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Research review paper

pH-Sensitive nano-systems for drug delivery in cancer therapy

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ABSTRACT

Nanotechnology has been widely used in the development of new strategies for drug delivery and cancer therapy. Compared to traditional drug delivery systems, nano-based drug delivery system have greater potential in a variety of areas, such as multiple targeting functionalization, in vivo imaging, combined drug delivery, extended circulation time, and systemic control release. Nano-systems incorporating stimulus-responsive materials have remarkable properties which allow them to bypass biological barriers and achieve targeted intracellular drug delivery. As a result of the active metabolism of tumor cells, the tumor microenvironment (TME) is highly acidic compared to normal tissues. pH-Sensitive nano-systems have now been developed in which drug release is specifically triggered by the acidic tumor environment. Studies have demonstrated that novel pH-sensitive drug delivery systems are capable of improving the efficiency of cancer treatment. A number of these have been translated from bench to clinical application and have been approved by the Food and Drug Administration (FDA) for treatment of various cancerous diseases.

Herein, this review mainly focuses on pH-sensitive nano-systems, including advances in drug delivery, mechanisms of drug release, and possible improvements in drug absorption, with the emphasis on recent research in this field. With deeper understanding of the difference between normal and tumor tissues, it might be possible to design ever more promising pH-responsive nano-systems for drug delivery and cancer therapy in the near future.

Contents

Abbreviations: AA, acrylic acid; ADPC, acryloyloxy dodecyl phosphorylcholine; ADH, adipic dihydrazide; ADR, adriamycin; Ala, alanine; ACP, amorphous calcium phosphate; Asn, asparagine; Asp, aspartate acid; ATRP, atom transfer radical polymerization; AuNP, gold nanoparticle; BSA, bovine serum albumin; C6-ceramide, N-hexanoyl-D-erythro-sphingosine; CA, chicken β-actin; CaP, calcium phosphate; CPT, camptothecin; CMC, carboxymethyl chitosan; CS, chitosan; Chol, cholesterol; CAD, cis-aconitic anhydride-DOX; CDDS, controlled drug delivery system; cyt c, cytochrome c; DAU, daunomycin; DNA, deoxyribonucleic acid; DTX, docetaxel; DDS, drug delivery system; DMAEMA, (dimethylamino)ethyl methacrylate; DMNP, drug-delivering magnetic nanoparticles; DOPC, 1,2-dioleoyl-sn-glycero-3-phospho-choline; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DOXO-EMCH, (6-maleimidocaproyl) hydrazone derivative of DOX; EAA, ethylacrylic acid; FDA, the Food and Drug Administration; FITC, fluorescein isothiocyanate; FA, folate; Glu, glutamic acid; GALA, glutamic acid–alanine–leucine–alanine; GMA, glycine methacrylamide; HAP, crystalline hydroxyapatite; HEMA, hydroxyethyl methacrylate; HEMA, hydroxyethyl methacry-late; HER, herceptin; HMA, hexyl methacrylate monomers; HMs, hollow microspheres; HPMA, N-(2-hydroxypropyl)methacrylamide; IPN, interpenetrating network; IR, infrared spectrum; KALA, lysine–alanine–leucine–alanine; LDI, L-lysine ethyl ester diisocyanate; Leu, leucine; Lys, lysine; MEND, multifunctional envelope-type nano device; MP, mastoparan; mPEG, monomethoxy polyethylene glycol; MSN, mesoporous silica nanoparticle; MTT, 3-(4,5)-dimethylthiahiazo(-z-y1)-3,5-di-phenytetrazoliumromide; NCCM, non-covalently connected micelle; NIPAM, N-isopropylacrylamide; NVP, N-vinyl-2-pyrrolidone; ODN, oligodeoxynucleotide; OSA, oligomeric sulfonamides; PA, pullulan acetate; PAA, poly(acrylic acid); PAGE, poly(allylglycidyl ether); PAH, poly(allylamine hydrochloride); PAH-Cit, poly(allylamine hydrochloride)-citraconic anhydride; PBAA, poly(butylacrylic acid); PbAE, poly (β-amino ester); PBLG, poly(γ-benzyl L-glutamate); PBS, phosphate buffered saline; PCL, poly(ε-caprolactone); PDEAEM, poly(N,N′-dimethylaminoethyl methacrylate); pDNA, plasmid DNA; PEAA, poly(ethylacrylic acid); PEG, poly(ethylene glycol); PEGylated, polyetheleneglycosylated; PEI, polyethylenimine; PEO, poly(ethylene oxide); PF-DNA, a proton-fuelled DNA nanomachine; PGA, poly(glutamic acid); PHis, poly(L-histidine); pHLIP, pH (Low) insertion peptide; PHP, PEG-b-poly(His-co-phenylalanine(Phe)); pkSer, poly(ketalized serine); PLA, polylactide; PLGA, poly(lactic-co-glycolic acid); PLGG, poly((lactic acid)-co-((glycolic acid)-alt-(L-glutamic acid))); PLL, poly(L-lysine); PLLA, poly(L-lactic acid); PMAA, poly(methacrylic acid); PNAs, peptide nucleic acids; PNiPAM/AA, poly(N-isopropylacrylamide)-co-acrylic acid; POSS, polyhedral oligomericsilsesquioxane; PPAA, poly(propylacrylic acid); PPADK, poly(1,4-phenyleneacetone dimethyleneketal); PPC, monomethoxyl poly(ethylene glycol)-b-poly-(allyl ethylene phosphate)-cysteamine; PPO, poly(propylene oxide); PSS, poly(styrenesulfonate sodium); PT, permeability transition; PTX, paclitaxel; PVA, poly(vinyl alcohol); PVP, poly (4-vinylpyridine); QD, quantum dot; R8, octaarginine peptide; RAFT, reversible addition–fragmentation chain-transfer polymerization; RNA, ribonucleic acid; ROMP, ring-opening metathesis polymerization; SDM, sulfadimethoxine; shGALA, short GALA; siRNA, small interfering RNA; TAA, 1,3,5-triazaadamantane; TAE, tri(aminomethyl) ethane; Tf, transferrin; TMAEMA, trimethylamino-ethylmethacrylate; TME, tumor microenvironment; β-CD, β-cyclodextrin.

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1. Introduction

Design and development of powerful new drug delivery systems has been relentless in recent years, with ever more attention devoted to developing new methods for realizing controlled drug release. In conventional drug delivery, the drug concentration in the blood rises quickly, and then declines. Each drug has a plasma level above which it is toxic and below which it is ineffective. The main aim of an ideal drug delivery system (DDS) is to maintain the drug within a desired therapeutic range after a single dose, and/or target the drug to a specific region while simultaneously lowering the systemic levels of the drug (Langer, 2003). As shown in Fig. 1, nano-systems can enhance the permeability and retention of drugs in solid tumors. Introducing different stimulus-responsive properties to DDSs is an efficient way to achieve these goals (Traitel et al., 2008). In recent decades, a myriad of nanoscale DDSs have been developed for better therapeutic applications (Wang and Zhang, 2012; Zhang et al., 2008). A large variety of nanomaterials responding to physical stimuli (temperature, electrical, electrochemical, light, magnetic, and ultrasonic) (Batrakova and Kabanov, 2008; Berndt et al., 2006; Ercole et al., 2010; Yan et al., 2013; Zhang and Choi, 2011), chemical stimuli (pH, ionic, and redox) (Felber et al., 2012; Ju et al., 2009; Liu et al., 2012a; Luo et al., 2011), or biological stimuli (enzymes, glucose, and inflammation) (Kang and Bae, 2003; Ulijn, 2006; Yui et al., 1992) have been synthesized and developed as effective delivery systems. Stimulus-responsive nanomaterials are termed as 'smart', 'intelligent', or 'environmentally sensitive', and have greater potential than traditional delivery systems (Gao et al., 2013; Kikuchi and Okano, 2002; Yavuz et al., 2009).

Among the different types of stimuli, pH sensitive system has been most widely used to design sensitive nano-systems for drug delivery in cancer therapy. It is well known that pH values vary significantly in different tissues or organs, such as stomach and liver, and in disease states, such as ischemia, infection, inflammation, and tumorigenesis. Due to the high rate of glycolysis in cancer cells, both in aerobic and anaerobic conditions, the pH in tumors is lower than in normal tissues. Tumors have been demonstrated to exhibit acidic pH values ranging from 5.7 to 7.8, while the pH of normal tissue is 7.4 (Engin et al., 1995; Stubbs et al., 2000). Even greater pH differences can be found at the subcellular level; late endosomes and lysosomes have much lower pH, in the range 4.5–5.5 (Lee et al., 2007a). This pH gradient is of particular importance, since several drugs and carriers for cancer therapy are internalized through endocytosis and trapped within endosomal and lysosomal compartments (Bae et al., 2012; Iversen et al., 2011). Therefore, pH-sensitive delivery systems are valuable for controlling drug delivery in cancerous diseases.

This review focuses on advances in the development of pH-sensitive nano-systems for drug delivery in cancer research. Furthermore, we discuss how the functional properties of different pH-sensitive materials and chemical bonds can be exploited to develop nano-systems that show improved cellular uptake and drug delivery. Overall, it is hoped that this review will provide both inspiration and impetus for the further design and development of pH-sensitive nano-systems for drug delivery application.

2. Mechanisms for pH-induced destabilization of nano-systems

For effective delivery of anticancer drugs, pH-sensitive nano-systems are expected to store and stabilize the drug at physiological pH, rapidly release the drug when the pH trigger point is reached, and ensure that the intracellular drug concentration reaches the therapeutic dose. In order to achieve such goals, several pH-responsive drug release approaches/strategies have been investigated.

One approach is to introduce "ionizable" chemical groups, such as amines, phosphoric acids and carboxylic acids among others, with nanomaterials. These groups, with different chemical structures and pKa values, can accept or donate protons and undergo pH-dependent changes in physical or chemical properties such as swelling ratio or solubility, resulting in drug release. According to their constituents, nanomaterials can be classified as organic, inorganic or hybrid. Polymers are an important class of material that can be used for the preparation of organic DDSs due to their abilities to encapsulate and protect cargoes, and to respond to specific stimuli (Stuart et al., 2010). pH-Sensitive polymers are a class of polyelectrolytes with ionizable groups in their backbones, side groups, or end groups. When the pH and the ionic composition of the aqueous medium changes, "smart" polymers are ionized and dramatically change their conformation. Several research groups have developed pH-sensitive polymers by using acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups, which either accept or release protons in response to changes in the pH of the physiological environment. These polymers can undergo pH-sensitive conformational changes in three different ways: a) dissociation, b) destabilization (via collapse or swelling), and c) changes of partition coefficient between the drug and vehicle.

pH-Sensitive fusogenic peptides are organic molecules that undergo fusion with the endosomal membrane when exposed to the low pH in the endosome. These peptides can potentially be used for highly efficient delivery of drugs and genes. For example, GALA (Glu-Ala-Leu-Ala) is the major repeat unit of a synthetic 30-amino acid peptide that can be used for delivery applications. At neutral pH, electrostatic repulsions between the carboxylic acid moieties of glutamic acid destabilize the helical structure of the peptide, whereas at pH 5.0 the neutralization of these groups promotes helix formation. Moreover, when the glutamic acid residues are protonated, the hydrophobicity of the glutamic acid side chain increases (Kim and Szoka, 1992). Thus, as the pH decreases, the structure of GALA changes from a random coil to an α-helix thereby increasing hydrophobicity, and consequently enhancing the interaction with lipid membranes. The most common feature of pH-sensitive lipids containing the same groups as polymers is that they display a net negative charge at neutral pH, allowing them to stabilize nanoparticles. However, in an acidic environment, the stabilizer becomes protonated, resulting in disintegration of the nanocarriers. Meanwhile, DNA with special sequence also

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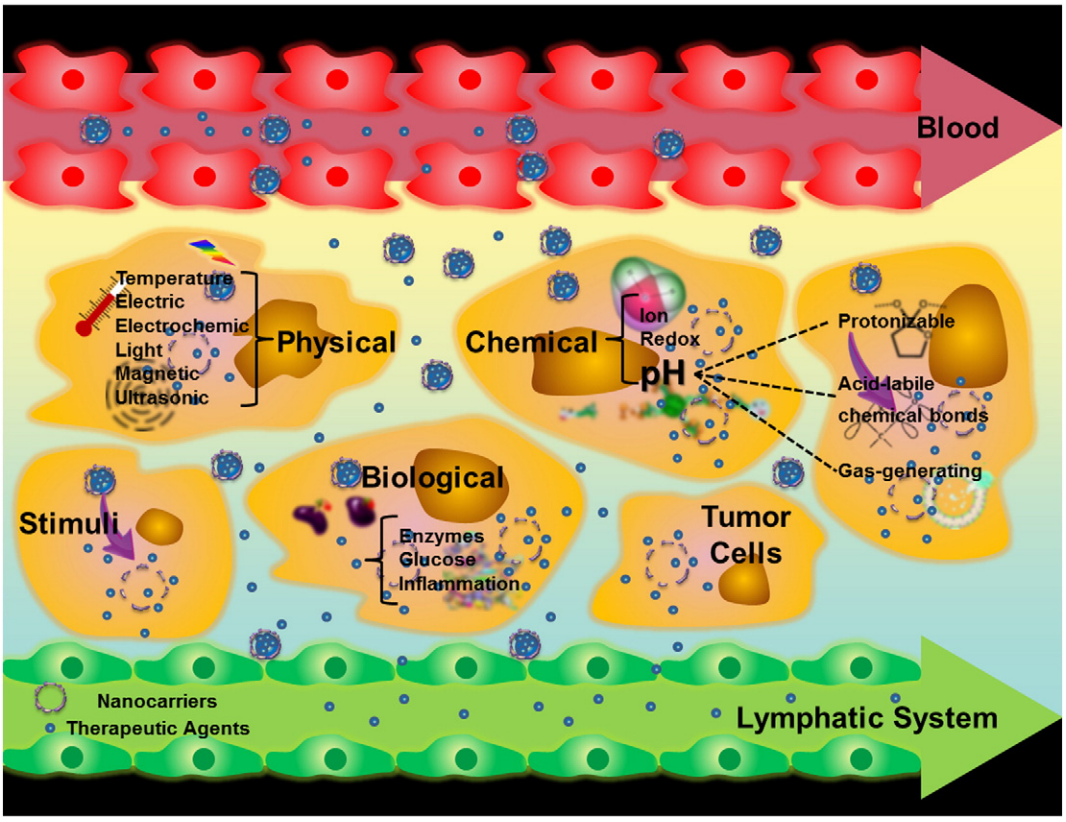

Fig. 1. Nanocarriers enhance the permeability and retention of drugs in tumors. The figure shows the different stimuli that can be used to trigger drug-release from appropriately responsive materials in tumor cells. The different approaches for pH-sensitive drug release are also shown.

has the ability to respond to pH. It can be fuelled by protons and undergo a rapid and highly reversible conformational switch between a four-stranded-motif structure in weak acids (pH < 6.0) and a random coil at higher pH (>6.4). Thus, drugs delivered by this type of DNA can be released rapidly at low pH. For inorganic nanoscale materials, some compounds, such as calcium phosphate (CaP), and zinc oxide (ZnO), are relatively insoluble at physiological pH, but can be dissolved as nontoxic ions in acidic microenvironments, such as endo/lysosomes and solid tumors (Banerjee et al., 2011).

Another approach is to use acid-labile chemical bonds either to covalently attach drug molecules directly onto the surfaces of existing nanocarriers, or to construct new nanocarriers. These acid-labile chemical bonds are stable at neutral pH but are degraded or hydrolyzed in acidic media. This unique property makes them promising candidates for the preparation of pH-sensitive DDSs. The acid-labile linkers most commonly used in previous studies are acetal, orthoester, hydrazone, imine, and cis-aconyl bonds. Their chemical structures and degradation products are illustrated in Table 1. The acetal linker is a group with two single-bonded oxygen atoms attached to the same carbon atom (or two carbon-bonded R groups in the case of ketal) (Knorr et al., 2008; Murthy et al., 2003; Tomlinson et al., 2003). In acidic conditions, the oxygen in the acetal group is protonated and activates the neighboring carbon, which facilitates the attack of water and finally results in the cleavage of the acetal linker to form an aldehyde and alcohol. Esters have a carbonyl adjacent to an ether linkage. The orthoester bond is a functional group containing three alkoxy groups attached to one carbon atom. Orthoester bonds are readily hydrolyzed in mild aqueous acid to form esters (Thambi et al., 2011). The hydrazone group contains a carbon–nitrogen double bond, with the nitrogen attached to an amine group. It is usually formed by the action of hydrazine on ketones or aldehydes. If the nitrogen is attached to another organic group or a hydrogen atom, it is known as an imine. Both are quickly hydrolyzed in acidic conditions to form esters (Ding et al., 2013; Gurski et al., 2010). The cis-aconityl linker, a derivative of natural aconitic acid, has a carboxylic acid (C-4) in cis-position of a hydrolytic bond (C-1). This linker undergoes intramolecularly-assisted C-4 acid-catalyzed hydrolysis at the C-1 bond, due to the proximity of the pendent carboxylic acid.

A novel approach to preparing pH-responsive DDSs is to incorporate carbon dioxide-generating precursors that will produce CO_2 gas in an acidic environment, leading to disintegration of the carrier and release of drug molecules (Liu et al., 2012a). This strategy is based on the fact that HCO_3^- reacts with acid to produce carbonic acid, which easily decomposes to yield carbon dioxide (CO_2) gas and water: $HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2\uparrow$. Common CO_2-generating agents include sodium bicarbonate (Ke et al., 2011) and ammonium bicarbonate (Liu et al., 2012a), both of which are compatible with normal cellular systems and the tumor microenvironment.

3. Ionizable pH-sensitive drug delivery systems for cancer treatment

In this section, we describe the three main classes of nanomaterial – organic, inorganic and hybrid (Fig. 2) – and the ways that they can be used to design pH-responsive nano-systems for delivery of therapeutic agents.

3.1. Organic nanoscale materials and the effects of protonation

3.1.1. Polymers

Biocompatible polymers that change their properties in different physiological environments have been used extensively to design and develop 'smart' delivery systems. pH-Sensitive polymers are important members of this category. Various polymer-based nano-systems have been developed for drug delivery applications, including polymeric micelles (Guo et al., 2010b), polymersomes (Chen et al., 2010), nanospheres (Makhlof et al., 2009), hydrogels (Bhattarai et al., 2010), liposomes (Yuba et al., 2008), dendrimers (Shen et al., 2012) and films

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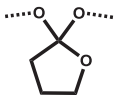
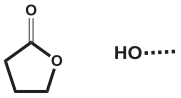
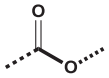
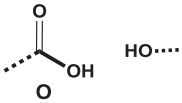
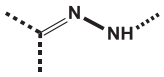
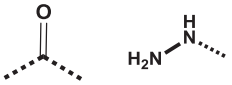
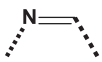
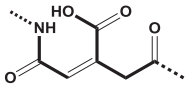
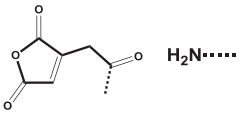
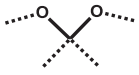
Table 1
Examples of acid-labile chemical bonds and their degradation products.

Name	Acid-labile chemical bonds	Degradation product
Orthoester		
Ester		
Hydrazone		
Imine		
Cis-aconityl		
Acetal/ketal		

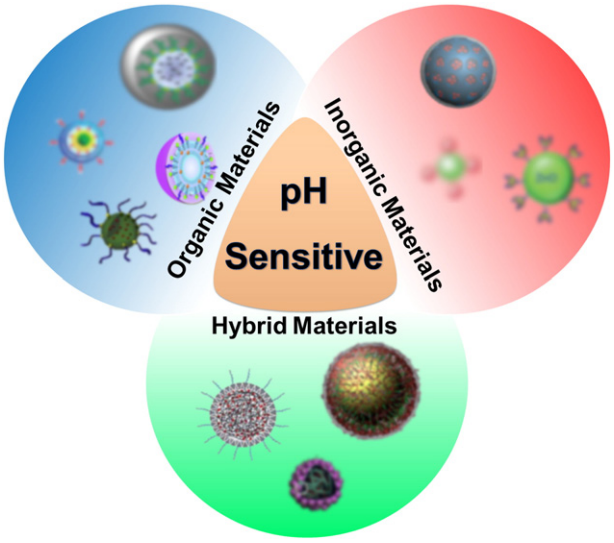


Fig. 2. The three different classes of pH-sensitive nanomaterials for drug delivery in cancer research.

(Tomita et al., 2008). A summary of the different types of nanocarriers based on pH-sensitive polymers is shown in Table 2. Both anionic and cationic polymers have been used to develop drug delivery systems.

Among the most commonly used pH-sensitive polymers are anionic polymers containing carboxylic groups, such as PAA, PMAA, PEAA, PPAA, PBAA, NIPAM, and PGA (Fig. 3A–G). In acidic conditions, these polymers are protonated and their backbones become relatively hydrophobic; in contrast, they are deprotonated at neutral or high pH and become hydrophilic (Bajaj and Singhal, 2011; Yue et al., 2009; Zignani et al., 2000). For example, PAA displays a relatively fast phase transition and a compact conformation due to the presence of carboxylic acid groups, which induce stronger hydrophobic interactions that promote aggregation. In a previous study, Eisenberg et al. has reported PAA-based hydrogels with the pH-sensitive swelling/deswelling behavior in 1950. Following that, polymer micelles made of PMAA grafted with poly(ethylene oxide) (PEO) with cross-linked polyanion core have pH-sensitive properties used for delivery of the cationic drug doxorubicin. DOX represents weak base and is positively charged at physiological conditions. In such complexes the ammonium group in the daunosamine part of DOX electrostatically binds to the carboxylic group of PMAA segment of PEO–PMA copolymer. And the hydrophobic interactions between the anthracycline residues of DOX provide for additional stabilization of the complex. At lower pH, protonation of carboxylic groups in the cores of the micelles at the acidic conditions resulted in the accelerated DOX release. DOX was liberated from the micelles significantly faster at pH 5.5 than at pH 7.4. During the first hour at pH 5.5 up to 50% of DOX-loaded into the micelles was released. However, there was no burst release of DOX at pH 7.4. The DOX-loaded cross-linked micelles exhibited pH-sensitive drug release character (Kim et al., 2009). Lu et al. also prepared a PEAA liposome as intracellular drug delivery carrier. The resulting PEAA liposomes are stable under physiological conditions and can fuse with adjacent membranes and release their contents upon acidification (Kuhn et al., 1950; Lu et al., 2012; Morishita et al., 2002).

Anionic polymers that change from being negatively charged to positively charged as the pH decreases are known as charge-reversal copolymers (Shen et al., 2010; Zhou et al., 2009). Charge-reversal copolymers can improve drug and gene delivery efficiency by enhancing endosomal escape. An example is PAH-Cit, an anionic caboxylate-functionalized polymer (Fig. 3H). When a vector constructed from PAH-Cit is trapped in acidic intracellular vesicles, charge conversion enhances its "proton sponge" capacity and facilitates its escape from endosomes by disrupting the membrane (Chen et al., 2013; Guo et al., 2010a).

Another type of pH-sensitive anionic polymer contains sulfonamide groups as shown in Fig. 3I (Na et al., 2004; Sethuraman et al., 2008). The acidic protons of sulfonamide groups are readily ionized as the pH increases, and the behavior of these polymers can be controlled over a narrower pH range close to physiological conditions, rendering them more sensitive than conventional carboxylic acid polymers (Kang and Bae, 2011). The first sulfonamide-based polymer was synthesized by copolymerizing a monomer derived from sulfamethazine with N,N-dimethylacrylamide (Park and Bae, 1999). Bae et al. investigated the weak acid sulfonamide as a trigger for extracellular delivery of the anticancer drug doxorubicin. Sulfonamide-carrying micelles were stable in neutral solution but in acidic conditions, the sulfonamide was further deprotonated and the micelles collapsed because they were no longer solvated. The encapsulated doxorubicin was then subsequently released (Huh et al., 2012).

Compared with anionic polymers, pH-sensitive cationic polymers have various advantages, such as their positive surface charges, which potentially enhances cellular uptake. A number of cationic polymers have been developed as DDSs, with a subset of them being successfully administered in clinical trials and even approved for clinical use because of enhanced therapeutic function. The tertiary amine group plays a crucial role in the pH-sensitivity of cationic polymers. It binds protons to form cationic groups under acidic conditions and releases protons under basic conditions. PDEAEM is a pH-sensitive cationic polymer with side chains that contain an ionizable tertiary amine group, as shown in Fig. 3J. A variety of PDEAEM copolymers have the ability to form pH-sensitive DDSs (Determan et al., 2007; Kavitha et al., 2013; Siegel et al., 1988; Sun et al., 2010). Drugs loaded into PDEAEM copolymer-based hydrogels can only be released at zero-order at pH 3–5, when PDEAEM is ionized, rather than at neutral pH. In recent years, the pH-sensitive polymer PbAE, which also has tertiary amine groups (Fig. 3M), has contributed to a novel class of biodegradable

Table 2
Illustrative examples of pH-responsive polymer-based nanoparticles used for drug and gene delivery.

Nanocarrier type	pH-Responsive polymer	Drug or gene	Ref
Micelles	PHis	DOX	Lee et al. (2003a)
Liposomes	NIPAM	Pyranine	Zignani et al. (2000)
Hydric nanoparticle	PNiPAM/AA	DOX	Hu et al. (2013)
Hydrogel	PAA	Crystal violet	Yue et al. (2009)
Film	PDEAEM	CPT	Kavitha et al. (2013)

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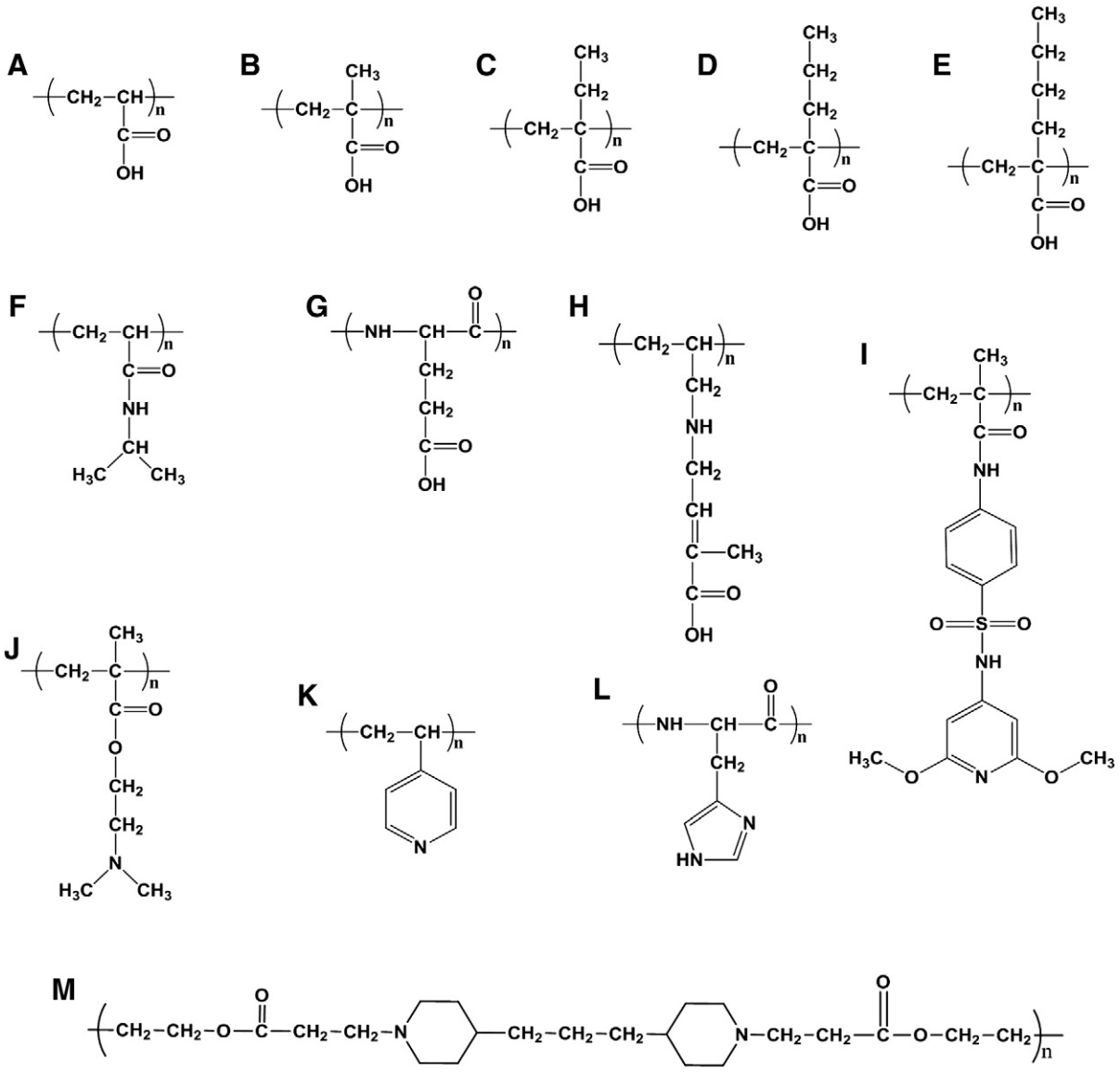

Fig. 3. Molecular formulae of representative pH-sensitive polymers. Anionic polymers: A) poly(acrylic acid) (PAA); B) poly(methacrylic acid) (PMAA); C) poly(ethylacrylic acid) (PEAA); D) poly(propylacrylic acid) (PPAA); E) poly(butylacrylic acid) (PBAA); F) N-isopropylacrylamide (NIPAM); G) poly(glutamic acid) (PGA); H) poly(allylamine hydrochloride)-citraconic anhydride (PAH-Cit); and I) polymers containing sulfonamide groups. Cationic polymers: J) poly(N,N′-dimethylaminoethyl methacrylate) (PDEAEM); K) poly(4-vinylpyridine) (PVP); L) poly(L-histidine) (PHis); and M) poly(β-amino ester) (PbAE).

cationic polymer for site-specific drug and gene delivery (Green et al., 2008; Kim et al., 2006; Lynn et al., 2001). PbAE is synthesized using bis(secondary amines) or primary amines and bis(acrylate ester) groups. This category of polymer undergoes a hydrophobic–hydrophilic phase transition as the pH decreases from basic to acidic, and can rapidly solubilize at pH values below its pKa. Therefore, in the acidic tumor microenvironment, PbAE-based nanostructures dissolve rapidly with a concomitant release of their contents. Several studies have demonstrated the non-cytotoxicity, degradation, high drug/gene delivery efficacy, pH sensitivity and tumor inhibition capability of PbAE nano-systems (Fang et al., 2012; Green et al., 2008; Song et al., 2012; Wang et al., 2005).

Another class of cationic polymer, including PVP and PHis, contains pyridine groups or imidazole groups. The pH response of PVP depends on deprotonation of the pyridine groups (Fig. 3K) (Risbud et al., 2000). Risbud et al. found that hydrogels based on chitosan and PVP with an amoxicillin payload underwent pH-dependent swelling, resulting in superior drug release in an acidic environment. The first polymer that was identified to have pH-dependent fusogenic properties was synthetic polypeptides such as poly(L-histidine) (Guo et al., 2010a). Poly(L-histidine) (PHis) forms an artificial cationic polypeptide, and has been extensively investigated for use in pharmaceutical carrier formulations because it is biocompatible and appropriately pH-sensitive (Lee et al., 2005b; Midoux et al., 2009). The hydrophobic imidazole ring of 'His' is a weak base that has the ability to acquire a cationic charge when the pH of the environment drops below 6, Fig. 3L, which induces destabilization of micellar structure (Guo et al., 2010b; Kim et al., 2008; Lee et al., 2005b, 2008; Midoux et al., 2009; H. Wu et al., 2013). Lee reported the synthesis of PEG-b-PHis via a coupling method. The copolymers formed micelles at pH 7.4 and became hydrophilic upon reduction of the solution pH below 7.4 (Lee et al., 2003b). And then, the mixed micelles prepared from a PEG-b-PHis/PEG-b-poly(L-lactic acid) (PLLA) blend were loaded with the anti-tumor drug DOX. They were destabilized at a pH range of 6.6–7.2, depending on the mixing content of PEG-b-PLLA. Minimal levels of cytotoxicity were observed at pH 7.4, but at pH below 6.8, cytotoxicity levels were nearly identical to that of free DOX, indicating a rapid release upon pH decrease, which is considered desirable (Fig. 4AB) (Lee et al., 2003a). To

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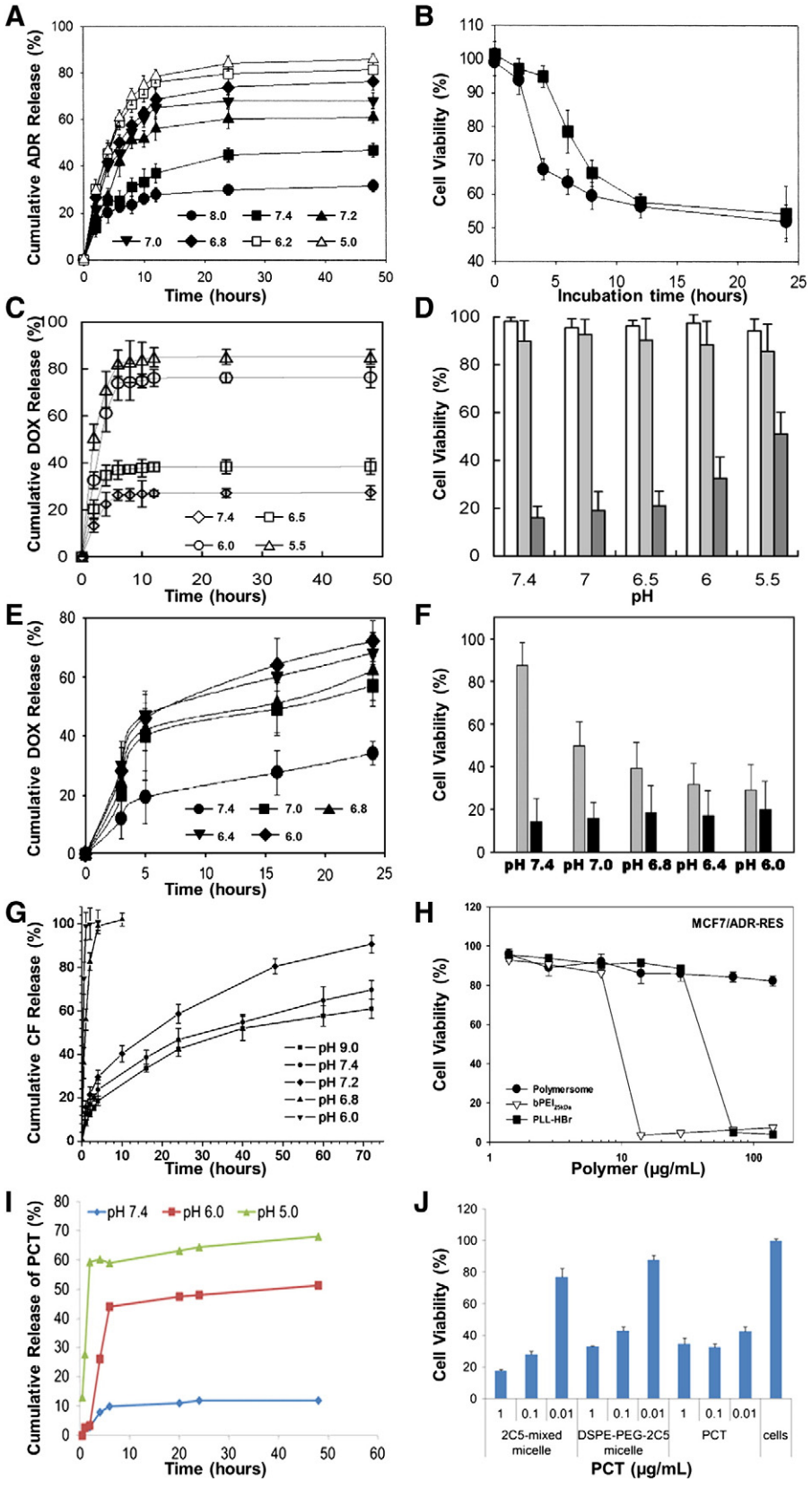
overcome multi-drug resistance (MDR) in cancer, PHis has been widely used for drug delivery (Kim et al., 2008; Lee et al., 2005a). Kim and coworkers designed optimized a mixed micelle that designed an optimized mixed micelle that was composed of PEG-b-poly(His-co-phenylalanine(Phe)) (PHP) and folate(FA)-PEG-b-PLLA, to target the early endosomal pH between tumor pH and lysosomal pH. The result showed accelerated DOX release triggered by an early endosomal pH 6.0. When the triggered release was combined with active internalization via FA receptor-mediated endocytosis, the micelle could effectively kill both wild-type sensitive and MDR cancer cell lines through



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an instantaneous high dose of DOX in the cytosol (Fig. 4CD) (Kim et al., 2008). Hydrophobic PLLA segments may be introduced into PEG-b-PHis to stabilize the micelle. At physiological pH 7.4, the triblock copolymer PLLA-b–PEG-b–PHis forms flower-like micelles. As the pH is decreased to pH 6.6, the micelles swell to form large particles that rapidly release DOX loaded in the micelles and promote cellular up-take of the drugs at pH 7.0 (Fig. 4EF) (Lee et al., 2007a). Recently, Yin et al. successfully synthesized 3-miktoarm mPEG-b–PHis2 copolymers that mimic phospholipid structures. The miktoarm copolymer self-assembled in aqueous environments to form nano-sized polymersomes with a strong proton buffering capacity and a low cytotoxicity; these polymersomes were stable above pH 7.4 but underwent a vesicle-to-micelle transition between pH 6.8 and pH 5.0 as a result of the gradual protonation of the imidazole groups. Drug-loaded polymersomes can thus provide pH-dependent drug release (Fig. 4GH) (Yin et al., 2012). Wu et al. reported PHis–PEG/DSPE–PEG copolymer micelles for cytosolic drug delivery. The low pH in endosomes induced destabilization of the micelle structure and triggered drug release, resulting in improved anti-cancer efficacy (Fig. 4IJ) (Wu et al., 2013a; Yin et al., 2012).

In summary, pH sensitivity of polymers is determined by the characteristic structure of ionizable groups and can be modulated by several structural and environmental factors (e.g., the nature of ionizable groups, the polymer composition, the ionic strength, and the hydrophilicity or hydrophobicity of the backbone polymer and side group). Anionic polymers can be divided into those with carboxylic acid groups and those with sulfonamide groups. Anionic polymers with carboxylic acid groups undergo pH-dependent polarity changes or charge-reversal, making them highly suitable for pH-sensitive drug delivery. Anionic polymers with sulfonamide group can also be utilized in DDSs. Cationic polymers containing tertiary amine group, pyridine groups, or imidazole groups undergo a pH-dependent phase transition, resulting in the release of drugs. However, the sensitivity of polymers to pH changes in the TME, the stability of polymeric nanostructures in biological fluids, and the interaction between anionic surfaces and cell membranes are parameters that still require optimization.

3.1.2. Peptides

Since the early 1980s, many studies have been performed on the membrane fusion activity of animal viruses and, as a result, many viral fusogenic peptide sequences have been identified (Wagner, 1999). However, non-viral delivery systems are preferable to viral transfer vectors because they are likely to be safer and easier to manufacture. pH-sensitive fusogenic peptides have been designed to facilitate endosomal escape (Table 3). GALA was the first peptide designed to interact preferentially with lipid bilayers at acidic pH (Subbarao et al., 1987). At low pH, the amino acid sequence of GALA yields a stable α-helix which can destabilize the lipid bilayer. This property of GALA has been utilized to enhance drug and gene delivery in vitro and in vivo (Futaki et al., 2005). The GALA motif can be covalently conjugated with suitable platforms, such as dendrimers or liposomes, to achieve an efficient delivery system. In many cases, the function of systems consisting of a drug or gene together with a nanocarrier and targeting ligands can be enhanced by pH-sensitive fusogenic peptides. As shown in Fig. 5A, these complexes bind to specific cell-surface receptors, triggering internalization through coated pit-mediated endocytosis; the drug or gene is then delivered into the cytoplasm in a pH-dependent manner (Hatakeyama et al., 2009; Toriyabe et al., 2013; Yamada et al., 2005). Yamada et al. developed a liposome-based DDS modified with GALA for selective delivery to the mitochondria of tumor cells. The liposomes contained mastoparan, a toxic peptide that permeabilizes mitochondria, causing apoptosis. Within the low-pH microenvironment of endosomes, GALA enhances the fusion between liposomes and endosomes, releasing mastoparan into the cytosol (Fig. 5B). The mastoparan peptides would then attack the mitochondria, thereby initiating antitumor activity (Yamada et al., 2005, 2013).

Table 3
Examples of pH-responsive fusogenic peptides and their sequence.

Fusogenic peptide	Sequence	Reference
HA2	GLFGAIAGFIEGGWTGMIDG	Takahashi (1990)
AcE4K	Ac-GLFEAIAGFIENGWEGMIDGK	Bailey et al. (1997)
GALA	WEAALAEALAEALAEHLAEALAEALEALAA	Subbarao et al. (1987)
shGALA	WEAALAEALAEALAEHLAEALA	Sakurai et al. (2011)
KALA	WEAKLAKALAKALAKHLAKALAKALKACEA	Guo et al. (2012)
EALA	AALAEALAEALAEALAEALAAAAGGC	Vogel et al. (1996)
GM225.1	GLFEALLELLESLWELLLEA	Collins et al. (2010)
ppTG1	GLFKALLKLLKSLWKLLLKA	Rittner et al. (2002)
INF3	GLFEAIEGFIENGWEGMIDGGGC	Plank et al. (1992)
JTS-1	GLLFEALLELLESLWELLLEA	Gottschalk et al. (1996)

A disadvantage of GALA-modified nanoparticles is that they are eliminated rapidly from circulating blood, possibly due to recognition of biomacromolecules. To circumvent this issue, the group of Hatakeyama has developed shGALA, a new and shorter version of GALA, which is masked by the aqueous layer resulting from PEG-modification (Sakurai et al., 2011). Along with the increased circulation time in vivo, shGALA still possesses ideal pH sensitivity membrane fusogenic ability to improve the endosomal escape, and demonstrates a substantial gene silencing in tumor tissue and an inhibitory effect against tumor growth without any remarkable toxicity in Fig. 5CD. It offers a higher potential for DDSs and future clinical application.

GALA itself cannot bind to nucleic acids directly, so its sequence has been modified to provide this functionality. For example, KALA is a synthetic cationic peptide that binds directly to nucleic acids such as DNA or siRNA. In KALA, the negatively-charged glutamic acid residues of GALA are replaced with positively-charged lysines. KALA is the first peptide designed to fulfill all the requisite criteria for efficient gene delivery without the aid of other components (Wyman et al., 1997). Indeed, a number of studies have utilized KALA for drug/gene delivery (Guo et al., 2012; Jeong et al., 2003; Lee et al., 2007b; Wyman et al., 1997). Once the anionic oligodeoxynucleotide (ODN) segments interact with the cationic KALA peptide, the KALA/ODN-PEG conjugate self-assembles into polyelectrolyte complex micelles in aqueous solution. Because of the pH-sensitive fusogenic activity of KALA, these complex micelles exhibit higher anti-proliferative activity (Jeong et al., 2003). Other peptides resembling GALA include EALA (Vogel et al., 1996), GM225.1 (Collins et al., 2010), ppTG1 (Rittner et al., 2002), INF3 (Plank et al., 1992) and JTS-1 (Gottschalk et al., 1996; Van Rossenberg et al., 2002). Studies on pH-sensitive fusogenic peptides and their analogs have been particularly revealing, especially regarding the requirement for a long amphipathic α-helical conformation to efficiently perturb lipid membranes. The mechanisms of membrane perturbation are fully understood, and further work is necessary to elucidate the function of these peptides.

Fig. 4. Various kinds of pH-sensitive nanosystem based on PHis for cancer therapy. A,B) pH-dependent cumulative ADR release from the mixed micelles composed of PEG-PHis and PEG-PLLA, and the cell killing rate against MCF-7 cells treated with the mixed micelle (●) and free ADR (■) at pH 6.8 (Lee et al., 2003a); C,D) pH-dependent DOX release profiles from the optimized mixed micelle that was composed of PEG-PHP and FA-PEG-PLLA, and cell viabilities determined by MTT assay of ovarian A2780/DOX^R multidrug (MDR) resistant carcinoma cells treated with micelles with folate: free DOX (white), DOX/FA-PEG-PLLA (gray), and DOX/mixed micelle (dark gray) (Kim et al., 2008); E,F) the pH-dependent cumulative DOX release from the PLA–PEG–PHis micelle, and the pH-dependent cytotoxicity of DOX-loaded flower-like micelles (black) or free DOX (gray) against MCF-7 cells (Lee et al., 2007a); G,H) In vitro release profiles of the encapsulated CF(5(6)-carboxyfluorescein) in the polymersome self-assembled from synthesized mimic phospholipid structures of 3-miktoarm mPEG-b–PHis2 copolymers at different pH, and the polymersome showed low cell cytotoxicity (Yin et al., 2012); I,J) The cumulative PCT(Paclitaxel) release from the pH-sensitive mixed micelles composed of PHis–PEG and DSPE–PEG at different pH, and cytotoxicity of PCT loaded-mixed micelles in 4T1 cells.

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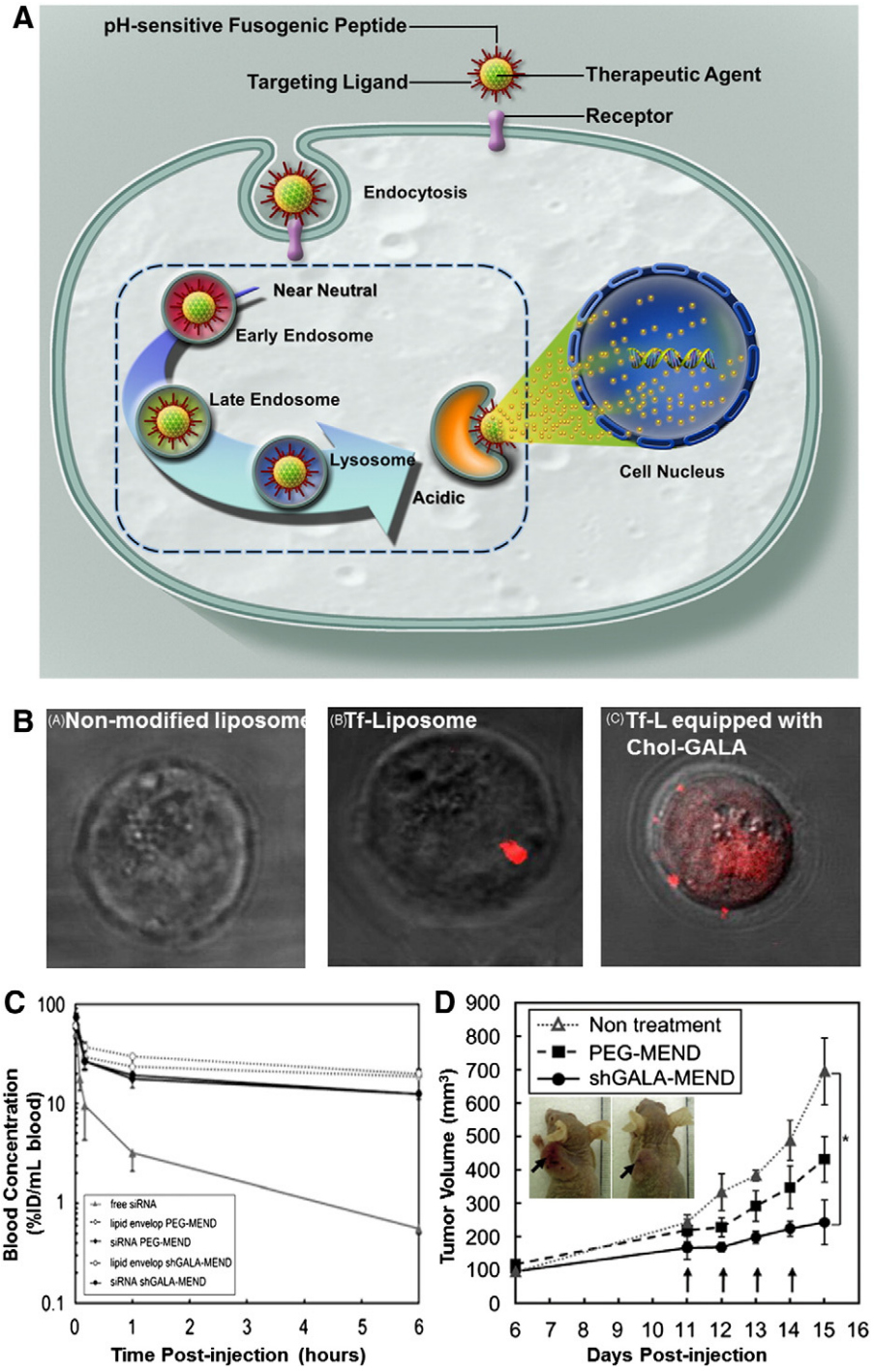

Fig. 5. A) Schematic model illustrating the strategy for drug or gene delivery by a multifunctional nanoparticle modified with targeting ligands and pH-sensitive fusogenic peptides. The strategy consists of three steps: i) binding of the targeting ligands on the surface of the nanoparticles to receptors on the cancer cell surface; ii) internalization of the nanoparticles via receptor-mediated endocytosis; iii) fusogenic peptide-mediated disruption of the membrane at low pH and release of the drug or gene from the endosome to the cytoplasm; B) Efficient cytosolic release of liposomally encapsulated sulforhodamine B from Tf-Liposome equipped with Chol-GALA in K562 cells analyzed by confocal laser scanning microscopy (Yamada et al., 2005); C,D) Blood clearance, and the time-dependent changes in tumor volume of a naked siRNA and the shGALA modified nanodevice (Sakurai et al., 2011).

In addition to the materials mentioned above, several other organic materials, such as lipids and DNA, have pH-sensitive properties that render them suitable for use in DDSs. Lipids can be used to generate liposomes, which at neutral pH can stably encapsulate highly water-soluble drugs, peptides, or nucleic acids. At low pH, the lipids are protonated, resulting in destabilization and formation of non-bilayer structures that are important intermediates in membrane fusion (Drummond et al., 2000).

3.2. Inorganic nanoscale materials

There have been rapid advances in the construction of pH-sensitive inorganic nano-systems for biomedical applications. Inorganic nano-systems can be divided into two types: hybrid nanoparticles, which use pH-sensitive chemical bonds, and nanoparticles made of inorganic materials which are themselves able to respond to pH changes. For example, calcium phosphate (CaP)-based nano-systems have considerable

potential for biomedical applications such as drug delivery. CaP is highly similar to amorphous calcium phosphate (ACP) and crystalline hydroxyapatite (HAP), both of which are major components of bone and tooth enamel. These compounds dissolve to give nontoxic calcium and phosphate ions in acidic microenvironments. This unique property provides a multifunctional platform for delivery of drugs, fluorescent dyes, or other organic cargo to a cell or organelle (Banerjee et al., 2011; Morgan et al., 2008). Kester et al. successfully encapsulated organic fluorophores and hydrophobic chemotherapeutics into CaP nanoparticles. CaP nanoparticles provide a pH-tunable method to deliver encapsulated molecules to targeted cells with minimal background release (Kester et al., 2008; Rim et al., 2011).

Similar to CaP nanoparticles, unprotected ZnO quantum dots (QDs) decompose completely at pH 5 in aqueous solution. Therefore, ZnO QDs can also be employed as platforms for targeted and pH-responsive intracellular delivery of anticancer drugs (Barick et al., 2010; Yuan et al., 2010b). Muhammad et al. demonstrated that ZnO QDs dissolve rapidly in the acidic environment of intracellular compartments in cancer cells, releasing DOX molecules into the cytosol and killing the cells (Muhammad et al., 2011).

Following these established examples, pH-sensitive inorganic materials can be used selectively to design drug delivery nano-systems for cancer therapy by modification with diverse chemical groups. In addition to synthesis, the functionalization, solubilization and assembly of inorganic nanomaterials are aspects of significant relevance that warrants future research.

3.3. Hybrid organic and inorganic nanomaterials

Organic and inorganic materials have complementary physical, chemical and biological properties, which can be exploited to develop hybrid nanomaterials for enhanced DDSs. Hybrid nanomaterials have recently emerged as promising platforms for therapeutic applications. This unique class of nanomaterial not only retains the favorable features of both the inorganic and organic components, but also provides the ability to systematically fine-tune the properties of the hybrid material via the combination of functional components (Wang et al., 2013).

By exploiting the pH-sensitivity of organic or inorganic components, hybrid nanoparticles can also respond to pH, resulting in drug release in acid conditions. Our group has developed several pH-responsive hybrid nanoparticles based on pH-sensitive organic compounds. We firstly demonstrated that gold nanoparticles (AuNPs) modified with organic polymers can effectively facilitate the release of drugs or nucleic acids in vitro and in vivo based on pH-induced charge-reversal (Guo et al., 2010a). Further, targeted knockdown of *MDR1* mRNA expression in drug-resistant breast cancer cells by this hybrid carrier is significantly more efficient than by PEI (Fig. 6A–D) (Han et al., 2012). The pH sensitivity of PAA hydrogels has attracted considerable attention in the last few years (Das et al., 2006). Hu et al. designed a facile pH- and temperature-responsive nanocarrier by employing a dually sensitive poly(N-isopropylacrylamide)-co-acrylic acid(PNiPAM/AA) hydrogel core enclosed in a silica shell with DOX as a model drug (Fig. 6E–G). Due to the relatively abrupt phase transition of AA, PNiPAM/AA@SiO_2 showed improved drug release efficiency in acidic medium, decreased cumulative drug release in neutral medium, and dramatically enhanced cell cytotoxicity (Hu et al., 2013; Peng et al., 2013; Su et al., 2013). In recent decades, the utilization of DNA as delivery vehicles has gained significant traction of the scientific community, largely due to its functionality and versatility, bridging the gap between materials sciences and biological systems (Shieh et al., 2010). Song and coworkers reported that proton-fuelled DNA formed stable complexes with DOX at pH 7.4, and released the drug at pH <5.3 (Song et al., 2013). The PF-DNA–DOX binding/release process was efficient, rapid and reversible. Conjugation of PEG-modified DNA to AuNPs produced a multivalent PF-DNA–AuNP nanocarrier that resisted non-specific adsorption and could be used for efficient delivery and pH-responsive release of DOX into cancer cells, leading to high cytotoxicity (Fig. 6H–J).

The inorganic components of hybrid nanomaterials can also confer pH sensitivity. Zhang et al. created hybrid nanoparticles using the non-toxic polymer polyacrylamide as a protective shell around ZnO QDs. In vitro studies showed that after the polyacrylamide had degraded, the ZnO QD core was responsive to low pH and released DOX to destroy glioblastoma cells effectively (Zhang et al., 2013). Khandare and co-workers reported a novel hybrid core-shell nanostructure fabricated with PAMAM-G4-NH_2 dendrimers as the core and calcium phosphate as the shell. The CaP shell prevented the encapsulated DOX from escaping under extracellular conditions, but dissolved within lysosomal compartments where the pH is near 5.0 (Khandare et al., 2013).

4. Nano-systems containing acid-labile chemical bonds

A number of chemical bonds are known to be unstable in strong acids or bases. Acid-labile chemical bonds have received widespread attention for use in pH-sensitive DDSs for cancer therapy. Systems containing acid-labile linkers, which can release the drug at slightly acidic pH, are proving popular for the design of intelligent carriers with a variety of architectures. Compounds containing acid-sensitive bonds can be used to construct nanocarriers or to couple drugs to suitable carriers as a way to trigger drug release in acidic environments, as shown in Fig. 7. In this section, we discuss the various smart drug delivery systems based on acid-labile chemical bonds, including acid-labile polymers and hydrogels, hybrid particles, self-assembled particles, and polymer-drug conjugates.

4.1. Applications of acid-labile chemical bonds in the construction of nanocarriers

pH-Responsive polymers with acid-labile chemical bonds are designed to remain stable at physiological pH, but degrade quickly in the mildly acidic environment of lysosomes, endosomes, or tumor tissues, leading to rapid drug release. The acid-sensitive chemical bonds are contained within the polymer structure, either in the backbone (including the junctions of block copolymers), or in the side chains. After these polymers are incorporated into nanostructures, they still retain their pH-responsiveness, resulting in the collapse of the entire nanostructure and release of the cargo.

Heller et al. first reported the synthesis of linear and cross-linked polyacetal by condensation of polyols with divinyl ethers (Heller et al., 1980). Polyacetals rapidly hydrolyze at acidic pH and therefore have the potential to act as biodegradable carriers for anticancer drug delivery (Gillies and Frechet, 2003; Kim et al., 2010). A pH-responsive drug delivery system was developed by PEGylating the commercially available aliphatic dendritic polyester Boltorn® H40 (H40), thus forming acetal linkages. The resulting star copolymer (H40-star-mPEG), with a hydrophobic H40 core and many hydrophilic mPEG arms, self-assembled into stable micelles in aqueous solution. In an acidic environment, drug release from DOX-loaded micelles was greatly accelerated (Fig. 8A) (Tu et al., 2013). Heffernan et al. used a novel hydrophobic polymer, poly(1,4-phenyleneacetone dimethyleneketal) (PPADK), containing ketal linkages in its backbone, to formulate polyketal nanoparticles. In acid conditions, the nanoparticles were hydrolyzed to low molecular weight hydrophilic compounds, and the encapsulated therapeutic molecules were released at an accelerated rate (Fig. 8B) (Heffernan and Murthy, 2005; Shim and Kwon, 2012).

Among the acid-sensitive polymers, polyorthoesters have the longest history since their inception in 1970 (Heller et al., 2002; Tang et al., 2011; Toncheva et al., 2003). Hydrophilic PEG and hydrophobic poly(γ-benzyl L-glutamate) (PBLG) can be combined to form an amphiphilic block copolymer bearing orthoester linkages that is capable of selectively releasing hydrophobic drugs in mildly acidic conditions (Fig. 8C). From in vitro cytotoxicity tests, it was found that DOX-loaded pH-sensitive micelles

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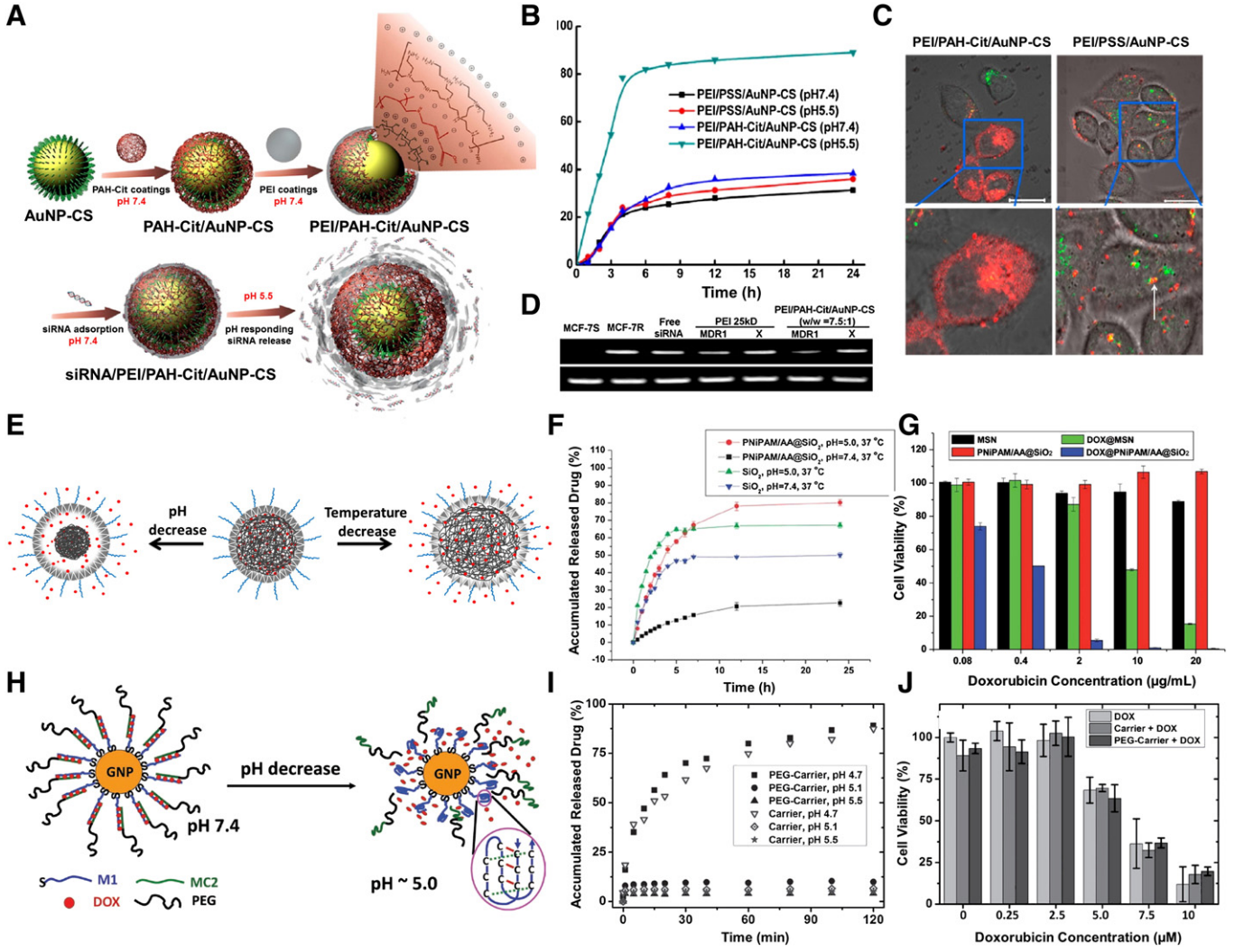

Fig. 6. Enhanced drug and gene delivery by hybrid nanoparticles. A) Scheme showing layer-by-layer assembly of AuNPs followed by pH-responsive release of siRNA(Han et al., 2012);B) Profile of siRNA release from siRNA/PEI/PAH-Cit/AuNP-CS complexes; C) Confocal images of HeLa cells incubated with cy5-siRNA (red) complexed with PEI/PAH-Cit/AuNP-CS, and PEI/PSS/AuNP-CS indicated the lysosome escape of siRNA; D) *MDR1* knockdown efficacy detected by PCR; E) Temperature- and pH-sensitive dual-responsive PNiPAM/AA@SiO_2 core–shell nanoparticles for controlled drug delivery (Hu et al., 2013); F) DOX release profiles from DOX@MSN, DOX@PNiPAM/AA@SiO_2 under different pH; G) The cytotoxi city of different nanoparticles to MCF-7 cells; H) Principle of the PF-DNA-GNP for pH-triggered drug delivery (Song et al., 2013); H) DOX release profiles from the carrier systems at pH 4.7, 5.1, and 5.5; J) MTT assay of HeLa cell viabilities after incubation with DOX, (Carrier + DOX) and (PEG-Carrier + DOX).

showed higher toxicity to SCC7 cancer cells than DOX-loaded micelles without orthoester linkers (Thambi et al., 2011; Yuan et al., 2011). The hydrazone bond is another pH-sensitive chemical bond that is widely used in DDSs (Ossipov et al., 2010; Patenaude and Hoare, 2012). Multi-block polyurethanes based on hydrazone bonds have been developed for the construction of intelligent nano-systems that undergo stepwise biodegradation. These polymers use PCL and pH-sensitive PCL-hydrazone-PEG-hydrazone-PCL macrodiol (PCLH) as the soft segment, L-lysine ethyl ester diisocyanate (LDI), L-lysine derivative tripeptide and 1,4-butandiol (BDO) as the hard segment and hydrazone-linked methoxyl-PEG (mPEG-Hyd) as the end-capper (Zhou et al., 2012). Using this copolymer, Ding et al. have designed and prepared a pH-sensitive DDS for targeted delivery of the drug paclitaxel (PTX) to tumor cells. This nanocarrier demonstrated unique properties, such as pH-dependent shell-detachment on arriving at the tumor site, and intracellular drug release in response to acidity within tumor cells. As a result, these nanoparticles could significantly improve the biodistribution and anticancer efficacy of chemotherapeutic drugs in vivo (Ding et al., 2013; Lin et al., 2010). Polyethylenimine (PEI) is yet another polymer that can be used as a gene carrier with high transfection efficiency. Kim et al. synthesized biodegradable PEI with acid-labile imine linkages as a vector for pDNA delivery. The PEI, which rapidly degraded in acidic conditions, showed a transfection efficiency close to that of PEI25K, but was much less toxic due to degradation of the acid-labile linkage. Therefore, acid-labile PEIs may be useful for the development of non-toxic polymeric gene carriers (Fig. 8D) (Ding et al., 2009; Kim et al., 2005; Quan et al., 2010; Wang et al., 2011a). Hu et al. combined a glycolipid-like conjugate (CS) with PEG via a pH-responsive cis-aconityl linkage to produce acid-sensitive PEGylatedCS conjugates (PCCS). Within in vitro environments, the release of DOX from PCCS micelles was more rapid in weakly acidic environments (pH 5.0 and 6.5 in Fig. 8E) (Hu et al., 2012).

In recent studies, biological molecules or nanoparticles, such as AuNPs, β-CD, and proteins, have been conjugated onto mesoporous silica nanoparticles (MSNs) through specific bonds including pH-sensitive linkages which function as gatekeepers for controlled drug release (Agostini et al., 2012; Aznar et al., 2007, 2009; Chen and Zhu, 2012; Wu et al., 2013b). These acidic-labile chemical bonds are indispensable for conferring pH sensitivity on nanocarriers (Lim et al., 2011). Liu et al. capped MSNs with AuNPs through an acid-labile acetal linker to create a pH-responsive MSN-based controlled release system. At neutral pH, the linker remained intact and the pores were blocked with AuNPs,

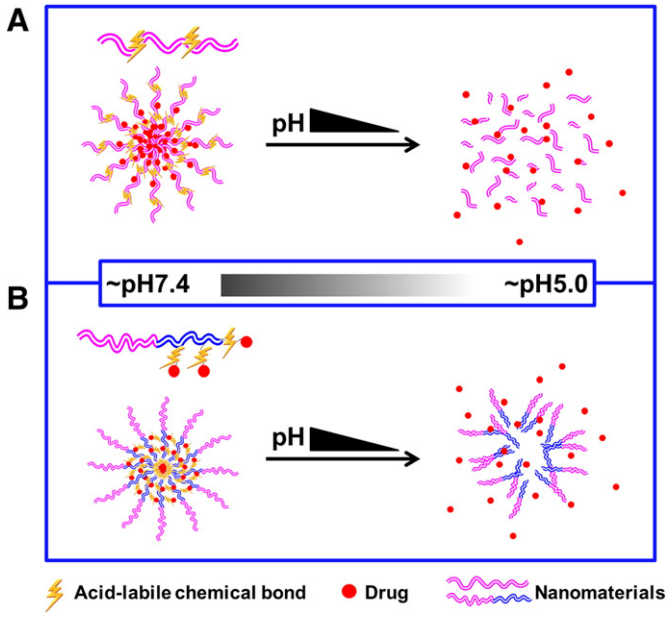

Fig. 7. Schematic representation of the mechanisms of drug release from acid-labile chemical bond-based nano-systems. A) Acid-labile chemical bonds used in the construction of a nanocarrier. B) Acid-labile chemical bonds used to conjugate drugs to nanocarriers.

inhibiting molecular diffusion. At acidic pH, the acetal group hydrolyzed, resulting in the removal of gold cap and escape of the molecules trapped within the MSN pores (Liu et al., 2010). Similar work was reported by Meng et al., who synthesized a novel MSN-based delivery system capable of delivering drugs based on the function of β-CD nanovalves that were responsive to the acidic endosomal microenvironment in human differentiated myeloid (THP-1) and squamous carcinoma (KB-31) cell lines. N-methylbenzimidazole stalks with optimized pKa endowed the nano-valves with the ability to bind the β-CD ring strongly at pH 7.4 and trap cargo molecules in the nanopores. During deprotonation at pH <6 in acidic endosomal compartments, the β-CD caps were dissociated and the cargo was released from the ring structure into the cytosol (Gan et al., 2012; Meng et al., 2010).

4.2. Conjugation of nanocarriers and drugs for prodrug therapy

Another strategy for pH-sensitive drug release is to use acid-labile linkers to conjugate drugs covalently to carriers molecules or to the surfaces of nanostructures, forming prodrugs that are inactive until the linker is hydrolyzed (Duncan, 2006). In this section we review work on the release of drugs from nanocarriers by cleavage of various chemical linkages.

Anthracyclines, such as doxorubicin (DOX) and daunorubucin (DAU), possess a primary amino group and a keto group that are suitable for covalent attachment to polymer chains via amide bonds (Du et al., 2013; Kakinoki et al., 2008) and hydrazone bonds (Lu et al., 2009; Rihova et al., 2001) respectively. The hydrazone bond formed between the C13 carbonyl group of anthracyclines and polymer hydrazides is one of the most commonly used for the preparation of nanocarrier–drug conjugates (Hruby et al., 2005; Kamada et al., 2004; Prabaharan et al., 2009b; Ulbrich et al., 2004). The conjugate of the (6-maleimidocaproyl) hydrazone derivative and DOX (DOXO-EMCH) is an albumin-binding prodrug with acid-sensitive properties that demonstrates superior antitumor efficacy. It was the first albumin-binding prodrug of DOX to enter clinical trials (Kratz, 2007). Since then, an increasing number of polymer-DOX prodrugs have been developed and evaluated as DDSs (Calderon et al., 2011; Rao et al., 2012; Zhan et al., 2011; Zhou et al., 2011). For example, Du et al. developed tailor-made dual pH-sensitive polymer–drug conjugate nanoparticles (PPC–Hyd-DOX–DA) for efficient anticancer drug delivery. DOX was conjugated to the polymer through an acid-labile hydrazine bond. These nanoparticles responded to both extracellular and intracellular pH environments, simultaneously enhancing cellular uptake and promoting acid-triggered intracellular drug release. With dual pH sensitivities, these nanoparticles showed enhanced inhibition of the progression of drug-resistant SK-3rd cancer stem cells, indicating their great potential for cancer therapy (Du et al., 2011). Recently, She and co-workers developed heparin-DOX conjugate-based nanoparticles as a pH-responsive delivery system for anticancer drugs. The DOX-conjugated nanoparticles showed pH-sensitive properties due to the presence of hydrazone bonds. Notably, these nanoparticles had strong antitumor and anti-angiogenesis effects, and induced significant apoptosis in the 4 T1 breast tumor model (She et al., 2013).

Attaching DOX to inorganic nanoparticles is also an effective way of constructing smart drug delivery nano-systems (Cui et al., 2012; Prabaharan et al., 2009a; Yang et al., 2011; Yuan et al., 2010a). Savla et al. designed a tumor-targeted, pH-responsive QD-mucin1 aptamer–DOX (QD-MUC1–DOX) conjugate for chemotherapy of ovarian cancer. DOX was attached to QDs via a pH-sensitive hydrazone bond in order to ensure that the complex was stable in the systemic circulation and released the drug only within the acidic environment inside cancer cells. The QD-MUC1–DOX conjugate had higher cytotoxicity than free DOX in multidrug-resistant cancer cells and preferentially accumulated in ovarian tumors (Lee et al., 2011; Savla et al., 2011). The group of Wang developed a drug delivery system in which DOX was tethered to the surface of AuNPs with a PEG spacer via an acid-labile linkage hydrazone bond (DOX–Hyd@AuNPs) in Fig. 9A. Using this system, they demonstrated that multidrug resistance in cancer cells could be circumvented by the combination of highly efficient cellular entry and pH-responsive intracellular release of DOX from the AuNPs in acidic organelles. Compared to free DOX, the DOX–Hyd@AuNPs achieved enhanced drug accumulation and retention in multidrug-resistant MCF-7/ADR cancer cells (Fig. 9BC) (Wang et al., 2011b).

Hydrazone bonds can also be used to link polymers with other anticancer drugs, such as cisplatin, which is widely used in the clinic for cancer therapy. To improve the therapeutic index of cisplatin and to minimize its adverse side effects, cisplatin analog Pt(IV) prodrugs have been synthesized (Dhar et al., 2008). Aryal et al. covalently conjugated Pt(IV) to PEG–PLA polymeric nanoparticles through a hydrazone bond, with the aim of minimizing drug loss while the nanoparticles were circulating in the blood. Once the particles were endocytosed by target cells, the drug was released in the low pH environment. The drug release profile suggested that these were promising nanoparticles for suppressing cancer cell chemo-resistance by rapidly releasing a high drug dose within the tumor cells, thereby improving the therapeutic efficacy of the drug payload (Fig. 9D–F) (Aryal et al., 2010). Paclitaxel (PTX) and docetaxel (DTX) are antineoplastic agents with high activity against various solid tumors. Etrych et al. described polymer prodrugs based on conjugation of PTX and DTX via hydrazone bonds with the copolymer HPMA. This polymer–drug conjugate was designed to achieve prolonged blood circulation and release of the active compound in target tumor cells. The PTX-containing conjugate showed enhanced antitumor efficacy in the 4T1 mammary carcinoma model than the parent drug and its derivative. The PTX-containing conjugate demonstrated highly activity in treating EL4T lymphoma cells (Etrych et al., 2010).

Besides hydrazone bonds, other pH-sensitive chemical bonds can also be used in nanocarrier–drug conjugates (Xie et al., 2007; Yoo et al., 2002; Zhang et al., 2005). Kakinoki et al. synthesized PVA–DOX conjugates containing cis-aconityl acid-cleavable bonds. When PVA–cis-DOX entered the cells and reached the lysosomal/endosomal compartments, DOX was released from the conjugate due to participation of the free carboxylic acid group in hydrolysis of the aconityl linker (Kakinoki et al., 2008). Liu et al. fabricated a novel type of multifunctional pH-disintegrable micellar nanoparticle by covalently conjugating DOX, folic acid (FA), and DOTA–Gadolinium moieties with asymmetrically functionalized β-cyclodextrin (β-CD)-based star copolymers for

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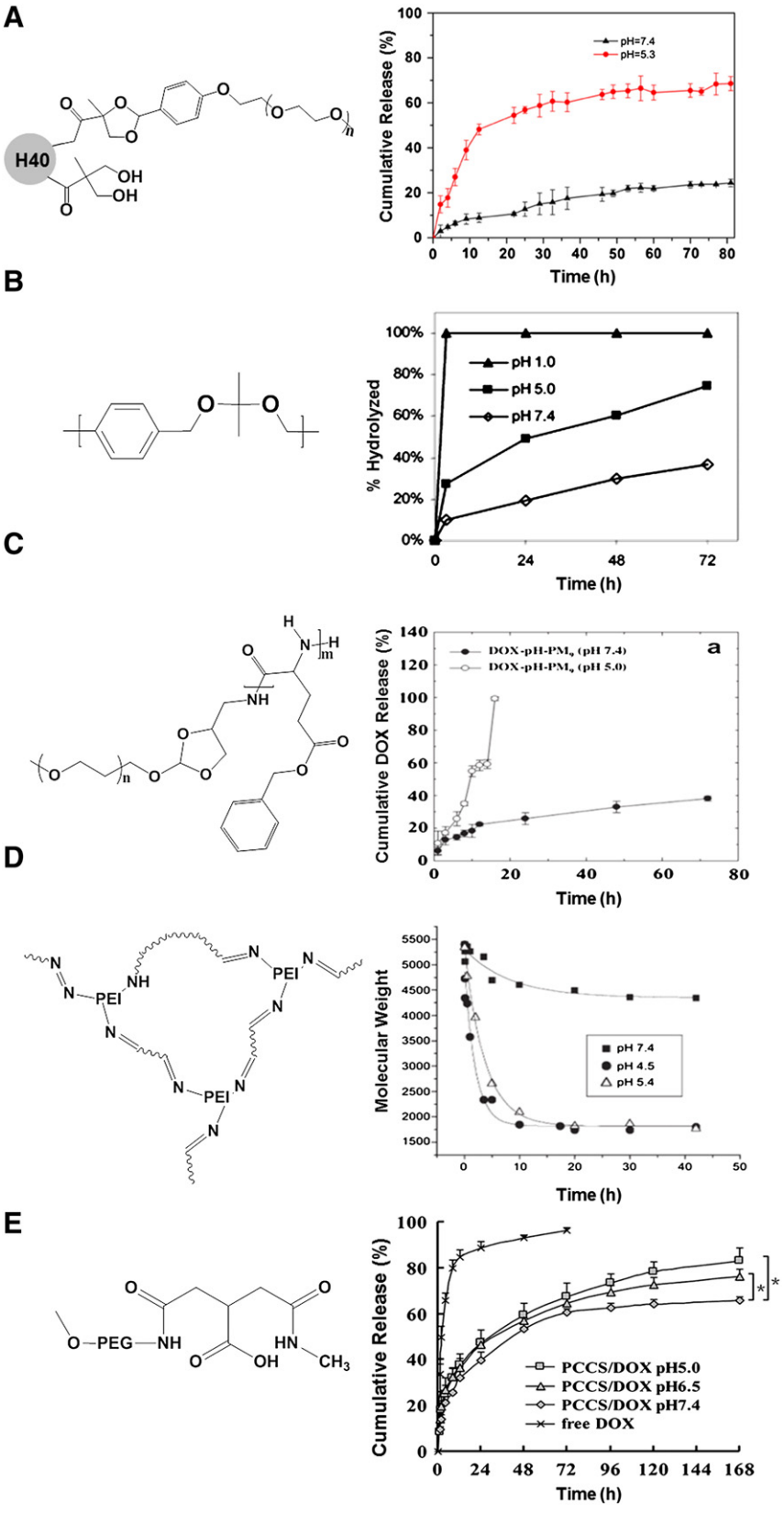

Fig. 8. Acid-labile chemical bonds used in the synthesis of polymer to construct the nanocarrier for drug delivery. A) Cumulative release curves of DOX from DOX-load H40-*star*-MPEG-2 under different pH values (Tu et al., 2013); B) Hydrolysis kinetics of PPADK (finely ground powder) at pH 1.0, 5.0, and 7.4 (37 °C) (Heffernan and Murthy, 2005); C) Release profiles of DOX from DOX-loaded micelles containing orthoester linkages (Thambi et al., 2011); D) Degradation of acid-labile PEI. Decreasing molecular weights due to hydrolysis of polymer as a function of time at pH 7.4, pH 5.4, and pH 4.5 (Kim et al., 2005); E) Release profiles of DOX from PCCS/DOX under different pH (Hu et al., 2012).

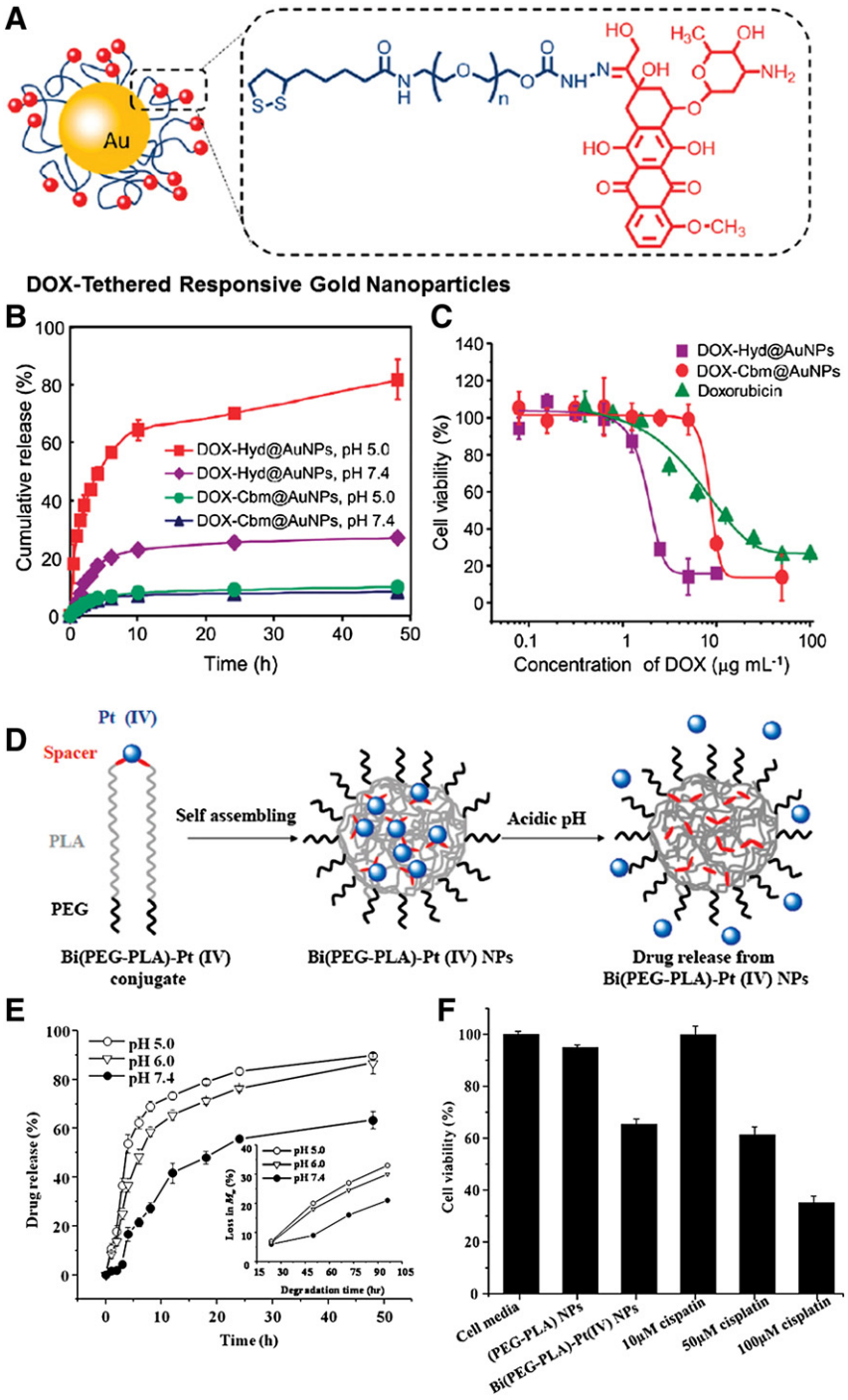

Fig. 9. Acid-labile chemical bonds used to conjugate drugs to nanocarriers. A) Schematic illustration of doxorubicin (DOX)-tethered responsive gold nanoparticles; B) Quantitative analyses of the in vitro release of doxorubicin from doxorubicin-tethered AuNPs at pH 7.4 or in acetate buffer at pH 5.0; C) Viability of MCF-7/ADR cells after treatment with free doxorubicin or doxorubicin-tethered AuNPs for 72 h (Wang et al., 2011b); D) Schematic illustrations of the structure of polymer cisplatin prodrug conjugate, the formation of Bi(PEG-PLA)-Pt(IV) NPs through self-assembling, and acid-responsive drug release from the NPs; E) Cisplatin release profile from Bi(PEG-PLA)-Pt(IV) NPs at different pH buffer at 37 °C. Inset: Hydrolytic degradation rate of PEG-PLA NPs at pH 5.0, 6.0, and 7.4; F) MTT assay to measure the cytotoxicity of Bi(PEG-PLA)-Pt(IV) NPs against A2780 human ovarian carcinoma cell line in comparison with cell culture media, PEG-PLA NPs and free cisplatin (10, 50, and 100 μM). The amount of cisplatin loaded in the Bi(PEG-PLA)-Pt(IV) NPs was equivalent to 7 μM free cisplatin drug(Aryal et al., 2010).

integrated cancer cell-targeted drug delivery and MRI contrast enhancement. The DOX molecules were covalently conjugated onto poly-*N*-(2-hydroxypropyl) methacrylamide (PHPMA) arms via acid-labile carbamate linkages and ester bonds. The in vitro DOX release profile from the micellar nanoparticles was highly pH-dependent, and the DOX-conjugated nanoparticles could effectively enter and kill HeLa cancer cells (Liu et al., 2012b). Recently, Du and coworkers prepared a FA-BSA–cis-aconitic anhydride–DOX prodrug, FA-BSA–CAD. DOX was attached to the BSA via a pH-sensitive linker, cis-aconitic anhydride, which was capable of being hydrolyzed in the acidic lysosomal environment. In vitro test results demonstrated pH-responsive drug release under different pH conditions. The therapeutic efficacy of the prodrug for FA-positive tumors was higher than non-conjugated DOX (Du et al., 2013).

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Acid-labile chemical bonds can be applied to many areas of DDS research. Different bonds can be used for a wide variety of applications depending on their synthetic capabilities. Indeed, hydrazone coupling is leading the way in the development of acid-cleavable nanocarrier–drug conjugates with a variety of different architectures. Every bond can be used to construct nanostructures for DDSs. Work carried out during the last decade has paved the way for a new generation of intelligent drug carriers, with tailored structures and delivery properties.

5. Gas-generating pH-sensitive nano-systems

Recently, a novel type of pH-sensitive nanoparticle has been developed, which can generate carbon dioxide (CO_2) gas. It is well known that HCO_3^- reacts with acid to produce carbonic acid, which easily decomposes to yield CO_2 gas and H_2O. Therefore, nanoparticles containing HCO_3^- has the potential to trigger selective drug release in an acidic environment. Sung and co-workers reported a novel smart system based on PLGA hollow microspheres (HMs) that could deliver anticancer drugs into tumor cells and quickly release the drug in acidic organelles. The key component of this system was sodium bicarbonate ($NaHCO_3$), which was incorporated into HMs together with an anticancer drug (DOX) using a double emulsion method. In an acidic environment, the $NaHCO_3$ reacts with hydrogen ions to generate CO_2 bubbles, which causing the microsphere wall to burst and thereby swiftly releasing the anticancer drug (Ke et al., 2011). The release of DOX from the $NaHCO_3$-containing HMs was dependent on the pH in the endocytic organelles. Once the HMs reached the lysosomal compartments, where the pH was near 5.0, DOX release was triggered promptly by the formation of CO_2 bubbles. The same drug delivery system was also used to overcome multidrug resistance. Multidrug-resistant cells often express high levels of the P-gp transporter protein, which rapidly transports drug molecules out of the cell. The PLGA HMs delivered DOX into MDR cells via the macropinocytosis pathway, thus bypassing P-gp-mediated efflux and releasing DOX promptly in acidic intracellular organelles. DOX is then rapidly accumulated in the nucleus above the threshold to kill the cancer cells (Ke et al., 2012, 2013). In our lab, we encapsulated DOX in a novel pH-sensitive liposome, which was prepared by a NH_4HCO_3 gradient method (Liu et al., 2012a). This was an improvement compared to the traditional $(NH_4)_2SO_4$ gradient method. The liposomes were able to release the drug at pH 5.0 by producing CO_2 gas. In vitro, the release of DOX from the pH-sensitive liposomes was pH-dependent. The cumulative amount of DOX released at pH 7.4 in 48 h was in the range of 25%, while at pH 5.0, about 60% of the drug was released in the first 2 h. More importantly, the drug-loaded liposomes were able to circumvent the DOX resistance of the breast cancer cells due to enhanced cellular uptake and endosomal escape (Fig. 10). In summary, this work provided new insights into resolving the issue of multidrug resistance of cancer cells using multifunctional liposomes.

Such pH-sensitive nano-systems can potentially be used for controlled release of drugs in acidic organelles. The gas-generating strategy, which harbors major advantages when preparing nano-systems, is considered to be a potentially useful method in the treatment of cancer.

6. Conclusion and future prospects

Harnessing the acidic pH of the cancer environment has proven to be a powerful and effective strategy for drug delivery by nano-systems. In this review, we have focused on the mechanism and design of pH-sensitive nano-systems. Several materials with pH sensitivity have shown great potential in constructing nano-systems for drug delivery, and acid-labile chemical bonds can be used flexibly in nano-system according to their properties. However, several challenges still remain, which needs to be addressed by future studies. The biocompatibility and biodegradability of the nano-systems must be improved and the

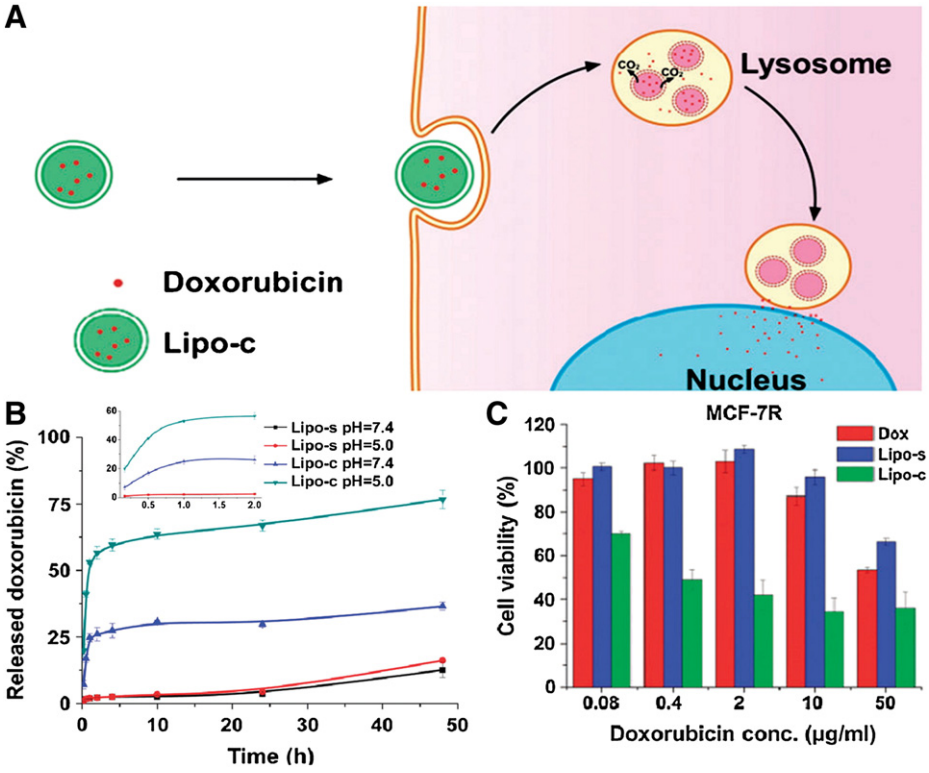

Fig. 10. A pH-sensitive liposome based on gas generating (Liu et al., 2012a). A) Schematic illustration of the novel doxorubicin-loaded liposomes, and intracellular release of doxorubicin into the cells due to the production of CO_2 in a pH-responsive way. B) Quantitative analysis of the released doxorubicin from pH-sensitive liposome (Lipo-c) and normal liposome (Lipo-s). C) Cell viability of the resistance MCF-7 cells after treatment with doxorubicin-loaded liposomes.

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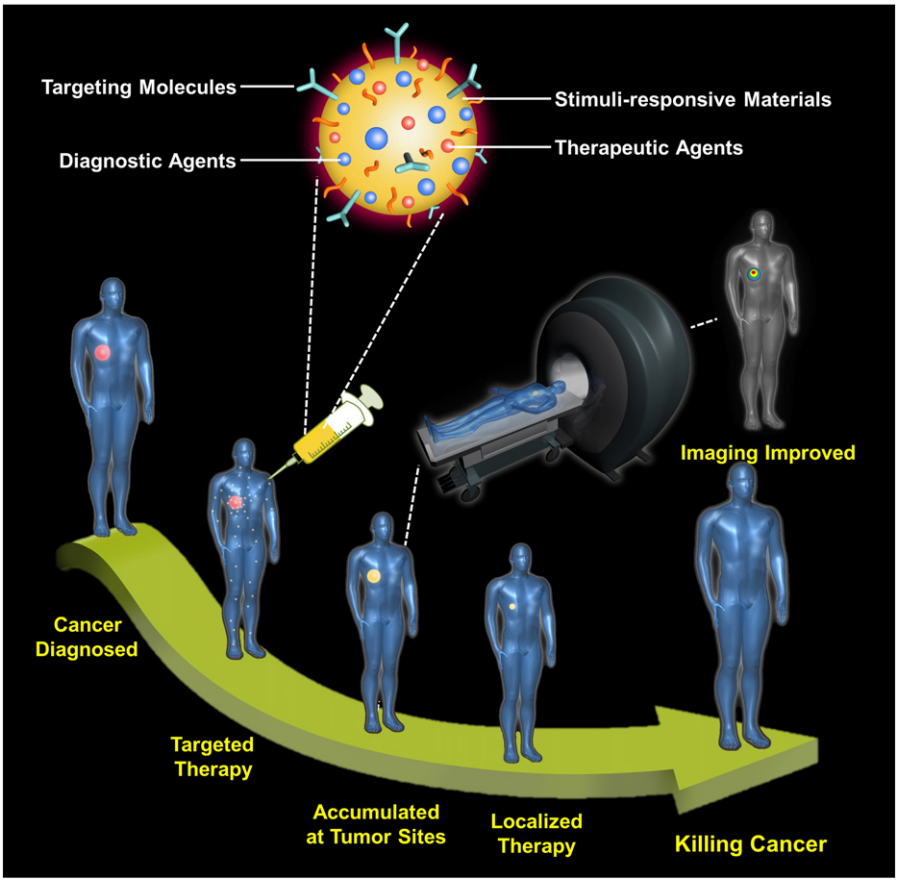

Fig. 11. An illustration of how "all-in-one" nano-systems may be used in the human body for cancer therapy in the future.

speed of the response to the pH stimulus must be tuned for certain applications. Certain ligands (e.g., antibodies, peptides, and nucleic acids) that actively target a tissue type can be conjugated onto the surfaces of nanoparticles to achieve highly efficient targeting and accumulation in cancer sites. Other stimuli may be combined with pH sensitivity to develop multifunctional drug delivery nano-systems. All-in-one systems combing diagnostic and therapeutic agents may be introduced to enable the visual tracking of cancer therapy, as shown in Fig. 11. In the near future, we anticipate that multifunctional drug delivery nano-systems for cancer therapy will be developed for actual clinical applications.

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