Bio-responsive smart polymers and biomedical applications

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Abstract
Bio-responsive polymers are the foundation for the construction of the smart systems that exhibit designed biomedical functions after receiving specific stimuli such as biological signals and pathological abnormalities. These stimulus-responsive systems have shown great promise of developing novel products in precision medicine, and relevant research has grown intensively in recent years. This review aims to outline the basic knowledge and recent progress in the advanced bio-responsive systems as well as the major challenges. The current bio-responsive systems mainly rely on physical, chemical and biological cues, and this review focuses on the strategies of molecular design for the incorporation of appropriate responsive building blocks. The potential applications, including controlled drug delivery, diagnostics and tissue regeneration, are introduced and promising research directions that benefit the medical translation and commercialization are also discussed.

With economic development, healthcare has attracted increased attention, which has stimulated explosive interest in the investigation of novel medical devices or treatment strategies. The foundation of the novel medical devices or treatment strategies is advanced biomaterials (most commonly biopolymers), and the interactions between the human body and the materials play the key roles. Great effort has been made to prepare new bulk polymers, modify the implants with functional coatings and design fancy modalities (i.e. hollow microspheres and nanorods) to regulate cellular behavior and improve tissue regeneration (figure 1). Despite their great success in biomedicine, those biomaterials are active rather than 'smart', and they cannot respond or adjust their functions according to the alternation of the microenvironment.

Nevertheless, the 'smart' characteristic is necessary in certain situations. For example, the drug carriers need to recognize the tumor tissues so that they can deliver the drug into cancer cells rather than kill the adjacent normal cells. To obtain such smart systems or devices, bio-responsive polymers that can respond to the surrounding stimuli are the key components, and it has become a hot research area. The bio-responsive functions are achieved by the incorporation of the responsive motifs in the desired formulations, and many reviews have described the details on the specific type of bio-responsive biopolymers, such as pH-[4, 5], redox-[6, 7], or enzyme-responsive [8] polymers. However, there are very few reviews that focus on the general introduction of the basic science and design principles for the different types of bio-responsive polymers. Therefore, in this review, we describe the commonly used stimuli in the physiological environment, basic principles for construction of bio-responsive formulations, and the potential applications, as well as discuss the factors that hinder the commercialization and medical translation. We hope that this review may help the researchers who would like to get a general picture of bio-responsive polymers or start the research in this field.

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1. Stimuli in physiological environment

There are various stimulation cues in the human body that can be used to stimulate biomaterials for specific responses and desired functions. Based on this nature, the triggers can be classified as physical, chemical and biological cues, which are discussed below.

1.1. Physical cues

pH value, which is an indicator of the acidity or basicity of a local environment, has been widely used for designing bio-responsive polymers. The local pH value in the human body varies from strong acidic (1–3.5) in the gastric fluid to weak alkaline (8.0–8.3) in the pancreatic fluid, and in the cellular level, the acidification of endosomes and endosome-lysosome fusion provides a pH gradient from 4.5 to 6.5 (table 1). Such variation in pH can act as an important signal to trigger physical or chemical changes of biomaterials for specific applications, especially for controlled drug delivery, which includes guiding the drug to the target site and programmed drug release profiles at the target site [9]. For example, tumor tissues exhibit strong metabolism owing to rapid cellular proliferation, which results in a higher level of glucose consumption and lactic acid accumulation than healthy tissues with the pH 0.5–1.0 units lower [5]. After the first discovery of acidosis in tumors in 1956 by Warbug et al [10], a further investigation of the pH distribution in the tumor tissues suggested that the acidosis is in the extracellular compartment of tumors because the intracellular pH values is similar to normal tissues as indicated by the $^{31}$P magnetic resonance spectroscopy [11]. This was proved by the subsequent study that showed that the plasma membrane transporters (e.g. bicarbonate/chloride exchangers and sodium-hydrogen exchanger NHE-1) could actively extrude protons and weak acids [12]. Thus, with a pH-response carrier that is stable at pH 7.4 and become fusogenic or soluble in the acid circumstance, the controlled release of antitumor drugs in the tumor region can be achieved to reduce the dosage of the cytotoxic drug and prevent multidrug resistance [5, 9].
Since poly(N-isopropylacrylamide) (PNIPAM) was discovered to undergo a sol-gel transition at 32 °C in 1960 [16], temperature-responsive polymers have been widely investigated for biomedical applications. The currently-found temperature-responsive polymers can typically be classified as lower critical solution temperature (LCST) polymers and upper critical solution temperature (UCST) polymers (figure 2). Among those polymers, most are the LCST type, i.e. the polymer exhibits phase separation from the homogenous solution with the temperature above the LCST. Such phase transition is decided by the free energy of mixing or the entropy of the polymer and solvent, and thus it is an energy-driven reversible process. Considering this characteristic, one important application for the temperature-responsive polymers is controlled drug delivery, and many investigations have shown that drugs loaded in a temperature-responsive polymeric carrier can be triggered to release by a small variation in surrounding temperature [17–20]. In most cases, those polymers are soluble, and the solution of the target drug can be swollen below the LCST. When the surrounding temperature increases above the LCST (e.g. administration in the human body, 37 °C), the polymeric carrier becomes insoluble and shrinks to expel the loaded drug.

For vascular stenosis or obstruction, pH or temperature-responsive carriers may not be a good choice for the delivery of the drug on the target. Regarding that the shear-stress at the site of the stenosis and obstruction of blood vessels is significantly higher than that of normal blood vessels, the abnormal high shear stress can be a new trigger to achieve the targeted release of drugs. Analysis of blood flow using a lamina flow model indicates that the blood flow follows a parabolic profile when the blood vessel wall and the blood are regarded as the solid boundary and viscous fluid, respectively. The relationship between the blood flux (Q) and the shear stress (τ) is

![Figure 2. Schematic phase diagram of LCST and UCST polymers.](image-url)

| Table 1. pH of different locations in the human body. The data is collected from Refs [13–15]. |
|---------------------------------|---------------------------------|
| Level                          | Location                        | pH     |
| Intracellular                  | Early endosome                  | 6.0–6.5|
|                                | Late endosome                   | 5.0–6.0|
|                                | Lysosome                        | 4.5–5.0|
|                                | Golgi complex                   | 6.0–6.7|
| Tissue or organ                | Gastrointestinal tract          | Saliva | 6.0–7.0|
|                                |                                 | Gastric fluid | 1.0–3.5|
|                                |                                 | Bile   | 7.8   |
|                                |                                 | Pancreatic fluid | 8.0–8.3|
|                                |                                 | Small-intestinal fluid | 7.5–8.0|
|                                |                                 | Large-intestinal fluid | 5.5–7.0|
|                                | Urinary tract                   | 6.5–8.0|
|                                | Vagina                          | 3.8–4.5|
|                                | Eye                             | Ocular surface | 7.1   |
|                                |                                 | Healthy tear | 7.3–7.7|
| Pathological microenvironment  | Plasma                          | 7.4    |
|                                | Extracellular tumor             | 6.3–7.2|
|                                | Inflamed tissue                 | 5.4    |
|                                | Fracture-related hematomas      | 4.7    |
|                                | Cardiac ischemia                | 5.7    |
When the responsive biopolymers are administrated in the human body, they are immediately exposed to a physiological environment containing various biological molecules. The variation in the level and types of the biological system itself, avoiding the requirement of external supply of the stimulus molecules. Since the enzymes control almost all physiological activities in living organisms, and due to the specificity and selectivity for the substrates, the use of enzymes as the trigger to change the properties of polymers has received increasing attention [8]. The distinct advantages of using enzymes as the stimulus include the high catalytic efficiency and inherent biocompatibility which make the enzyme-responsive systems especially suitable for biomedical applications. In addition, the targeted enzymes exist in the body and can be provided by the biological system itself, avoiding the requirement of external supply of the stimulus molecules. Since the physiological reactions or processes are accurately regulated by the presence, level and activity of the specific enzymes, the abnormal expression of the targeted enzyme in pathological conditions can be easily recognized by the appropriately designed enzyme-responsive system [26].

The selection of the appropriate enzyme as a stimulus based on the specific biomedical requirements as well as the properties of the responsive polymers. There are plenty of enzymes that can be chosen, such as proteases, endonucleases, kinases, and phosphatases. Proteases are a class of enzymes that hydrolyze peptide bonds, and endonucleases act to break phosphodiester bonds in a polynucleotide chain. Thus, the protease- and endonuclease-responsive materials are good candidates for controlled drug delivery and biosensors [27, 28]. Kinases catalyze the transfer of phosphate groups to the substrate (phosphorylation), and phosphatases, which complementary to the kinase functions to remove phosphate groups from the substrate (dephosphorylation). This antagonistic interplay benefits the construction of reversible or dynamic responsible systems [29]. In addition, there are also some enzymes that act to catalyze the formation of covalent bonding (e.g. transglutaminase and glycosyltransferases), which are suitable to stimulate the crosslinking of the drug carriers (figure 4).
Besides enzymes, adenosine-5′-triphosphate (ATP), which acts to provide the energy for cellular metabolism, is another trigger signal to induce the materials’ responses. The intracellular level of ATP is 1–10 mM while the level in extracellular environment is only less than 5 μM [30]. Such a difference in the ATP level is significant enough to trigger the responses of materials. For example, the nanocarrier consisting of ATP-binding aptamer was loaded with doxorubicin, and the exposure of the nanocarriers in an ATP-rich environment resulted in the competitive binding of ATP to the ATP aptamer, which subsequently dissociated the duplex structure in the carrier and released the loaded doxorubicin [31]. In addition to the competitive binding effect, the hydrolysis of ATP into adenosine-5′-diphosphate (ADP) provides energy to induce conformational changes of proteins, resulting in the disassembly of the initial supermolecular structure and release of the cargo molecules [32].

All the living organisms contain nucleic acids that act to create, encode and store information in the nucleus as well as transmit and express the information outside the nucleus. Nucleic acids are the polymers of nucleotides and include ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) depending on the structure of the sugar component in the nucleotides. MicroRNAs (miRNAs) refer to short (∼22 nucleotide length) non-coding RNAs that act in RNA silencing and regulation of gene expression, and the expression profiles of miRNAs in tumor tissues are significantly different from that of the healthy tissues, which serve as a potential trigger for cancer therapy [33]. A notable example of the miRNA-responsive therapy is the mesoporous silica nanocarrier with doxorubicin loaded in the nanopores, and the nanopores are capped with the DNA hybrids containing antisense oligonucleotides to prevent the release of doxorubicin. When such a mesoporous silica nanocarrier is enriched in tumor tissues that contain a high level of the oncogenic miRNA (miR-21), the miR-21 competitively binds to the antisense oligonucleotide part and disassembles the DNA hybrids away from the mouth of the nanopore, resulting in the release of doxorubicin (figure 5) [34]. Besides RNA, DNA can also trigger the changes in the properties of nanomaterials via hybridization effect. For example, immobilization of single-strand DNA chains on the surface of gold nanoparticles leads to the assembly of the nanoparticles, and the addition of the DNA molecules that contains the sequences supplementary to the single-stranded section in the central part of the linker disassembles the nanoparticle aggregates [35].
2. Principles for designing bio-responsive systems

2.1. pH-responsive drug carrier

Based on the pH difference between the target site and surroundings, pH-responsive delivery systems can be designed to achieve intracellular and extracellular release. This is accomplished by the controlled protonation of the functional groups in the polymer and pH-responsive bond cleavage (figure 6) [9]. For polymer protonation, ionizable groups such as the carboxylic group, tertiary amine, and pyrrolidine groups accepted protons at low pH and loss protons at high pH. The protonation/de-protonation transition significantly changes their hydrophilicity to induce a pH-responsive behavior of the drug carrier such as precipitation-solubilization transition, swelling-shrinking transition, and morphological change, resulting in controlled drug release. For the method of pH-induced bond cleavage, drugs can be released by direct dissociation from the carrier or breaking up the carrier’s topological structure, depending on the strategy of drug loading (i.e. covalent linking or physical entrapment). Chemical bonds that are cleavable for pH-responsive materials includes hydrazine [36], oxime [37], amide [38], imine [39], ketal or acetal [40], orthoester [41], and phenyl vinyl ether [42]. When drugs are linked to the carrier by these bonds, the cleavage of these bonding in an acidic environment leads to the drug release (figure 6). Readers can refer to the Review paper [9] for the detailed characteristics of each bonding for the construction of pH-responsive materials.

The materials designed and chosen for pH-responsive carriers also depend on the characteristics of the target drugs. For an instance, to deliver the drugs that are degradable in an acid environment (i.e. proton pump inhibitor), polyanions containing —COOH groups may be a proper carrier. Those polymers become less soluble in an acidic environment, which is helpful to prevent the drug from gastric degradation, while when they arrive at alkaline intestine (table 1), the polymers are easy to dissolve and release the encapsulated drug [43]. For non-viral gene delivery, cationic polymers are promising because they can easily form complexes with the negatively charged nucleotides via electrostatic interaction. Polyethylenimine is a polycation that can be used for gene delivery, and to improve its efficiency and safety, Anderson et al developed the semi-automated synthesis and screening of a library of polyl(3-amino esters) for the establishment of cationic polymers [44]. With the aim of using the physiological pH gradients (i.e. endosome-lysosome fusion) to achieve sequential delivery of drugs, the carriers containing pH-sensitive charge conversion motifs or cell penetrating peptides would be a good choice [45–47].

2.2. Temperature-responsive drug carrier

For the temperature-responsive drug carrier, the phase transition temperature is the key performance indicator, and it must match a set of conditions for a specific application. The phase transition temperature needs to be between room temperature and body temperature for inherent temperature sensitivity towards the physiological conditions. LCST polymers form hydrogen bonds with surrounding water, and the hydrogen bonding weakens with increasing temperature, which result in the expelling of water and aggregation of the partially dehydrated polymer chains. The balance between polymer-polymer interactions and polymer-solvent interactions affects the phase transition temperature, i.e. the increase in the polymer-polymer attractive interactions or decrease in the polymer-solvent interactions can decrease the phase transition temperature. For the most-investigated temperature responsive polymer, PNIPAM, the copolymerization of polar or ionic
monomers increased the transition temperature \([48]\), and the copolymerization of hydrophobic monomers shifted the transition temperature to lower temperatures \([49]\). Besides the chemical structure, the solutes, especially salts in the surrounding solution, may also affect the transition temperature. The salts that increase the hydrophobic interaction decrease the transition temperature and vice versa \([50]\).

2.3. Shear stress-responsive polymers

As mentioned in section 1.1, the significant increase in shear stress caused by physiological stenosis can drive the shearing stress-responsive drug carriers to release drugs near the stenosis area. To achieve this, one strategy is to use the aggregates of nanoparticles assembled through non-covalent bonding between the nanoparticles, and the aggregates can be disassembled by the high shear stress near the stenosis area (figure 7). Since the hemodynamic force that moves the particles along the flow is proportional to the square of the particle size, the disassembled nanoparticles adhere more efficiently to the surrounding vascular wall than the micro-sized aggregates, and the unaffected nanoparticle aggregates are pulled away by the blood flow \([51]\). Another strategy for shear-stress response is microcapsules, microvesicles, and liposomes that deform and increase the permeability to release the loaded drug when subjected to high shear-stress \([52, 53]\).
With the adhesion of nanoparticles on the surfaces of red blood cells (RBCs), the nanoparticle-RBC complexes can also achieve shear-stress response because the nanoparticles would fall off the RBC’s membrane surface to release drugs under the condition of high shear stress at the vascular stenosis site [54, 55]. The combination of nanoparticles and RBCs fully uses the advantages of nanoparticles and RBCs such as high efficiency of drug loading and a long period of circulation to accomplish shear stress response. However, the specific interactions between nanoparticles and RBCs remains unclear, which makes it difficult to precisely regulate the interactions. As a result, it is difficult to effectively regulate the binding strength and shear response behavior of nanoparticles and RBCs. Therefore, further investigations on these interactions by preparing model nanoparticles with controllable structure and surface properties are required.

Supramolecular self-assembled hydrogels with macroscopic reversible properties or self-healing functions can also be used to design shear stress-responsive drug delivery system. The supramolecular systems usually rely on non-covalent cross-linking, self-assembly interactions and subject-guest interactions. Those self-assembled hydrogels can release more drugs when shear stress is applied to break the supramolecular interactions (figure 7) [56, 57].
2.4. Redox-responsive polymeric system

Based on the nature of the redox stimuli, redox-responsive polymeric systems can be further divided into reduction-responsive systems and oxidation-responsive systems. For the reduction-responsive system, it commonly contains disulfide and diselenide linkages which will be broken with a significant increase in the level of surrounding reducing agents such as GSH. Common methods to incorporate disulfide linkage in the system includes direct formation of disulfide linkage and crosslinking by a disulfide-containing crosslinker (figure 8). Disulfide can be introduced in the polymer as the end group by living or controlled polymerization (e.g. atom transfer radical polymerization and reversible addition-fragmentation chain transfer polymerization) [58]. Compared to the relative harsh conditions for the living/controlled polymerization, the thiol-disulfide exchange reaction is another effective strategy with milder conditions (e.g. at room temperature), which is widely used to prepare reduction-responsive prodrugs and gene carriers [25]. On the other hand, the polymeric micelles that contain drugs can also be crosslinked by disulfide-containing crosslinkers (using bis(2,2′-hydroxyethyl)disulfide, dithiodipropionic acid and their derivatives) to prevent drug leakage, and after the micelles reach the target, the disulfide linkers break to release the drugs [59].

Replacement of the disulfide linkage with the diselenide linkage is a facile way to further improve the sensitivity of the reduction-responsive system because the bond dissociation energies of the Se-Se (172 kJ mol\(^{-1}\)) and C-Se (244 kJ mol\(^{-1}\)) bonding are lower than those of S-S (251 kJ mol\(^{-1}\)) and C-S (272 kJ mol\(^{-1}\)) bonding.

Figure 8. Illustration of the common strategies to introduce disulfide bonds in the polymeric systems.
Nevertheless, introduction of the diselenide linkage in the polymeric system is not as easy as that of the disulfide linkage, and further investigations on the efficient synthetic methods are still required [60]. Oxidation-responsive systems primarily respond to ROS, the byproducts from aerobic metabolism. Sulfur-based materials represent a type of oxidation-responsive material. Poly(propylene sulfide) (PPS) can be oxidized by ROS to form sulfoxide to achieve hydrophobic-hydrophilic transition [61]. The major limitation of the sulfur-containing materials is the relative high stability of the sulfur, and the response to ROS may not be so sensitive. Incorporation of selenium, which is more reactive than sulfur in the polymers, raises the sensitivity of the response to ROS [62]. Ferrocene-containing polymers are another major class of the oxidation-responsive polymers due to its oxidation sensitivity, and ferrocene can be incorporated in the backbone, side chain and terminal group of the polymers [6, 63]. To extend the applications, emerging motifs such as boronic ester groups, tetrasialafuvalene, and oligoproline have also been investigated for the construction of novel oxidation-responsive polymers [64, 65].

2.5. Enzyme-responsive polymeric system
The synthesis of enzyme-responsive polymers for biomedical applications should follow some basic rules. Specific conditions (e.g. aqueous environment containing various ions and the pH at 7.4 or moderately basic or acid) are required for enzymes to exhibit their functions, and the enzyme-responsive polymers need to tolerate these conditions. Besides the presence of the substrate or substrate-mimic unit for the targeted enzyme to react, the actions of the targeted enzymes need to induce a change in the polymers’ properties for the specific functions. The enzyme’s action and the final material’s response can be carried out simultaneously or in a step-by-step way. For example, the DNA nanoparticles were prepared using peptides as the crosslinker, and degradation of the peptide by proteases immediately destroys the nanoparticles [66]. In another example, enzymatic cleavage of a protection group leads to the rearrangement of the amyloid β-derived peptides, which then fold and self-assemble into fibrillar aggregates [67]. Enzymes control bond formation and cleavage, substrate oxidation and reduction, and isomerization reactions in the living organisms, and the first two types of the reactions have been used in designing enzyme-responsive materials (figure 6). The enzymatic bond formation can be used to covalently link amino acids and peptides as well as crosslinking the polymers with amino acids as the side groups, while the bond cleavage reaction has been used to break the peptide and ester bonds between polymers and/or small molecules, which is useful in controlled drug release and implant biodegradation. The enzymatic bond formation and cleavage can also be used to generate reversibly responsive materials using the kinase/phosphatase system which catalyze the phosphorylation and dephosphorylation reactions on the substrates. Many natural and artificial polymers have been explored as the matrix materials for the construction of enzyme-responsive systems, such as chitosan, dextran, alginate, polyacrylamide, polyethylene glycol and poly(butyl methacrylate). The detailed information is provided in the review papers [8, 26, 68].

2.6. Multi-responsive system
With the progress of the investigations on the stimuli-responsive system, it has been found that the system with single responsiveness may not achieve the desired goals due to the complexity of the real physiological microenvironment. For example, drug-delivery efficiency is reduced by a hierarchy of barriers such as blood brain barrier, mononuclear phagocyte system, cell internalization and endosome escape existing in organs, tissues, and cells. Thus, polymeric systems with multi-stimuli responsiveness have been designed for biomedical applications.

It is easy to provide pH responsiveness by introducing ionizable groups in the polymer, and thus the current multi-stimuli responsive systems are commonly constructed via adding a responsiveness property to a pH-responsive system, including pH-reduction responsive, pH-diol responsive, pH-light responsive, and pH-temperature responsive systems [69]. Such multi-responsive systems can be obtained in the forms of particles, films or hydrogels. The multi-stimuli responsive films are commonly prepared via the layer-by-layer (LBL) assembling or by using polymer brushes. LBL assembling involves alternatively depositing different polymers on a substrate, and the deposited polymers can be assembled into the LBL coating via various interactions such as electrostatic interactions, host-guest interactions, hydrogen bonding and coordination bonding [70]. For the polymer brush strategy, the initiator is anchored to the substrate and the polymer brushes with different functions are then formed via the surface-initiated living polymerization [71]. Hydrogels are crosslinked hydrophilic polymer networks with large amounts of water absorbed in the network, which can not only encapsulate cells and bioactive cytokines but also be highly permeable for oxygen and nutrients. Multi-stimuli responsive hydrogels can be easily obtained by crosslinking the polymers with different responsiveness properties, and the hydrogels are programmed to swell, shrink, or dissociate in response to various stimuli [72, 73]. A representative example is the pH and redox-responsive hydrogel prepared by crosslinking poly...
multidrug resistance for the anticancer drug compromise the therapeutic effect. Reacts with the endogenous H2O2 at the tumor site to level of hyaluronidase. For example, the tumor tissues have mild acidity, high GSH concentration and elevated sensitivity of the drugs towards neoplastic cells remarkably improves the prognosis and quality of life for the patients, a major challenge remains the lack of recent progress in chemotherapy leads to the appearance of various new drugs for cancer treatment and to prepare a temperature and pH-responsive hydrogel, which is assembled on a layer of gold-coated polydimethylsiloxane. The changes in solution temperature and pH induce the modulation of the hydrogel solvation state, which subsequently results in a unique bidirectional bending behavior. The bilayers could be used as temperature- and pH-induced grippers for the controlled delivery of small molecules, which is useful for various biomedical applications.

3. Biomedical applications of bio-responsive polymers

3.1. Drug delivery

Most bio-responsive systems focus on controlled drug release, especially for cancer treatment. Although the recent progress in chemotherapy leads to the appearance of various new drugs for cancer treatment and remarkably improves the prognosis and quality of life for the patients, a major challenge remains the lack of sensitivity of the drugs towards neoplastic cells. The possible fatal systemic adverse effect and the presence of multidrug resistance for the anticancer drug compromise the therapeutic effect. Further development of the chemotherapy requires sufficient drug release at the tumor site and the prevention of endosomal entrapment of the drug-carriers, and the construction of appropriate stimulus-responsive systems has exhibited great promise on these aspects. This is based on the fact that the microenvironment of tumor tissues can provide multiple endogenous stimuli. For example, the tumor tissues have mild acidity, high GSH concentration and elevated level of hyaluronidase, and thus the pH-, redox- and enzyme-responsive drug carriers or their combination (to further improve the drug release performance) have been widely investigated. A novel illustration is the human serum albumin (HSA)-coated MnO2 nanoparticles as the intelligent carrier of cis-platinum. The MnO2 reacts with the endogenous H2O2 at the tumor site to in situ produce O2 to overcome the drug resistance induced by local hypoxia, and simultaneously, the nanoparticles are able to degrade in an acidic environment to release cis-platinum. In another design, the poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) was used to prepare a nanogel, and the hydrophilic rhodamine B was covalently linked to the PDMAEMA through disulfide bonds to release the hydrophilic cargo drug.

In recent decades, there has been a tremendous increase in developing bio-responsive drug carriers for control release, and further improvement of release efficiency results in the dual and multiple-responsive systems that can deliver more than one drugs for programmed site-specific drug delivery. The various designs of the bio-responsive delivery system aim to overcome the key challenges in drug delivery: drug loading, stability in physiological environment, tumor-targetability, efficient uptake by cancer cells, and programmed intracellular drug release. Although there is much excellent research, most of it focuses on one point of the challenges and remains at the early stage of concept-proof. To translate the research into clinical practices, the problems associated with most of the current bio-responsive drug delivery systems must be solved such as low capacity of drug loading, biodegradability, the ability to retain circulation and enrich in the targeted tissues (e.g. tumor). In addition, further investigations should be conducted on the microcosmic in vivo performance of the bio-responsive systems and the effect of systemic physiological factors on drug release.

3.2. Diagnostics

The development of biomedical research significantly expands the understanding of the human body and the mechanisms of the physiological activities and diseases. Therefore, besides disease treatment, another important goal is diagnostics where bio-responsive materials have also exhibited great promise to detect low levels of biochemicals, proteins and genes which serve as specific markers of diseases. Those markers are conventionally measured on various expensive chromatography systems such as high-performance liquid chromatography and gas chromatography-mass spectrometry, but with the stimulus-responsive systems, simple, fast, sensitive and low-cost detection strategies can be developed. For example, in magnetic resonance imaging, iron oxide nanoparticles (IONs) with the size <4 nm can significantly enhance T1 contrast while their aggregation resulted in T2 contrast enhancement due to inhomogeneous of the magnetic field around the aggregates. Thus, such IONs have been used as a T2 contrast agent for the diagnosis of liver diseases. However, they are insensitive for the diagnosis of small hepatocellular carcinomas (SHC), and the
successful diagnosis is critically important to increase the median five-year survival rate for the patients [81]. When the ION was functionalized with i-Motif DNAs that can transform from single-stranded state to intercalated quadruple-helical structure in an acid environment, the decrease in pH would disperse the aggregates of the functionalized IONs. With these functionalized IONs, SHC can be detected because the acidity of the tumor stimulated the disassembly of the ION aggregates and switched the MRI module from T2 to T1 enhancement to improve the distinction between normal liver and the SHC tissues [82]. Another interesting example is the pH-responsive surfaces composed of nanoparticles with a coating of amino group-containing silane. An acidic environment results in the protonation of the amino groups, which makes the surfaces very hydrophilic, while an alkali condition changes the surfaces into a very hydrophobic state. With this surface, the level of glucose in the saliva and urine can be accurately measured in one second by recording the contact angle of the liquid sample, based on the produced gluconic acid after the addition of glucose oxidase in the sample [83]. This non-invasive, low-cost, rapid glucose detection method is beneficial to overcome the limitations of the traditional invasive diagnosis of diabetes such as pain and infection risk.

Although the current investigations have shown the promise and success of the stimuli-responsive system in preclinical tests for diagnostic applications, most of the constructed system cannot meet the requirements for clinical practices. This is due to a great diversity of compounds in the real samples harvested from the patients of various conditions (e.g. different diet, ages, and lifestyles) which significantly interfere with the accuracy and sensitivity of the measurement [84]. Besides detecting the level of the biochemicals, their local distribution in the human body and continuous monitoring which are difficult to achieve may be also needed. Thus, the stimuli-responsive diagnostic systems remain in the early stage, and further investigations are needed for the commercialization in clinical management of diseases.

3.3. Tissue engineering and regenerative biomedicine

The research on tissue engineering and regenerative biomedicine aim at replacing the necrotic or pathological tissues, and the general requirements of the corresponding materials including biodegradability, proper physical properties, bioactive ligands and the ability to control suitable cellular behaviors. For the synthetic scaffold which is relative low cost and has predefined properties, it is important to mimic the matrix metalloproteinases (MMP)-mediated cellular invasion which regulates the balance between scaffold degradation and cell ingrowth. Incorporation of the integrin-binding sites and the substrates of MMP in hydrogels can provide the enhanced cell adhesion and controllable biodegradability. In a polyethylene glycol (PEG) hydrogel functionated with MMP-degraded oligopeptides, thymosin β4 (Tβ4), and human umbilical vein endothelial cells (HUVECs), the Tβ4 can stimulate the encapsulated HUVECs to secrete MMP-2 and MMP-9 to degrade the hydrogel, and such degradation promotes the release of Tβ4 in return [85]. In another study, four-armed PEG with arginylglycylaspartic acid (RGD) peptide units was crosslinked by MMP-sensitive crosslinkers to form microparticles, and a porous and injectable scaffold was formed by annealing those microparticles with each other. Such an enzyme-responsive scaffold is beneficial for maintaining the balance between the rates of the scaffold biodegradation and tissue regeneration, and the rapid cutaneous-tissue regeneration was found within five days [86]. Besides the molecular design, spatiotemporal control of the hydrogel’s physical and chemical properties is also important, and photochemical strategies including photocatalysis and photocleavage are useful tools for dynamic tuning [87].

Besides scaffolds, another important application of the bio-responsive materials is to construct intelligent surfaces or coatings on medical devices. For example, to prevent the implant-related infections, nanotubes were formed on the surfaces of titanium implants and antibiotics were loaded in the nanotubes. The nanotubes were then capped with 1,4-bis (imidazol-1-ylmethyl) benzene (BIB) using metal ions as the coordination linkage between the titanium and BIB. When bacteria attach on the titanium implant, the acidic metabolism products break the coordination linkage, resulting in the release of the loaded antibiotics to kill the bacteria. The loaded antibiotics ceased to release when the attached bacteria are completely killed [88]. However, compared with bioresponsive scaffolds, there is much less research on the bio-responsive coating.

4. Conclusion and outlook

In past decades, there has been an explosive growth in the research on bio-responsive polymers which have exhibited the significant influence in materials science, molecular pharmaceutics and nanobiotechnology. The variation in pH, temperature, stress, redox, enzyme and ATP can trigger various responses in the materials such as swelling, shrinkage, assembly, disassembly, degradation, sol-gel transition and crosslinking, and the stimuli-responsive systems exhibit many promising applications. The stimuli-responsive functions are achieved through proper molecular design including introduction of protonated groups, polar side chains, reducing groups and enzyme substrate units as well as supramolecular self-assembly. Most of the stimulus-responsive
systems are designed for controlled drug delivery to achieve programmed release and overcome the shortcomings associated with systemic administration of drugs, and the increasing attention is gained on the development of novel materials for diagnostics and tissue engineering. Besides the system that can only respond to a single stimulus, dual or multiple stimuli-triggered bio-responsive systems have also been developed to further improve the responsive efficiency.

The construction of bio-responsive systems depends on several integrated steps such as the design of the responsive forms, determination of the biological stimuli, and incorporation of the responsive units. The prepared system should exhibit a desired responsive performance with high sensitivity and selectivity, and as a material for biomedical applications, the system should also have satisfied stability and biocompatibility. Taking drug delivery as an example, the drug carriers are designed to stabilize in the circulatory system and interact with the microenvironment of the target tissues. Good biocompatibility is required to avoid the possible systematic toxicity and immunogenicity, and it is important to control the timing for sufficient interaction between the carrier and the target tissues. Sometimes, it would be useful to incorporate dual or multi-stimuli or step-by-step function for the precise spatiotemporal control of drug delivery.

Despite the rapid growth in the research on bio-responsive biopolymers, it remains very difficult to get the products commercialized or even into the stage of clinical trials. Practical commercialization usually requires the potential of scale-up production and strong evidence to illustrate the clinical safety and efficiency. Thus, the key polymers in the bio-responsive system should have a simple molecular structure or can be synthesized by routine strategies. Unfortunately, this aspect has restricted the commercial potential of most published polymers in the bio-responsive system should have a simple molecular structure or can be synthesized by routine strategies. Unfortunately, this aspect has restricted the commercial potential of most published investigations due to their ‘overdesigned’ characteristics with the sophisticated structures and complex responsive mechanisms. Further exploration on the discovery of simple polymers or facile synthetic routes with defined responses is needed.

Clear demonstration of the safety and efficiency of the bio-responsive systems requires the full understanding of the in vivo behavior of the materials. It should be noted that the biological environment and the level of the target cues are different between the animal model and human body or even among the individual patients. It is urgently needed to develop fundamental biochemical and physiological research and for the evaluation of the influence of the variation in the biological situations and discovery of novel in situ imaging techniques for analyzing the interaction between the bio-responsive system and the target tissues. The information on the various biological cues should also be intensively gathered and analyzed in detail. In addition, the development of bioinspired or biomimetic systems to mimic the natural bio-responsive phenomena in the human body is promising. A representative example is the insulin-loaded synthetic vesicles that mimic the structure of granules or vesicles in pancreatic β cells and thus achieve a fast response for glucose-responsive insulin release [89]. Another promising strategy to overcome the limitation of the inconsistent parameters of the endogenous stimuli is the use of exogenous stimuli that can be manually controlled such as light, ultrasound and magnetic field. Recently, researchers also try to modulate the physiological microenvironment or generate the biochemical triggers in combination with the exogenous stimuli. For example, light was used to produce hypoxic conditions at the chosen position and time, which subsequently resulted in the dissociation of the carrier and drug release [90]. This strategy requires the incorporation of the functional building blocks that can respond to exogenous stimuli, which may increase the complexity of the system, but it would significantly promote the responsive sensitivity. Furthermore, the use of implanted wireless biochips or wearable devices may help to continuously monitor the local physiological conditions or amplify the bio-stimuli for the precise modulation of the bio-responsive behavior. Therefore, with further development of the basic sciences and advanced technologies, we believe that more and more bio-responsive smart systems will appear on the market to significantly change the current strategies of diagnosis and the treatment of diseases as well as people’s lifestyles.

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References

[1] Wilson D et al 2019 Antigens reversibly conjugated to a polymeric glyco-adjuvant induce protective humoral and cellular immunity Nat. Mater. 18 175–85
[2] Park Y et al 2018 Protection of tissue physicochemical properties using multifunctional crosslinkers Nat. Biotechnol. 37 73–83
[3] Roberts S et al 2018 Injectable tissue integrating networks from recombinant polypeptides with tunable order Nat. Mater. 17 1154–63
[4] Kocak G, Tuncer C and Büttün V 2017 pH-responsive polymers Polym. Chem. 8 141–76
[5] Pang X, Jiang Y, Xiao Q, Leung A W, Hua X and Xu C 2016 pH-responsive polymer–drug conjugates: design and progress J. Controlled Release 222 116–29
[6] Zhang X, Han L, Liu M, Wang K, Tao L, Wan Q and Wei Y 2017 Recent progress and advances in redox-responsive polymers as controlled delivery nanoplatforms Mater. Chem. Front. 1 807–22
[7] Fukino T, Yamagishi H and Aida T 2017 Redox-responsive molecular systems and materials Adv. Mater. 29 1603888
[8] Hu Q, Katti P S and Gu Z 2014 Enzyme-responsive nanomaterials for controlled drug delivery Nanoscale 6 12273–86
[9] Kanamala M, Wilson W R, Yang M, Palmer B D and Wu Z 2016 Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery a review Biomaterials 85 152–67
[10] Weinhouse S, Warburg O, Burkh D and Schade A L 1956 On respiratory impairment in cancer cells Science 124 267–72
[11] Denny W A and Wilson W R 1986 Considerations for the design of nitrophenyl mustards as agents with selective toxicity for hypoxic tumor cells J. Med. Chem. 29 879–87
[12] Madshus I H 1988 Regulation of intracellular pH in eukaryotic cells Biochem. J. 250 1–8
[13] Yoshida T, Lai T C, Kwon G S and Sako K 2013 pH- and ion-sensitive polymers for drug delivery Expert Opinion on Drug Delivery 10 1497–513
[14] Schmaljohann D 2006 Thermo- and pH-responsive polymers in drug delivery Adv. Drug Deliv. Rev. 58 1655–70
[15] Lu Y, Aimetti A A, Langer R and Gu Z 2016 Bioresponsive materials Nat. Rev. Mater. 2 16075
[16] Scarp J S, Mueller D D and Klotsz I M 1967 Slow hydrogen–deuterium exchange in a non-alpha.-helical polypeptide JACS 89 6024–30
[17] Timko B P et al 2014 Near-infrared-activated devices for remotely controlled drug delivery PNAS 111 1349–54
[18] Amiram, Luginbuhl K M, Li X, Feingols M N and Chilkoti A 2013 Injectable protease-operated devices of glucagon-like peptide-1 provide extended and tunable glucose control PNAS 110 2792–7
[19] Wang C, Stewart R J and Kopecek J 1999 Hybrid hydrogels assembled from synthetic polymers and coiled-coil protein domains Nature 397 417–20
[20] Xia J W, Xie R, Ju X J, Wang W, Chen Q and Chu L Y 2013 Nano-structured smart hydrogels with rapid response and high elasticity Nat. Commun. 4 2226
[21] Nesbitt W S, Westen E, Tovar-lope F I, Tolouei E, Mitchell A, Fu J, Carberry J, Fours A and Jackson S P 2009 A shear gradient-dependent platelet aggregation mechanism drives thrombus formation Nat. Med. 15 665–73
[22] Cheng R, Feng F, Meng F, Deng C, Feijen J and Zhong Z 2011 Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery J. Controlled Release 152 2–12
[23] Kuppusamy P, Li H, Ilangovan G, Cardonnel A J, Zweier J L, Yamada K, Krishna M C and Mitchell J B 2002 Noninvasive imaging of tumor redox status and its modification by tissue glutathione levels Cancer Research 62 307–12
[24] Quinn J F, Whitaker M R and Davis T P 2017 Glutathione responsive polymers and their application in drug delivery systems Polym. Chem. 8 97–126
[25] Huo M, Yuan J, Tao L and Wei Y 2014 Redox-responsive polymers for drug delivery: from molecular design to applications Polym. Chem. 5 1519–28
[26] Zelzer M, Todd S J, Hirst A R, McDonald T O and Uljin R V 2013 Enzyme responsive materials: design strategies and future developments Biomaterials Science 1 11–39
[27] Cheng Y, Huang F, Min X, Gao P, Zhang T, Li X, Liu B, Hong Y, Lou X and Xia F 2016 Protease-responsive prodrug with aggregation-induced emission probe for controlled drug delivery and drug release tracking in living cells Anal. Chem. 88 8913–9
[28] Jiang Y, Lu J, Wang Y, Zeng F, Wang H, Peng H, Huang M, Jiang H, Luo C and Huang T 2014 Molecular-dynamics-simulation-driven design of a protease-responsive probe for in-vivo tumor imaging Adv. Mater. 26 8174–8
[29] Phillips D J, Wilde M, Grobe F and Gibson M J 2015 Enzymatically triggered, intracellularly responsive polymers: reprogramming poly(oxyethylene glycols) to respond to phosphatase Biomacromolecules 16 3256–64
[30] Mo R, Jiang T and Gu Z 2014 Enhanced anticancer efficacy by ATP-mediated liposomal drug delivery Angewandte Chemie International Edition in English 53 5815–20
[31] Mo R, Jiang T, Di Santo R, Tai W and Gu Z 2014 ATP-triggered anticancer drug delivery Nat. Commun. 5 3364
[32] Biswas S, Kimbara K, Niwa T, Taguchi H, Ishii N, Watanabe S, Miyata K, Kataoka K and Aida T 2013 Biomolecular robotics for chemomechanically driven guest delivery fuelled by intracellular ATP Nat. Chem. 5 613–20
[33] Calin G A and Croce C M 2006 MicroRNA signatures in human cancers Nat. Rev. Cancer 6 587–66
[34] Zhang P, Cheng F, Zhou R, Cao J, Li J, Burda C, Min Q and Zhu J J 2014 DNA-hybrid-gated multifunctional mesoporous silica nanocarriers for dual-targeted and microRNA-responsive controlled drug delivery Angewandte Chemie International Edition in English 53 2371–5
[35] Ohta S, Glancy D and Chan W C 2016 DNA-controlled dynamic colloidal nanoparticle systems for mediating cellular interaction Science 351 841–5
[36] Coboi I, Li M, Sumerlin B S and Perrier S 2015 Smart hybrid materials by conjugation of responsive polymers to biomacromolecules Nat. Mater. 14 143–59
[37] Jin Y, Song L, Su Y, Zhu L, Pang Y, Qiu F, Tong G, Yan D, Zhu B and Zhu X 2011 Oxime linkage: a robust tool for the design of pH-sensitive polymeric drug carriers Biomacromolecules 12 3460–6
[38] Zhu S, Hong M, Tang G, Qian L, Lin J, Jiang Y and Pei Y 2010 Partly PEGLyated polyamidoamine dendrimer for tumor-selective targeting of doxorubicin: in the effects of PEGLyation degree and drug conjugation style Biomaterials 31 1360–71
[39] Kang Y, Ha W, Liu Y Q, Ma Y, Fan M M, Ding L S, Zhang S and Li B J 2014 pH-responsive polymer-drug conjugates as multifunctional micelles for cancer-drug delivery Nanotechnology 25 335101
[40] Wu Y, Chen W, Meng F, Wang Z, Cheng R, Deng C, Liu H and Zhong Z 2012 Core-crosslinked pH-sensitive degradable micelles: a promising approach to resolve the extracellular stability versus intracellular drug release dilemma J. Control. Release 164 338–45
[41] Huang Z, Guo X, Li W, MacKay J A and Snoka F C Jr 2006 Acid-triggered transformation of diortho ester phospholiposome JACS 128 60–1
Kim H-K, Thompson D H, Jiang H-S, Chung Y J and Van den Bossche J 2013 pH-responsive biodegradable assemblies containing tunable phenyl-substituted vinyl tetrafluoroethers for use as efficient gene delivery vehicles ACS Applied Materials & Interfaces 5 5648–58

Koettig M C, Guido J F, Gupta M, Zhang A and Peppas N A 2016 pH-responsive and enzymatically-responsive hydrogel microparticles for the oral delivery of therapeutic proteins: Effects of protein size, crosslinking density, and hydrogel degradation on protein delivery J. Controlled Release 221 18–25

Anderson D G, Lynn D M and Langer R 2003 Semi-automated synthesis and screening of a large library of degradable cationic polymers for gene delivery Angewandte Chemie International Edition in English 42 3133–9

Cheng C J et al 2013 MicroRNA silencing for cancer therapy targeted to the tumour microenvironment Nature 518 107–10

Li H J et al 2016 Stimuli-responsive clustered nanoparticles for improved tumor penetration and therapeutic efficacy PNAS 113 4164–9

Pacarro D B, Ligler F S and Gu Z 2015 Programmable nanomedicine: synergistic and sequential drug delivery systems Nanoscale 7 3381–91

Ma Y, Qiao S L, Wang Y, Lin Y X, An H W, Wu X C, Wang L and Wang H 2018 Nanoantagonists with nanophase-segregated surfaces for improved cancer immunotherapy Biomaterials 156 248–57

Zhuang J, Gordon M R, Ventura J, Li L and Thayumanavan S 2013 Multi-stimuli responsive macromolecules and their assemblies Chem. Soc. Rev. 42 7421–55

Qiao S and Wang H 2018 Temperature-responsive polymers: synthesis, properties, and biomedical applications, Nano Research 11 2400–23

Korin N et al 2012 Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels Science 337 738–42

She S, Li Q, Shan B, Tong W and Gao C 2013 Fabrication of red-blood-cell-like polyelectrolyte microcapsules and their deformation and recovery behavior through a microcapillary Adv. Mater. 25 5814–8

Natsume T and Yoshimoto M 2014 Mechanosensitive liposomes as artificial shear-chambers for shear-driven acceleration of enzyme-catalyzed reaction ACS Applied Materials & Interfaces 6 5671–9

Anselmo A C, Kumar S, Gupta V, Pearce A M, Ragusa A, Muzykantov V and Mitragotri S 2015 Exploiting shape, cellular–hitchhiking and antibodies to target nanoparticles to lung endothelium: synergy between physical, chemical and biological approaches Biomaterials 68 1–8

Anselmo A C, Gupta V, Zern B J, Pan D, Zakrewsky M, Muzykantov V and Mitragotri S 2013 Delivering nanoparticles to lungs while avoiding liver and spleen through adsorption on red blood cells ACS Nano 7 11129–37

Feng Q, Wei K, Lin S, Xu Z, Sun Y, Shi P, Li G and Bian L 2016 Mechanically resilient, injectable, and bioadhesive supramolecular gelatin hydrogels crosslinked by weak host–guest interactions assist cell infiltration and in situ tissue regeneration Biomaterials 101 217–28

Kaplan J A, Barthélémy P and Grinstaff M W 2016 Self-assembled nanofiber hydrogels for mechanoresponsive therapeutic anti-TNFα antibody delivery Chem. Commun. 52 8660–3

Siegrist D J, Oh J K and Matyjaszewski K 2012 ATRP in the design of functional materials for biomedical applications Prog. Polym. Sci. 37 18–37

Zhang S and Zhao Y 2010 Rapid release of entrapped contents from multi-functionalizable, surface cross-linked micelles upon different stimulation JACS 132 10642–4

Xu H, Cao W and Zhang X 2013 Selenium-containing polymers: promising biomaterials for controlled release and enzyme mimics Acc. Chem. Res. 46 1647–58

Napolí A, Valentini M, Tirelli N, Muller M and Hubbell J A 2004 Oxidation-responsive polymeric vesicles Nat. Mater. 3 183–9

Liu J, Pang Y, Zhu Z, Wang D, Li C, Huang W, Zhu X and Yan D 2013 Therapeutic nanocarriers with hydrogen peroxide-triggered drug release for cancer treatment Biomacromolecules 14 1627–36

Staff R H, Gallet M, Mazurowski M, Rehahn M, Berger R, Landfester K and Crespy D 2012 Patchy nanocapsules of poly(vinylferrocene)-based block copolymers for redox-responsive release ACS Nano 6 9042–9

Broaders K E, Grandhi S and Frechet J M 2011 A biocompatible oxidation-triggered carrier polymer with potential in therapeutics JACS 133 756–8

de Gracia Lux C, Joshi-Barr S, Nguyen T, Mahmoud E, Schopf E, Fomina N and Almutairi A 2012 Biocompatible polymeric nanoparticles degrade and release cargo in response to biologically relevant levels of hydrogen peroxide JACS 134 15758–64

Santiana J J, Sui B, Gomez N and Rouge J L 2017 Programmable peptide–cross-linked nucleic acid nanocapsules as a modular platform for enzyme specific cargo release Bioconjugate Chem. 28 2910–4

Dos Santos S, Chandravarkar A, Mandal B, Minna R, Murat K, Sauède L, Tella P, Tuchscherer G and Mutter M 2005 Switch-peptides: controlling self-assembly of amyloid β-derived peptides in vitro by consecutive triggering of acyl migrations JACS 127 11888–9

Hu J, Zhang G and Liu S 2012 Enzyme-responsive polymeric assemblies, nanoparticles and hydrogels Chem. Soc. Rev. 41 5933–49

Fu X, Hosta-Rigau L, Chandravarkar R and Cui J W 2018 Multi-stimuli-responsive polymer particles, films, and hydrogels for drug delivery Chem 4 2084–107

Cao Z Q and Wang G J 2016 Multi-stimuli-responsive polymer materials: particles, films, and bulk gels Chem. Rev. 16 1398–435

Oliveir A, Meyer F, Raquez J M, Dammann P and Dubois P 2012 Surface-initiated polymerization of block copolymers for redox-responsive release ACS Nano 6 9042–9

Badeau B A, Comerford M P, Arakawa C K, Shadish J A and DeForest C A 2018 Engineered modular biomaterial logic gates for environmentally triggered therapeutic delivery, nature Chemistry 10 251–81

Sun Y, Liu S, Du G, Gao G and Fu J 2015 Multi-responsive and tough hydrogels based on triblock copolymer micelles as multi-functional macro-crosslinkers Chem. Commmun. 31 5812–5

Xue B, Kozlovskaya V, Liu F, Chen J, Williams J E, Campos–Gomez J, Saeed M and Kharlampieva E 2015 Intracellular degradable hydrogel cubes and spheres for anti-cancer drug delivery ACS Applied Materials & Interfaces 7 13633–44

Li X, Cai X, Gao Y and Serpe M J 2017 Reversible bidirectional bending of hydrogel–based bilayer actuators J. Mater. Chem. B 5 2804–12

Cao Y, DePinho R A, Ernst M and Voukden K 2011 Cancer research: past, present and future Nat. Rev. Cancer 11 749–54

Patel N R, Pattni B S, Abouzeid A H and Torchilin V P 2013 Nanopreparations to overcome multidrug resistance in cancer Adv. Drug Delivery Rev. 65 1748–62

Chen Q, Feng L, Liu J, Zhu W, Dong Z, Wu Y and Liu Z 2016 Intelligent albumin–MnO2 nanoparticles as pH/H2O2-responsive dissociable nanocarriers to modulate tumor hypoxia for effective combination therapy Adv. Mater. 28 7129–36

Cao Z, Zhou X and Wang G 2016 Selective release of hydrophobic and hydrophilic cargos from multi-stimuli-responsive nanogels ACS Applied Materials & Interfaces 8 28888–90

Cheng B, Meng F, Deng C, Klok H A and Zong Z 2013 Dual and multi-stimuli-responsive polymeric nanoparticles for programmed site-specific drug delivery Biomaterials 34 3647–57
[81] Llovet J M, Burroughs A and Bruix J 2003 Hepatocellular carcinoma Lancet 362 1907–17
[82] Lu J, Sun J, Li F, Wang J, Liu J, Kim D, Fan C, Hyeon T and Ling D 2018 Highly sensitive diagnosis of small hepatocellular carcinoma using pH-responsive iron oxide nanocluster assemblies JACS 140 10071–4
[83] Gao Z F, Sann E E, Lou X, Liu R, Dai J, Zuo X, Xia F and Jiang L 2018 Naked-eye point-of-care testing platform based on a pH-responsive superwetting surface: toward the non-invasive detection of glucose NPG Asia Mater. 10 177–89
[84] Jung I Y, Kim J S, Choi B R, Lee K and Lee H 2017 Hydrogel based biosensors for in vitro diagnostics of biochemicals, proteins, and genes Adv. Healthcare Mater. 6 1601475
[85] Krachenbuehl T P, Ferreira L S, Zammaretti P, Hubbell J A and Langer R 2009 Cell-responsive hydrogel for encapsulation of vascular cells Biomaterials 30 4318–24
[86] Griffin D R, Weaver W M, Scumpia P O, Di Carlo D and Segura T 2015 Accelerated wound healing by injectable microporous gel scaffolds assembled from annealed building blocks Nat. Mater. 14 737–44
[87] DeForest C A and Anseth K S 2011 Cytocompatible click-based hydrogels with dynamically tunable properties through orthogonal photoconjugation and photocleavage reactions Nat. Chem. 3 925–31
[88] Wang T, Liu X, Zhu Y, Cui Z D, Yang X J, Pan H, Yeung K W K and Wu S 2017 Metal ion coordination polymer–capped pH-triggered drug release system on titania nanotubes for enhancing self-antibacterial capability of Ti implants ACS Biomaterials Science & Engineering 3 816–25
[89] Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, Ligler F S, Buse J B and Gu Z 2015 Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery PNAS 112 8260–5
[90] Qian C, Yu J, Chen Y, Hu Q, Xiao X, Sun W, Wang C, Feng P, Shen Q-D and Gu Z 2016 Light-activated hypoxia-responsive nanocarriers for enhanced anticancer therapy Adv. Mater. 28 3313–20