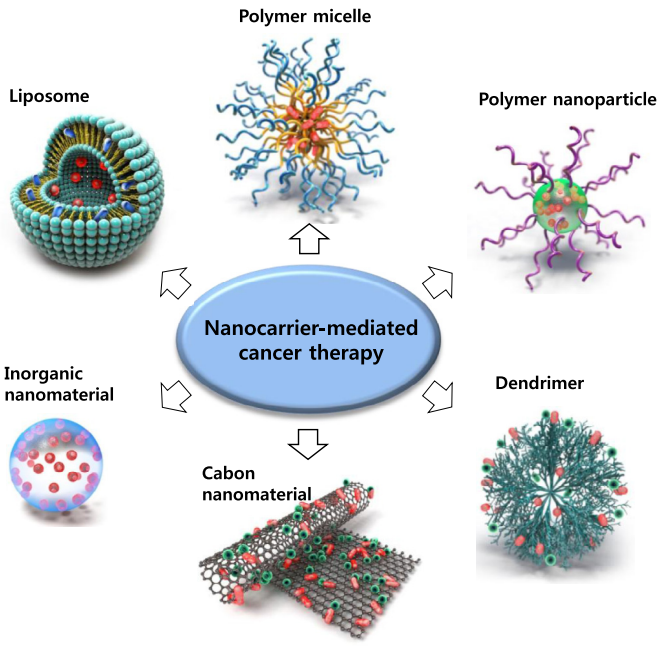

Fig. 1. Schematic diagram of NCs for cancer therapy.

exploring conventional research strategies and cases. We also highlight recent research trends in the development of new functional NCs devised to offer improved targeting efficiency and therapeutic efficacy.

Typical approaches to NC-mediated drug delivery

Targeting strategy

An attractive NC feature is size-motivated tumor selectivity after administration, which provides a passive targeting strategy for cancer therapy [12,13]. Neovascular structures within tumor tissue are generally disorganized with a number of defects ranging in size from 100 to 600 nm in diameter. As such, tumor neovasculature is distinctly different from the vasculature found in normal tissue. Specifically, endothelial cells are often inadequately aligned or disordered, while perivascular cells and basement membranes are frequently vacant or abnormal owing to rapid angiogenesis within the tumor tissue. These conditions result in leaky channels that allow permeation of nano-sized materials (normally less than 200 nm of hydrodynamic size) into the tumor region from circulating matrices [14,15]. In addition, the tumor neovasculature possesses wide lumens and a poorly operating lymphatic drainage system, resulting in the retention and accumulation of nanomaterials for prolonged periods of time compared to other small molecules. The term "enhanced permeability and retention (EPR) effect" has been coined to describe this size-motivated tumor selectivity of NCs [12,13]. It should be noted that EPR-mediated tumor selectivity can only be achieved if the NCs are stable in the circulating blood without RES filtration; therefore, careful consideration of both the size and nature of a NCs surface should be taken into account when designing NCs [16–19]. Nanoparticles that are surface modified, or "decorated," with polyethylene glycols (PEGs) are a representative example of passively targeted NCs that avoid unwanted filtration in the blood stream after administration, attributable to the tiny size and antifouling characteristics of PEG molecules [20].

In addition to passive targeting, decorated NCs can also provide active tumor targeting [21]. Active tumor targeting strategies take advantage of specific receptors or antigens that are overexpressed on cancerous cells and distinguishable from the surrounding normal cells; various targeting moieties have been chemically and physically introduced onto NCs to impart a specific binding to cancer cells, resulting in further enhancement of the tumor-targeting efficiency of NCs [22]. For example, folic acid (FA) has been conjugated with NCs to offer specific binding to folate receptors overexpressed on various cancer cells including ovarian cancer cells, osteosarcoma, meningioma, and choriocarcinoma [23–25]. FA-conjugated NCs loaded with anti-cancer drugs reportedly enhance targeting efficiency and therapeutic efficacy of the chemotherapeutic agent [26–29]. Besides FA, various types of specific cellular-targeting moieties have been reported, including hyaluronic acid (HA), a biocompatible/non-immunogenic biomolecule that targets the CD44 receptor [30–36]; transferrin (Tf), a glycoprotein that targets the Tf receptor (TfR) [37–39]; epidermal growth factor (EGF) that targets the EGF receptor (EGFR) [40]; and aptamer, a type of oligonucleotide or peptide [41–43]. Representative examples of targeting moieties for active targeting strategies are summarized in Table 1.

Systemic delivery

Numerous NC formulations have been produced to carry a variety of therapeutic cargoes such as proteins, nucleic acids, or small molecule drugs. Of these, NCs that encapsulate hydrophobic cancer

Table 1
Targeting moieties for active tumor targeting.

Targeting moieties	Targets	Formulation	Type of cancer	Ref.
Folic acid (FA)	FA receptor	Graphene oxide	MCF-7, MGC803 cells	[26,27]
		Metal oxide NP	KB cells	[28]
		Nanogel	Ovarian cancer	[29]
Hyaluronic acid (HA)	CD44 receptor	Polymeric micelle	SCC7, MDAMB-231, HCT116, and MCF-7 cells	[30–34]
		Nanogel	B16F10 cells	[35]
		Liposome	B16 cells	[36]
Transferrin (Tf)	Tf receptor	Silica NP	A549, PANC-1, BT-549, and MDA-MB-435 cells	[37,39]
		Gold NP	Neuro2A cells	[38]
Aptamer	PSMA	Gold NP	LNCaP cells	[41]
	Nucleolin	Polymeric micelle	C6 glioma cells	[42]
		Gold NR	MCF-7 cells	[43]
NGR motif peptide	CD13	Polymeric micelle	MCF-7 cells	[44]
		Liposome	Renal cell carcinoma (RCC)	[45]
RGD peptide	Integrin $\alpha_v\beta_3$	Graphene oxide	U87MG cells	[46]
		Nanogel	RCC	[47]

PMSA: Prostate specific membrane antigen, NP: nanoparticle, NR: nanorod.