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SHORT COMMUNICATION

Stimuli-responsive nanocarriers for precision cancer therapy: a short communication

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The cancer is still one of the world's biggest public health problems due to its diversity (tumor), multiresistance, and non-specific delivery by drugs like chemotherapy. Oncological precision medicine is changing treatment paradigms towards targeted therapies with high specificity and low-toxicity options for patients' use. Among them, stimuli-responsive nanocarriers are smart drug delivery systems that release drugs in response to endogenous stimuli, pH, redox potential, enzymes, reactive oxygen species, and hypoxia, or exogenous stimuli (light, magnetic fields, ultrasound, and temperature). The intelligent nanovehicles utilize properties specific to tumors' environment that allow precise targeting with targeted delivery mechanisms, resulting in better penetration rates as well as lower toxicity levels within tissues. Nanotech innovations allow for multi-functional devices that incorporate anticancer drugs as well as genetic treatments; immune responses are also incorporated to provide diagnostics on one device platform. Though there are some favorable results from laboratory studies as well as successful trials with nanoparticles medicines, there are problems such as production difficulties for drugs' approval process, variation among individuals due to genetics, etc. The paper reviews current developments concerning stimulus-responsive nanoparticles; it also describes how these agents work as a means to treat cancers precisely.

Keywords: stimuli-responsive nanocarriers, precision oncology, targeted drug delivery, tumor microenvironment, smart nanoparticles, cancer nanomedicine

Introduction

Despite significant progress on diagnostics as well as treatments, cancer is still a major cause of death globally. Chemotherapy usually has low specificity for tumors; it's quickly metabolized by kidneys, leading to high toxicity rates, as well as multiresistant populations developing over time, which makes treatment unsuccessful. The complexity of the tumor microenvironment (TME), characterized by acidic pH, high levels of glutathione, hypoxia, altered enzyme expression, and oxidative stress, also limits the efficacy of conventional treatments. The problems are leading to advances in nanomedicines that target tumors more precisely without affecting other organs as much (1–5).

Nanocarriers that are stimuli sensitive are among the best ideas for targeted cancer treatment, as discussed in **Table 1**. In contrast with traditional nanomaterials "smart" devices are not subject to systemic transport; they only respond when stimulated by an internal (endogenous) and/or external trigger. This level of precision increases absorption rates; it also facilitates better penetration through tissues while minimizing side effects at a cellular level substantially. Also, multi-functional nanoparticles that can simultaneously deliver anticancer drugs as well as genetic material (nucleotides), proteins, etc. (6–10).

TABLE 1 | Types of stimuli-responsive nanocarriers used in precision cancer therapy.

Stimulus	Mechanism	Representative nanocarriers	Major applications
Ph	Drug release in acidic tumor microenvironment (TME)	Liposomes, polymeric nanoparticles, micelles	**Breast, lung, colon cancers**
Redox	Cleavage of disulfide bonds by intracellular glutathione	Polymeric nanoparticles, dendrimers	**Intracellular chemotherapy and gene delivery**
Enzyme	Enzyme-mediated degradation of carrier	Polymeric nanoparticles, hydrogels	**Matrix metalloproteinase-rich tumors**
Hypoxia	Activation under oxygen-deficient conditions	Polymeric nanocarriers	**Pancreatic and liver cancers**
Light	Near-infrared (NIR) or ultraviolet (UV)-triggered release	Gold nanoparticles, liposomes	**Photothermal and photodynamic therapy (PDT)**
Ultrasound	Acoustic cavitation-mediated drug release	Liposomes, microbubbles	**Deep-seated solid tumors**
Magnetic field	Magnetically guided targeting	Iron oxide nanoparticles	**Targeted chemotherapy and magnetic resonance imaging (MRI)**
Temperature	Heat-induced structural transition	Thermosensitive liposomes	**Hyperthermia-assisted therapy**

Stimuli-responsive nanocarriers in precision cancer therapy

Nanocapsules are stimuli-sensitive and can be programmed to release drugs only where needed (tumor). As opposed to passively transported nanoparticles they are "active" and can be stabilized through blood flow while undergoing biochemical modifications that lead towards targeted delivery of medications towards tumors via a stimulus-induced mechanism, as shown in **Figure 1**. Spatial as well as time-based management enhances treatment effectiveness, reduces side effects of drugs at a broader range. Targeting ligand incorporation as well as tracer molecules along with several drugs is also beneficial for this purpose. The recent progress made by materials science, particularly nanotechnology, is leading towards the creation of multi-functional nanoparticles that can cross cell membranes, which is a problem for cancer cells (solid) (11–15).

Endogenous stimuli-responsive nanocarriers

The environment around a tumor is really different from healthy tissues in many ways—it's more acidic, has more oxidative stress, and has different levels of enzymes and glutathione, a powerful antioxidant. Also, the amount of oxygen available is often lower. All these differences can be used as signals to trigger the release of drugs in a targeted way, which is a promising approach for cancer treatment.

Among endogenous stimuli, pH-responsive nanocarriers are the most extensively investigated. The extracellular pH of solid tumors (approximately 6.5–6.8) and intracellular lysosomal pH (4.5–5.5) are considerably lower than physiological pH (7.4). Nanocarriers fabricated using acid-labile polymers, hydrazone bonds, or pH-sensitive lipids exploit these differences to achieve site-specific drug release.

Liposomes, polymeric micelles, mesoporous silica nanoparticles, and polymeric nanoparticles as shown in **Figure 2** have demonstrated enhanced accumulation and intracellular release of chemotherapeutic agents such as doxorubicin, paclitaxel, and cisplatin under acidic conditions, thereby improving antitumor efficacy while reducing systemic exposure (16–18).

One key approach is to use special tiny carriers called nanocarriers that can respond to changes in their surroundings, like the high levels of a molecule called glutathione found in cancer cells. These nanocarriers are designed with special links that keep them stable while they're moving through the bloodstream, but when they get inside a cancer cell, these links break apart quickly, releasing the medicine or genetic material they're carrying. This method has shown a lot of potential for treating cancer from inside the cells, silencing faulty genes, and delivering new therapies based on a powerful tool called clustered regularly interspaced short palindromic repeats (CRISPR). By targeting cancer cells in this way, these nanocarriers can help get treatments exactly where they're needed, which could lead to more effective and targeted cancer therapies.

Another promising platform is enzyme-responsive nanoparticles. Tumors overexpress matrix metalloproteinases, hyaluronidase, cathepsins, phospholipases, and other proteolytic enzymes that selectively degrade enzyme-sensitive polymers and thereby allow localized drug release. These systems allow for better penetration into tumor tissues and reduce premature drug leakage.

Similarly, hypoxia-sensitive nanocarriers take advantage of the low oxygen levels in fast-growing tumors. The bioreducible polymers comprising nitroimidazole,

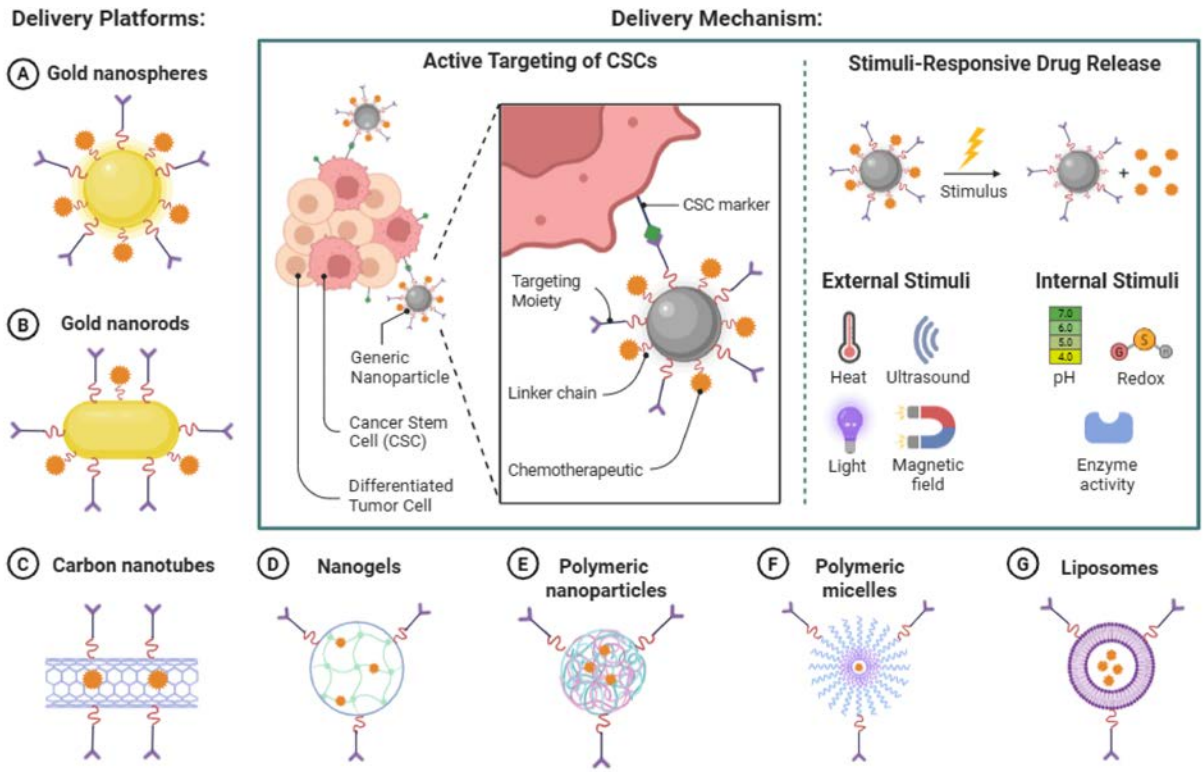

FIGURE 1 | Schematic representation of targeted and stimuli-responsive nanocarriers. Design principles of stimuli-responsive nanocarriers for cancer stem cell-targeted drug delivery. Nanocarriers decorated with cancer stem cell (CSC)-specific targeting moieties selectively accumulate within the TME and release therapeutic payloads in response to endogenous (pH, redox, and enzymatic activity) or exogenous (heat, ultrasound, light, and magnetic field) stimuli, improving therapeutic precision and reducing systemic toxicity.

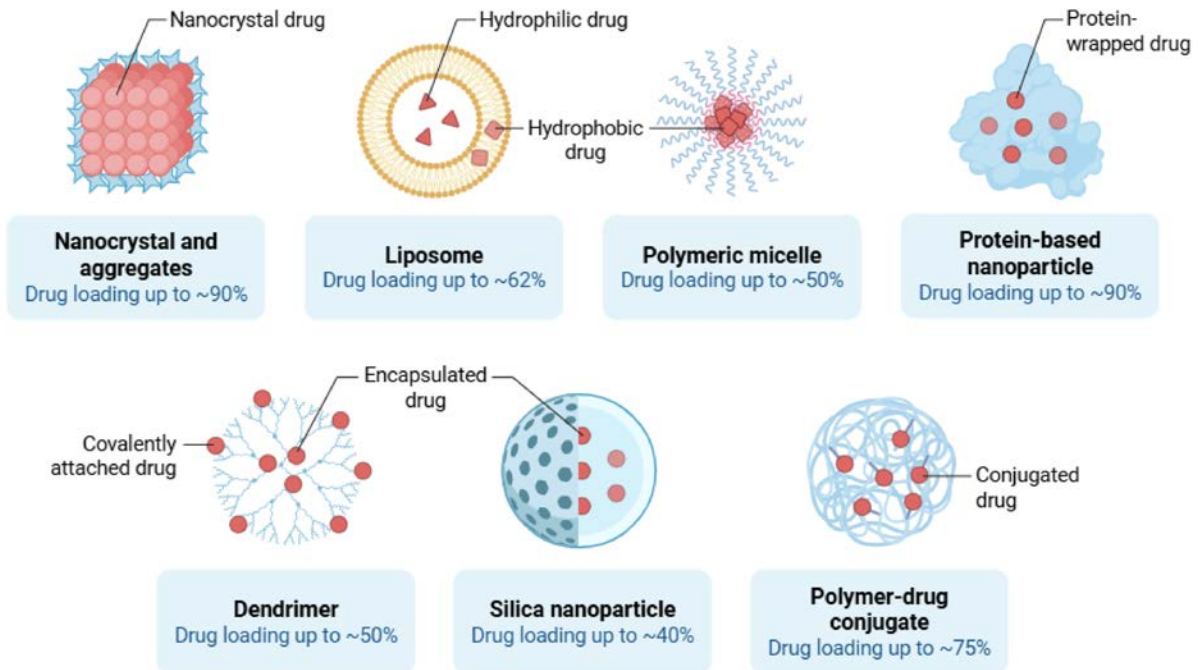

FIGURE 2 | Schematic illustration of representative nanoscale drug delivery platforms for small-molecule therapeutics. Representative nanoscale drug delivery platforms for small-molecule therapeutics, including nanocrystals, liposomes, polymeric micelles, protein-based nanoparticles, dendrimers, silica nanoparticles, and polymer–drug conjugates. These carriers can be engineered for targeted and stimuli-responsive drug release triggered by pH, redox, enzymes, reactive oxygen species (ROS), hypoxia, light, heat, ultrasound, or magnetic fields to enhance therapeutic efficacy and minimize systemic toxicity.

azobenzene, or quinone derivatives are converted to a different structure in the hypoxic condition, leading to the controlled release of the anticancer agents. In pancreatic, liver, and breast cancers, where severe hypoxia has contributed to therapeutic resistance, these systems have shown promising results.

Exogenous stimuli-responsive nanocarriers

Clinicians can use external physical stimuli to exert more control over when and where drugs are released, thereby improving the precision of treatment (19, 20).

Among these approaches, light-responsive nanocarriers have received great attention. Gold nanoparticles, graphene oxide, and photosensitive liposomes absorb near-infrared (NIR) light and convert the optical energy into localized heat or reactive oxygen species. This mechanism allows for photothermal therapy (PTT), photodynamic therapy (PDT), and co-chemotherapy, which together produce synergistic anticancer effects and decrease the damage to adjacent healthy tissues (21).

Magnetic-responsive nanocarriers contain superparamagnetic iron oxide nanoparticles, which can be directed to the tumor sites by external magnetic fields. Besides improving the localization of drugs, these nanoparticles can also be used as contrast agents for magnetic resonance imaging (MRI) and can enable magnetic hyperthermia, where localized heating triggers apoptosis of malignant cells. Combination approaches of magnetic hyperthermia with chemotherapy have demonstrated enhanced therapeutic effects in preclinical models.

Another promising approach for deep-seated tumors is ultrasound-responsive systems. Ultrasound waves cause acoustic cavitation, which increases vascular permeability and breaks down the structures of nanoparticles, leading to local drug release. Ultrasound can penetrate deeper into tissue than optical techniques and can be combined with microbubbles or liposomes to enhance drug internalization in cells (22).

Similarly, thermosensitive nanocarriers release their therapeutic payload at a mild hyperthermia (around 40–42°C). Localized heating methods coupled with thermosensitive liposomes formulated from phospholipids with defined phase-transition temperatures have been shown to enhance tumor-specific drug delivery. This strategy shows a promising clinical potential to improve the therapeutic efficacy of traditional chemotherapy. Collectively, these externally triggered systems, as discussed in **Table 2**, provide clinicians with precise spatiotemporal control over therapeutic delivery, making them particularly attractive for personalized cancer treatment and image-guided interventions.

Clinical translation and current challenges

Stimuli-responsive nanocarriers have shown great therapeutic efficacy in preclinical studies, but their successful translation to the clinic is limited. Although many nanoparticle-based formulations, such as liposomal doxorubicin, albumin-bound paclitaxel, and lipid nanoparticle platforms, have been approved for clinical use, only a few advanced stimuli-responsive systems have progressed beyond early-phase clinical trials. This translational gap is mainly due to the complexity of the nanoparticle design, reproducibility of their manufacturing, regulatory requirements, and interpatient variability in nanoparticle biodistribution (23, 24).

The heterogeneity of the TME is one of the major biological challenges. Factors such as vascular density, stromal composition, immune-cell infiltration, and variability in pH, enzyme expression, and hypoxia vary greatly between patients and even within different regions

TABLE 2 | Representative stimuli-responsive nanocarriers for precision cancer therapy.

Stimulus	Nanocarrier	Therapeutic cargo	Cancer type	Major advantages
Acidic pH	Polymeric nanoparticles	Doxorubicin	Breast cancer	**Site-specific intracellular drug release**
Redox	Disulfide-linked micelles	Paclitaxel, siRNA	Ovarian cancer	**High intracellular drug release**
Enzyme	Gelatin nanoparticles	Docetaxel	Melanoma	**Selective degradation by tumor enzymes**
Hypoxia	Nitroimidazole nanoparticles	Doxorubicin	Pancreatic cancer	**Drug activation in hypoxic regions**
NIR light	Gold nanoparticles	Doxorubicin	Breast cancer	**Combined chemo-photothermal therapy (PTT)**
Ultrasound	Liposomes	Cisplatin	Liver cancer	**Controlled deep-tissue drug release**
Magnetic field	Iron oxide nanoparticles	Paclitaxel	Glioblastoma	**Magnetic targeting and MRI imaging**
Temperature	Thermosensitive liposomes	Doxorubicin	Soft tissue sarcoma	**Hyperthermia-triggered drug release**

of the same tumor. Therefore, the responsiveness of smart nanocarriers is not always predictable, leading to inconsistent therapeutic performance. In addition, the enhanced permeability and retention (EPR) effect, which is well documented in experimental animal models, is much more heterogeneous in human tumors and thus restricts passive nanoparticle accumulation (25, 26).

Another big problem is producing it and producing more of it. Multifunctional nanocarriers usually involve multiple synthetic steps using polymers, targeting ligands, imaging agents, and responsive linkers. However, producing such systems at a large scale poses some technical challenges, especially concerning particle size, surface charge, drug loading efficiency, stability, and batch-to-batch reproducibility. Production is further complicated and made more expensive by adherence to Good Manufacturing Practice (GMP) and Chemistry, Manufacturing and Controls (CMC) guidelines.

Long-term safety is also an important consideration. Although many biodegradable polymers exhibit excellent biocompatibility, the long-term persistence of inorganic nanoparticles, unexpected immune reactions, complement activation, and the off-target accumulation in organs such as the liver and spleen need to be carefully investigated. Therefore, extensive pharmacokinetic, biodistribution, immunogenicity, and toxicity studies are required to gain regulatory approval.

However, the advances in artificial intelligence (AI)-assisted nanoparticle design, biomimetic cell membrane-coated nanoparticles, personalized nanomedicine, and microfluidic manufacturing technologies are expected to accelerate the clinical translation despite these limitations. Simplification of the nanoparticle architecture without compromising therapeutic performance could improve reproducibility, reduce manufacturing costs, and facilitate regulatory approval (27).

Conclusion and future perspectives

The development of stimuli-responsive nanocarriers as a new generation of intelligent drug delivery systems can overcome many of the limitations associated with conventional chemotherapy. These nanocarriers enable controlled and site-specific drug release using endogenous stimuli such as acidic pH, redox gradients, enzymes, and hypoxia in conjunction with externally applied triggers such as light, ultrasound, magnetic fields, and temperature. Such programmed delivery can greatly improve therapeutic efficacy and decrease systemic toxicity, thus helping the goals of precision oncology (28–31). The recent progress in the combination of chemotherapy, immunotherapy, gene therapy, and diagnostic imaging into multifunctional nanoplatforms further exemplifies the transformative potential of smart nanomedicine.

However, many challenges remain to be solved for wider clinical use. Major barriers in tumor heterogeneity, variability in EPR effect, manufacturing scalability, regulatory approval pathways, quality control, and long-term biosafety still need to be addressed before commercialization.

The solution to these problems will require the close cooperation of pharmaceutical scientists, materials engineers, oncologists, clinicians, and regulatory agencies to define standardized methods for characterization and clinically relevant evaluation models.

Future studies should focus on the development of simplified but multifunctional nanocarriers with increased targeting accuracy, scalable manufacturing processes, and improved clinical reproducibility. Integration of artificial intelligence for nanoparticle optimization, machine learning-assisted patient stratification, CRISPR/Cas-based gene editing, mRNA therapeutics, biomimetic nanoparticles, and real-time theranostic monitoring are anticipated to define the next generation of precision cancer therapeutics. These advances could transform the management of cancer, opening the door to personalized, safer and more effective treatment strategies that are tailored to the molecular characteristics of individual tumors.

Abbreviations

AI; artificial intelligence
CMC: chemistry, manufacturing and controls
CRISPR: clustered regularly interspaced short palindromic repeats
CSC: cancer stem cell
EPR: enhanced permeability and retention
GMP: good manufacturing practice
HIF: hypoxia-inducible factor
MRI: magnetic resonance imaging
mRNA: messenger ribonucleic acid
NIR: near-infrared
PDT: photodynamic therapy
PTT: photothermal therapy
ROS: reactive oxygen species
siRNA: small interfering ribonucleic acid
TME: tumor microenvironment
UV: Ultraviolet

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Clinical trial

Not applicable.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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