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STIMULUS-RESPONSIVE NANOCARRIERS FOR CANCER THERAPY

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ABSTRACT

Stimuli-responsive nanomedicine has emerged as a promising strategy to improve the efficacy and safety of cancer therapy through controlled and site-specific drug delivery. These smart nanocarriers are designed to respond to endogenous stimuli and exogenous stimuli. On activation, they enable drug release at tumor sites, increasing therapeutic efficacy while reducing systemic toxicity. Recent advances in polymeric, lipid-based, inorganic, and hybrid nanocarriers have expanded their applications in chemotherapy, immunotherapy, gene therapy, and combination treatments. In addition, technologies such as biomimetic nanoparticles, artificial intelligence-assisted nanomedicine design, and multifunctional therapeutic and diagnostic platforms are accelerating the development of next-generation cancer therapeutics. This review highlights the fundamental mechanisms, recent developments, therapeutic applications, and challenges of stimuli-responsive nanocarriers, showing their potential to improve precision oncology and personalized cancer treatment.

KEYWORDS: stimuli-responsive nanocarriers, nanomedicine, cancer therapy, targeted drug delivery, smart nanoparticles, and immunotherapy.

INTRODUCTION

One of the biggest threats to global health, cancer, is predicted to overtake all other causes of death. Poor drug solubility, fast clearance, non-specific drug distribution, systemic toxicity, multidrug resistance, and inadequate drug accumulation at the illness site are some of the

common problems with conventional systemic therapy for cancer, inflammatory diseases, and genetic disorders. To address these problems, targeted drug delivery has evolved into an advanced therapeutic strategy that enables precise control over the location, timing, and manner of drug release. Nanocarriers have promising delivery systems because they improve drug stability, modify pharmacokinetics, increase circulation time, increase solubility, protect sensitive therapeutic molecules, and improve tissue distribution. Approved nanomedicines have shown that nanoscale formulations can increase therapeutic efficacy and reduce toxicity by improving drug distribution instead of developing new drug targets. Clinical examples include liposomal doxorubicin, albumin-bound paclitaxel, liposomal irinotecan, and liposomal cytarabine/daunorubicin.[1] Anyhow, the first generation of nanomedicines depended significantly on passive targeting via the Enhanced Permeability and Retention (EPR) effect.

According to the EPR principle, nanoparticles tend to collect in tumor tissues due to characteristics like leaky blood vessels and compromised lymphatic drainage. Although this effect has been extensively seen in preclinical investigations, its dependability in clinical settings remains debated because human tumors show significant variability in vascular density, blood flow, pressure from surrounding tissues, lymphatic functionality, macrophage behavior, and transport within the interstitial space. Consequently, the accumulation of nanoparticles through EPR can differ greatly among various tumor types, individual patients, and even distinct lesions in the same patient. These challenges suggest that a one-size-fits-all approach to nanocarriers that relies exclusively on passive targeting is unlikely to consistently produce positive clinical results. To overcome these limitations, stimuli-responsive nanocarriers have been developed as advanced drug delivery systems that can react to specific biological or external signals. In contrast to conventional nanocarriers, which mainly rely on passive accumulation, these intelligent systems undergo structural, chemical, or physical changes when exposed to defined stimuli. These responses may include swelling, breakdown, bond cleavage, charge switching, membrane disruption, pore formation, drug release, degradation of the carrier, or phase transitions.[2] The stimuli may arise from the tumor microenvironment, such as acidic pH, high glutathione levels, enzyme overexpression, reactive oxygen species, and hypoxic conditions. Alternatively, external triggers such as localized heat, near-infrared light, ultrasound, magnetic fields, and radiation can be used to initiate drug release. This responsive behavior allows precise control over when and where drugs are released, thereby improving treatment accuracy.[3]

In nanomedicine, nanocarriers are crucial for transporting therapeutic agents, minimizing side effects, streamlining administration, and enhancing treatment results. Among these systems, stimuli-responsive nanocarriers have garnered significant interest due to their ability to infiltrate tissues and deliver therapeutic agents when triggered by internal or external stimuli. In contrast to traditional chemotherapy, these advanced systems can minimize systemic side effects and enable regulated drug release at tumor locations, rendering them extremely beneficial for cancer treatment.[4]

Stimuli-responsive nanocarriers are designed to undergo structural, chemical, or physical changes upon exposure to stimuli. This reactivity allows for accurate spatiotemporal regulation of drug release and improves therapeutic efficacy.

Despite their promising potential, the clinical application of stimuli-responsive nanocarriers remains challenging. Numerous systems excel in controlled lab settings but struggle to replicate those outcomes in the intricate human body. In Vivo, the stimuli that trigger responses are frequently diverse, changing, and at times inadequate to completely activate the carriers, constraining their therapeutic effectiveness. This review aims to provide a comprehensive summary of stimuli-responsive nanocarriers used in cancer treatment. The review encompasses the design principles, action mechanisms, and categorization of nanocarriers that respond to internal stimuli like pH, redox states, enzymes, reactive oxygen species, and hypoxia, as well as external stimuli such as light, temperature, ultrasound, magnetic fields, and radiation.[4]

1.1 Fundamentals of Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers play an important role in nanotechnology and disease treatment.

They are designed to mimic the natural responses of cells and living organisms to various physical and chemical stimuli present in their environment. The implementation of this approach has driven significant progress in biomedical technologies, enabling precise drug delivery, site- specific release of bioactive compounds, enhanced imaging and diagnostic capabilities, and integrated theranostic platforms.

While conventional nanotherapeutics have shown substantial therapeutic potential in preclinical and clinical investigations, their ability to achieve targeted and site-specific drug

delivery remains limited. The major Drawback of traditional nanocarriers is the release of therapeutic agents into healthy tissues, which can result in toxicity. These intelligent nanocarrier systems are designed to recognize and respond to disease-associated physiological and biochemical triggers, including pH gradients, temperature fluctuations, and enzyme overexpression, thereby enhancing therapeutic precision and efficacy.[2]

1.2 Core Design Principles

To build a functional stimuli-responsive nanocarrier, four main principles must be balanced:

- **Colloidal Stability:** The carrier must remain structurally stable in systemic circulation, resisting protein adsorption and immune clearance (e.g., via PEGylation) during transit.
- **Responsiveness (The "Trigger" Sensitivity):** The linker or matrix must possess an optimal threshold. It needs to be stable in physiological conditions (pH 7.4, 37° C) but rapidly transition upon encountering the targeted stimulus.
- **Biocompatibility & Biodegradability:** The building blocks (such as lipids, biodegradable polymers, or mesoporous silica) must be non-toxic and easily cleared by the body after their cargo is released.

Active or Passive Targeting: Carriers are frequently functionalized with specific ligands (antibodies, peptides, or aptamers) to ensure they accumulate at the disease site before the stimulus is applied.[2][5]

1.3 Mechanism of Action

Stimuli-responsive nanoparticles remain stable and inactive while circulating in the bloodstream, thereby preventing premature drug release and reducing adverse effects on healthy tissues. Once they accumulate at the tumor site, they respond to endogenous triggers such as acidic pH or elevated enzyme expression.

pH-responsive nanocarriers are designed to respond to the acidic conditions characteristic of the tumor microenvironment, where protonation of ionizable groups or cleavage of pH-sensitive linkages induces carrier disassembly and controlled drug release. In contrast, enzyme-responsive nanoparticles leverage the elevated activity of tumor-specific enzymes, especially matrix metalloproteinases (MMPs), to trigger degradation of protective barriers or cleavage of peptide-based linkers. These processes promote localized drug activation, enhance intratumoral penetration, and improve therapeutic efficacy while minimizing off-target effects.

As a result, these nanoparticles achieve selective activation within tumor tissues, increasing drug availability at the target site, improving tumor penetration, and reducing systemic toxicity. This targeted mode of action highlights their significant potential as an advanced strategy for cancer therapy.[5]

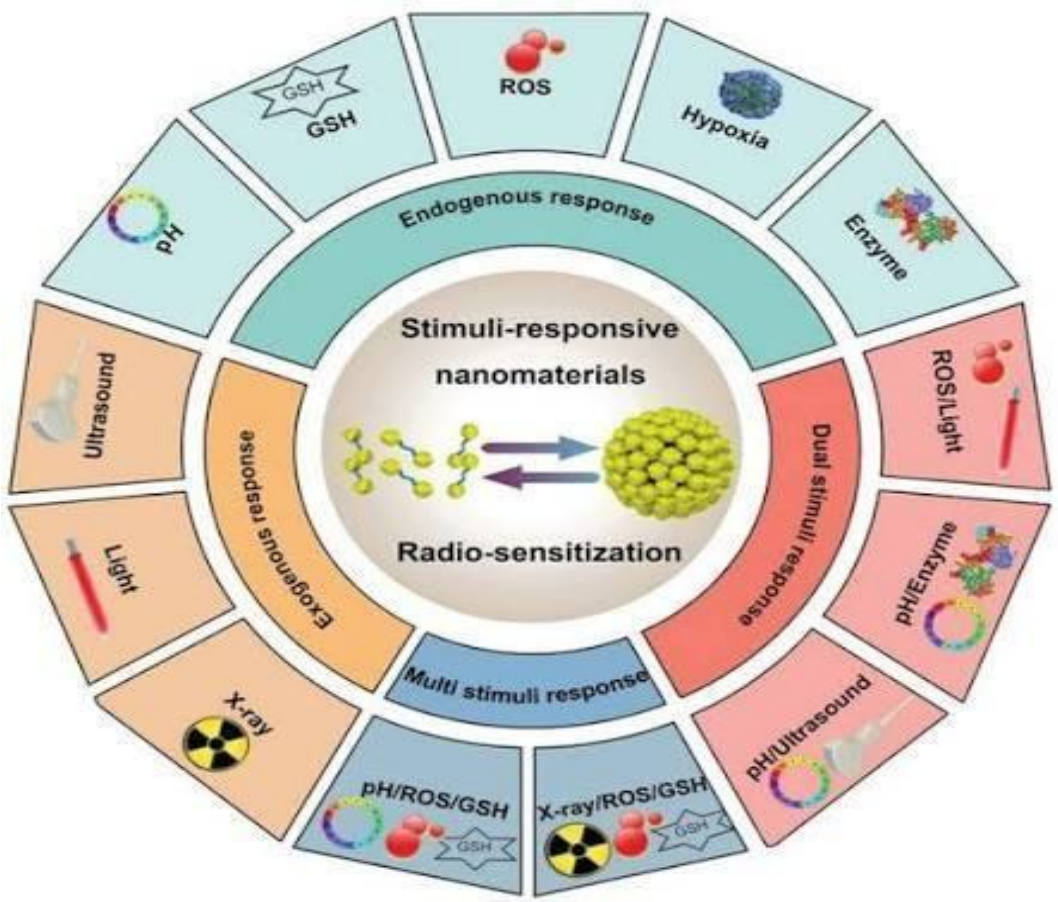

FIG. 1: Exogenous and endogenous stimuli for drug delivery systems.

2. Endogenous Stimuli

Biochemical traits that are either naturally occurring in tumors or produced during immune responses are the source of endogenous stimuli. These include changes in oxygen availability, pH, redox conditions, and enzyme expression. In nanomedicine, these intrinsic variables have been extensively used to precisely control drug delivery and activation in both space and time. Acidic pH, high enzyme concentrations, reducing conditions, and tumor hypoxia are some of these stimuli that have been widely used to release or activate immunotherapeutic drugs.[6]

2.1 Nanoparticles Activated by pH

One of the most popular methods for delivering targeted cancer drugs is pH-responsive nanoparticles. Because of poor blood circulation and increased lactic acid generation by

cancer cells, the tumor microenvironment (TME) is more acidic than normal tissues. Even lower pH levels are found in intracellular spaces like lysosomes and endosomes. These acidic environments are powerful catalysts for the activation of nanoparticles.

These nanoparticles are made with acid-sensitive linkers or ionizable groups that react to low pH by releasing their payload or altering their structure. Drugs can therefore be released precisely at the tumor site with the least amount of impact on healthy tissues.[6]

2.2 Nanoparticles Activated by Redox

For targeted drug delivery, redox-activated nanoparticles make use of the increased glutathione (GSH) levels found in tumor cells. These nanoparticles are made with GSH-sensitive disulfide bonds, which break down in the tumor environment to release therapeutic agents under controlled conditions while remaining stable in healthy tissues.

Numerous redox-responsive nanoparticles have been created for immunotherapy and cancer treatment. For instance, by encouraging immune responses and gene silencing, nanoparticles containing cytokines, anticancer medications, and siRNA have demonstrated successful tumor suppression. To improve tumor removal, some systems have also been coupled with CAR-T cell therapy.

Redox-responsive nanoparticles are frequently combined with near-infrared (NIR) light-responsive therapies to increase therapeutic efficacy.

These multipurpose systems have the ability to inhibit tumor growth, induce tumor cell death, boost immune responses, and deliver medications all at once.

Overall, by taking advantage of the aberrant redox environment of tumors, redox-activated nanoparticles offer a targeted and effective approach to cancer treatment.[7]

2.3 Nanoparticles Activated by Enzymes

To achieve targeted drug release, enzyme-activated nanoparticles employ enzymes that are overexpressed in tumors. Matrix metalloproteinases (MMPs), caspases, hyaluronidases, and cathepsins are frequently used enzymes for this purpose. Therapeutic agents are released directly into the tumor microenvironment when these enzymes degrade particular parts of the nanoparticles.

One of the most extensively researched of these enzymes is MMP-2. When exposed to the enzyme, nanoparticles with MMP-2-sensitive linkers can release immune-modulating medications like PD-L1 and IDO inhibitors, boosting antitumor immune responses. To achieve more effective drug release and therapeutic effects, some systems combine MMP-2 activation with other stimuli, such as acidic pH and high glutathione (GSH) levels.

Additionally, chemotherapy and immunotherapy have been combined with enzyme-responsive nanoparticles. These multipurpose systems enhance tumor destruction, boost immune responses, and improve drug delivery. For instance, immunosuppressive M2 macrophages were successfully transformed into antitumor M1 macrophages by pH-gated nano systems containing the TLR7/8 agonist imiquimod (IMQD), enhancing immune activation and tumor control.

All things considered, enzyme-activated nanoparticles are promising platforms for cancer immunotherapy and combination therapies because they use tumor-associated enzymes to provide selective and controlled drug release.[8][9]

3. External Stimuli

External stimuli like light, magnetic fields, or ultrasound can activate exogenous stimulus-responsive nanoparticles. Controlled drug release at the intended location and time is made possible by these stimuli. Additionally, they can boost the immune system's ability to fight cancer and destroy tumor cells.

3.1 The Magnetic Field

External magnetic fields are used by magnetic field-responsive nanoparticles to enhance cancer immunotherapy and targeted drug delivery. The ability to direct and focus therapeutic nanoparticles at particular tumor sites is a key benefit of this strategy, improving treatment efficacy while lowering side effects.

For instance, magnetic nanoparticles have been affixed to T cells and natural killer (NK) cells, increasing their anticancer activity and enabling them to accumulate more effectively at tumors under a magnetic field. When directed by external magnets, magnetic nanocarriers containing medications like doxorubicin have also demonstrated enhanced tumor accumulation and drug release.

In addition, magnetic nanoparticles can be used for imaging, observing immune responses,

and increasing drug penetration into deep tumor tissues. Some magnetic systems can trigger cancer cell death, stimulate immune activation, and enhance the effectiveness of immunotherapy.[10]

3.2 Light-Responsive Nanoparticles

Light-responsive nanoparticles regulate drug release and cancer treatment by using light, particularly near-infrared (NIR) light. The ability to precisely control the location, timing, and intensity of treatment is a key benefit of this strategy, as it reduces harm to healthy tissues.

When exposed to light, these nanoparticles can release medications, produce heat, or create reactive oxygen species (ROS), which can destroy tumor cells and boost immune responses.

Photothermal therapy, photodynamic therapy, immunotherapy, and controlled drug delivery have all made use of light-triggered systems.

Furthermore, light-responsive nanoparticles can produce long-term antitumor immune memory, enhance tumor penetration, stimulate immune cells, and prevent tumor growth and metastasis.[7]

3.3 Nanoparticles Responsive to Ultrasound

Ultrasound waves are used by ultrasound-responsive nanoparticles and microbubbles to enhance cancer treatment. By increasing blood vessel permeability, ultrasound can improve the delivery of medications, immune cells, and therapeutic agents to tumors.

Additionally, tumor cells can be damaged by microbubble cavitation, which releases tumor antigens that activate antigen-presenting cells and trigger immune responses. Furthermore, under ultrasound guidance, oxygen-loaded microbubbles can directly deliver oxygen to hypoxic tumors, increasing the efficacy of cancer treatments.

All things considered, ultrasound-responsive systems offer a targeted, non-invasive method for improving medication delivery and cancer immunotherapy.[6]

4. Various Polymeric Nanocarriers That Respond to Stimuli

In intricate tumor environments, single stimulus-responsive nanocarriers frequently encounter difficulties. In order to respond to two or more triggers, such as pH, redox conditions (GSH), temperature, ROS, enzymes, light, or UV irradiation, researchers have created multiple

stimuli-responsive polymeric nanocarriers. These systems offer better tumor targeting, more accurate drug release, and increased therapeutic efficacy.

pH/redox dual-responsive nanoparticles, which have acid-sensitive and disulfide linkages that react to the acidic tumor environment and increased glutathione levels, are a typical example.

Anticancer medications can be released under controlled conditions within tumor cells thanks to these systems.

Additionally, scientists have created light- and ROS-responsive polymeric micelles, in which near-infrared (NIR) radiation produces heat and reactive oxygen species that cause nanoparticle degradation and quick drug release. For better treatment results, these systems combine photothermal or photodynamic therapy with chemotherapy.[1]

5. Nanomedicines

Nanomedicines are nanometer-scale (1 to 100(0) nm) formulations aimed at diagnosing and treating diseases, including cancer.

Table 1: Nanomedicines in Clinical Cancer Care.

Product	Drug	Nanocarrier Type	Application
ADI-PEG 20	Arginine deaminase	Polymeric	Hepatocellular carcinoma
Doxil	Doxorubicin	Polymeric/Liposomal	Leukemia, lymphoma, carcinoma
AP5280	Platinum	Polymeric	Solid tumors
DepoCyt	Cytarabine	Liposomal	Lymphomatous meningitis
MAG-CPT	Camptothecin	Polymeric	Solid tumors
Visudyne	Verteporfin	Liposomal	Macular degeneration
Oncaspar	L-Asparaginase	Polymeric	Acute lymphoblastic leukemia
PNU166945	Paclitaxel	Polymeric	Solid tumors
Lipoplatin®	Cisplatin	Liposomal	Non-small cell lung cancer
XMT-1001	Camptothecin	Polymeric	Gastric and lung cancer
Onco-TCS	Vincristine	Liposomal	Relapsed non-Hodgkin lymphoma
OSI-211	Lurtotecan	Liposomal	Head, neck, and ovarian cancer
SPI-077	Cisplatin	Liposomal	Head, neck, and lung cancer

6. BARRIERS

6.1 Biological Barriers

Tumor heterogeneity, macrophage uptake, high interstitial fluid pressure, and poor diffusion within tumor tissues are some of the challenges nanoparticles must overcome to reach tumors.

Additionally, the reticuloendothelial system (RES) and the kidneys' quick clearance lessen the buildup of nanoparticles at tumor sites.

6.2 Difficulties in Translation

Only a small number of nanomedicines are successfully used in clinical settings, even though many exhibit excellent results in laboratory studies. Their translation from research to clinical practice is limited by differences between human tumors and experimental models, as well as challenges in large-scale production.

6.3 Regulatory Obstacles

High research and development costs, complicated manufacturing procedures, unclear regulatory guidelines, and safety concerns all hinder the development and approval of nanomedicines.

Commercialization is difficult because of these factors.[11]

CONCLUSION

Stimuli-responsive nanomedicine has emerged as a transformative approach in cancer therapy by enabling precise, targeted, and controllable drug delivery while minimizing systemic toxicity.

The evolution from passive targeting strategies to intelligent, immune-integrated nanocarriers represents a significant paradigm shift in oncology, where the immune system is no longer avoided but actively harnessed for therapeutic benefit. Nanocarriers designed to respond to tumor-specific biological signals or external stimuli offer enhanced tumor penetration, improved drug bioavailability, and the ability to overcome multidrug resistance. Moreover, immune cell–targeted nanoplatforms provide the additional advantage of inducing long-term antitumor immune memory, thereby reducing the risk of disease recurrence.

Despite these promising advances, challenges such as biosafety concerns, large-scale manufacturing, regulatory approval, and clinical translation remain significant barriers. However, continuous progress in nanotechnology, immune engineering, and personalized medicine is steadily bridging these gaps. With further optimization and interdisciplinary collaboration, stimuli-responsive and immuno-nanomedicine strategies are expected to significantly expand the current anticancer arsenal, paving the way for safer, more effective,

and patient-specific cancer therapies in the future.

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