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Mini review

Biological stimuli-responsive cyclodextrin-based host–guest nanosystems for cancer therapy

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ABSTRACT

Stimuli-responsive nanosystems are of particular interest in cancer therapy, owing to their impressive capability to enable the on-demand drug release in response to specific biological stimuli in tumor microenvironments (such as pH, redox and enzyme, etc.). Cyclodextrin (CD)-based host–guest interactions provide a flexible and powerful platform for the development of multifunctional nanosystems. This article highlights the current progress of CD-based host–guest nanosystems (CHNs) with biological stimuli-responsive properties in cancer therapy. We summarize the composition, structure and design of various CHNs in response to specific stimuli in tumor, and focus on their performance in controlled drug delivery and cancer therapy. These recent advances make it a promising and intelligent drug delivery system to improve the anticancer efficacy.

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1. Introduction

Compared to the traditional cancer therapies, nano-based drug delivery systems provide significant advantages such as improved drug targeting and therapeutic effectiveness (Petros and DeSimone, 2010). Nanosystems can preferentially deliver a wide range of therapeutics to a tumor by exploiting the enhanced permeability and retention (EPR) effects (Bertrand et al., 2014; Chauhan and Jain, 2013; Jain and Stylianopoulos, 2010). However, owing to the extremely complicated and abnormal microenvironment in tumor tissue, the supply, penetration and distribution of nanosystems to tumor are often limited by the physiological barriers, which cannot be overcome by the EPR effects alone (Chauhan and Jain, 2013; Ernsting et al., 2013; Mura et al., 2013; Petros and DeSimone, 2010). Recently, stimuli responsive nanosystems are developed to enable the on-demand drug release by employing the physiological and pathological conditions in tumor to improve the cancer therapy (Mura et al., 2013; Torchilin, 2014; Wang et al., 2014b). The commonly utilized biological stimuli mainly involve the lower interstitial pH values, high levels of reductive molecules, and altered expression of specific enzymes (Hogg, 2013; Medeiros et al., 2011; Mura et al., 2013; Torchilin, 2014; Wang et al., 2014b). These disparate conditions between tumor and normal tissues can be exploited to trigger the responsive drug release in tumor tissues or intracellular compartments to achieve the desired therapeutic efficacy (Fleige et al., 2012; Torchilin, 2014).

Cyclodextrin (CD) based supramolecular assembly is a powerful platform for development of multifunctional nanosystems via the host–guest interactions (Hu et al., 2014; Wang et al., 2013; Zhang and Ma, 2013), and have been successfully employed in drug and gene delivery applications (Mateen and Hoare, 2014; Su et al., 2014; Yuan et al., 2013; Zhang and Ma, 2013). Recently, CD has been used as functional component for fabrication of biological stimuli responsive nanocarriers to achieve the desired drug release behavior in cancer cells and improve the therapeutic efficacy (Hu et al., 2014). Moreover, the guest molecules such as adamantine (Ad) can also be linked to polymer or anti-cancer drugs with stimuli-responsive properties (Luo et al., 2012a; Ping et al., 2013). The CD-based host–guest nanosystems (CHNs) can be elegantly fabricated in response to intracellular pH, redox and enzymes to trigger the specific drug release, thereby overcome the intrinsic biological barriers and improve the cancer therapy

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(Namgung et al., 2014; Zhang et al., 2013a). The topics about CD-based multifunctional materials, design and formation of CD-based nanoassemblies, and their applications in drug delivery have been reviewed elsewhere (Hu et al., 2014; Kang et al., 2014; Moya-Ortega et al., 2012; Wang et al., 2013; Zhang and Ma, 2013). However, the approaches of biological stimuli-responsive CHNs in cancer therapy have not been specifically summarized.

In this review, we focus on the current progress of biological stimuli-responsive CHNs in cancer therapy (Table 1). We mainly summarize the components, structure and design of various biological responsive CHNs, and emphasize on their potential performance in inhibiting cell proliferation and tumor growth. Other stimuli-responsive CHNs including light, temperature and voltage, etc., are not included in this mini-review (Liu et al., 2010; Suzaki et al., 2007; Wang et al., 2007; Yan et al., 2010).

2. Biological stimuli-responsive CHNs

2.1. pH-responsive CHNs

The dysregulated pH variation in tumor is one of the most widely used stimuli for design of stimuli-responsive nanosystems (Fig. 1A) (Banerjee et al., 2012; Jin et al., 2011; Ouahab et al., 2014). The extracellular pH is 6.7–7.1, which is slightly lower than that in normal tissues or blood (~7.3–7.4) (Webb et al., 2011). Moreover, at cellular level, the pH values is around 6.3 in early endosome, then lowered to 5.5 in late endosomes and 4.7 in lysosomes (Casey et al., 2010). The pH-responsive capabilities are mainly motivated by the mildly acidic pH stimuli for specific release of therapeutic agents in tumor tissues or intracellular compartments.

In the pH-responsive CHNs, the controlled drug release behavior can be achieved by destabilization of the nanosystem structure or degradation of the acid-sensitive bonds linked to CD molecules (Fig. 1B). For example, CD can be linked with a pH-sensitive poly(2-(dimethylamino) ethyl methacrylate) (pDMAEMA) polymer chain to develop the CD-based pH-sensitive star polymer, and then used to encapsulate the anti-cancer drug of doxorubicin (DOX) via the host–guest interactions (Xiong et al., 2014; Zhang et al., 2013b). The nanosystem exhibited a controllable release, enhanced cellular uptake and cytotoxicity in HeLa and Hep G2 cancer cells, and higher inhibitory effects on tumor growth. On the other hand, DOX can be conjugated to the guest Ad molecules with pH-cleavable hydrazine bonds to trigger the responsive drug release under endosomal pH environments, thereby enhances the cellular uptake and anti-cancer efficiency in HeLa cells (Luo et al., 2012a).

On the other hand, the guest moiety itself can also be designed with pH-responsive capability to achieve the pH-controlled drug release (Fig. 1B). Benzimidzole (BM), a typical guest molecule with β-CD, is hydrophobic at the physiological pH (~7.4) and can bind to β-CD via the host–guest interactions (Koner et al., 2011). Interestingly, under endosomal/lysosomal pH environment (pH <6), BM becomes hydrophilic due to the protonation effects, thereby leading to the disassembly of BM/β-CD binding and controlled release of encapsulated drugs (Xue et al., 2011). Based on the pH-stimuli responsive properties of BM, Chen et al. designed BM modified poly(3-caprolactone) (BM-PCL) and β-CD terminated dextran (Dex-b-CD), then further assembled into micelles loading DOX (Zhang et al., 2013c). The nanosystem exhibited pH-stimuli controllable drug release in mildly acidic conditions mimicking the endosomal/lysosomal environments, and significantly enhanced the in vitro anti-cancer activities in Hep G2 cells. Moreover, the BM/β-CD binding can also be used as pH responsive nanovalves to accelerate the drug release in endosomal acidic conditions. Nel et al. reported BM modified mesoporous silica nanoparticles (MSN) loading DOX in the pores (Fig. 1C) (Meng et al., 2010). Then, β-CD was binding to BM via the host–guest interactions and functionalized as nanovalves to control nanopore opening, thereby manipulate the drug release from pores of MSN. Due to the protonation of BM in acidic conditions, the capped β-CD could be removed from the surface of MSN to trigger the release of encapsulated DOX. MSN with pH-responsive nanovalves enabled its specific drug delivery to the endosomal acidification conditions in THP-1 and KB-31 cancer cells.

Table 1
Summary of the stimuli, host, guest, drugs, design and performance of various CHNs in cancer therapy.

Stimuli	Host	Guest	Drug	Design	Peformance	References
pH	β-CD	DOX	DOX	Linking pH-sensitive polymer of PDMAEMA to β-CD.	Enhance cytotoxicity in Hep G2 and HeLa cancer cells, and in vivo inhibitory effects on tumor growth.	Xiong et al., 2014; Zhang et al., 2013b
pH	β-CD	Ad	DOX	Linking DOX to Ad with pH-cleavable hydrazine bonds.	Enhance cellular uptake and cytotoxicity in HeLa cells.	Luo et al., 2012a
pH	β-CD	BM	DOX	Linking PCL pH sensitive BM molecules.	Enhance in vitro cytotoxicity in Hep G2 cells.	Zhang et al., 2013c
pH	β-CD	BM	DOX	Anchoring BM to the surface of MSN.	Enable specific endosomal/lysosomal drug delivery in THP-1 and KB-31 cancer cells.	Meng et al., 2010
Redox	β-CD	Ad	DNA	Linking multiple cationic pDMAEMA to β-CD via disulphide linkages.	Improve gene transfection efficiencies and in vivo inhibitory effects on tumor growth.	Hu et al., 2013
Redox	β-CD	Ad	Therapeutic DNA	Linking multiple cationic star polymer to β-CD via disulphide linkages.	Intracellular gene delivery, enhance gene transfection efficiency in MCF-7 cells.	Wen et al., 2014
Redox	β-CD	Ad	DNA	Linking PEG to Ad via disulphide linkages.	Enhance the transfection efficiency in vitro and in vivo, tumor targeted gene delivery.	Ping et al., 2013
Redox	β-CD	Camptothecin	Camptothecin	Immobilizing PEI/β-CD onto magnetic nanoparticles via disulfide linkage.	PEI/β-CD as a molecular reservoir for specific intracellular drug delivery.	Luo et al., 2012b
Redox	α-CD	[2]rotaxanes	DOX	Anchoring [2]rotaxanes onto hollow MSN via disulfide linkage.	Induce apoptosis and death of HeLa cells, enhance tumor targeting and inhibit the tumor growth with minimal side effects in vivo.	Luo et al., 2013
Redox	γ-CD	PTX	PTX and DNA	γ-CD-PEI conjugated with folic acid via disulfide linker.	Efficient gene delivery into FR+ cancer cells and induce a significant cell apoptosis.	Zhao et al., 2014
Ester enzyme	β-CD	PTX	PTX	Conjugating PTX or β-CD to polymer via ester bonds.	Enhance cytotoxicity in cancer cells, inhibit tumor progression and extend survival rate.	Namgung et al., 2014
Enzyme and redox	β-CD	Ad	DOX	Linking β-CD to MSN with disulphide linkage; grafting RGD motif, PLGVR peptide and protection polymer to Ad.	Tumor-targeting drug delivery with programmed stimuli responsive capability.	Zhang et al., 2013a
pH and H_2O_2	β-CD	Ferrocene	DOX	Conjugating PEG to ferrocene, linking DOX to β-CD with hydrazone bonds.	Dual responsive drug release.	Wang et al., 2014a

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