Volume 26 June 2020
Indian Journal of Biological Sciences
(A Peer Reviewed Journal)
ISSN 0972-8503

An overview on the interior and exterior stimuli-responsive biomaterials designed for cancer therapy

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Abstract

Cancer is the prime cause of mortality worldwide. There are so many limitations in the use of conventional chemotherapeutic agents for cancer treatments. Due to the development of materials chemistry and the ability to deliver drugs in different directions, the concept of stimuli-responsive devices has gained widespread acceptance. These devices can be used in combination with other drugs to deliver a specific therapeutic agent. There is a greatly promising role of stimuli-responsive nanomaterials for cancer drug delivery in the future. This review aims to provide an overview of the various stimuli-oriented developments of prodrug-based nanomaterials for cancer treatment. Several types of bio-based materials are currently being developed that can respond to various external stimuli such as the thermal, light, and magnetic fields and internal stimuli such as enzymes, pH, redox potential, and hypoxia. These can also be used to deliver drugs to the targeted areas of cancer cells. They can additionally trigger the activation of multiple bioactive compounds and improve the efficiency of their drug delivery. In addition to being able to deliver drugs, these materials can help in the development of accurate diagnosis and treatment.

Keywords: Nanomaterials, Cancer therapy, Stimuli-responsive, Drug delivery, Tumor microenvironment

Introduction

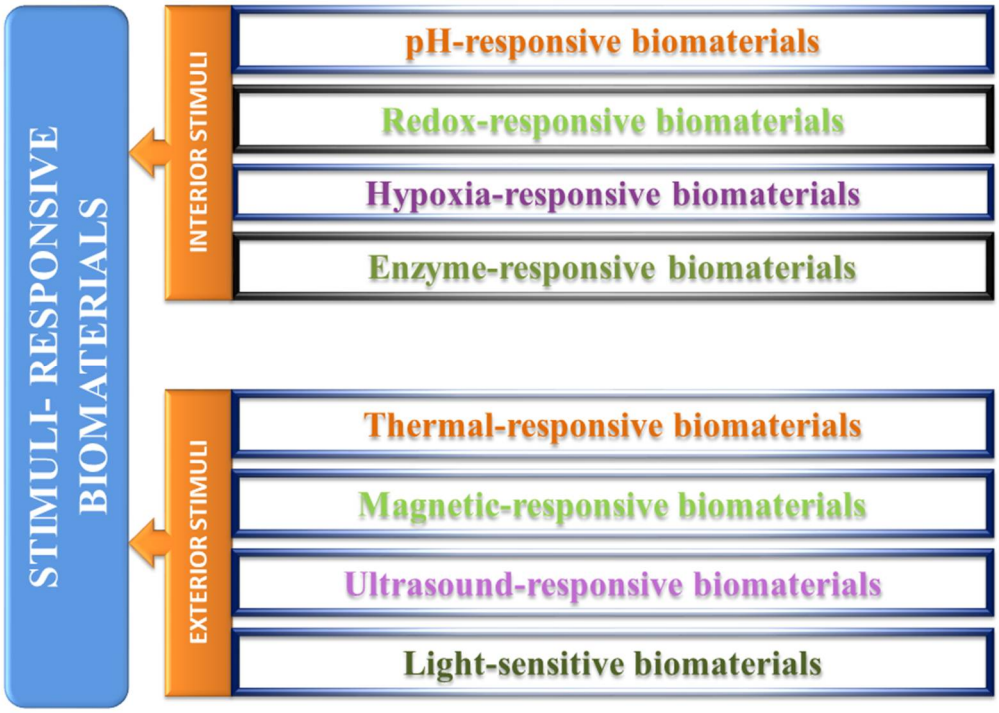
Cancers are a collection of diseases characterized by the uncontrolled growth of malignant cells in the body's tissues, which can infiltrate tissues and spread to other

parts of the body. Cancer-related deaths accounted for roughly 10 million deaths in 2020, according to the World Health Organization, and the incidence of cancer is anticipated to rise significantly to 28.4 million new cases in 2040 (Sung *et al.*, 2021). Nanotherapeutics, a growing sector of nanotechnology that blends nanoscience, biological science, material science, and pharmaceutical science to produce innovative anticancer medicines, could be a viable alternative to current cancer therapies such as chemotherapy, surgery, and radiation (Wang *et al.*, 2020). To extend therapeutic action, nanoparticles (NPs) can modify the pharmacokinetic and pharmacodynamic characteristics of chemotherapeutic medicines. Nanoparticles take advantage of leaky tumor vasculature and a malfunctioning lymphatic drainage system, which is mediated by the increased permeability and retention (EPR) effect, to increase their accumulation and retention time inside tumors (Martin *et al.*, 2020). Although most of thenanotherapeuticshas improved the solubility and pharmacokinetic profile of anticancer medications in clinical tests, only a few have improved the survival rate (Rosenblum *et al.*, 2018). In the microenvironment, there are several variations in endogenous stimuli between tumor cells and normal tissues. By endowing the nanocarrier with redox, pH, enzyme, and reactive oxygen species (ROS) responsiveness, stimuli-responsive nanomaterials have been used to design and construct nanocarriers to optimize drug delivery at specified areas and limit leakage in unexpected regions (Hirata *et al.*, 2017). pH-sensitive drug delivery systems (DDSs) are relatively mature at the moment, while redox-sensitive DDSs have a lot of promise among those DDSs that respond to internal microenvironment stimuli. Researchers used uneven amounts of glutathione (GSH), which is overexpressed in cancer cells' cytoplasm, to produce target-specific DDSs (Phillips *et al.*, 2014). The precision distribution and potent effects of this method provide several major benefits to redox-sensitive DDSs. In the absence of additional endogenous or exogenous signal stimulation, this delivery technique may even outperform desired outcomes such as no blood leakage, tumor-targeting delivery, and rapid drug release. In comparison to other forms of nanomaterials, prodrug-based nanomaterials can respond to stimuli intelligently and sensibly, releasing the desired medicines. Several prodrug-based nanomaterials with various chemical modifications have emerged as the corresponding stimuli-responsive devices, including the interior tumor microenvironment (TME) stimuli e.g., pH, redox environment, enzymes, hypoxic, etc. (Sun *et al.*, 2018; Chi *et al.*, 2017; An *et al.*,

2016) as well as the exterior environmental stimuli (e.g., light, thermal, ultrasound, and magnetism field, etc.) (Liu *et al.*, 2016; Li *et al.*, 2017). The key to designing satisfactory prodrug-based nanomaterials is to choose the right type of stimuli and chemical changes for varied scenarios. This review will cover the most important features of stimuli-responsive prodrugnanomaterials in cancer therapy, such as different types of prodrug-based nanoparticles, diverse stimuli, problems, perspectives, and current clinical advancements.

Stimuli-Responsive Biomaterials

The broad stimuli-responsive biomaterials have been classified here according to their stimulus responses including both inside and outside stimuli.



Interior Stimuli-Responsive Biomaterials

Enzymes, ATP, low pH, redox-potential, and hypoxia, among other biological variables in the tumor microenvironment or inside cancer cells, could be specific

triggers for controlled drug release, endosome/lysosome escape, prodrug activation, tumor specific imaging, and therapy (Qian *et al.*, 2016).

pH-responsive biomaterials

Due to the nature of low pH inside cancer cell organelles (e.g., lysosomes and endosomes) and in the tumor microenvironment, pH-responsive biomaterials have been extensively utilized. In general, the pH of cytoplasm, blood, and normal tissues is around 7.0 to 7.4, while endosomal/lysosomal organelles have a pH of 6 to 4, and the tumor microenvironment has a pH of 6.5 to 6.8 (Helmlinger *et al.*, 1997). Until now, a variety of pH-sensitive biomaterials have been used for imaging, intracellular drug delivery, charge conversion, and controlled drug release in the tumor microenvironment, including $CaCO_3$ nanoparticles (Wang *et al.*, 2018), calcium phosphate (CaP) biomaterials (Huang *et al.*, 2019), inorganic nanoparticles or crystals(Liu *et al.*, 2016), polymer-drug conjugates (Pang *et al.*, 2016), polymeric micelles(Li *et al.*, 2018), liposomes (Vila-Caballer *et al.*, 2016), polymersomes (Chen *et al.*, 2010), nanogels (Huang *et al.*, 2019) and dendrimers (Mingming *et al.*, 2015), and others. Meanwhile, various pH-sensitive polymers have been developed for the fabrication of pH-responsive biomaterials (Deirram *et al.*, 2019), including Poly (2-(pentamethyleneimino) ethyl methacrylate) (PC6A), poly (2-(hexamethyleneimino) ethyl methacrylate) (PC7A), poly (-amino ester) (PAE), polysulfadimethoxine (PSD), poly (L-histidine) (PHis), poly (4-vinyl benzoic acid) (PVBA), poly (2- vinylpyridine) (P2VP) (Chen *et al.*, 2015). Meanwhile, pH-sensitive chemical bonds have been used for drug conjugation, confirmation/size change, and charge conversion, among other things, to promote pH-triggered drug release and biomaterial disassociation inside cancer cells or in the tumor microenvironment (Wu *et al.*, 2018). For the purpose of releasing cargo from cancer cells, several intercellular biomaterials with pH triggers have been created (Hou *et al.*, 2018). Due to the protonation of the cationic materials, pH-triggered charge conversion biomaterials have also been engineered for intracellular drug delivery, where neutral or negatively charged biomaterials could turn positively charged by responding to low pH in endosomes/lysosomes for disrupting endosomes/lysosomes (Wang *et al.*, 2019). Certain chemical groups, such as citraconic anhydride, 2, 3-dimethylmaleic anhydride (DA), cis-aconitic anhydride, carboxydimethylmaleic anhydride (CDM), and cis-4-cyclohexene-1,2-dicarboxinic anhydride, could be used

to achieve pH-triggered charge conversion. Intracellular delivery of antibodies (Lee *et al.*, 2010), proteins, siRNA (Tangsangasaksri *et al.*, 2016), and DNA (Lee *et al.*, 2008) is facilitated by the charge conversion approach, as is tumor build-up of biomaterials, etc (Ranneh *et al.*, 2018). Furthermore, by conjugating ligands (e.g., biotin) to tumor pH-sensitive polymers, it was possible to hide the targeting ligands inside the Polyethylene Glycol (PEG) shell during circulation (i.e., pH 7.4) and ligands present in the tumor microenvironment (i.e., pH 7.0), avoiding unspecific internalization and uptake of ligands and improving tumor active targeting efficacy (Lee *et al.*, 2008). (**Table 1**)

Redox-responsive biomaterials

Due to the drastically variable reduction potentials and capacities in tumors, redox-responsive biomaterials have been widely used for drug delivery. For example, the glutathione (GSH) level inside cancer cells (2-10 mM) is significantly higher than that in normal regions (2-10 μM). Several redox-sensitive biomaterials, such as nanocapsules (Kim *et al.*, 2010), mesoporous silica nanoparticles (Luo *et al.*, 2011), polymer-drug conjugates (Mi *et al.*, 2017), polymersomes (Zou *et al.*, 2016), polymeric vesicles (Chang *et al.*, 2014), polymeric micelles (Liu *et al.*, 2019), nanogels (Elkassih *et al.*, 2019), gold nanoparticles (Kim *et al.*, 2014), and hybrid nanoparticles (Qiu *et al.*, 2018), have been produced to date. GSH can cleave disulfide bonds into sulfhydryl groups (Guo *et al.*, 2018), but diselenide bonds (Se-Se) are equally susceptible to redox potential but have lower bond energy than disulfide bonds (Ma *et al.*, 2010). Furthermore, H_2O_2-responsive biomaterials have been created for tumor therapy (Lin *et al.*, 2019), including the treatment of hypoxic (Chen *et al.*, 2019) and multidrug-resistant malignancies (Chen *et al.*, 2015). (Table 1)

Hypoxia-responsive biomaterials

Hypoxia (low oxygen level) is prone to develop inside solid tumors due to inadequate vascularization, which plays a crucial role in cancer progressions, such as loco-regional spread and distant metastasis (Keith *et al.*, 2007). Hypoxia promotes a malignant phenotype, which has a deleterious impact on prognosis and therapy and leads to drug resistance (e.g., radiotherapy, chemotherapy). As a result, numerous techniques for treating hypoxic tumors have been used, including raising oxygen levels and employing hypoxia activated pro-drugs, among others (Brown *et al.*,

2004). Liposomes (Liu *et al.*, 2017), silica nanoparticles (Im *et al.*, 2019), up-conversion nanoparticles (UCNPs), layer-by-layer nanoparticles (Poon *et al.*, 2011), nanovesicles, polymeric micelles (Zhen *et al.*, 2019), polymersomes (Kulkarni *et al.*, 2018), albumin nanoparticles(Yang *et al.*, 2019), cell membrane coated metal-organic framework (MOF) (Li *et al.*, 2017), solid-state sensors CaP nanoparticles (Mi *et al.*, 2016), and other biomaterials have all been engineered for drug delivery to hypoxic tumors (Liu *et al.*, 2018). Meanwhile, various cargos, such as imaging agents (e.g., contrast agents), prodrugs (e.g., dihydrochloride (AQ4N)), anticancer drugs (e.g., doxorubicin), siRNA, and photosensitizers (e.g., ICG), could be loaded inside the hypoxia-activated biomaterials, demonstrating high performance in hypoxic tumor imaging and effective therapy by overcoming drug resistance (Liu *et al.*, 2014). However, some underlying issues, such as modifying the hypoxic tumor microenvironment, enhancing drug penetration and oxygen levels, as well as clinical translation of hypoxia-responsive biomaterials will be addressed in future investigations. (Table 1)

Enzyme-responsive biomaterials

Enzymes play a crucial part in biological activities, and the uncontrolled expression of certain enzymes in neoplastic circumstances could be used to trigger the release of enzyme-responsive drugs. Several enzyme-sensitive biomaterials, such as mesoporous silica nanoparticles (Liu *et al.*, 2015), dendrimers (Zhang *et al.*, 2017), magnetic nanoparticles (Huang *et al.*, 2015), polymeric micelles (Gu *et al.*, 2019), and liposomes (Fu *et al.*, 2015), have been developed to achieve regulated release of cargos in tumors and cancer cells (Chandrawati *et al.*, 2016), as well as prodrug/ligand activation and morphological modification. Biomaterials may interact withoxidoreductases (e.g., peroxidases) (Van den Mooter *et al.*, 1994), transferases (e.g., creatine kinase), and hydrolases, such as matrix metallo-proteinases (MMPs) (Callmann *et al.*, 2015), human recombinant caspase3 (Xin *et al.*, 2018), proteinase K (Nosrati *et al.*, 2018), intestinal protease, cathepsin B (Cai *et al.*, 2018), trypsin(Zhang *et al.*, 2015), and among others, which are up-regulated in the tumor microenvironment and cancer cells (Hu *et al.*, 2014). (Table 1)

Exterior Stimuli-Responsive Biomaterials

The fate of biomaterials inside biological systems may be affected by external stimuli such as heat, magnetic field, electronic field, ultrasound, and light. It permits

the enhancement of biomaterial accumulation in desirable places with outer forces (e.g., magnetic field), regulated release, intracellular drug administration, as well as triggered imaging and therapy with exterior stimuli.

Thermal-responsive biomaterials

Temperature-sensitive biomaterials are also commonly used for drug delivery and cancer treatment. In general, biomaterials are designed to be stable in normal temperatures up to 37°C and sensitive to higher temperatures (>40°C) with considerable changes in properties due to the narrow temperature shift. Liposomes (Liu *et al.*, 2019), polymeric micelles (Araki *et al.*, 2018), nanocomposites (Hervault *et al.*, 2016), nanocapsules (Lee *et al.*, 2008), nanogels (Ruan *et al.*, 2019), and vesicles (Zheng *et al.*, 2019), among other thermosensitive biomaterials, have been developed to date. Thermal-sensitive biomaterials are made from materials that can change their physicochemical properties as a result of temperature changes (van Elk *et al.*, 2014). Poly (N-isopropylacrylamide) (PNIPAM) (Barhoumi *et al.*, 2014), poly (N-inylisobutyramide) (PAMAM) (Kono *et al.*, 2011), poly (2-oxazoline) (POxs) (Osawa *et al.*, 2017), and poly [2-(2-methoxyethoxy) ethyl methacrylate] (PMEOMA) (Yang *et al.*, 2010) are among the temperature-sensitive materials. Incorporating thermal-unstable elements inside biomaterials is also an approach for achieving thermal sensitivity. For example, the NH_4HCO_3 incorporated liposome could produce CO_2 after local hyperemia (42°C) caused the liposome to swell and collapse (Chen *et al.*, 2013), resulting in drug release for efficient intracellular drug delivery. (Table 1)

Magnetic-responsive biomaterials

The magnetic-responsive biomaterials were created because magnetic nanoparticles have intrinsic magnetic field tropism for tumor targeting, as well as the ability to generate local hyperthermia under an alternating magnetic field for drug release and tumor ablation. Magnetic nanoparticles (Yan *et al.*, 2018), liposomes (Di Corato *et al.*, 2015), super-paramagnetic iron-oxide nanoparticles (SPIONs) (Smith *et al.*, 2015), polymeric micelles (Thorat *et al.*, 2016), albumin nanocapsules (Li *et al.*, 2015), magnetic biomaterials (Chiang *et al.*, 2016), and magnetic nanogels (Cazares-Cortes *et al.*, 2017) are among the numerous magnetic-responsive biomaterials now being developed. Magnetic materials, such as iron oxide nanoparticles (e.g., Fe_3O_4 nanoparticles) (Zhang *et al.*, 2017), iron oxide hybrid nanoparticles (e.g.,

graphene/Au/ Fe_3O_4hybrids) (Chen *et al.*, 2013), and other magnetic nanomaterials, are commonly used in biomaterials to achieve magnetic sensitivity (e.g., $ZnFe_2O_4$) (Yin *et al.*, 2016). Magnetic resonance imaging could be used to image tumors using the inserted magnetic materials (Yao *et al.*, 2017). Contrast agents (Wang *et al.*, 2017), anticancer medicines (Wu *et al.*, 2018), plasmids (Yin *et al.*, 2016), antibodies (Zhang *et al.*, 2017), and photosensitizers (Di Corato *et al.*, 2015) could all be integrated into magnetic-sensitive biomaterials to achieve numerous functions or multimodal therapeutic effects. Furthermore, the biomaterials could be tailored for passive tumor targeting via the EPR effect (Meikle *et al.*, 2016), as well as for active cancer cell targeting by targeting moieties (e.g., folic acid) (Li *et al.*, 2015). (Table 1)

Ultrasound-responsive biomaterials

Ultrasound is a type of high-frequency sound wave that can influence biomaterials and allow for controlled medication release in sick areas (i.e., tumors). For various purposes, the ultrasonic intensity might be varied. It could be used for imaging at low ultrasonic frequencies (less than 20 kHz), or for disrupting biomaterials to release cargos or boosting the permeability of cancer cell membranes at high ultrasound frequencies (more than 20 kHz) (Wang *et al.*, 2016). Albunex, Optison, Definity, Imagent, Levovist, and Sonazoid are only a few of the microbubbles that have been commercialised so far (Son *et al.*, 2014). Microbubbles, on the other hand, are limited in their access to vascular compartments in tumour tissues and deep penetration due to their enormous size (1-10 μm), short half-life, and low stability. Nanobubbles (Delogu *et al.*, 2012), calcium carbonate ($CaCO_3$) nanoparticles (Min *et al.*, 2015), liposomes (Geers *et al.*, 2012), nanodroplets (Cao *et al.*, 2018), vesicles (Huang *et al.*, 2016) and nanoparticles (Min *et al.*, 2013), and other size switchable microbubbles (i.e., from microbubbles to nanobubbles) (Huynh *et al.*, 2015) or biomaterials have been engineered for ultrasound imaging(Kang *et al.*, 2010), ultrasound triggered drug delivery (Wang *et al.*, 2014), and ultrasound triggered cancer theranostics. Generally, gas or contrast agents (Shapiro *et al.*, 2014), such as air, N_2, and perfluorocarbons, are incorporated into ultrasound-sensitive biomaterials, or gas is generated in the biological milieu (Jin *et al.*, 2017), such as $CaCO_3$ nanoparticles (Min *et al.*, 2015). (Table 1)

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Light-sensitive biomaterials

Light is an appealing stimulus with the ability to change the irradiation wavelength, power, and impacting region, hence biomaterials that can respond to light have been extensively researched (Yan *et al.*, 2016). Light irradiation, such as UV-Vis and near-infrared light (NIR), can alter light-sensitive biomaterials in biological systems at a distance (e.g., cancer cells, or tumors). Meanwhile, light-activated tumor therapy could be carried out with precision by limiting the irradiation range to avoid or minimize any injury to normal organs and tissues. Until recently, light-responsive biomaterials such as poly-ion complex vesicles (PICsomes) (Chen *et al.*, 2014), polyplexes (Nomoto *et al.*, 2014), nanoparticles (Jin *et al.*, 2013), polymeric micelles (Yen *et al.*, 2014), upconverting nanoparticles (UCNPs) (Boyer *et al.*, 2010), polymersomes (Qian *et al.*, 2017), liposomes (Luo *et al.*, 2016), nanogels (Khatun *et al.*, 2015), nanorods (Yang *et al.*, 2016), and nanorattles are being used. Meanwhile, light-responsive cargos/materials, such as photosensitizers (e.g., IR780) (Li *et al.*, 2017), gold nanocomposites (gold nanoparticles) (Zhang *et al.*, 2016), UCNPs, organic molecules (e.g., azobenzene) (Zhao *et al.*, 2009), grapheme (Khatun *et al.*, 2015), carbon nanotubes (Wang *et al.*, 2017), and two-dimensional (2D) transitional metal nanomaterials (e.g., MoS_2, WSe_2 and WS_2) (Wang *et al.*, 2015; Yang *et al.*, 2015), could be used to make light-sensitive biomaterials. Biomaterials could respond to light for a variety of reasons: (1) to alert the conformation of certain molecules, such as azobenzene, spiropyran, dithienylethene, and diazonaphthoquinone (Zhao *et al.*, 2012); (2) to cleave light-sensitive chemical bonds for biomaterials disassociation; (3) to trigger therapeutic release from biomaterials in diseased regions (Luo *et al.*, 2016); (4) to light-activated imaging (e.g., photoacoustic (PTT) (Moon *et al.*, 2015). (Table 1)

Table 1: representative interior and exterior stimuli-responsive biomaterials

Nanocarriers	**Stimuli-responsive mechanism/materials**	**Cargos**	**Applications**
pH-responsive biomaterials (Deirram *et al.*, 2019); (Pang *et al.*, 2016); (Huang *et al.*, 2019); (Liu *et al.*, 2016)			
Nanoparticles	Poly (ethylene glycol)-block-poly (propylene glycol)-poly (ethylene glycol)	Paclitaxel and Doxorubicin	Cancer therapy

Nanoparticles	Poly (n-isopropylacrylamide-*co*-propylacrylic acid-*co*-butylacrylate	Fibroblast growth factor	Cancer therapy
Nanoparticles	Poly(acrylamide)-g-carrageenan and sodium alginate	Ketoprofen	Colon-targeted delivey
Nanoparticles	Alginate and chemically modified carboxymethyl chitosan	Protein drug	For oral drug delivery
Redox-responsive biomaterials (Kim *et al.*, 2010); (Luo *et al.*, 2011); (Mi *et al.*, 2017); (Zou *et al.*, 2016); (Chang *et al.*, 2014); (Liu *et al.*, 2019); (Elkassih *et al.*, 2019).			
Nanocapsules	Disulfide bonds response to DTT) and GSH	Carboxyfluorescein	Redox-potential triggered drug release inside cancer cells
Mesoporous silica nanoparticles	Disulfide bonds	Doxorubicin	Controlled drug release and tumor active targeted therapy
Polymer-drug conjugates	Disulfide bonds	^{10}B-based sodium borocaptate	Efficient tumor targeted therapy, deep penetration, GSH-triggered drug release
Polymersomes	Disulfide bonds in poly (trimethylene carbonate-co-dithiolanetrimethylene carbonate)	Doxorubicin	Lung cancer chemotherapy
Micelles	Disulfide bonds	siRNA	Cross-linked micelles with improved stability for siRNA delivery
Nanogels	Disulfide bonds	Camptothecin	Tumor therapy
Hypoxia-responsive biomaterials (Liu *et al.*, 2017); (Im *et al.*, 2019); (Poon *et al.*, 2011); (Zhen *et al.*, 2019); (Kulkarni *et al.*, 2018); (Yang *et al.*, 2019); (Li *et al.*, 2017).			
Liposomes	The prodrug of banoxantronedihydrochloride (AQ4N) could be activated	Ce6, AQ4N	Cancer therapy

	in hypoxic environment caused by PDT		
Upconversion nanoparticles (UCNPs)	Oxygen indicator [Ru(dpp)3]2+Cl2 for hypoxia detection as UCNPs provided the excitation light of [Ru(dpp)3]2+Cl2 by upconversion process at 980 nm	[Ru(dpp)3]2+Cl UCNPs	Imaging hypoxic regions or oxygen changes in cells and zebrafish
Nanoparticles	PEG-azo(azobenzene)-PEI-DOPE block copolymer	siRNA	siRNA delivery and tumor RNAi
Cancer cell membrane coated MOFs	The porphyrinic MOFs could generate toxic ROS for PDT and cause hypoxic regions for activating TPZ	Porphyrinic metal organic framework, TPZ	Tumor targeted PDT and chemotherapy
Polymeric micelles	The metronidazole (MN) grafted in polymers could change hydrophobicity in hypoxic conditions for drug release	Doxorubicin	Tumor chemotherapy and radiotherapy
Enzyme-responsive biomaterials (Liu *et al.*, 2015); (Zhang *et al.*, 2017); (Huang *et al.*, 2015); (Gu *et al.*, 2019); (Fu *et al.*, 2015).			
Nanoparticles	Hollow mesoporous silica/poly(L-lysine) particles	Fluorescein and cytosine-phosphodiest er-guanine oligodeoxynucleo tide (CpG ODN)	Hydrolases (α-Chymotrypsi n), Tumor chemotherapy
Nanoparticles	PEGylatedpDNA-nanoparticles	Nucleic acid	Hydrolases (Elastase), cancer therapy
Nanoparticles	Low molecular weight protamine and conjugated it to PEG-PCL nanoparticles	Paclitaxel	Hydrolases (MMPs), cancer therapy
Nanoparticles	Methotrexate-conjugated magnetic nanoparticles and glycine coated magnetic nanoparticles	Glycine and methotrexate	Proteinase K, Tumor chemotherapy
Thermal-responsive biomaterials (Liu *et al.*, 2019); (Araki *et al.*, 2018); (Hervault *et al.*, 2016).			

Liposomes	The incorporated NH4HCO3 could response to local hyperemia for drug release	Doxorubicin, NH4HCO3	Temperature-controlled drug release
Nanogels	PNIPAM grafted chitosan nanogels response to temperature for drug release	Curcumin	Temperature-triggered drug release, intracellular drug delivery
Polymersomes	Thermal-sensitive PNIPAM gel in side pH-sensitive polymersomes	Doxorubicin	Dual-thermal, pH-responsive drug release, tumor therapy
Magnetic-responsive biomaterials (Yan *et al.*, 2018); (Di Corato *et al.*, 2015); (Smith *et al.*, 2015); (Thorat *et al.*, 2016); (Li *et al.*, 2015); (Chiang *et al.*, 2016).			
Albumin nanocapsules	Magnetic guided tumor targeting	Fe3O4, hydrophilic drugs	Targeting cervical cancer cells
Mesoporous iron oxide nanoparticles	Burst gas generation and on-demand drug release upon high-frequency magnetic field exposure	Iron oxide nanoparticles, paclitaxel, perfluorohexane	Tumor active targeted thermos-chemo-therapy
Polymeric micelles	Generate magnetic hyperthermia and controlled drug release	$La_{0.7}Sr_{0.3}MnO_3$, doxorubicin	Effective breast cancer theranostics
Liposomes	Induce local hyperthermia by response to alternating magnetic field	Magnetic nanoparticles, rhodamine, photosensitizer	Ultimate hyperthermia and photodynamic therapy combined tumor ablation
Ultrasound-responsive biomaterials (Delogu *et al.*, 2012); (Min *et al.*, 2015); (Geers *et al.*, 2012); (Cao *et al.*, 2018); (Huang *et al.*, 2016).			
$CaCO_3$ nanoparticles	The $CaCO_3$ could generate CO_2 in the acidic tumor microenvironment	Doxorubicin	Tumor ultrasound imaging, drug release and tumor therapy
Liposome	Containing NH_4HCO_3 to generate gas in tumors	Docetaxel and NH4HCO3	Dual ligand targeted triplex

			therapy, and ultrasound imaging
Nanorattles	Perfluoropentane for ultrasound-sensitive	Perfluoropentane	Ultrasound and photoacoustic imaging, photothermal therapy
Gas vesicles	Genetically encoded gas nanostructures from microorganisms	Gas	Ultrasound and multimodal imaging, molecular biosensors
Light-sensitive biomaterials (Chen *et al.*, 2014); (Jin *et al.*, 2013); (Luo *et al.*, 2016); (Khatun *et al.*, 2015); (Yang *et al.*, 2016); (Yang *et al.*, 2015).			
Polyion complex vesicles (PICsomes)	Light-triggered release of photosensitizer, photochemical internalization	Al (III) phthalocyanine chloride disulfonic acid (AlPcS2a)	PDT of tumors, photoinduced cytoplasmic delivery of drugs
Nanoparticles	Photosensitizer Ce6 for light-triggered size reducing, and generation of O21 (ROS)	Camptothecin, Ce6	Enhanced tumor penetration for combined therapy
Liposome	Porphyrin for light-responsive phototherapy	Doxorubicin, porphyrin	Chemotherapy and phototherapy of tumors
Vesicle	The structure change of azobenzene makes disassociation with β-CD	β-CD, azobenzene	Mimic for cell aggregation
Nanorods	Gold nanorods for thermal sensitivity	DNA, doxorubicin	Treatment of multidrug resistant cancer cells
2D transitional metal Nanomaterials	Photothermal effects of MoS2	Doxorubicin	Photothermal and chemotherapy of tumor

Conclusions and Future Perspectives

The development of triggered drug delivery should use stimuli-responsive materials, which have been used successfully in the creation of various drug delivery systems and devices. Smart drug delivery systems with controlled spatiotemporal drug distribution have been designed and developed as a result of having access to a wide range of physical, chemical, and biological stimuli. There is still a need for next-generation stimuli-responsive drug delivery systems and devices with more precise and on-demand distribution, despite the enormous advances made by smart drug delivery systems for cancer using a variety of stimuli triggers. It's important to note that the majority of published stimuli-responsive medication delivery methods and devices are only tested *in cellulo* or *in vitro* environments rather than *in vivo* under actual pathophysiological circumstances. There is still plenty of room for the development of next-generation multifunctional smart drug delivery systems and devices that are biocompatible and biodegradable in addition to being spatiao-temporal, target specific, and for on-demand delivery. This is true even in wake of contemporary advancements in stimuli-responsive smart delivery devices.

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