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Precision Polymeric Nanoparticles for Hypoxia-Targeted Cancer Therapy

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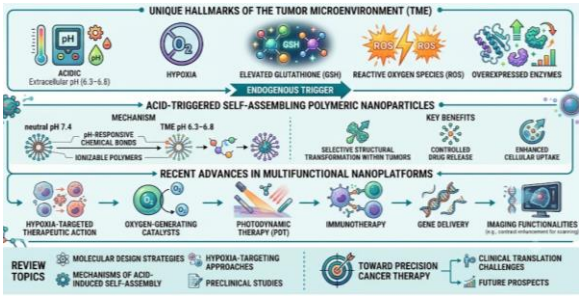
Abstract

The acidic tumor microenvironment (pH 6.3–6.8) provides a powerful endogenous trigger for targeted nanomedicine. Acid-triggered self-assembling polymeric nanoparticles leverage pH-responsive chemical bonds and ionizable polymers to undergo structural transformations selectively within tumors. This enables controlled drug release, improved cellular uptake, and targeted hypoxia therapy. Recent innovations integrate these pH-sensitive platforms with hypoxia-responsive moieties, oxygen generation, photodynamic therapy, immunotherapy, gene delivery, and imaging capabilities. This review highlights molecular design strategies, self-assembly mechanisms, and multifunctional nanoplatforms while evaluating current preclinical progress, clinical translation challenges, and future perspectives for precision cancer therapy.

Infographic abstract



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Background

Cancer remains among the leading causes of mortality worldwide despite significant advances in chemotherapy, immunotherapy, radiotherapy, and targeted molecular therapy. Conventional anticancer drugs exhibit limited tumor specificity, systemic toxicity, multidrug resistance (MDR), and poor penetration into hypoxic tumor cores. The tumor microenvironment differs markedly from normal tissues due to: Extracellular acidity, Hypoxia, High ROS, Elevated glutathione, Abnormal vasculature, Dense extracellular matrix. These characteristics provide endogenous biochemical triggers for intelligent nanocarriers. Acid-triggered polymeric nanoparticles represent one of the most promising precision drug delivery systems because they remain stable during circulation (pH 7.4) but rapidly transform inside acidic tumors. Cancer remains one of the leading causes of mortality globally, primarily due to the limitations of conventional systemic therapies, including off-target toxicity, insufficient intratumoral drug accumulation, and the rapid emergence of therapeutic resistance. A major driver of these clinical challenges is the complex and heterogeneous architecture of the **tumor microenvironment (TME)**. As solid tumors outgrow their surrounding vasculature, disorganized and dysfunctional blood vessel networks fail to adequately supply oxygen and nutrients, giving rise to two interrelated biological hallmarks: severe intratumoral **hypoxia** (low oxygen partial pressure) and extracellular **acidosis** pH - 6.2–6.8, compared to physiological pH- 7.4.

Hypoxia acts as a major driver of tumor aggressiveness, fueling epithelial-to-mesenchymal transition (EMT), metastasis, immune evasion, and resistance to standard chemotherapy and radiation. Concurrently, the accelerated anaerobic glycolysis of tumor cells under hypoxic stress—commonly referred to as the Warburg effect—leads to an accumulation of lactic acid, creating an acidic extracellular milieu. While hypoxia presents a formidable biological barrier to conventional treatments, the unique physiological gradients of the TME also offer an unprecedented opportunity for

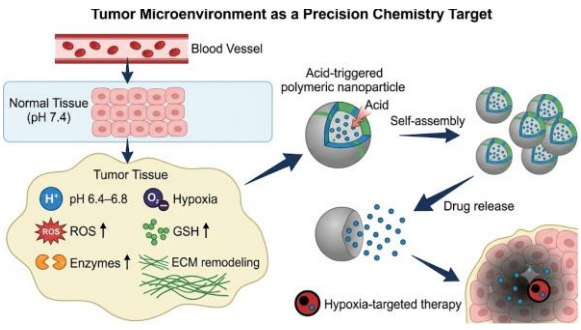
precision chemistry and stimuli-responsive nanomedicine design (Jin et al., 2024).

Polymeric nanoparticles have emerged as versatile platforms to overcome traditional drug delivery hurdles by extending systemic circulation times via the enhanced permeability and retention (EPR) effect. However, static nanocarriers often suffer from premature cargo leakage, poor deep-tissue penetration, and inefficient localized activation. To address these limitations, recent paradigms have shifted toward **smart, stimuli-responsive nanomaterials** that dynamically adapt their chemical structures, charge, or spatial assembly in direct response to TME-specific biological cues (Jin et al., 2024).

Among various TME triggers, extracellular acidity serves as an ideal bio-orthogonal signal for localized nanomedicine activation. By exploiting **acid-triggered self-assembly**, amphiphilic block copolymers equipped with pH-sensitive chemical moieties (such as ionizable tertiary amines, hydrazones, or orthoesters) undergo protonation or structural realignments upon encountering the mildly acidic extracellular tumor space pH-6.5. This sharp physical transition drives the *in situ* self-assembly or morphological transformation of small, circulating unimers or loose structures into higher-order nanostructures. This localized structural transition significantly enhances intratumoral retention, prevents rapid lymphatic drainage, and promotes deep-tissue penetration into poorly perfused hypoxic cores (Thambi et al., 2014).

Furthermore, integrating hypoxia-targeted therapeutic moieties—such as 2-nitroimidazole derivatives or azobenzene linkages—into these acid-responsive polymeric architectures enables a sophisticated, multi-stage delivery strategy. Once localized within the acidic tumor tissue, these nanoparticles penetrate deep into oxygen-depleted hypoxic niches, where overexpressed reductases selectively cleavage or reduce the hypoxia-sensitive moieties to trigger rapid, on-demand drug release or photo/radiosensitizer activation (Thambi et al., 2014).

Herein, we report a dual-stage precision chemistry strategy featuring **acid-triggered self-assembling polymeric nanoparticles** optimized for **hypoxia-targeted cancer therapy**. By coupling acidic pH sensitivity for site-specific physical transformation with hypoxia-responsive chemical moieties for deep-tissue cargo release, this platform achieves high-precision, spatiotemporally controlled drug delivery. In this study, we detail the synthesis, chemical characterization, pH-dependent self-assembly kinetics, and hypoxia-activated therapeutic efficacy of these nanocarriers *in vitro* and *in vivo*, demonstrating a robust strategy to overcome microenvironmental barriers and enhance solid tumor therapy.



The Acidic Tumor Microenvironment (TME)

The solid tumor microenvironment (TME) is characterized by pronounced extracellular acidosis (pH approx 6.3–6.8), sharply contrasting with the tight homeostatic physiological pH of healthy tissues pH7.35–7.45 (Lee & Griffiths, 2020). Extracellular acidity functions as a driver of cancer evolution, aggressive behavior, and therapeutic recalcitrance.

Self-Assembling Polymeric Nanoparticles

Self-assembling polymeric systems undergo spontaneous hierarchical organization driven by non-covalent, reversible interactions. This eliminates the need for harsh organic crosslinkers during synthesis (Beach et al., 2024).

Supramolecular Driving Forces

Hydrophobic Interactions: Amphiphilic block copolymers (e.g., Polyethylene glycol-poly(L-lactic acid) [PEG-PLA]) self-assemble in aqueous media to shield hydrophobic segments into an inner core while extending hydrophilic PEG chains outward.

Hydrogen Bonding: Directional hydrogen bonds yield rigid

nanostructures such as supramolecular hydrogels and peptide-based assemblies.

Electrostatic Interactions: Oppositely charged polyelectrolytes form polyion complex (PIC) micelles, ideal for encapsulating charged macromolecules like siRNA, mRNA, or plasmid DNA.

pi–pi Stacking: Aromatic interactions between polymer backbones (e.g., poly(histidine) or phenylalanine derivatives) and planar drug molecules (e.g., doxorubicin, paclitaxel) substantially increase loading efficiency.

Host–Guest Interactions: Macrocyclic hosts such as cyclodextrins, cucurbit[n]urils, and calixarenes bind specific guest moieties (e.g., adamantane, ferrocene) to form reversible inclusion complexes.

Van der Waals Forces: Ubiquitous attractive dispersion forces stabilize assemblies once functional groups are brought into close spatial proximity.

Key Pharmacological Advantages

High Drug Loading & Encapsulation: Non-covalent core entrapment protects unstable active pharmaceutical ingredients (APIs) from pre-systemic degradation.

Improved Pharmacokinetics & EPR Effect: Hydrophilic outer shells reduce opsonization and reticuloendothelial system (RES) clearance, taking advantage of the Enhanced Permeability and Retention (EPR) effect for passive tumor accumulation.

Triggered Assembly/Disassembly: Polymer structures can be engineered to undergo rapid morphological transitions (e.g., micelle-to-fiber or sphere-to-aggregate) upon encountering TME signals such as low pH.

In Situ Self-Assembly: Advanced designs infiltrate tumors as small monomeric or micellar entities ($<20\text{ nm}$), then assemble *in situ* into larger networks ($>100\text{ nm}$) upon activation by pH_e or enzymatic cues. This strategy enhances deep tissue penetration while inhibiting premature lymphatic clearance (Beach et al., 2024).

Hypoxia-Targeted Cancer Therapy

Tumor hypoxia arises when rapid cellular proliferation outpaces structural angiogenesis, resulting in localized oxygen partial pressures (pO_2) falling below 10 mmHg (Li et al., 2021)

Molecular Signaling & Pathophysiology

Under normoxia, proline residues on HIF-1 alpha are hydroxylated by prolyl hydroxylase domain proteins (PHDs), marking for von Hippel-Lindau)-mediated proteasomal degradation. Under hypoxic stress, PHD activity ceases:

HIF-1alpha Stabilization: HIF-1alpha translocates to the nucleus, heterodimerizes with HIF-1beta, and binds to Hypoxia-Response Elements (HREs).

VEGF & Neovascularization: Transcriptional activation of VEGF triggers chaotic, highly permeable, and non-functional blood vessel formation.

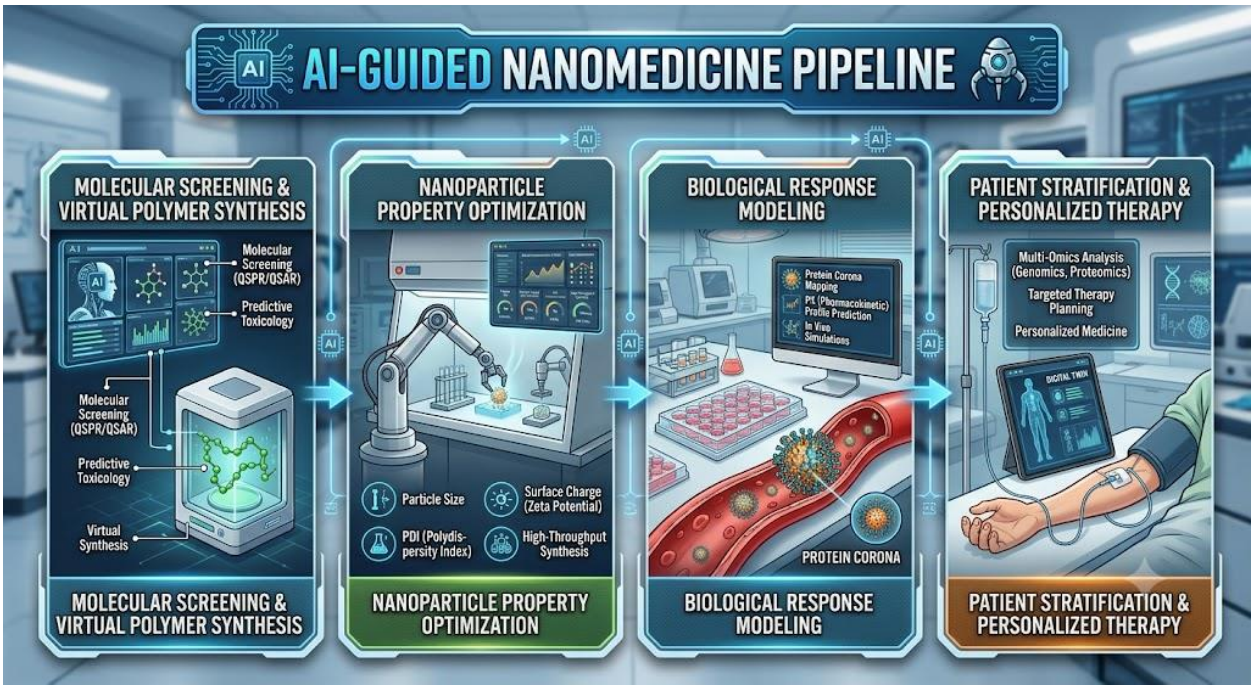
CAIX and GLUT1 Activation: Promotes glycolytic flux (Glucose Transporter 1) and extracellular proton accumulation (CAIX).

Multidrug Resistance (MDR): Transcriptional activation of P-glycoproteinP-gpMDR1 actively pumps chemotherapeutic agents out of malignant cells.

Radioresistance: The absence of molecular oxygen prevents the permanent "fixation" of radiation-induced DNA free radical damage.

Artificial Intelligence & Machine Learning in Precision Nanomedicine

Integrating artificial intelligence (AI), machine learning (ML), and deep learning (DL) into nanomedicine design helps streamline development by shifting from trial-and-error experimentation to predictive, data-driven formulation (Chou, 2025).



Machine Learning Applications across the Development Cycle

Polymer Screening and Synthesis: Quantitative Structure-Property Relationship (QSPR) models screen virtual polymer libraries to evaluate biocompatibility, degradation rates, and pH-responsive protonation behavior before laboratory synthesis (Chou, 2025).

Molecular Docking and Dynamics: AI-accelerated molecular dynamics (MD) simulations model non-covalent interactions (π–π stacking, hydrogen bonding) between polymeric carriers and hydrophobic payloads, predicting drug loading capacities and encapsulation stability.

Formulation Design & Property Optimization: Supervised learning algorithms—such as Random Forests, XGBoost, and Artificial Neural Networks (ANNs)—map complex formulations (e.g., lipid-to-polymer ratios, surfactant concentrations) to target physical properties like particle size, zeta potential, and polydispersity index (PDI).

Predicting Protein Corona Composition: Machine learning classifiers leverage surface properties (e.g., hydrophobicity, spatial charge

distribution) to forecast plasma protein adsorption patterns, predicting *in vivo* circulation clearance (Chou, 2025).

Pharmacokinetic (PK) Modeling & Digital Twins: Deep learning models integrate high-throughput multi-omics data, physiological tumor parameters, and real-time imaging to create "digital twins." These computational models simulate individual patient responses, optimizing therapeutic schedules and personalized dosing regimens.

Mthodology

This review was conducted using a structured and reproducible literature review methodology to comprehensively evaluate recent advances in **acid-triggered self-assembling polymeric nanoparticles for hypoxia-targeted cancer therapy**. The review focused on the chemistry of tumor microenvironment (TME)-responsive nanocarriers, self-assembly mechanisms, polymer engineering, drug loading strategies, hypoxia-responsive systems, therapeutic efficacy, translational challenges, and future research directions.

Literature Search Strategy

A comprehensive search of peer-reviewed literature was performed using the following electronic databases: PubMed, Scopus, Web of Science Core Collection, ScienceDirect, Google Scholar, Wiley Online Library, SpringerLink, Nature Portfolio, and ACS Publications. The literature search covered publications from **2015 to June 2026**, with seminal earlier papers included when necessary to explain the development of polymeric nanomedicine.

Inclusion Criteria

Studies were included if they met the following criteria: Published in peer-reviewed journals, written in English,Focused on polymeric nanoparticles exhibiting pH-responsive or hypoxia-responsive behavior,Investigated self-assembling nanostructures for cancer therapy, reported experimental, preclinical, translational, or review findings relevant to tumor microenvironment-responsive drug delivery,Discussed

polymer chemistry, nanocarrier design, or precision drug delivery.

Exclusion Criteria

The following publications were excluded: Conference abstracts without full articles,Editorials and opinion papers,Non-English publications,Studies unrelated to polymeric nanocarriers,Articles lacking sufficient methodological or experimental details,Nanoparticles designed exclusively for imaging without therapeutic relevance.

Results and Discussion

Acidic Tumor Microenvironment as a Precision Trigger for Polymeric Self-Assembly

The tumor microenvironment (TME) is characterized by extracellular acidosis (pH 6.4–6.8), intracellular hypoxia, elevated glutathione (GSH), reactive oxygen species (ROS), and overexpressed enzymes. Among these hallmarks, acidic pH has emerged as one of the most reliable endogenous triggers for precision nanomedicine. Acid-triggered polymeric nanoparticles remain stable in physiological blood pH (7.4) but rapidly undergo protonation, structural transformation, or self-assembly in acidic tumor tissues, leading to selective drug accumulation and release.

This "off-to-on" activation minimizes premature leakage while enhancing therapeutic specificity. Recent polymer systems employing hydrazone, acetal, imine, β-thiopropionate, and cis-aconityl linkages demonstrate controlled disassembly under acidic conditions, significantly improving intratumoral drug concentration compared with conventional nanocarriers.

Self-Assembling Polymeric Nanoparticles Enhance Tumor Penetration

A major finding across recent studies is that **in situ self-assembly** improves nanoparticle retention and penetration within hypoxic tumors. Initially, polymeric prodrugs circulate as small molecular precursors or loosely assembled nanoparticles. After exposure to acidic TME, intermolecular hydrogen bonding, π–π stacking, hydrophobic interactions,

or electrostatic interactions induce self-assembly into larger supramolecular nanostructures.

This dynamic transformation provides several therapeutic advantages: prolonged tumor retention, enhanced intracellular uptake, deeper penetration into poorly vascularized hypoxic regions, sustained drug release,release, and reduced systemic toxicity. Compared with permanently assembled nanoparticles, stimulus-induced self-assembly demonstrates superior therapeutic efficiency because particle transformation occurs only inside tumor tissue rather than during circulation.

Synergistic Targeting of Acidity and Hypoxia

Hypoxia and extracellular acidity are closely interconnected biological phenomena. Oxygen deficiency shifts cancer metabolism toward glycolysis, increasing lactate production and lowering extracellular pH. Consequently, nanoparticles simultaneously responsive to hypoxia and acidity exhibit superior selectivity compared with single-stimulus systems.

Several dual-responsive polymers incorporate:
azobenzene,nitroimidazole,nitrobenzyl,quinone,N-oxide derivatives together with acid-labile linkers. After entering acidic tumors, nanoparticles first expose targeting ligands through acid-induced charge reversal. Subsequently, hypoxia activates reductive cleavage of azo or nitro groups, triggering complete drug release specifically within oxygen-deficient tumor regions. This sequential activation substantially reduces off-target toxicity while overcoming multidrug resistance.

Table 1. Major Acid-Responsive Polymeric Strategies for Hypoxia-Targeted Therapy

Polymeric strategy	Trigger	Mechanism	Therapeutic advantage
Hydrazone-linked polymers	Acidic pH	Bond cleavage	Controlled drug release
Imine (Schiff-base) polymers	Low pH	Hydrolysis	Selective intracellular activation
Acetal/Ketal polymers	Acidic lysosomes	Polymer degradation	Enhanced chemotherapy
pH-responsive block copolymers	Protonation	Self-assembly/disassembly	Improved tumor accumulation
Charge-conversion polymers	Acidic TME	Surface charge reversal	Increased cellular uptake
Dual pH/Hypoxia polymers	Acid + Hypoxia	Sequential activation	High therapeutic precision

Future Perspectives

Future research should focus on: Personalized nanomedicine, Multi-

stimuli-responsive polymers, AI-driven nanoparticle engineering, Clinical-scale manufacturing, Biomarker-guided patient selection, Integration with immunotherapy, Regulatory harmonization.

Conclusion

Acid-triggered self-assembling polymeric nanoparticles represent a transformative strategy for precision cancer therapy by exploiting the acidic and hypoxic features of the tumor microenvironment. Their ability to remain stable in circulation while undergoing selective activation within tumors enables targeted drug release, improved penetration, and reduced systemic toxicity. Integrating pH-responsive polymers with hypoxia-sensitive chemistries, oxygen-modulating systems, and multifunctional therapeutic payloads offers a powerful platform to overcome tumor heterogeneity and treatment resistance. Continued progress in polymer chemistry, supramolecular engineering, artificial intelligence-assisted nanomedicine design, and clinically scalable manufacturing is expected to accelerate translation from laboratory research to personalized oncology

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