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REVIEW

Stimuli-responsive nanocarriers for intracellular delivery

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Abstract
The emergence of different nanoparticles (NPs) has made a significant revolution in the field of medicine. Different NPs in the form of metallic NPs, dendrimers, polymeric NPs, carbon quantum dots and liposomes have been functionalized and used as platforms for intracellular delivery of biomolecules, drugs, imaging agents and nucleic acids. These NPs are designed to improve the pharmacokinetic properties of the drug, improve their bioavailability and successfully surpass physiological or pathological obstacles in the biological system so that therapeutic efficacy is achieved. In this review I present some of the current approaches used in intracellular delivery systems, with a focus on various stimuli-responsive nanocarriers, including cell-penetrating peptides, to highlight their various biomedical applications.

Keywords Nanocarrier · Drug delivery · Stimuli-responsive · Intelligent materials · Nanomedicine

Introduction

Nanotechnology research has made a progressive impact in the field of medicine. Nanomaterials, such as liposomes, dendrimers, polymers, metallic nanoparticles (NPs), quantum dots, nanogels and peptidic NPs are now being developed as intracellular carriers for drug and gene delivery. These nanocarriers are developed using a carrier platform and target ligands and payload for sensing, imaging or therapy. Their applications have been primarily focused on either therapy, diagnosis, or both, a field now referred to as "theranostics" (Koo et al. 2011; Lehner et al. 2013). These intelligent carrier systems have been developed because of their responsive nature to one of the various external stimulus, such as pH, temperature, light or ultrasound (Frenkel 2008; Liu et al. 2009). Modern diagnostic and therapeutic platforms are now utilizing the molecular machinery of these nanocarriers for different clinical applications (Shim and Kwon 2012). These intelligent nanocarriers are purposely designed to improve the efficacy and enhance the safety profiles of drug delivery systems and, in particular, to increase target specificity for non-viral drug gene delivery (Jeong et al. 2007). Different payloads, such as drugs, imaging agents, proteins, small interfering RNA (siRNA) and functional genes, for cancer therapies are now being used in both in vitro and in vivo studies (Yokoyama 2002; Waehler et al. 2007).

In general, carrier systems enhance the solubility of poorly water-soluble drugs, increase their bioavailability, protect drugs or functional genes from harsh conditions or release them in a sustained or triggered fashion at the desired site of the organism. It has been reported that certain polymeric nanocarriers have the potential to accumulate in specific tissues, such as tumors, through an enhanced permeation and retention (EPR) effect which is largely attributed to the leaky vasculature and lack of efficient lymphatic drainage (Maeda et al. 2000). The EPR effect has been observed in chronic inflammations and infections, highlighting the potential therapeutic application of these nanomachines. The design of these carrier systems is an essential factor that will dictate their ability to possess the appropriate particle size, ensure biocompatibility and stealth properties, optimize specificity and achieve the controlled release functionality in the biological system. A main focus of current research is the development of stimuli-responsive—or intelligent—drug carriers that are able to release their cargo at the desired target site in a controlled or programmed fashion. Many pathological conditions, such as malignant neoplasms, are characterized by abnormal changes in the microenvironment, including changes in pH, temperature, levels of expressed enzymes and oxygen concentration (Yokoyama 2014; Koo et al. 2011). These characteristics have been widely exploited to develop stimuli-responsive drug carriers that

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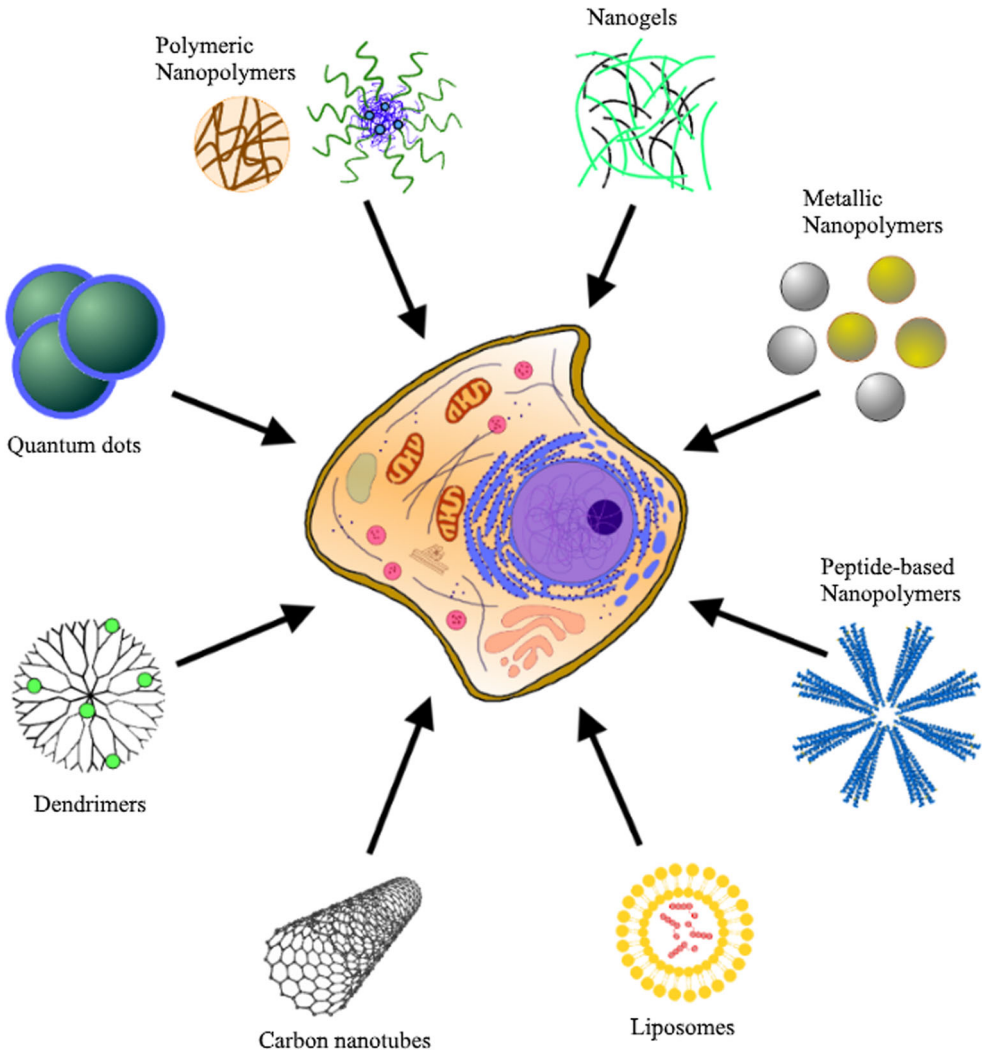

Fig. 1 Representation of the various nanoparticle (NP) platforms used for intracellular delivery

disintegrate and release their cargo in response to the stimuli at the disease site (Pärnaste et al. 2017). Moreover, the release of active agents from the drug carriers can be manipulated externally from the outside the living organism using devices which generate light, ultrasound or even a magnetic field (Liu et al. 2017).

Once these molecular machines arrive at the target site inside the living organism, several barriers must be overcome. Nanocarriers are believed to be internalized by endocytic processes (Canton and Battaglia 2012). These cellular uptake processes involve vesicular internalization. The most widely studied endocytic pathways are clathrin-mediated endocytosis, caveolae-mediated endocytosis and macropinocytosis, but other cellular pathways have been recently identified, including clathrin- and caveolae-independent endocytosis and phagocytosis (Doherty and McMahon 2009). Following cellular uptake, molecules which are internalized by the cell membrane will follow the intracellular endocytotic pathway involving early endosomes or progress to late endosomes and lysosomes. If the payload targets the nucleus, the nuclear membrane is another difficult obstacle that will be encountered. Physicochemical factors, such as size, shape, surface charge and ligand coating, influence internalization of these systems (Zhao et al. 2011). The design of the nanocarriers are of prime importance for effective delivery of their cargo. Different covalent linkages (e.g. ester, disulfide, hydrazine, etc.) have been utilized to conjugate drugs/nucleic acids, for encapsulation or even for complexation processes for unmodified therapeutics (Ding and Li 2017). In this review article I discuss different nanocarrier platforms which are used for the design and construction of stimuli-responsive machineries for controlling intracellular delivery. Figure 2 shows a pictorial representation of stimuli-responsive systems used for intracellular cargo delivery.

In addition to the above-mentioned stimuli-responsive properties of different nanocarriers, site-specific delivery at the cellular level can be achieved by functionalizing surfaces of NP carriers with antibodies, biomolecules and peptides (Allen 2002; Kamaly et al. 2012). The functional groups introduced on the surface of NPs enhanced cellular interaction of these carriers, leading to enhanced intracellular delivery of

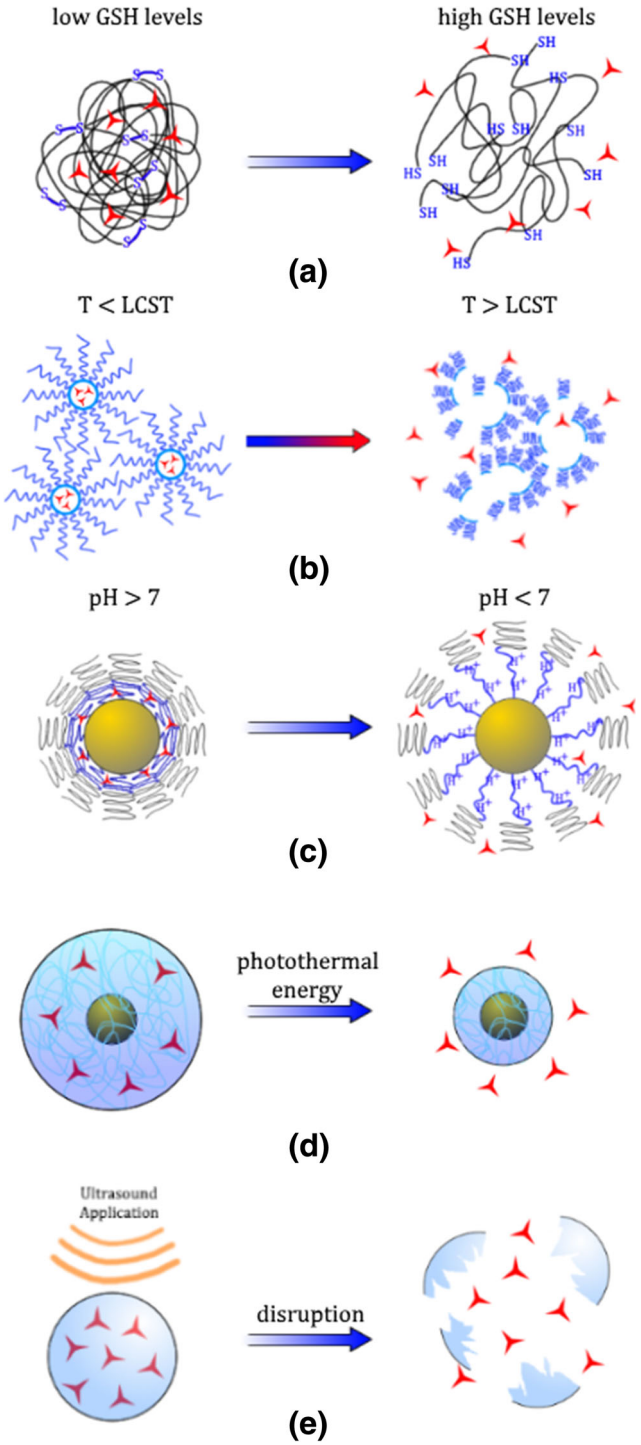

Fig. 2 Representation of the various stimuli-responsive systems utilized in the construction of NPs for biomedical applications. **a** Redox-responsive, **b** temperature-responsive, **c** pH-responsive, **d** photo-responsive, **e** ultrasound-responsive. GSH Glutathione, T temperature, LCST lower critical solution temperature, GSH

the cargo (Li and Huang 2008). In the past years, cell-penetrating peptides (CPPs) have been extensively studied for drug and gene delivery applications. CPPs may contain or correspond to protein transduction domains (5–30 amino acid residues) that allow permeation through the cell membrane. Various molecules, such as proteins, anti-sense oligonucleotides, siRNAs, drugs, fluorescent compounds, NPs and other substances, have been transported into cells via CPP conjugation (Duchardt et al. 2007; Tashima 2017). Different NP surfaces are now modified with CPPs either by covalent or by non-covalent bond formation. Moreover, CPPs are metabolically degraded after delivery of the accompanied cargo and they exhibit favorable pharmacokinetic behavior. Currently, there is no criteria for classifying CPPs, although according to their physicochemical properties they are categorized into three classes: cationic, amphipathic and hydrophobic peptides. Although CPPs have been used to promote cellular internalization of NP carriers, mechanisms have not been fully clarified. The differing physicochemical properties, size and concentration of the diverse CPPs in cargos have a significant impact on their intracellular delivery. Moreover, it has become apparent that a single CPP can possibly have different routes to entering cells and that these internalization routes may occasionally operate concomitantly, such as direct penetration or energy-dependent endocytosis. Several studies on nanomaterials containing CPPs have been recently published for cellular delivery of siRNA, insulin, plasmids and other drugs. Target specificity and efficient delivery are demonstrated when CPPs are surface-conjugated on NPs. Studies on CPPs demonstrate high efficacy of cargo delivery in different cells and biological systems (Dowaidara et al. 2017; Mesken et al. 2017).

Nanocarrier platforms

Liposomes

Liposomes are spherically shaped structures which are composed of a phospholipid bilayer that entirely surrounds an aqueous core. These carrier systems can range from nanometer to micrometer dimensions and are capable of delivering various types of molecules to the target, including drugs.

The diameter of small liposomes range between 60 and 80 nm while large ones are defined as having a diameter of 200 nm. Various sizes have been used to deliver therapeutics in different biological systems (Joshi et al.2017). Different lipids with varying fatty acid chain lengths and different head groups have been used, resulting in a broad range of achievable physicochemical characteristics, such as minimal micellar concentration or melting temperature, allowing the creation of environmentally sensitive (e.g. temperature-sensitive, pH-sensitive, mechano-sensitive) liposomes. Several liposome-based cancer drugs have entered clinical trials carrying different anthracycline analogues. Liposomes together with the drug doxorubicin have been studied extensively in the form of nano-capsules. Molecular modeling has been done on

different shapes (sphere, cylinder and ellipsoid) of liposomal doxorubicin clusters to optimize favorable properties needed when designing drug carriers (Sumetpipat and Baowan 2014). In addition to becoming approved agents, liposomal chemotherapeutics are finding their way into clinical trials (Immordino et al. 2006). A significant direction for these liposomes is the development of receptor targeting for cell-specific delivery of cargo. Early trials by scientists have reported difficulties with the various responses of the immune system to these carriers. Liposomes, however, are interesting carrier candidates for delivery because their inner aqueous core offers a protection from the surrounding body fluids following injection into the biological system (Elegbede et al. 2008). Furthermore, many liposomes have already been modified into intelligent nanosystems by combining a wide variety of stimuli-responsive functionalities, such as temperature, light, pH, ultrasound, enzymatic response or even as a drug delivery system for radiation-sensitive NPs (Suzuki et al. 2010; Gao et al. 2011; Liu et al. 2017).

Metallic NPs

Metallic NPs, such as iron oxide, gold and silver, have been developed and modified for both therapeutic and diagnostic purposes. Metallic NPs with superparamagnetic properties have been produced from their oxides (e.g. Fe_3O_4, Fe_2O_3) and are evident when a magnetic moment is induced upon the application of a magnetic field (Chan et al. 1993; Frimpong and Hilt 2010). This large magnetic moment offers a strong signal change in magnetic resonance imaging diagnostics. Iron oxide NPs have also been used for tumor treatment via magnetically induced hyperthermia. Other metallic NPs of gold and silver have been experimentally used for drug delivery because of their inertness and suitable mechanical properties; however size-dependent toxicity needs to be considered before their application (Patra et al. 2007). Studies have shown that not all metallic NPs comply with the proposed and generally accepted size of ≥100 nm for biomedical applications (Kumar et al. 2017). Some of the reported shapes include rods, spheres, stars and cubes. Experiments on Au NPs demonstrated that diameters ranging between 1 and 200 nm are readily internalized by cells via receptor-mediated endocytosis. Cytotoxicity studies with Au NPs in three diameters, namely 2–4, 5–7 and 20–40 nm, showed that both an decreased size and increased concentration induced cellular death (Jia et al. 2017). On the other hand, metallic NPs can be functionalized on their surface to diminish cytotoxicity and improve their specificity for their biological targets, which allows them to have a wide range of properties, such as pH sensitivity and redox responsiveness. Some potential disadvantages include their bioaccumulation, elimination pathways in the organism and potential threat to the environment (Han et al. 2007).

Carbon quantum dots

Carbon quantum dots (CQDs) are small carbon nano-crystals which display excellent optical and electronic properties for biomedical applications. They come in elliptical, spherical or triangular-shaped nanostructures (Derfus et al. 2007; Zintchenko et al. 2009), including good conductivity, high chemical stability, broadband optical absorption, low toxicity and strong photoluminescence emission. They were first discovered by chance during purification of single-walled carbon nanotubes (Xu et al. 2004). CQDs can now be synthesized using physical, chemical, or electrochemical methods. Modification of CQDs enable them to acquire good surface characteristics that are crucial for solubility and selected biomedical applications. They are also suitable for surface passivation and chemical modification with different polymeric, inorganic, organic or biological materials. Both their physical and fluorescence properties can be further improved by surface passivation. Their application has primarily focused on bioimaging and optical sensing, but more recently studies on drug and siRNA delivery have been reported in the literature (Luo et al. 2012). CQDs have been reduced in size to enhance cellular uptake of their cargo and reduce cytotoxicity, and particle sizes of ≥ 10 nm have been used in medicine for cellular imaging, clinical diagnostics and also for drug/gene delivery (Namdari et al. 2017). Nowadays, many studies have used CQDs with different delivery strategies that utilize polymers, peptide mediators, nanochannels and nanoinjection strategies for delivery in different cell lines; these CQD delivery systems have shown to be several fold superior in delivering drugs to target cells (Namdari et al. 2017).

Polymeric systems

Polymeric nanomaterials have gained increasing attention in the field of drug delivery and non-viral gene delivery. They modify the pharmacokinetics of both “biologicals” and drugs. A wide range of materials fall into this class, which includes polymeric micelles, hydrogels and dendrimers. Toxicities from these systems are mostly dependent on the type of polymers employed for the synthesis of nanocarriers. The particle size employed for biomedical applications of polymeric NPs are in the range 10–200 nm and occur as spheres or ellipsoids (Shih et al. 2017). Nowadays, different types of polymers are being used for the formation of polymeric micelles and polymeric vesicles as drug delivery systems (Ginn et al. 2013). Polymeric micelles can be built by self-assembly of amphiphilic-block copolymers exhibiting a hydrophilic outer shell and a hydrophobic core, properties which can enable the transport of water-insoluble drugs to their specific target. Several important anticancer drugs, such as paclitaxel, tamoxifen or campthotecin, are highly water insoluble. The relatively small size of polymeric micelles (10–100 nm) compared to polymeric vesicles enhances their ability

to accumulate in tumor tissues through the EPR effect (Maeda et al. 2010). Cationic polymers have received attention in past decades as non-viral vectors for gene delivery in cells. The drawback with most cationic polymers, including polyethylenimine), is their potential cytotoxicity with increasing surface charge (Jewell and Lynn 2008; Tamura et al. 2010; Tian et al. 2012). Studies have shown that conjugating these cationic polymer to polyethylene glycol (PEG) enhances the biocompatibility of the polyplexes (cationic polymer and DNA complex). Other polymers, such as chitosan, poly-lactic acid and poly-L-lysine have also been observed to reduce the cytotoxicity of cationic polymers in non-viral gene delivery (Kunath et al. 2003; Naeye et al. 2010). The conjugation of PEG to various polymers has also reduced protein adsorption and blood cell adhesion. This is essential for the development of non-fouling polymers for various biomedical applications. The non-specific adsorption of proteins, such as fibrinogen and various clotting enzymes, is the first interaction event to initiate full-scale platelet adhesion and activation leading to thrombosis and embolism at the blood-material interface. Hence, protein-resistant surfaces have been widely examined with the aim to eliminate blood clot formation (Chang et al. 2011). The retention of bound water molecules surrounding the functional groups of the material interfaces is now recognized to play a key role in surface resistance during non-specific protein adsorption (Jiang and Cao 2010). Moreover, it has been reported that surface-grafted PEG brushes lose their protein-repulsive properties at physiological temperatures. In this regard, it is of great advantage to have alternative non-fouling material systems other than PEG. Zwitterionic polybetaines are gaining popularity for their application as blood-inert polymers since they can inhibit plasma protein adsorption, blood platelet adhesion and activation and thrombus formation. Zwitterionic polymers, such as polyphosphobetaine, polysulfobetaine and polycarboxylbetaine, possess cationic and anionic charged moieties on the same side chain, which is responsible for the overall charge neutrality (Zhang et al. 2006).

Nanogels are a three-dimensional polymeric network formed either physically via hydrogen bonding, Van der Waals forces and electrostatic interactions or chemically via covalent bonding. The hydrophilicity of these nanogels allows them to swell and encapsulate high volumes of water in aqueous solution. Due to their polymeric nature, a broad range of chemical modifications is possible. Through spontaneous processes, such hydrogels can entrap a large number of biological molecules, such as DNA, RNA, proteins and drugs; this property renders them well suited for drug delivery. For site-specific tissue targeting within the body, the surface structure of nanogels can be chemically modified with different ligands (Dumville et al. 2011; Skulason et al. 2012).

Dendrimers are large, complex and monodispersed macromolecules which display a regular branching tree-like architecture. Dendrimers are synthesized through a repeated sequence of chemical reaction steps that leads to predictable alterations in their size that is determined by each generation (Tomalia et al. 1985; Paleos et al. 2010). The size of typical dendrimers ranges from 1 to 10 nm, and each dendrimer contains a hydrophobic inner compartment which enables drug delivery of hydrophobic drugs. Poly-(amidoamine), or PAMAM, is the most well-known dendrimer studied for many biological applications (Navarro and Tros de Ilarduya 2009; Pavan et al. 2010). Similar to the other cationic polymers used in non-viral gene delivery, cationic PAMAM dendrimers exhibit cytotoxic effects, which have been thought to result from their interaction with negatively charged molecules. Zwitterionic PAMAM dendrimers joined by a phosphorylcholine surface efficiently lower the cytotoxicity compared with the native PAMAM dendrimers (Jia et al. 2011). At the present time, researchers face the challenge to develop intelligent nanoscale systems based on dendrimers for clinical applications, possibly due to the uncertainty of commercial development, its regulatory path and clinical success outcomes.

Stimuli-responsive nanocarrier systems

Light-responsive systems

Light-responsive polymeric nanomaterials typically consist of photochromic moieties. Upon light exposure these moieties undergo photochemical changes, such as photoisomerization, photodimerization or photocleavage, with subsequent disruption of the nanocarrier and the release its cargo. Several research groups have reported the use of photo-responsive systems for drug delivery due to the ready manipulability of light for the efficient temporal and spatial control needed for drug delivery. Furthermore, light sources can be easily manipulated from the outside of the organism's body (Tomatsu et al. 2011; Fomina et al. 2012). Polymeric NPs which are photo-responsive in the ultraviolet (UV), visible and near-infrared (NIR) regions have been extensively studied for drug delivery applications. Light in the NIR region is important for biomedical applications since NIR radiation penetrates deep into tissues, ranging from millimeter to centimeters, and is less damaging to the biological system than UV light (Saravanakumar and Kim 2014). Some of the strategies used by researchers for designing light-sensitive nanocarriers involve the proper selection of photochromic functional groups on block copolymers which can shift the hydrophilic–hydrophobic balance in their micellar structure upon exposure to different wavelengths of light (Babin et al. 2009; Zhao 2012). Another strategy is to disrupt the micellar structure by breaking the photolabile functional groups introduced between the hydrophobic pendant and the main chain, or at the junction of the hydrophobic and hydrophilic segments. It is also possible to utilize surface plasmon and other photothermal effects to

trigger the release of payloads in targeted cells (Zhao 2007). Nanocapsules based on cross-linked polyamide, constructed via interfacial polymerization, have been used to create a photo-responsive polymer (Marturano et al. 2015). This study highlights the ability to control the size of the encapsulating particles, tailor swelling kinetics and to precisely design light-controlled release systems (Marturano et al. 2015).

The plasmon absorption in these nanostructures can be successfully tuned so that these systems can be activated with almost any desired excitation wavelength ranging from UV up to the NIR region. However, photo-thermal effects using Au nanostructures would need relatively effective illumination powers, which can be harmful to biological specimens. Recently, Bouchaala et al. (2017) achieved the light-induced release of a fluorescent dye from lipid nanodroplets under visible light conditions. Using auto-emulsification process these authors prepared nanoemulsion droplets of 32 nm size encapsulating NR668 (hydrophobic analogue of Nile Red) and tested this system on cultured cells and zebra fish embryo. The results suggest that dye-loaded lipid nanodroplets may be a prospective platform for the preparation of light-triggered nanocarriers of active molecules (Bouchaala et al. 2017).

pH-responsive systems

The important property in the pH-sensitivity of a polymer is the presence of ionizable pendant groups which are attached to the hydrophobic chain of the polymer. Therefore, pH-sensitive polymers form a class of polyelectrolytes with ionic functional groups that are either weakly acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. amines, imidazole and pyridine) (Manchun et al. 2012; Pang et al. 2016). These pendant moieties are capable of accepting or donating H^+ ions in response to pH changes in the environment. Protonation/deprotonation of these groups changes the extent of ionization and the overall charge on the polymer chains (Liu et al. 2017). As a consequence of these changes in the electrostatic charge, alteration of the polymeric chains leads to disruption of a system's hydrodynamic volume and conformation. Increasing the net charge on the chains generates electrostatic repulsion of the chain, thereby causing the system's conformation to shift from a collapsed to an expanded state. On the other hand, a decrease in the chains' net charge will result in their transition from the expanded to the collapsed configuration. Selecting a polymer with a critical pH that matches the desired pH range for its application is a major factor in designing an ideal pH-sensitive system. Thus, understanding the chemical structure of the polymer's ionizable moieties, and their respective pKa (negative logarithm of the acid dissociation constant) is necessary for the design and synthesis of appropriate pH-sensitive drug delivery systems. These pH-responsive NPs are also one of the most widely studied stimuli-responsive NPs due to the changes in pH condition at the site of diseased tissue (Gao et al. 2010; Wang and Zhang 2012). The pH profile of pathological tissues is significantly different from that of normal tissues. For example, the pH is lower in the extracellular environment of a solid tumor (6.5–7.2) and at certain inflammation sites in the body compared to healthy tissue (~ 7.4). The lowered pH in the tumor microenvironment is derived from the "Warburg effect" and is due to production of acidic metabolites under hypoxic conditions. This pH difference between neoplastic and normal tissues has stimulated researchers to develop pH-responsive NPs for anti-cancer therapeutics (Tayo et al. 2015; Shih et al. 2017). Other studies have also correlated pH variations in the body in various organs (stomach and vagina), tissues (cancerous and inflamed) and sub-cellular organelles. Taking into account the differences in pH in the body, nanocarriers can be designed utilizing these smart particles. Currently, various pH-responsive nanosystems have been synthesized using block copolymers, dendrimers, polymer-drug conjugates, nanogels, polymerosomes and even multiple core shell complexes and micellar structures (Bazban-Shotorbani et al. 2017). Cytotoxicity has been alleviated by conjugating synthesized particles with PEG or with any of the zwitterionic polybetaines (Lee et al. 2008; Rao et al. 2011; Wei et al. 2013; Liu et al. 2017; Shih et al. 2017).

Redox-responsive systems

Redox potential gradients between the intracellular and extracellular environments occur in biological systems. This scenario has enabled researchers to study redox-responsive polymers. One of the aims of these systems is to incorporate disulfide bonds in these nanocarriers. Polymeric nanocarriers containing reducible disulfide bonds offers a good potential for intracellular delivery of drug or functional genes in targeted tumors and other tissues. The glutathione (GSH) concentration is higher in the cytosol and subcellular compartments than in the extracellular environment (Meng et al. 2009; Cheng et al. 2011; Son et al. 2011). Disulfide bonds present in these nanocarriers are generally intact in the oxidizing extracellular environment during circulation, but they are readily cleaved off in the GSH-elevated and consequently reducing intracellular environment, triggering the cytosolic release of the drugs. Many scientific studies have published results showing that GSH is expressed at relatively higher levels in tumors compared with normal tissues (Son et al. 2010; Kuppusamy et al. 2002). The efficacy of this system to deliver anti-cancer substances, such as doxorubicin, trastuzumab and p53 tumor suppressor gene, is significantly increased when different polymeric nanocarriers with cleavable disulfide linkers are used (Kumar et al. 2017). Studies have also utilized different NP platforms, including inorganic materials, multi-block polymers, micelles and other combinations, for effective drug and gene delivery (Han et al. 2017; Lin et al. 2017).

Temperature-responsive systems

Thermo-responsive polymers that are used for various biomedical applications display either a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST), which are the respective critical temperature points below and above which the polymeric system becomes completely miscible with the water/solvent. Among these, LCST-based polymers have been investigated for drug delivery applications. Poly(*N*-isopropylacrylamide), or PNIPAM, has received a great deal of interest as a component of temperature-responsive carriers. It has been incorporated in many block copolymers to attain desirable properties for drug delivery applications. Hyperthermia in pathological tissues compared to normal tissues has been described in the literature, leading to the development of thermo-responsive systems for this type of biological environment. Although the temperature gradient from physiological environments (~ 37 °C) to disease sites (~ 40–42 °C) exhibits a narrow range, it is a must that the materials used for these systems should change their hydrophobicity–hydrophilicity balance accurately and quickly with the suitable LCST (Zhang et al. 2005; Cheng et al. 2008; Liu et al. 2017). Nanocarriers in this category should maintain a stable loaded cargo at normal body temperature and collapse their intact structure and rapidly release their cargo when they are delivered to local hyperthermal tissues (Chilkoti et al. 2002; Schmaljohann 2006).

Ultrasound-responsive systems

Microbubbles have been used as ultrasound (US) contrast agents for several decades, and their therapeutic application for intracellular delivery of drugs and genes are now being widely studied (Kooiman et al. 2014). Microbubbles collapse rapidly at inertial cavitation under high US exposure. The power generated from this collapse would have the capacity to enhance the permeability of drugs or functional genes to tumor tissue delivery (Yan et al. 2013). However, some of the negative properties of microbubbles include their short circulation time and relatively large size, limiting their possible clinical application. Studies on US-responsive nanobubbles which were loaded with siRNA and an anticancer drug using a hetero-assembling strategy involved their exposure to intermittent low-frequency US at tumor sites during drug delivery. The results of this study showed that US-responsive nanocarriers penetrated the deep locations of the tumor effectively (Wang et al. 2016). Several recent publications by Baghbani et al. showcased various NPs platforms utilizing US for the enhanced delivery of therapeutics in different forms of cancer (Baghbani et al. 2017a, b; Baghbani and Moztarzadeh 2017).

Concluding remarks

The design, production and application of intelligent nanocarriers for intracellular delivery have undergone an explosion of interest recently due to molecular engineering. Stimuli-responsive NPs in the field of medicine have emerged as powerful tools to aid in the diagnosis or to enhance therapeutic efficacy by the appropriate delivery and release of drugs and genes in diseased cells. The inherent stimuli in the biological system, such as pH, temperature and oxidizing/reducing conditions, are the primary triggers of the release of payloads by altering the hydrophilic–hydrophobic balance and/or disintegration of cleavable moieties incorporated in the NP carriers. External stimuli, on the other hand, such as light and US enable the release of therapeutics to be regulated in a remote but controlled way at the target site of action. Furthermore, it is also important to realize that cytotoxicity is minimized or, if not minimized then localized in a controlled manner at the target site. Although these new approaches have resulted in spectacular improvements to therapeutic delivery at the preclinical stage, further development of these systems remains a challenge. Scientists need a deeper understanding of the biochemical and physiological differences between normal and diseased tissues and they have to establish appropriate criteria for evaluating the results of studies using nanodelivery systems. Some internal stimuli are unreliable, such as the upregulation of protein expression in normal cells and inaccurate pH range in various types of tumor tissues. Rapid advances in biomolecular engineering may lead to the discovery of novel internal stimuli in the future that can used for the design of nanocarriers. Rationally designed carriers with a combination of stimulus sensitivity can be constructed to offer more effective therapy while minimizing toxicity. In general, the field of nanodelivery systems has made a significant progress in the field of medical area, and further studies will continue to help realize their applications up to the higher stages of clinical trials.

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Compliance with ethical standards

Conflict of interest Lemmuel L. Tayo declares that he has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

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