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REVIEW

Design of pH-Responsive Nanomaterials Based on the Tumor Microenvironment

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Abstract: The metabolic activity of tumor cells leads to the acidification of the surrounding microenvironment, which provides new strategies for the application of nanotechnology in cancer therapy. Researchers have developed various types of pH-responsive nanomaterials based on the tumor acidic microenvironment. This review provides an in-depth discussion on the design mechanisms, drug-loading strategies, and application pathways of tumor acidic microenvironment-responsive nanodrug delivery systems. These materials trigger drug release upon reaching the tumor microenvironment, enhancing therapeutic targeting and reducing toxicity to healthy cells. pH-responsive nanomaterials include organic nanomaterials, inorganic nanomaterials, and composite nanomaterials. Additionally, this review outlines the drug-loading strategies, application prospects, and challenges of pH-responsive nanomaterials, aiming to promote the development and clinical translation of this field.

Keywords: tumor microenvironment, pH response, nanocarriers, drug-loading strategies, drug delivery system

Introduction

The complexity of the tumor microenvironment has become a consensus in the scientific community. It not only provides conditions for tumor growth and metastasis but also poses significant challenges for cancer treatment. This environment is characterized by hypoxia, mild acidity, increased interstitial pressure, elevated reactive oxygen species (ROS), and immune tolerance, all of which are closely related to tumor initiation, progression, and metastasis.[1,2] At the same time, these features provide opportunities for developing novel cancer treatment strategies.[3] In particular, the mildly acidic conditions within the tumor microenvironment have become a critical target for designing novel therapeutic strategies. In recent decades, researchers have identified various pH-related membrane transport proteins or pathways that play key roles in regulating the acidity of the tumor microenvironment, such as proton pumps (V-ATPases)[4] and monocarboxylate transporters (MCTs).[5] These discoveries provide the potential to directly inhibit tumor growth and enhance the effectiveness of traditional therapies (such as chemotherapy, radiotherapy, and immunotherapy) by modulating the acidic environment at tumor sites. Designed mildly acidic-responsive nanoparticles, such as $CaCO_3$ and MnO_2, can regulate the acidic tumor environment by consuming H^+ in the tumor extracellular matrix. Nanoparticles could remain stable at normal physiological pH while triggering drug release under low pH conditions, making them highly promising for cancer therapy.[6]

Therefore, the development of nanodrug delivery systems that respond to the acidity of the tumor microenvironment can both enhance treatment targeting and efficiency and reduce side effects on normal tissues, offering new strategies for

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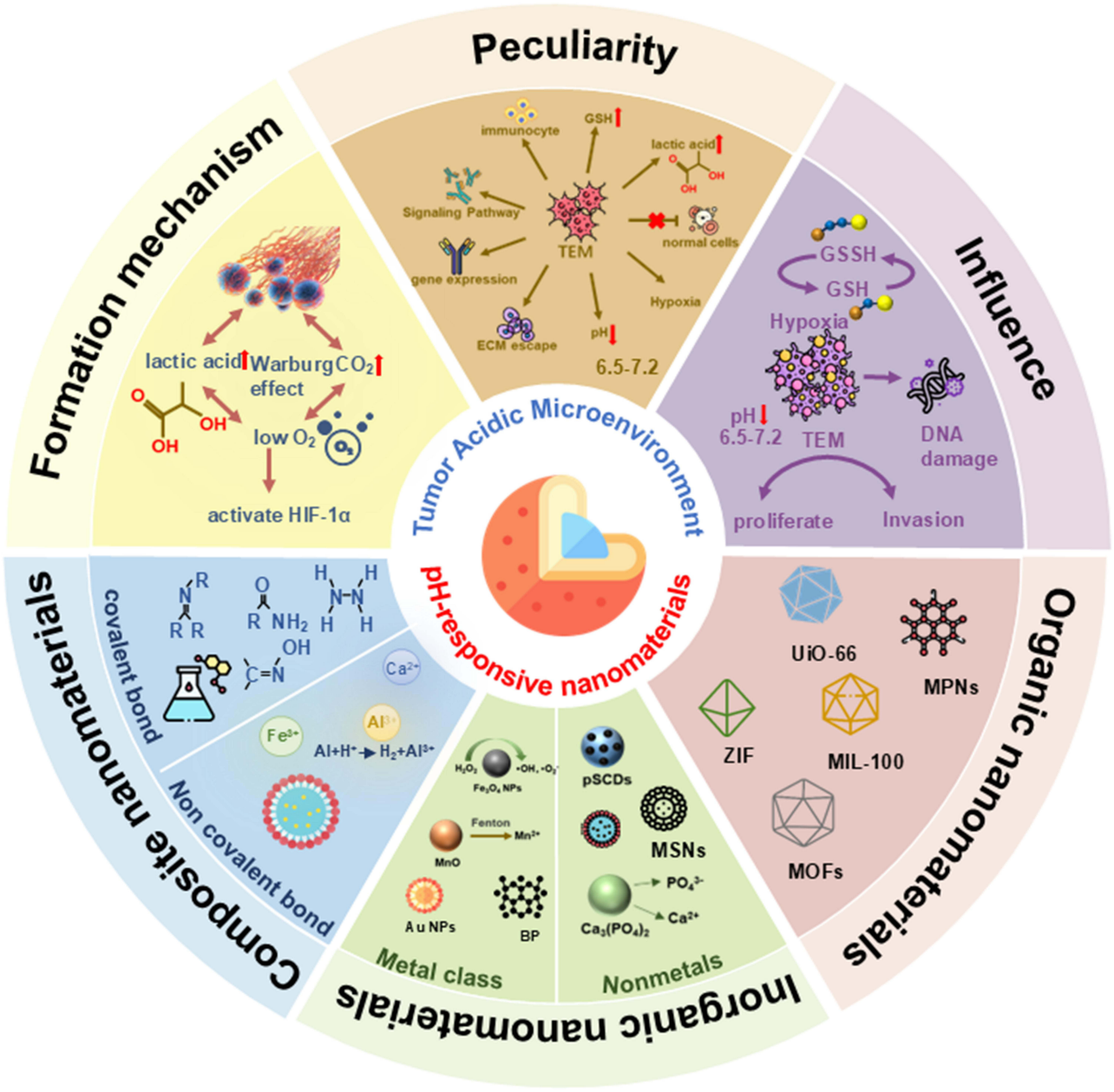
cancer therapy. Research needs to further explore the mechanisms of these systems, optimize their design, and assess their clinical application potential in the future. The research work includes understanding the interactions between nanodrug delivery systems and the tumor microenvironment, improving the stability and biocompatibility of these systems, and conducting more preclinical and clinical research to verify the safety and efficacy of these novel therapies. Once these challenges are addressed, nanodrug delivery systems based on the tumor acidic microenvironment are expected to become an important tool for cancer treatment (scheme 1).

Tumor Acidic Microenvironment

The more acidic microenvironment surrounding tumor cells compared to normal tissues is referred to as the tumor acidic microenvironment. This characteristic arises from the unique metabolism of tumor cells, which, even under adequate oxygen conditions, tend to metabolize energy through lactic acid fermentation, producing large amounts of lactic acid



Scheme 1 Strategies for designing and modifying pH-responsive nanomaterials based on the tumor microenvironment.

and lowering the pH of the microenvironment.[7] Moreover, poor blood circulation within tumors exacerbates lactic acid accumulation due to the resulting hypoxic conditions. The tumor acidic microenvironment not only affects the survival and proliferation of tumor cells but also impairs the function of surrounding healthy cells and immune cells, further influencing tumor progression and response to therapy. Therefore, in-depth research into the tumor acidic microenvironment can not only lead to a better understanding of tumor growth and metastasis mechanisms but also offer new insights for developing novel anti-tumor treatment strategies.[8]

Mechanism of Tumor Acidic Microenvironment Formation

Recent research progress on the mechanisms underlying the formation of the tumor acidic microenvironment has revealed a more complex and diverse set of biochemical processes. The discovery of the Warburg effect was a major breakthrough in understanding tumor cell metabolism, showing that tumor cells prefer lactic acid fermentation even in the presence of sufficient oxygen, producing large amounts of lactate and leading to local acidification.[9] This metabolic reprogramming mechanism not only reflects an adaptive strategy for tumor survival but also promotes tumor aggressiveness and drug resistance. Further research has shown that tumor cells produce not only lactate but also other acidic metabolites, such as carbon dioxide. These metabolites influence the tumor microenvironment, further promoting tumor growth and metastasis. For instance, lactate can directly stimulate tumor cell proliferation and also affect the function of surrounding immune cells, creating an immunosuppressive environment that helps tumor cells evade immune surveillance and eliminate.[10] Moreover, tumor cells regulate the formation and function of surrounding micro vessels, exacerbating hypoxia in the microenvironment. This hypoxic condition not only enhances tumor cell lactic acid fermentation but also activates a series of hypoxia-responsive factors (such as HIF-1α),[11] promoting tumor growth, angiogenesis, and metabolic reprogramming. The tumor acidic microenvironment can affect drug stability and cellular uptake through various mechanisms, thereby reducing the effectiveness of chemotherapy and radiotherapy.[12,13] Disordered energy metabolism, inadequate blood supply, and uncontrolled proliferation collectively cause the physicochemical composition of the tumor microenvironment to differ from that of the typical stroma in normal tissues. The primary molecules involved in pH regulation in the tumor microenvironment include the following: Monocarboxylate Transporter protein (MCT);[14,15] Na^+/H^+ exchange agent (NHE);[5,16] Anion exchange agent (AE); Carbonic Anhydrase (CA);[17–19] Na^+/HCO_3^- cotransporter protein (NBC); HCO_3^- transporter protein (BT); Organelles: Acidic lysosomes/endosomes with V-type ATPase[20,21] (Figure 1).

Characteristics of the Tumor Acidic Microenvironment

The characteristics of the tumor acidic microenvironment are a key focus in cancer treatment research, with its complexity having profound implications for tumor progression and therapy. The detailed mechanisms by which the tumor acidic microenvironment affects tumor cells and surrounding normal cells have been revealed, offering new targets for cancer therapy. Tumor cells demonstrate their adaptability to acidic environments through unique metabolic mechanisms.[24,25] Firstly, tumor cells enhance survival mechanisms in acidic conditions to promote their growth and proliferation, allowing them to maintain malignancy even in harsh microenvironments by modulating specific signaling pathways and gene expression. Normal cells lack these adaptive mechanisms, making them more vulnerable to damage in low pH conditions, which leads to impaired tissue function. Secondly, increased activity of extracellular matrix (ECM) degrading enzymes in the acidic microenvironment facilitates tumor cell invasiveness and enhances metastatic potential. The characteristics of the tumor microenvironment include acidity, hypoxia, elevated lactate concentrations, reduced glucose levels, secretion change, and the recruitment of stromal and immune cells.[26,27]

The Impact of the Tumor Acidic Microenvironment on Tumor Growth and Treatment

The impact of the tumor acidic microenvironment on cancer development and treatment strategies has become a major focus in cancer research in recent years. The acidic microenvironment not only promotes tumor cell growth, invasion, and metastasis but also affects the efficacy of current cancer therapies.

(1) The acidic microenvironment promotes tumor cell growth and metastasis through multiple mechanisms.

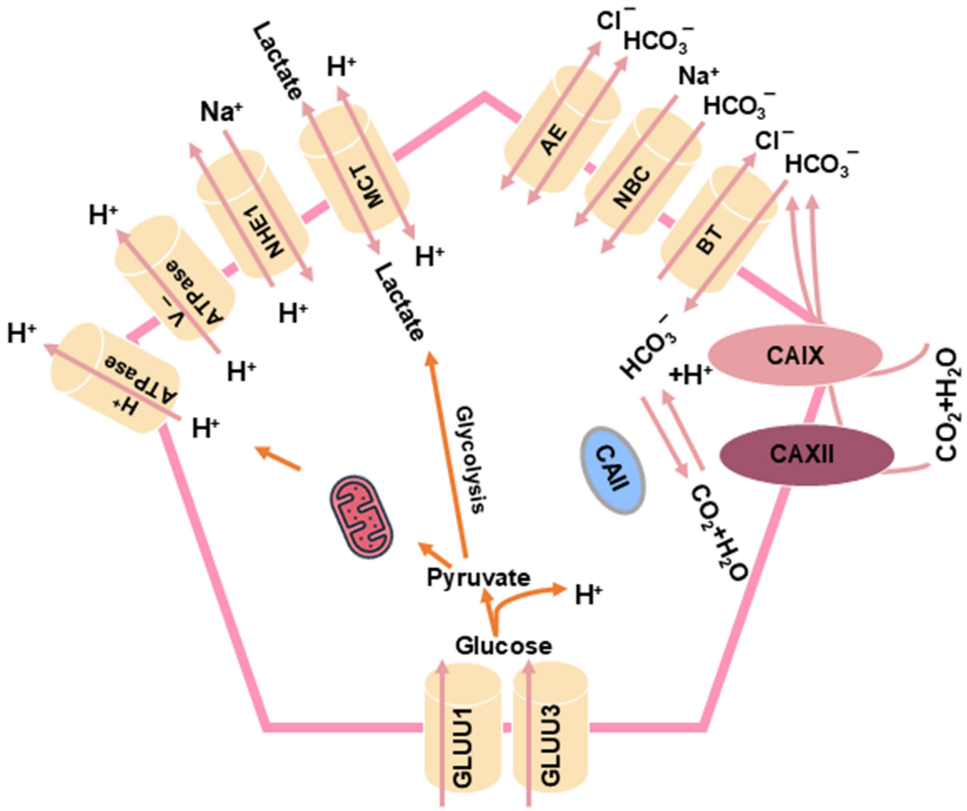


Figure 1 The primary molecules involved in pH regulation within cancer cells include: MCT; NHE; AE; CA; NBC; BT; Organelle: V-type ATPase.
Note: Adapted from Swietach P. What is pH regulation, and why do cancer cells need it?. Cancer Metastasis Rev. 2019;38(1-2):5-15, Creative Commons (http://creativecommons.org/licenses/by/4.0/) and Damaghi M, Wojtkowiak JW, Gillies RJ. pH sensing and regulation in cancer. Front Physiol. 2013;4:370. Creative Commons.[22,23]

First, the acidic microenvironment at low pH can activate certain receptors on tumor cell surfaces, inducing signaling pathway changes that promote cell growth and division. Secondly, the acidic environment enhances the degradation of the extracellular matrix (ECM), facilitating tumor cell invasiveness and metastasis. Additionally, the acidic microenvironment suppresses immune cell activity, creating an immunosuppressive environment that weakens the immune system's ability to attack tumor cells, allowing them to evade immune surveillance.[28]

(2) The tumor acidic microenvironment has a significant impact on cancer treatment.

In chemotherapy, many drugs lose stability under acidic conditions, leading to reduced drug activity and diminished therapeutic efficacy. Furthermore, the low pH environment can affect drug absorption and distribution within cells, further limiting therapeutic effectiveness. In radiotherapy, the acidic environment is believed to enhance certain tumor cells' resistance to radiation, as DNA damage repair mechanisms are more efficient under low pH conditions.

Given the significant influence of the tumor acidic microenvironment on tumor growth and therapy, it is crucial to develop novel therapeutic strategies that specifically target this acidic environment. In recent years, nanotechnology has shown great potential in this field. By designing pH-responsive nanodrug delivery systems, drugs can be precisely released in the tumor acidic microenvironment, improving therapeutic efficacy and reducing toxic side effects on normal tissues. These nanodrug delivery systems can intelligently modulate drug release based on the acidic characteristics of the tumor microenvironment, ensuring the drug acts where it is most needed, maximizing therapeutic outcomes while minimizing overall toxicity to the patient.

The tumor acidic microenvironment is a key factor affecting cancer treatment outcomes. Understanding its mechanisms and impacts, and designing nanomedicine and drug delivery systems based on these characteristics, provides new targets and strategies for cancer therapy, showing great potential for research and clinical applications.

pH-Responsive Nanomaterials

Acid-responsive nanodrug delivery systems are a type of intelligent nanotechnology designed to recognize and respond to the acidic conditions of the tumor microenvironment. Tumor tissues typically exhibit a more acidic environment compared to surrounding normal tissues due to their high metabolic activity.[29,30] This feature enables acid-responsive nanodrug delivery systems to achieve precise drug release at the tumor site through physical or chemical changes triggered by the acidic environment. This not only enhances the efficiency and specificity of drug delivery but also reduces potential toxic effects on normal tissues. The acidic tumor microenvironment is conducive to the Fenton reaction in nanomaterials for chemodynamic therapy (CDT). These classifications and functionalization strategies of nanodrug delivery systems play a crucial role in designing pH-responsive drug delivery system (DDS) based on the pH variation between healthy and tumor cells. The pH differences between healthy and tumor tissues within endosomal and lysosomal compartments can play as internal stimuli to trigger drug release, enhancing the therapeutic response to cancer. pH-responsive nanocarriers release their therapeutic molecules based on pH changes, specifically in tumor tissues (~6.5), endosomes (~5.5), and lysosomes (~5.0), thereby improving the therapeutic efficacy of antitumor drugs. In recent years, nanoparticles have been applied in cancer therapy due to their excellent enhanced permeability and retention (EPR) effect.[31–34] However, the EPR effect can lead to the accumulation of nanoparticles in tumor tissues, causing poor cellular internalization and insufficient drug release. pH-sensitive nanoparticles can encapsulate hydrophobic drugs at physiological pH and trigger drug release at the slightly acidic pH of tumor sites. pH-responsive nanocarriers are designed for prolonged circulation in the bloodstream, promoting drug accumulation at tumor sites and preventing premature release before reaching the target.[35] pH-responsive nanomaterials mainly include organic nanomaterials, inorganic nanomaterials, and composite nanomaterials.

pH-Responsive Organic Nanomaterials

Organic nanomaterials include liposomes, polymeric micelles, polymer capsules, nanogels and dendrimers. pH-sensitive chemical bonds are relatively stable in neutral or alkaline environments but undergo hydrolysis or cleavage in acidic tumor microenvironments. The formation of unstable bonds between drugs and polymers, or within polymers, in the presence of acid is a key design strategy for pH-responsive organic nanomaterials, enabling drug delivery to tumor tissues and drug release at acidic pH through the disruption of acid-labile bonds.[36,37] In pH-sensitive organic nanomaterials, typical acid-labile bonds include covalent bonds such as hydrazone, imine, acetal, oxime, amide, and ester bonds, metal ion coordination bonds and non-covalent bonds. The reaction rates and pH response values of each type of chemical bond vary, and this diversity of responses offers more options for precision and versatility in drug delivery.

Covalent Bond

Hydrazone/acylhydrazone bonds: Hydrazone/acylhydrazone bonds are formed by the condensation reaction between hydrazine (-HH-NH_2) or acylhydrazine (-CONH-NH_2) and ketones or aldehydes. This reaction is relatively stable at pH 7.4, but becomes sensitive under mildly acidic conditions (pH=5). Based on this, hydrazone/acylhydrazone bonds can be used in drug delivery and the design of pH-responsive hydrogels.

Lin, CX, etc. prepared dynamic hydrogels with self-healing and injectable capabilities by crosslinking biopolymer frameworks through dual pH-sensitive dynamic covalent bonds, which can be used as controlled and sustained-release carriers for protein drugs. The oxidized konjac glucomannan (OKGM) crosslinked with polyaspartic acid hydrazide (PAHy) and N-carboxyethyl chitosan (CEC) forms dynamic hydrazone and imine bonds, imparting pH responsiveness and dynamic behavior to the hydrogel. PAHy promotes the formation of hydrazone bonds, enhances mechanical properties and pH sensitivity, and reduces hydrogel degradation under physiological conditions.[38] Fu et al utilized hydrazone-modified nanocovalent organic frameworks (NCOFs) as a pH triple molecular switch, covalently loading doxorubicin and coating with soy phospholipid (SP) on the HNTs-NN-DOX surface, showing better efficacy at pH 5.2 than 7.4. Novel hydrazone-functionalized NCOF NP conjugated with doxorubicin have the ability to respond to endosomal/lysosomal pH stimuli and release the drug.[39] Appiah et al prepared pH-responsive HPMA copolymers of bradykinin (P-BK) and significantly altered the release kinetics through substitutions near the hydrazone bond. The release constant of methyl-substituted P-BK (P-MeBK) was about 4 and 80 times higher than that of cyclopropyl-

substituted P-BK (P-CPBK) and phenyl-substituted P-BK (P-PhBK), respectively, providing insights into designing pH-responsive nanodrugs with desired release properties for targeting acidic lesions.[40] Shi Yongli conjugated DOX to PEG chains via acylhydrazone bonds to synthesize DHPD polymers, and prepared pH-responsive DHPD NP to study their biosafety and antitumor activity in vivo. The acylhydrazone bonds were cleaved in the acidic microenvironment of 4T1 cells, increasing the delivery of DOX to tumor cells and enhancing in vivo antitumor efficacy.[41]

Imine bond: the delocalization effect of the π-electrons stabilizes the C=N bond, making it a pH-sensitive dynamic covalent bond. The carbon-nitrogen double bond structure is formed by the "Schiff base" condensation reaction between an aldehyde or ketone and a primary amine. This structure is stable in alkaline or neutral environments but becomes sensitive in an acidic environment at pH 6.8, leading to an accelerated hydrolysis/cleavage rate, making imine bonds insufficiently stable under physiological conditions (pH 7.4 and 37°C).[42] Modifying the substituents can regulate the pH sensitivity and stability of the linker, such as forming a benzylidene imine bond by combining with p-p bonds to enhance stability and achieve optimal release behavior. Basutkar et al combined ring-opening polymerization (ROP) with click chemistry to synthesize amphiphilic PEG-PCL three-arm star copolymers containing visible light-cleavable BODIPY groups and pH-responsive imine bonds. DOX micelle assemblies were prepared by coupling PEG-BODIPY via imine bonds, enabling controlled release via visible light and pH triggers.[43] Liang Na et al introduced 4-(diphenylamino) benzaldehyde derivatives (DBA-CHO), imine bonds, and folic acid (FA) into chitosan (CS). They synthesized amphiphilic polymers FA-CS-DBA-CHO with aggregation-induced emission (AIE) characteristics, facilitating the self-assembly of the polymers into micelles. Paclitaxel (PTX) was encapsulated in the hydrophobic core, and the pH-sensitive imine bond enabled precise drug release in acidic environments.[44] Aram et al developed pH-sensitive, shell-removable magnetic Fe_3O_4@SiO_2 NP coated with polyethyleneimine (PEI) and PEG. The PEG chain was linked to PEI via a pH-sensitive benzylidene imine bond, and PEI loaded curcumin (Cur) through van der Waals interactions. Drug release was induced under tumor pH conditions by the shedding of the hydrophilic PEG corona. The Cur-loaded magnetic nanoparticles (C-LMNs) released more at tumor pH 5.6 than at physiological pH 7.4.[45] Tan et al used hydroxypropyl chitosan (HPC), caffeic acid-functionalized chitosan (CCS), and oxidized dextran (ODex) to form crosslinked dynamic imine bonds. They designed a sprayable chitosan-based hydrogel (HPC/CCS/ODex-IGF1) capable of pH-responsive behavior in acidic microenvironments and controlled release of insulin-like growth factor-1 (IGF1).[46]

Acetal/ketal bond: Ketals differ from acetals by having one more central carbon substituent, with two alkoxy groups attached to the same carbon in their structural formulas.[47,48] Under acidic conditions, an oxygen atom is protonated, activating the adjacent carbon atom and leading to bond hydrolysis and cleavage. Polymers containing acetal/ketal bonds can degrade into soluble monomers in the acidic pH of the tumor microenvironment. Acetal/ketal bonds are widely used in pH-responsive polymeric nanoparticle DDS.

Andrade-Gagnon et al suggest that benzaldehyde acetal (BzAA) is an optimal choice for acid-labile linkers. Nanostructures formed by linking PEG-based block copolymers with BzAA can undergo slow degradation at tumor pH, while rapidly disintegrating at endosomal/lysosomal pH, and remaining colloidally stable at physiological pH. This enhances tumor-targeting drug delivery through improved endocytosis.[49] Quadrado et al synthesized aldehyde-functionalized hydroxyethyl cellulose via acetal functionalization and acid deprotection, quickly forming a hydrogel in situ with carboxymethyl chitosan. This approach avoids pyran ring breakage issues caused by introducing aldehyde groups into polysaccharides using the periodate method. The resulting hydrogel exhibited rapid stress relaxation, self-healing, and pH sensitivity, and could control the release of encapsulated model drugs based on the medium's pH.[50] Lee et al developed cellulose nanocrystal (CNCs)-reinforced polyvinyl alcohol (PVA)-based hydrogels, which were cross-linked with glutaraldehyde (GA) at low pH (2.0, 2.5). The nano-blocking and nano-locking effects of CNCs significantly enhanced the drug (salicylic acid) adsorption and sustained release in hydrogels prepared at low pH with high CNCs content. This system is suitable for sustained DDS with desired physical and mechanical properties.[51]

Oxime bond: -C=N-O-. Similar to the imine bond, it is a reversible dynamic covalent bond with pH sensitivity, responding at pH values between 4.8–5.0. The condensation of aldehyde or ketone with a hydroxylamine group is a common method for preparing oxime bonds.[52] In acidic conditions, the hydroxylamine group hydrolyzes into aldehydes, ketones, and hydroxylamine. Oxime bonds can be used to synthesize pH-responsive polymers. Sen et al developed a DOX delivery system based on a PEG-functionalized TAT-derived cell-penetrating peptide (G(2)RQR(3)QR

(3)G(3)S), where DOX was linked to the mPEG-peptide system through an acid-labile oxime bond. DOX release was pH-programmed, with 68% release at pH 5.0 and 28% at pH 7.4.[53] Vrettos et al exploited the pH sensitivity of the oxime bond to the acidic tumor microenvironment and the GnRH-R GPCR-mediated internalization in cancer cells. They developed a fast (1-hour) and cost-effective "click" oxime bond platform to guide drug release at different rates in PDCs.[54] Smyth et al synthesized a pH-responsive nanoparticle by RAFT polymerization of phenylaldehyde-functionalized amphiphilic block copolymers of 2-(diisopropylamino) ethyl methacrylate (DPA), PEG-based oligo (ethylene glycol) methacrylate (OEGMA), and p-formylphenyl methacrylate (pFPMA). The surface phenylaldehyde groups formed oxime bonds with Alexa Fluor 488 hydroxylamine dyes, enabling fluorescent tracking of intracellular fate or antibody-based targeted therapy.[55]

Amide bond: C=O-N-,Amides are an important component in medicinal chemistry, with over 25% of drugs in medicinal chemistry databases containing amide bonds. During synthesis, active carboxylic acid derivatives such as acyl chlorides, anhydrides, esters, and azides are generally used for the initial preparation, followed by acylation with reactants like alcohols, aldehydes, and alkynes under amine catalysis, with a pH response range of 4.5–6.0. Some amide bonds with special side chains undergo hydrolysis and cleavage under weakly acidic conditions,[56] such as maleic acid, cis-aconitic acid, and dimethylmaleic anhydride. As a result, amide bonds are widely used in pH-responsive polymers.[57–59] Yang C et al used a disulfide/α-amide-bridged doxorubicin dimer prodrug (DDOX) model to validate a pH/GSH dual-triggered doxorubicin DDS, showing different pH/GSH dual-triggered drug release properties based on the aggregate structure.[60] Chinapaka R et al synthesized a series of N-acyl GABAs (C8-C18), which exhibited higher efficiency and release properties than DPPC liposomes under physiologically relevant pH conditions.[61]

Ester bonds: -COOR. The structure of ester bonds or orthoster bonds is similar where one carbon atom is connected to two or three oxygen atoms. The pH sensitivity value is 5.0–6.0,[62,63] and it degrades faster in acidic environments compared to acetal, ketone, or hydrazone bonds. It has been extensively studied and applied in pH-responsive polymers. Common ester bond structures include polyacrylic acid (PAA), polymethacrylic acid (PMAA), and polyethylacrylic acid (PEAA). Qu LM et al developed a novel dual-functional polymer coating consisting of copolymer brushes made from N-vinylpyrrolidone (NVP) and 3-(acrylamidophenyl)boronic acid, with antibacterial and antifouling properties. Through acid-responsive boronate ester bonds, it binds Cur as an antibacterial molecule. Hydrophilic poly(N-vinylpyrrolidone) (PVP) effectively prevents bacterial adhesion and aggregation at the initial stage, improving antifouling performance. Poly(3-(acrylamidophenyl)boronic acid) (PAPBA) forms acid-responsive boronate ester bonds that provide binding sites for Cur. When bacteria overcome the anti-adhesion barrier, the disruption of boronate ester bonds releases Cur, which interferes with biofilm formation, providing a multilayer biofilm protection system.[64] Yu Y et al synthesized a pH-responsive self-healing hydrogel from chitosan (CS-BA) and PVA grafted with 3-carboxyphenylboronic acid. The self-healing property is achieved through dynamic boronate ester bonds and intermolecular hydrogen bonding.[65] Wang WQ et al developed an injectable hydrogel that responds to acidic conditions, ROS, and high glucose levels in the microenvironment of diabetic wounds. It sustainably delivers tannic acid (TA), enhancing antibacterial, anti-inflammatory, and antioxidant activities. The triple response is achieved by introducing dynamic acylhydrazone and phenylboronic ester crosslinks into modified hyaluronic acid (HA). The pH/ROS/glucose triple-responsive OAH@TA hydrogel triggers the controlled release of TA, enhancing antibacterial, anti-inflammatory, and antioxidant properties, promoting diabetic wound healing.[66]

Finally, we provided a comprehensive summary of the design, mechanisms, and applications of pH-sensitive chemical bonds (Table 1) and analyzed their degradation rates across various cellular compartments and physiological conditions (Table 2).

Non-Covalent Bonds

Intermolecular non-covalent interactions are also reversible binding forms, including hydrophobic interactions, hydrogen bonding, dipole interactions, electrostatic interactions, and/or π-π stacking charge interactions.

Metal ion coordination bonds: Transition metal cations form coordination bonds with molecules or ionic ligands containing lone pairs of electrons, such as Fe^{3+}, Al^{3+} and Ca^{2+}, which respond to changes in pH.[73] The reaction mechanism can be referenced from the Lewis acid-base theory. Metal ions and protons belong to Lewis's acids; protons

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Table 1 Design, Mechanism, and Application of pH Sensitive Chemical Bonds

Type		Author	Design	Mechanism	Application	Ref
PH sensitive chemical bonds	Hydrazone/ acylhydrazone bonds	Lin、CX et al	PAHy-l-OKGM-l-CEC hydrogel	Imide and acylhydrazone bonds as dual pH responsive dynamic covalent chemical bonds	PH responsive hydrogel	38
		Fu et al	NCOFs-NN-DOX@SP	Hydrazone bond formed by mixing acid unstable substances with NCOFs-$NHNHNH_2$	PH sensitive nanoparticles	39
		Shi Yongli et al	DHPD polymer	DOX combined with polyethylene Synthesis of DHPD polymer via acylhydrazone bond using ethylene glycol (PEG) chain	PH responsive nanoparticle polymer	41
PH sensitive chemical bonds	Imine bond -C=N-	Basutkar et al	FA-CS-DBA-CHO	Using triphenylamine derivatives (DBA-CHO) to bind with CS via pH sensitive imine bonds sensitive imine bonds	PH sensitive nanoparticles	43
		Aram et al	Fe_3O_4/SiO_2/PEI-PEG/curcumin	PEG chains are attached to the PEI layer through benzoic acid imine bonds	PH sensitive nanoparticles	45
		Tan et al	HPC/CCS/ ODex-IGF1	The amino groups of HPC and CCS react with the aldehyde groups of ODex to form a pH responsive dynamic Schiff base network	PH responsive hydrogel	46
PH sensitive chemical bonds	Acetal/ketal bond	Andrade Gagnon et al	PEG-BzAA-PBM	Benzaldehyde formaldehyde aldehyde (BzAA) is the best choice for acid unstable linkers	Drug delivery nanocarriers	49
		Quadrado et al	HEC-Ald /CMCHT hydrogel	Schiff imine crosslinking between aldehydes and amines	PH responsive hydrogel	50
	Oxime bond -C=N-O-	Sen et al	MPEG-oxime-DOX	DOX is connected to the mPEG peptide carrier system through acid cleavable oxime bonds	PH responsive nanoparticle polymer	53
		Smyth et al	P(OEGMA-st-pFPMA)-b-PDPAblock copolymer	Surface benzaldehyde groups form oxime bonds with Alexa Fluor 488 hydroxylamine dye	PH sensitive nanoparticles Fluorescence tracking Targeted therapy	55
PH sensitive chemical bonds	Amide bond C=O-N-	Yang C et al	DDOX	DDOX bridged by disulfide/α - amide	PH sensitive nanoparticles	60
		Chinapaka R et al	NPGABA/DPPC liposomes	GABAsSynthesis of N-acyl GABAs containing 8–18 carbon atoms in acyl chains	PH sensitive nanoparticles	61
	Ester bonds-COOR	Qu-LM et al	Ti-PVP-PB@Cur coating	NVP and 3- (acrylamide phenyl) boronic acid form acid responsive boronic ester bonds	Dual functional polymer coating	64
PH sensitive chemical bonds	Ester bonds-COOR	Yu Y et al	CS-BA/PVA/TAFe hydrogel	The - NH_2 on CS is coupled with the - COOH of BA on CS through amidation reaction to obtain CS-BA. Then, CS-BA reacts with diols on polyethylene Alcohol (PVA) forms reversible dynamic boronic ester bonds	PH responsive self-regulation device Healing hydrogel using CS as skeleton	65
		Wang WQ et al	OHA-APBA/TA	Hydrogels functionalized by phenylboronic acid to oxidize HA (OHA-APBA), HAAD and TA are crosslinked by acylhydrazone and phenyl borate ester bond	pH responsive hydrogel	66

compete with metal ions for binding to ligands (Lewis bases) under acidic conditions, leading to the breaking of metal ion coordination bonds.[74] For example, Fe^{3+} form coordination bonds with imine or carboxyl groups, and the protonation of these bonds with Fe^{3+} under weak acidic conditions can cause bond cleavage.

Zhang ZZ et al developed pH-responsive, iron-coordinated polymer nanoparticles (PPA/TF) that encapsulate the mitochondria-targeting drug α-tocopheryl succinate (α-TOS), promoting the release of the drug in the mildly acidic intracellular environment of tumors. Imidazole-grafted micelles can prolong blood circulation and improve the delivery efficiency of the hydrophobic drug α-TOS, and PPA assists in delivering Fe^{3+} for CDT.[75] Liang Y et al first discovered that biodegradable monometallic Al can be used as a Fenton-like biocatalyst for tumor therapy. They prepared pH-sensitive aluminum nanoparticles (Al@P), which react with H^+ to form H_2 and Al^{3+}, disrupting redox balance and ion homeostasis, inducing the generation of ROS and activating ROS-responsive prodrugs, effectively treating tumors

Table 2 Reaction Kinetics of pH-Sensitive Chemical Bonds Under Physiological Conditions and pH Values in Different Cellular Compartments

Type		Physiological Conditions (~7.4)	Responsiveness to Varying pH Levels in Different Compartments of TEM			Ref
			Tumor Tissue (~6.5)	Endosome (~5.5)	Lysosome (~5.0)	
PH sensitive chemical bonds	Hydrazone/ acylhydrazone bonds	–	+	++	+++	38,67
	Imine bond -C=N-	-	++	++	+++	68
	Acetal/ketal bond	-	+	+++	+++	49,69
	Oxime bond -C=N-O-	-	+	++	+++	70
	Amide bond C=O-N-	-	+	+++	+++	71
	Ester bonds -COOR	-	+	++	+++	72

Notes: - Expressing stability, + Indicates degradation rate.

without affecting normal cells.[76] Cheng YY et al constructed a CT@hCuS NIR photothermal nano-platform using hollow CuS nanoparticles (hCuS) coated with a TA surface layer, where the TA/Ca^{2+} complex loads Ca^{2+}, which is released in response to the mildly acidic pH of the tumor microenvironment. Upon 1064 nm laser irradiation, CT@hCuS provides precise photothermal activation of TRPV1, triggering intracellular Ca^{2+} influx, destroying tumor vasculature, and inducing immunogenic tumor cell death.[77]

Hydrogen bond: a force between permanent dipoles, established by weak electrostatic attraction between a hydrogen atom acting as a donor and a highly electronegative, small-radius atom (such as N, O, F) acting as an acceptor. Hydrogen bonds are weak and dynamic bonds that form and break reversibly, often used in assembling stimulus-responsive supramolecular networks, and are stronger than van der Waals interactions between alkyl chains. Electron-rich π systems are often used to construct stable supramolecular structures, such as hydroxyl-containing aromatic compounds, which form π-π stacking interactions, offering higher in vivo stability and drug release kinetics.[78] Li HC prepared composite nanoparticles (CNPs) encapsulating tea polyphenol (-)-epigallocatechin gallate using corn starch (CS) and β-cyclodextrin (β-CD). The CNPs showed remarkable stability under diverse conditions, including varying pH levels, ion concentrations, heating, and storage. They exhibited complete release under alkaline conditions, enabling precise targeting of specific sites, thus highlighting their pH-responsiveness and potential for intestinal-targeted delivery.[79] Yuan H prepared a TCS10/PUE fibrous network composite hydrogel containing hydrogen bonds and disulfide bonds, with dual sensitivity to pH and glutathione (pH/GSH).[80] Sarfaraz S et al used hollow nanocapsules as drug delivery carriers for the anticancer drugs nitrosourea (NU) and fluorouracil (FU). Quantum theory (QTAIM) and non-covalent interaction (NCI) analyses revealed that the FU@Capsule and NU@Capsule complexes are primarily composed of hydrogen bonds and van der Waals interactions. The anticancer drugs are more easily released from the target site carriers (nanocapsules) because the low pH of cancer cells.[81]

Protonation Mechanism

Aside from linking pH-sensitive acid-unstable bonds to the polymer main or side chains, another approach to making nanodrug carriers pH-sensitive is through protonation mechanisms. In the acidic tumor microenvironment, protonated substances trigger one of the most common mechanisms for pH-responsive drug delivery.[82] Chemical groups that cause surface charge changes in response to environmental pH (protonation or deprotonation) are introduced into nanomaterials, letting polymers to alter their charge properties as the pH varies. These kinds of groups include amino, phosphate, and carboxyl groups. These have distinct chemical structures and pKa values, allowing them to accept or donate protons and undergo physical or chemical changes related to pH.[83] Swelling or solubility changes can cause polymers containing pH-sensitive groups such as amine, sulfonamide, or imidazole to undergo protonation under acidic conditions, leading to charge reversal or hydrophilic-hydrophobic transitions, altering the polymer's physicochemical properties or structural conformation and releasing the drug. Polymers containing amino groups generally exhibit specific pH responsiveness,

where altering the polymer's ionic state can induce protonation or deprotonation of amines in different environments. Nanoparticles with imidazole groups remain stable at pH 6.8 but fully degrade at pH 6.0.

Polymers are classified as cationic, anionic, or zwitterionic based on their charge. Most cationic polymers contain ionized amino groups, anionic polymers contain organic acids, and zwitterionic polymers carry both cationic and anionic groups on the same polymer chain. Cationic nanoparticles are more easily absorbed by cells compared to anionic and neutral nanoparticles, but they may be cleared from systemic circulation after binding with serum components in the blood. Charge-switchable polymers exhibit negative charges under physiological conditions (pH 7.4), minimizing specific interactions with serum components and reducing clearance by the reticuloendothelial system. The polymer's negative charge switches to positive, enhancing uptake by tumor cells in the acidic tumor microenvironment.[5,84]

pH-Responsive Inorganic Nanomaterials

In recent years, pH-responsive DDS based on inorganic materials have emerged as promising carriers due to their unique properties, such as thermal stability, biocompatibility, morphology control, size, and structure. pH-responsive inorganic nanomaterials can be categorized into metallic and non-metallic types. Typical pH-responsive inorganic materials used as drug delivery carriers include iron oxides, manganese oxides, gold nanostructures (nanorods, nanocages, nanoshells), molybdenum disulfide, carbon-based nanostructures (carbon dots, graphene, carbon nanotubes), mesoporous silica, and calcium-based nanostructures ($CaCO_3$, $Ca_3(PO_4)_2$).

Metallic

pH-responsive metallic inorganic nanomaterials mainly include iron oxides, manganese oxides, gold nanoparticles, and molybdenum disulfide. Iron oxides (such as FeO, Fe_2O_3, Fe_3O_4) dissolve under acidic conditions and are thus commonly used for pH-sensitive drug delivery. Fe_3O_4 can be used to prepare superparamagnetic iron oxide nanoparticles, combining pH and magnetic dual functionalities for DDS. In 2009, the FDA approved the use of the iron oxide nanoparticle injection, Ferumoxytol. Özcan Z et al developed polydopamine-coated iron oxide nanoparticles loaded with vinorelbine (VNB). These nanoparticles function as multifunctional therapeutic agents, combining chemotherapy and photothermal therapy (PTT). They exhibited different drug release profiles in vitro at pH 5.5 and 7.4 and showed photothermal activity under 808 nm NIR laser irradiation.[85]

Manganese oxides have properties such as controllable shape and high surface area, similar to iron oxides, and exhibit acid sensitivity and magnetic resonance effects. Zhou X et al designed a multifunctional manganese-doped mesoporous magnetic nanodrug carrier. When loaded with DOX, the carrier forms a Schiff base bond with pullulan oxide, creating oMMNPs/DOX nanocomposites. These nanocomposites exhibit excellent controlled drug release, high 808 nm NIR photothermal conversion efficiency, good biodegradability, and targeted drug delivery capability. The generated Mn^{2+}, via a Fenton-like reaction, responds to the overexpression of glutathione (GSH) in the tumor microenvironment, enabling CDT. oMMNPs/DOX, as a magnetically targeted and a pH/GSH/NIR triple-responsive drug carrier, enables synergistic PTT/CDT/DT therapy.[86]

Gold nanoparticles possess excellent photothermal efficiency and surface modification capabilities. In recent years, multi-responsive gold nanocomposites have emerged as a research hotspot due to their ability to be triggered simultaneously by NIR and other stimuli (such as pH, enzymes, and molecular recognition).

Costa-e-Sá F et al designed an NIR light-triggered nanodelivery system based on lipid-gated mesoporous silica-coated gold nanorods and chitosan/alginate nanogels. Sequential NIR-triggered drug delivery can provide different drug combinations targeting multiple sites within the tumor microenvironment.[87] Farahavr G et al used anti-MUC18 single-chain antibody-modified PEG to modify AuNCs, whose negatively charged surface achieved a MEL loading rate of 93%, used for a MEL-targeted delivery system for melanoma. (AuNC@scFv-lip) facilitates dual-release triggered by acidic pH and NIR.[88]

Dong Q et al designed a mixed nanocapsule targeting gold nanostructured chitosan (PLA-co-GA) containing human epidermal growth factor receptor 2 (Her2), encapsulating perfluorooctyl bromide, superparamagnetic iron oxide nanoparticles, and doxorubicin (Her2-GPDH nanocapsules). It serves as a therapeutic agent for bimodal ultrasound/magnetic

resonance imaging and synergistic photothermal chemotherapy of Her2 breast cancer cells, with pH-responsive and near-infrared light-triggered gradual release of doxorubicin.[89]

Black phosphorus (BP) is an allotrope of phosphorus with excellent drug-loading capacity and photothermal conversion efficiency, and it is increasingly used in drug delivery and PTT. BP has a negatively charged surface under physiological conditions, and its two-dimensional nanosheets provide a large surface area for drug loading through π-π stacking or electrostatic interactions. After protonation at acidic pH, the electrostatic interactions between black phosphorus and the drug change, inducing drug release. Ling K et al designed a Mn^{2+}/CpG oligodeoxynucleotide (ODNs) co-loaded black phosphorus nanosheet (BPNS@Mn^{2+}/CpG platform). The coordination with Mn^{2+} significantly improved the stability of BPNS and the adsorption of CpG ODNs. The acidic TME and endosomes can disrupt the Mn^{2+} coordination, triggering the pH-responsive release of CpG ODNs and Mn^{2+}, and activating the Toll-like receptor 9 and STING pathway.[90]

Non-metallic

1.Carbon dots (CDs) are a new type of fluorescent nanomaterial with carboxyl or other functional groups as the outer layer.[91] CDs are spherical particles with a diameter of less than 10 nm, classified as natural materials, exhibiting good dispersibility and suitability for large-scale production. CDs have unique properties compared to other organic dyes, semiconductor quantum dots, and upconversion nanoparticles (UCNPs). The unique characteristics of fluorescent CDs include biocompatibility, ease of preparation, good water solubility, tunable emission, strong photostability, and high quantum yield. CDs with good electrical conductivity, photochemical stability, low toxicity, and environmental friendliness are being increasingly explored.

Li Q et al loaded doxorubicin (DOX) onto functionalized orange-emitting carbon dots (CDs) with a nuclear localization sequence (NLS), delivering DOX to the nuclei of tumor cells to enhance its antitumor activity. The CDs NLS can efficiently target the cell nucleus, achieving a high drug-loading efficiency (59.4%) after loading DOX, and releasing DOX in a mildly acidic environment through hydrazone bond cleavage.[92]

Meng QX prepared carbon dots (CDs) by modifying folic acid, and loaded doxorubicin (DOX) to create a poly (methacrylic acid) DDS (DOX@CDs@HPMAA), which is responsive to pH and glutathione, achieving effective tumor treatment through combined chemotherapy and sonodynamic therapy.[93] Wu et al developed a pH- and temperature-responsive drug delivery carrier (CDs/PNVCL@HMSNs), using selective etching to synthesize hollow mesoporous silica nanoparticles (HMSNs). At room temperature (pH=7.4, T=25°C), PNVCL extends, allowing free transport of DOX in the mesopores. PNVCL becomes fold in the bloodstream (pH=7.4, T=37°C), and encapsulating DOX to form PNVCL@HMSNs-DOX CDs are grafted onto CD/PNVCL@HMSNs-DOX. Schiff base bond was cleavage after the drugs upon reaching the acidic tumor environment, and causing the shell to shed and DOX to be released.[94]

Mesoporous silica nanoparticles (MSNs) possess excellent properties such as high surface area, thermal stability, tunable pore size, chemical inertness, good biocompatibility, biodegradability, and antioxidant properties, and have been widely used in DDS in recent years.[95]

Wang XN developed a novel mesoporous silica-based drug delivery system, dual-modified with tumor-homing peptide iRGD (CRGDKGPDC) and the pH-responsive polymer poly(2-ethyl-2-oxazoline) (PEOz), for the treatment of triple-negative cancer. It penetrates deep into tumor tissues through NRP-1 receptor-dependent internalization, and the drug release rate of the PEOz-modified formulation is pH-dependent, allowing rapid drug release in the acidic cytosol.[96] Qiu et al investigated the immobilization and release behavior of MSN using hyaluronidase, bromelain, and collagenase (Coll). A series of cationic MSNs (CMSNs) with large and tunable pore sizes were synthesized to enhance tumor penetration.[97] Liu C et al introduced Ca^{2+} into the MSN framework and designed a Ca-doped nanoplatform carrying the chemotherapeutic drug Dox, enabling the doped nanoplatform to enhance chemotherapy and activate antitumor immune responses.[98]

Calcium phosphate-based nanomaterials: Calcium salts can react with H^+ and degrade, and calcium phosphate nanoparticles decompose into Ca^{2+} and PO_4^{3-} in acidic environments. They exhibit good biocompatibility, relatively slow biodegradability, high safety, and ease of availability, making them significant in pH-sensitive drug delivery and pH-responsive design.[99]

Liu et al prepared bilayer HPCaCO$_3$/CaF$_2$ hollow nanospheres using yeast cells. Biomolecules secreted were used as regulators and stabilizers to control the biosynthesis of HPCaCO$_3$/CaF$_2$ by yeast cells. The product features a hierarchical porous structure, abundant channels, and a large specific surface area, which improve drug loading and extend sustained drug release through hierarchical pore-by-pore diffusion. The pH-sensitive HPCaCO$_3$ can controllably release DOX in the acidic tumor microenvironment.[100] Tian T et al prepared a Gela/PAA-CaCO$_3$/NaF hydrogel by inducing charge reversal in amphoteric gelatin nanoparticles via pH changes. This approach induces tumor regression and inhibits tumor recurrence and metastasis through immune microwave hyperthermia.[101] He JN et al developed pH-responsive conjugated polymer calcium composite nanoparticles (PFV/CaCO$_3$)/PDA@PEG), enabling synergistic tumor treatment through ROS-triggered calcium overload and PDT. It rapidly decomposes in the acidic tumor microenvironment, effectively releasing Ca^{2+} and the photosensitizer PFV-COOH. Elevated extracellular Ca^{2+} concentrations promote dimer formation between adjacent cadherin domains, thereby strengthening cell-to-cell adhesion and potentially inhibiting tumor metastasis.[102]

pH-Responsive Composite Nanomaterials

Composite nanomaterials include metal-organic frameworks (MOFs) and metal-phenol networks. MOFs are materials with an infinitely extending network structure, formed by organic ligands connecting with metal ions (clusters) through self-assembly or coordination bonds, and they have features such as high surface area, tunable properties, large encapsulation capacity, and controlled release effects. Metal-phenol networks are structures formed by the coordination of phenolic hydroxyl groups in polyphenols with various metal ions. They exhibit good biocompatibility and poor biological fouling resistance.

MOFs were discovered by Robson in 1989. They are crystalline hybrid materials formed by the coordination of metal ions (transition metals or lanthanides) with organic ligands (such as carboxylates, azolates, or phosphonates). Their surface chemical structure is controllable, featuring high surface area, high porosity, hydrothermal stability, and reversible structural flexibility. MOFs can stably and effectively encapsulate various types of drugs, including hydrophobic drugs, hydrophilic drugs, and proteins.[103] They have extensive applications in drug delivery, catalysis, and materials science. General pH-sensitive MOF materials include zeolitic imidazolate frameworks (ZIF), UiO-66, and MIL-100.

Yang CL et al encapsulated interleukin-4 (IL-4) within a zeolitic imidazolate framework (ZIF-8) and coated it with a diselenide block copolymer to obtain IL-4@ZIF-8@Se-Se polymer.[104] This polymer achieves redox-responsive release of IL-4 through the diselenide copolymer, while ZIF-8 facilitates pH-triggered release. Binaeian E et al prepared a pH-sensitive MOF prodrug by the Schiff base reaction between UiO-66-NH$_2$ and 3.4-dihydroxybenzaldehyde (DHBD).[105] Sun BY et al constructed Oxa@Mil-100 (Fe) nanocomposites, which can release Fe^{3+} and the encapsulated Oxa under external stimuli.[106]

Stimuli-responsive metal-phenol networks (MPNs). MPNs are a novel organic-inorganic hybrid network system developed in recent years, which exhibit various properties such as anti-inflammatory, antioxidant, and antibacterial activities through the coordination between phenolic ligands and metal ions. Xiangyu Meng et al prepared a multifunctional nanocomposite material based on a metal-phenol network (PID@Fe-TA), which has pH responsiveness and can generate ROS and release drugs. PCA rapidly self-assembles with Fe^{3+} to form a metal-phenol network under different pH conditions, and SA is added to prepare an SA/PCA/Fe hydrogel with delivery capabilities, used for synergistic cancer therapy involving CDT/PTT/chemotherapy.[107] Nie WD et al assembled iron ions with TA onto the surface of OMVs and utilized iron-based "prisons" to undergo local collapse under low pH and high ATP conditions in the tumor microenvironment (TME). MPNs are used to reduce the toxicity of OMVs and induce immunogenic cell death (ICD) through chemical dynamics effects, thereby providing tumor antigens. In the TME, released iron ions promote ICD of cancer cells through Fenton reactions, generating a large amount of tumor antigens. By fusing with OMVs, in situ vaccines are prepared, successfully inhibiting bilateral tumor models with good biosafety.[108] Zhao SL et al used a one-step method to coordinate and self-assemble SA, TA, and Fe^{3+} ions to prepare microenvironment-responsive nanogels (STF) composed of Fe^{3+}/sodium alginate (SA)-based nanogels and Fe^{3+}/TA-based MPNs, used for synergistic treatment of bacterial infections through PTT and CDT.STF nanogels exhibit photothermal-enhanced peroxidase-like activity

through the photothermal effects of MPNs. The degradation of Fe^{3+} chelators and the reduction of TA produce more Fe^{2+}, thereby enhancing Fenton reaction activity.[109]

Conclusion and Outlook

Nanomedicine systems developed to target the acidic microenvironment of tumors can exploit the differences between normal and cancer cells to achieve selective treatment, marking a significant advance in cancer therapy. Research on the differences in the tumor microenvironment primarily focuses on pH, redox environment, enzyme activity, and receptor expression. By utilizing the mildly acidic environment of tumor tissues, strategies such as designing pH-sensitive chemical bonds or introducing protonable groups have been employed to develop pH-responsive nanomaterials and DDS These systems enable controlled release and targeted delivery of drugs under acidic conditions, thereby enhancing treatment efficacy, reducing damage to normal tissues and systemic side effects, and demonstrating significant advantages in improving anti-tumor treatment outcomes.

Despite the significant achievements of nanomedicine systems in responding to the acidic tumor microenvironment, they still face some limitations and challenges. Firstly, improving the targeting and selectivity of nanomedicine systems to ensure precise action on tumor cells while minimizing impact on healthy tissues is one of the key future research directions. Secondly, enhancing the stability and biocompatibility of nanomedicine systems in vivo, and optimizing their pharmacokinetics and biodistribution characteristics are also crucial research directions. In clinical applications, it is also important to focus on the long-term safety, potential immunogenicity, resistance, and efficacy evaluation of nanomedicine systems. Developing new synthesis methods and production processes, reducing the production costs of nanomedicine systems, and improving their clinical feasibility and accessibility are important research directions for achieving industrialization. How to combine with photothermal, magnetic resonance, redox, and immunotherapy modalities to fully leverage their respective advantages for combination treatments is also an important area of research.

In summary, nanomedicine systems exhibit great potential and advantages in responding to the acidic tumor microenvironment, providing new ideas and methods for cancer treatment. By overcoming existing challenges and limitations, future research is expected to further enhance the therapeutic effects and clinical prospects of these systems, bringing more hope and possibilities to cancer patients.

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Disclosure

The authors declare that they have no competing interests.

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