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Research Progress on Responsive Formulations for Cancer Prevention and Early Diagnosis

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Abstract

Malignant tumors have become an urgent public health challenge worldwide. A wealth of clinical evidence indicates that intervening during the precancerous stage is the most cost-effective means of reducing the risk of cancer and improving patients' long-term survival rates. Conventional cancer prevention formulations generally suffer from shortcomings such as insufficient targeting capability, short retention time at the lesion site, and low bioavailability in vivo. Furthermore, pharmacological prevention and lesion diagnosis are not integrated, making it difficult to meet the practical clinical needs for targeted intervention in precancerous lesions [6]. Stimulus-responsive (smart) formulations can recognize characteristic signals in the microenvironment of precancerous lesions and early-stage tumors, including pH changes, elevated levels of reactive oxygen species, elevated glutathione levels, high expression of specific proteases at the lesion site, and specific enzymes produced by gut microbiota. By responding to microenvironmental triggers to achieve localized, targeted drug release at the lesion site while simultaneously activating imaging signals, these formulations have opened up new avenues for early cancer prevention and early screening [16]. This article reviews the recent advances in stimulus-responsive formulations for cancer prevention and early diagnosis. It discusses targeted delivery systems for small-molecule chemopreventive agents, oral formulations responsive to the intestinal microenvironment, and mucosal delivery systems for the prevention and control of epithelial cancers. It also summarizes microenvironment-responsive imaging probes, biomarker-activated theranostic prodrugs, and nanosensor-based diagnostic technologies for body fluid samples, and introduces multifunctional nanoplatforms that combine preventive and diagnostic functions. Finally, it analyzes the practical challenges associated with biosafety, large-scale production, and clinical translation [4], and discusses future directions for the development of next-generation smart responsive formulations, with the aim of informing the development of novel formulations for cancer prevention and early diagnosis.

Keywords

stimulus-responsive formulations; nanodelivery; cancer chemoprevention; precancerous lesions; early cancer diagnosis; theranostics

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1. Introduction

1.1 The Clinical Value of Cancer Prevention and Early Intervention

Malignant tumors continue to pose a threat to human life and health, and global cancer incidence and mortality rates remain at high levels. Most malignant tumors do not develop overnight but undergo a lengthy, multistep process, which may involve stages ranging from precancerous lesions and early-stage cancer to local invasion and distant metastasis. The progression from precancerous lesions to invasive cancer often takes several years or even more than a decade, and this stage represents a critical window for intervention. If intervention is carried out during this window, there is an opportunity to halt or even delay the carcinogenesis process, thereby reducing the likelihood of malignant tumor development at its source [18].

At present, most clinical treatment regimens are targeted at patients with mid- to late-stage tumors. Once a tumor becomes invasive or metastasizes, surgery, radiation therapy, and chemotherapy are often highly invasive and associated with considerable adverse effects, with 5-year survival rates often remaining low for many advanced cancers. In contrast, implementing chemoprevention and immunoprevention strategies for high-risk populations together with early cancer screening and intervention before lesions progress to invasive cancer can reduce the incidence of malignant tumors. For typical precancerous lesions such as colorectal adenomas, oral leukoplakia, and cervical intraepithelial neoplasia, early identification and localized intervention can significantly reduce the risk of cancer progression. In contrast, highly malignant tumors such as pancreatic and lung cancers exhibit very subtle early symptoms, and most patients are already in advanced stages by the time of diagnosis. If detection and intervention can be carried out during the precancerous stage, it may greatly improve the management of these tumors. Therefore, establishing a established, integrated technical system for cancer prevention and early diagnosis holds significant clinical significance for cancer control and prevention, and is also a hot research topic at the intersection of pharmacy, materials science, and oncology [18].

1.2 Practical Limitations of Conventional Formulations in Cancer Prevention and Early Diagnosis

Drugs and active substances investigated for cancer chemoprevention include small molecules such as nonsteroidal anti-inflammatory drugs, natural polyphenols, and vitamin derivatives. These may exert their effects through anti-inflammatory, antioxidant, and immune-modulating mechanisms and are being explored for use in preventing cancer development in high-risk populations. However, conventional formulations present several challenges that limit their clinical application.

After systemic administration, small-molecule drugs often show limited selective accumulation in target tissues and are widely distributed in normal organs. Long-term use may cause gastrointestinal injury and adverse effects on liver and kidney function. Furthermore, small molecules are easily metabolized and degraded by enzymes in the body, resulting in drug may undergo rapid enzymatic metabolism, preventing drug concentrations at lesion sites from reaching effective levels thereby significantly reducing their preventive efficacy [23].

For gastrointestinal tumors, chemopreventive drugs may be released prematurely from conventional oral formulations and undergo degradation in the stomach and upper gastrointestinal tract, making it difficult for them to accumulate at target sites such as the colon and thus limiting their ability to act locally on intestinal precancerous lesions. Drug formulations administered locally to mucosal surfaces are continuously washed away by mucus, resulting in limited drug retention. Drug penetration through the dense mucosal barrier is also limited. These formulations therefore have limited efficacy against precancerous epithelial lesions, including oral leukoplakia and those affecting the bladder, cervix, and other body cavities. [19].

At the level of early diagnosis, ordinary contrast reagents and fluorescent probes lack tumor tissue selectivity, and the signal discrimination between normal tissues and lesions is weak. The sensitivity of routine reagents for body fluid detection is insufficient, and early tumor markers with very low content in blood and urine are difficult to detect, with a high risk of false negative [26]. In addition, the traditional model split preventive drug administration and lesion detection into two sets of independent programs, which cannot achieve “synchronous detection and intervention”, and the clinical process is cumbersome, which is not conducive to the long-term follow-up management of high-risk populations. In general, the shortcomings of

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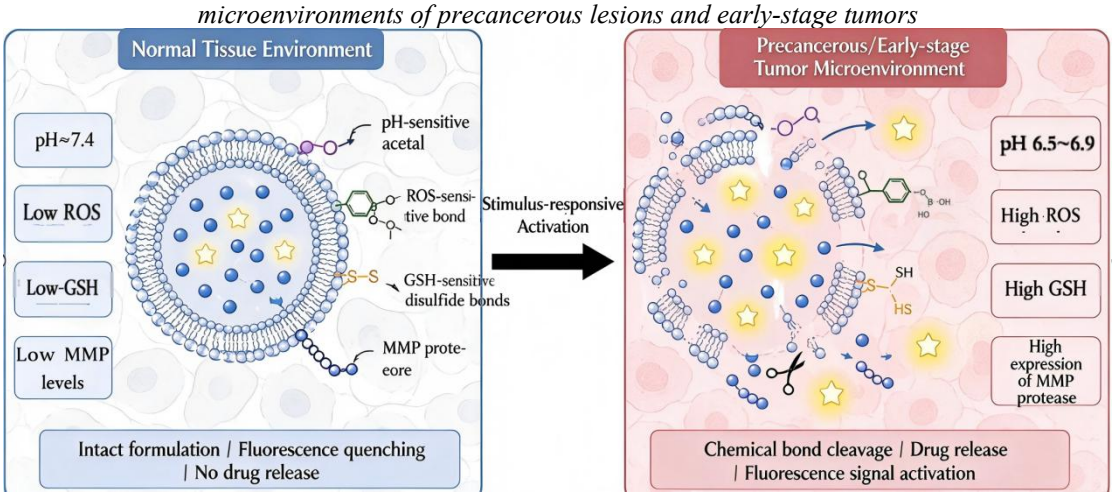
traditional agents are prominent in targeted enrichment, controlled release at lesion sites, and multifunctional coupling, and it is urgent to develop new intelligent agents to break through the above bottlenecks [6].

1.3 Basic Characteristics of Stimulus-responsive Preparations

Stimulus-responsive agents are also often called intelligent agents. Such systems can recognize in vivo and in vitro microenvironmental signals, change their own structure accordingly, and realize drug release, fluorescence signal activation and other functions. In recent years, they have been widely used in tumor prevention, diagnosis and treatment research [6]. According to their source, trigger signals can be divided into exogenous stimuli and endogenous stimuli. Temperature, light and magnetic fields are exogenous stimuli, which need to be applied by external equipment. Endogenous stimulation relies on the biochemical characteristics of precancerous lesions and early tumors without external equipment intervention, which is more suitable for in situ lesion identification and controlled drug release in vivo, and is also the mainstream idea for the design of formulations for early prevention and early diagnosis of tumors [16].

Compared with normal tissues, the microenvironment of precancerous lesions and early tumors shows a series of characteristics: tissue pH shifts to a weakly acidic range (pH 6.5–6.9), the level of reactive oxygen species (ROS) increases, the concentration of intracellular glutathione (GSH) increases, and the expression of matrix metalloproteinases such as MMP2 and MMP9 increases. Some tissues also have characteristic signals such as specific enzymes of intestinal flora [7]. Researchers construct responsive formulations by introducing various sensitive chemical bonds into carriers, probes, or prodrug molecules. Acetal bonds, imine bonds and boronate ester bonds are mostly used in pH-responsive systems, and these bonds will be broken to release the active components under acidic conditions. Phenylboronic ester, thioketal and other groups are used for ROS response. The disulfide bond is broken in the reducing environment with a high concentration of GSH. The enzyme response system depends on the polypeptide substrate sequence, which is recognized and cleaved by the highly expressed protease of the lesion, and then activates the probe or releases the drug [20].

Figure 1: Schematic diagram illustrating the mechanism of action of a multi-stimulus-responsive formulation in the microenvironments of precancerous lesions and early-stage tumors



As shown in Figure 1, in a normal tissue microenvironment (pH ~7.4, low ROS levels, low GSH concentrations, and low MMP levels), the nanoformulation remains intact, with its fluorescence quenched and no drug released. In the microenvironments of precancerous lesions and early-stage tumors (pH 6.5–6.9, high ROS levels, high GSH concentrations, and high MMP levels), stimuli-sensitive chemical bonds are cleaved, triggering drug release and activation of the fluorescent signal.

Agents that rely on only a single signal trigger are prone to be disturbed by the physiological environment in vivo, and their specificity is often insufficient. In order to address this defect, multi-stimuli-responsive preparations have been gradually developed, which have a “logic gate”-like recognition mechanism. Only when two or more signals characteristic of lesions exist at the same time will the preparations be activated, which significantly reduces the risk of non-specific activation in normal tissues and improves the specificity and safety of preparations [13]. Nanocarriers are the most commonly used platform for stimulus-responsive preparations, covering various types such as liposomes, polymer nanoparticles, inorganic nanoparticles, and

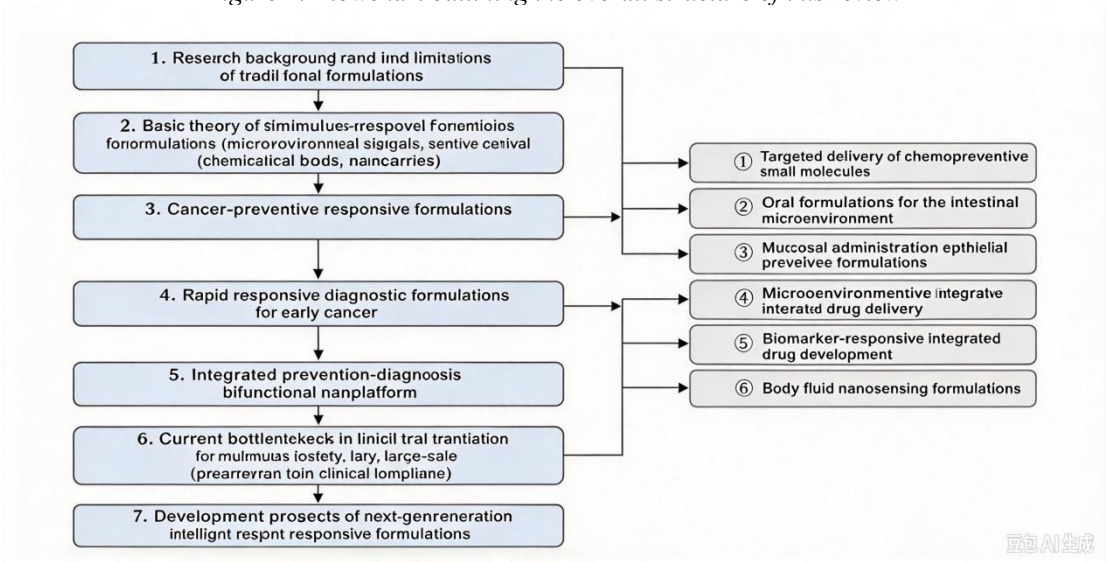
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host-guest assembled nanostructures [14]. Nano-carriers can not only protect active molecules from enzymatic degradation, but also achieve targeting through surface modification, and can also be loaded with drugs, fluorescent molecules, immune adjuvants and other components at the same time, providing a structural basis for the realization of multifunctional integration of prevention and diagnosis [23].

1.4 Approach to This Review and Scope of the Literature Search

This article reviews the research progress of stimulus-responsive agents in the direction of tumor prevention and early diagnosis. The literature retrieval databases included Web of Science, PubMed, CNKI and Wanfang database. The Chinese and English search keywords were set as stimulus-responsive preparation, nano-delivery, cancer chemoprevention, precancerous lesions, early diagnosis of tumors, tumor microenvironment-responsive probe, theranostics, mucosal nano-preparation, intestinal microflora-responsive nanomedicine, etc. The time span of literature screening was mainly 2019–2026, with priority given to high-quality reviews and frontier original research papers, while also considering relevant results in domestic Chinese core journals.

Figure 2: Flowchart outlining the overall structure of this review



As shown in Figure 2, this flowchart illustrates the logical structure of the review. Starting from the research background and the limitations of traditional formulations, it sequentially introduces preventive formulations, early-diagnosis formulations, and integrated dual-function formulations. It then analyzes existing bottlenecks and finally proposes future directions.

From the research background and the defects of traditional preparations, this article sorted out the responsive preparations for cancer prevention, responsive preparations for early diagnosis, and prevention–diagnosis integrated nano platform. Then, the bottleneck encountered in the clinical translation of agents was analyzed, and the development direction of the next generation of intelligent responsive agents was discussed. In this paper, the responsive agents for cancer prevention are divided into targeted delivery of small molecules for cancer chemoprevention, oral preparations in the intestinal microenvironment, and mucosal delivery agents for epithelial cancer. Early diagnosis preparations include microenvironment-responsive imaging probes, marker-activated integrated prodrugs, and body fluid nanosensing preparations. Then, the bifunctional nano platform for both prevention and intervention was described. Finally, the difficulties in biological safety, large-scale preparation and clinical translation are discussed, and views on the subsequent research and development direction are put forward, hoping to provide reference for the development of intelligent agents for early prevention and early diagnosis of tumors [4].

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2. Research Progress on Stimulus-Responsive Formulations for Cancer Prevention

2.1 Targeted Delivery Formulations for Small-Molecule Chemopreventive Agents

Chemopreventive small molecules include non-steroidal anti-inflammatory drugs, vitamin derivatives, natural polyphenols, etc. These drugs are used to block carcinogenesis in high-risk populations, but their long-term application will encounter systemic toxic side effects and insufficient bioavailability. The emergence of nanotechnology provides a new path for precise intervention in precancerous lesions [9]. Nano-carriers can co-load antigens, immune adjuvants and chemopreventive drugs to ensure the simultaneous delivery of multiple active components to antigen-presenting cells (APCs), avoid the rapid diffusion of active molecules in the body, and improve the enrichment efficiency of components in draining lymph nodes.

Delivery systems such as liposomes, polymeric nanoparticles, and inorganic nanoparticles not only protect small-molecule drugs from enzymatic degradation but also enable active targeting of specific tissues through surface modification [10]. For example, dendritic cell (DC)-targeted nanodelivery systems and artificial antigen-presenting cell (APC) nanovaccines developed for high-risk populations activate the body's immune surveillance capabilities during the precancerous stage by mimicking the structure of natural immune synapses [10]. This nanotechnology-mediated immunoprevention strategy can interrupt the chain of tumor initiation and progression at an early stage and marks a shift in cancer prevention research from traditional systemic administration toward a new approach based on precise immune intervention [9].

Commentary: However, most findings in this area have been validated only in animal models. Further experimental data are needed to clarify differences in efficacy across precancerous lesion models and to establish appropriate dose ranges.

2.2 Oral Cancer-preventive Preparations Responsive to Intestinal Microenvironment

The occurrence of colorectal cancer and other gastrointestinal tumors is highly related to the disorder of the intestinal microenvironment. Common oral cancer-preventive agents are prone to degradation and early release in the gastrointestinal tract, which makes it difficult to maintain an effective drug concentration in colon lesions. In view of this pain point, the intestinal microenvironment-responsive oral nano-preparations have been extensively studied [11].

Some studies have constructed a microbiota-responsive nano-amifostine system (CS/PEC-AMF NPs). After coupling amifostine and pectin, the outer layer is coated with chitosan to achieve release triggered by both pH and intestinal flora enzymes [15]. After the nanoparticles reach the colon, intestinal flora-specific enzymes degrade the pectin shell and release amifostine locally, which exerts anti-inflammatory and radioprotective effects. Animal experiments confirmed that the preparation could alleviate radiation-induced intestinal injury, repair intestinal epithelium and protect intestinal stem cells. The results of metagenomic and metabolomic tests showed that the preparation could help restore the diversity of intestinal flora, promote the production of short-chain fatty acids, and induce the polarization of macrophages to the anti-inflammatory M2 phenotype. In the orthotopic colorectal cancer animal model, this system can inhibit tumor growth and prolong the survival time of model animals [15].

In addition to drug delivery, engineered oral commensal bacteria-based nanovaccines use intestinal commensal bacteria as a carrier to activate mucosal local immunity through oral administration, and further induce systemic anti-tumor immune responses, providing a new idea for mucosal immune prevention of gastrointestinal tumors [5].

Commentary: These oral formulations are highly dependent on the state of the gut microbiota. Interindividual differences in the microbiota can directly alter drug release behavior, which is a challenge that must be addressed in subsequent clinical translation.

2.3 Mucosally Administered Formulations for Epithelial Cancer Prevention

Most precancerous lesions of epithelial origin such as oral leukoplakia and cervical intraepithelial neoplasia, as well as most early cancer lesions of the digestive tract, are confined to the mucosa. Mucosal administration preparations can directly form a drug depot at the lesion site, avoid the first-pass effect in the liver, and reduce the toxic and side effects caused by systemic administration [19].

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For oral leukoplakia, a host-guest-assembled trans-mucosal spherical nucleic acid (SNA) delivery system has been studied and developed [21]. The spherical nucleic acid has a special three-dimensional structure, and the outer layer is densely packed with oligonucleotides, which can resist nuclease degradation and help drugs penetrate the mucosal barrier. The efficient retention and delivery of immunomodulatory drugs in oral mucosa and local immune intervention for precancerous lesions are achieved by host-guest interaction [21]. In the prevention and control of bladder cancer, mucoadhesive and tissue-penetrating nanomedicine can prolong the residence time of the preparation on the mucosal wall and penetrate into the depth of the lesion to achieve combined chemotherapy and immune intervention [24]. The above-mentioned mucosa-responsive preparations fully consider the physiological barrier characteristics of epithelial tissue, and provide intervention strategies with translational potential for local block of epithelial precancerous lesions [24].

3. Research and Development of Early Cancer Rapid-response Diagnostic Agents

3.1 Tumor Microenvironment Signal-responsive Fluorescent/contrast Probe Preparation

The complexity and heterogeneity of the tumor microenvironment are a major obstacle to early detection of cancer [18]. Compared with normal tissues, the lesions will be characterized by weak acidity, increased ROS and high expression of GSH [16]. Intelligent responsive probes developed based on such endogenous signals can achieve the “in situ fluorescence activation” imaging effect at the lesion location [7].

The pH-responsive probes rely on acid-sensitive linkers such as imine bonds, acetal bonds, and boronate ester bonds to break and release fluorescent groups in an acidic microenvironment. Thioketal and phenylboronic ester groups were introduced into the ROS-responsive probe. GSH-responsive probes utilize the cleavage of disulfide bonds in a highly reducing environment to activate fluorescent signals [7]. Single-signal-responsive probes are prone to non-specific activation, while multi-responsive probes learn from the logic gate recognition idea and identify a variety of microenvironmental signals at the same time, which significantly improves the probe recognition specificity [13]. For pancreatic cancer, which has dense stroma and is difficult to image, the MRI nano strategy based on superparamagnetic iron oxide nanoparticles (SPIONs) relies on the microenvironmental signal response to detect PanIN precancerous lesions [1]. Near-infrared fluorescence–MRI multimodal probes further take into account the imaging sensitivity and tissue penetration depth.

3.2 Integrated Prodrug–Diagnostic Preparations Activated by Early Cancer Markers

In the field of early cancer screening, the integration of diagnosis and intervention functions in the same molecule or on the same nano platform, that is, the integration of diagnosis and treatment, is a current research hotspot. Stimulus-responsive peptides showed prominent advantages in this direction [20].

Take the MMP enzyme-responsive polypeptide probe as an example: it uses high expression of MMP2/MMP9 proteases in the lesion as a trigger condition. After the probe reaches the early lesions, it is specifically cleaved by the enzymes, and the fluorophore is activated to realize the visualization of lesions, and at the same time, the active prodrug is released to exert the intervention effect. A single system can complete the detection and intervention simultaneously [8]. Depending on the flexible design of polypeptide sequences, responsive prodrug probes can be customized for different tumor markers (proteases, receptors, and nucleic acid sequences) to track and block the process of carcinogenesis at the molecular level [17].

Comment: At present, most of the studies on this type of polypeptide probes focus on animal models. The non-specific cleavage by enzymes in vivo will bring the risk of false positives, and the molecular design needs to be further optimized.

3.3 Responsive Nanosensing Preparation for Rapid Testing of Body Fluids

Liquid biopsy using body fluid samples such as blood, urine and saliva is a non-invasive or minimally invasive detection method, which is very suitable for large-scale cancer high-risk population screening [26]. In order to achieve highly sensitive and rapid detection of trace tumor markers in body fluids, researchers have developed a series of responsive nanosensing agents.

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For example, a ROS-responsive fluorescent sensor array is used to complete tumor recognition with the help of pH-regulated multicolor gold nanoclusters [12]. The system combined the fluorescence characteristics of gold nanoclusters and ROS-sensitive groups to output multi-color fluorescence signals in simulated tumor microenvironment conditions. With the help of a pattern recognition algorithm, the fluorescence pattern was analyzed to distinguish normal samples from tumor samples, and a high-sensitivity sensing scheme was provided for rapid testing of body fluids [12]. In addition, smart nano platforms combine functional nanomaterials with biological recognition elements, which can simultaneously detect exosomes, circulating tumor DNA (ctDNA), RNA, protein and other markers. Artificial intelligence and machine learning algorithms are introduced to analyze complex body fluid data to further improve the accuracy of early diagnosis and disease prediction ability [26].

4. Integrated Preparation: Dual-function System for Both Prevention and Early Intervention

4.1 Diagnosis–Prevention Dual-drug-loaded Nanocarriers

The traditional model of cancer prevention and control often separates prevention, diagnosis and treatment from each other. The goal of integrated preparations is to build a multi-functional intelligent platform to integrate multiple functions. Taking lung cancer prevention and control as an example, both early lesion identification and local immune regulation are indispensable.

The smart nano platform integrates nanomaterials and biological recognition components to detect exosomes, DNA, RNA, protein and other markers to complete early recognition. On the other hand, targeted immune activation can be achieved through checkpoint inhibition, nanovaccines, and microenvironment reprogramming, and the platform can simultaneously play a role in detection and preventive intervention [22]. Dual-drug-loaded nanocarriers can simultaneously carry imaging probes and immunomodulatory agents such as STING agonists and immune checkpoint inhibitors [22]. When the tumor microenvironment or early cancer markers are identified, the components are released by the carrier in the lesion in situ, which not only completes the visualization and confirmation of the lesion, but also initiates immune clearance at the location of precancerous and early lesions, forming a closed-loop mode of "intervention upon recognition" to improve the timeliness and accuracy of clinical intervention [22].

4.2 In Situ Responsive Prodrug Systems for Prevention and Treatment

To enable continuous monitoring and immediate interruption of carcinogenesis, in situ responsive prodrug systems have been developed. Many of these systems incorporate self-amplifying positive feedback loops that rely on stimuli in the tumor microenvironment to achieve cascade drug release and signal amplification.

Some studies have reported a pH/ROS dual-responsive self-amplifying ROS-replenishing delivery system: the high ROS environment of the lesion promotes the cleavage of the thioketone bond, exposing the PBAE groups, which undergo protonation in response to the local acidic environment. Relying on the ROS positive feedback amplification mechanism, the intracellular drug release efficiency and ROS generation are improved, and the synergistic effect of chemotherapy and ferroptosis is achieved, while retaining the imaging tracer ability [25]. To address the challenge of cGAS–STING pathway activation, pH-responsive nanocarriers such as ZIF-8 can co-deliver drugs that damage telomeric DNA and TIM-3 blocking antibodies to release DNA fragments at the tumor site to activate the cGAS–STING pathway and relieve immunosuppression. The adaptive immune response is initiated [3]. This kind of dual-responsive, self-amplifying prodrug system integrates prevention, diagnosis and intervention into the same system [3].

The triggering signals, routes of administration or detection methods, core functions, and applicable lesion types for various microenvironment-responsive formulations are listed in Table 1.

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Table 1: Classification and Characteristics of Microenvironment-Responsive Formulations for Precancerous Lesions and Early-Stage Tumors

Formulation Categories	Primary Triggering Signals	Route of Administration	Core Functions	Applicable Lesion Types
Targeted delivery formulations for small-molecule chemopreventive agents	pH, ROS, GSH	Intravenous / local injection	Chemoprevention, immune activation	Precancerous lesions of multiple tissue origins
Oral formulations responsive to the intestinal microenvironment	pH, gut microbiota-derived enzymes	Oral	Local anti-inflammatory effects in the gut, microbiota regulation	Colorectal precancerous lesions
Mucosal delivery formulations	MMPs, pH	Mucosal / intracavitary administration	Local drug retention, mucosal penetration	Oral leukoplakia and epithelial lesions of the cervix and bladder
Microenvironment-responsive fluorescent and contrast-enhancing probes	pH, ROS, GSH	Intravenous injection	Fluorescence / MRI imaging of lesions	Imaging-based identification of early-stage solid tumor lesions
Biomarker-activated theranostic prodrugs	Proteases such as MMPs	Intravenous / local administration	Imaging-based detection + in situ drug release	Early intervention for various solid cancers
Nanosensor formulations for body fluid analysis	ROS, pH	In vitro testing of body fluid samples	Non-invasive screening for tumor markers	Large-scale initial screening of high-risk populations
Dual-function integrated nanoplatforms	Multisignal logic gates	Multiple routes	Closed-loop detection and preventive intervention	Various precancerous lesions and early-stage tumors

5. Existing Bottlenecks and Future Development Directions

5.1 In Vivo Safety and Biocompatibility Issues

Although stimulus-responsive nanoformulations have shown good potential in preclinical studies, in vivo safety risks are still the primary factor limiting clinical translation [6]. There is individual heterogeneity in the tumor microenvironment, and there are differences in response thresholds between different patients and even different lesions in the same patient, which will lead to early release of drugs in non-target sites or insufficient release in target sites, and it is difficult to stably exert drug effects [2].

The long-term accumulation of nanomaterials in vivo, potential immunogenicity, and organ toxicity caused by nonspecific uptake by the reticuloendothelial system of the liver and spleen all require systematic toxicological evaluation [2]. For example, if the activation of potent immune pathways such as cGAS–STING becomes uncontrolled, it may induce serious adverse reactions such as cytokine storm [3]. Subsequent studies need to systematically analyze the metabolism and toxicology of nano-preparations in vivo, give priority to the development of degradable and highly biocompatible carrier materials, and establish a design strategy with a controllable response threshold to ensure the safety and controllability of the therapeutic window of the preparation [6].

5.2 Difficulties in Large-scale Preparation and Formulation Stability

There are many process obstacles for scale-up of nano-preparations from laboratory scale to industrial kilogram-scale production. Multi-component assembly (host-guest complexation, peptide synthesis, liposome encapsulation) process steps are complicated and prone to large batch-to-batch variations, low yield, and high production costs [4]. In addition, acid-sensitive bonds and ROS-sensitive groups are prone to hydrolysis and oxidation during storage and transportation, resulting in decreased stability and shortened shelf life of the

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preparations [27]. For mucosal drug delivery preparations, how to maintain adhesion ability and structural integrity under complex physiological fluid conditions is also a problem that must be solved in the translation of preparations [24]. In the future, new preparation processes such as microfluidics and continuous flow synthesis can be used to establish standardized quality control schemes, and freeze-drying, solid state dispersion and other preparation technologies can be combined to improve storage stability [27].

5.3 Ideas for Clinical Translation and Medication Compliance Optimization

In addition to technical breakthroughs, practical factors such as patient compliance and medical economics need to be taken into account when nano-agents go to clinical practice [4]. Complicated dosing regimens such as frequent intravenous injections, coupled with potential adverse reactions, may easily lead to dropout of subjects. The development of minimally invasive and non-invasive dosage forms such as oral formulations and mucosal patches, prolonging the dosing interval and simplifying the dosing regimen are important ways to improve compliance [4]. At the same time, it is necessary to conduct standardized clinical trials to verify the advantages of these agents in survival benefit, quality of life, and cost-effectiveness compared with traditional regimens. Companion diagnostics should be established to identify patients likely to benefit from the preparation, and precision prevention and early screening should be implemented to promote the completion of clinical translation of the technology [4].

6. Summary

Cancer prevention and early intervention are key strategies for reducing the incidence of malignant tumors and improving patient prognosis. Traditional formulations lack sufficient targeting capability, exhibit significant systemic toxicity and side effects, have limited capacity for controlled release at the lesion site, and have separate preventive and diagnostic functions, making it difficult to meet the needs for precise prevention and control of precancerous lesions.

This article systematically reviews the research progress of stimulus-responsive intelligent agents in the field of early cancer prevention and early diagnosis. The microenvironment of precancerous lesions has biochemical characteristics that distinguish it from normal tissues, such as pH shift, increased reactive oxygen species, up-regulated glutathione, high expression of specific proteases, and intestinal flora disorder. Stimulus-responsive formulations developed based on these features can achieve lesion-specific drug release and simultaneously activate imaging signals.

In the direction of cancer prevention, the targeted delivery of chemopreventive small molecules mediated by nanocarriers promotes the transformation of cancer prevention from traditional systemic drug administration to precise immune intervention. Oral preparations responsive to the intestinal microenvironment rely on the dual signals of pH and microflora enzymes to release active substances in the colon to achieve the prevention and control of colorectal precancerous lesions. Mucosal drug formulations break through the limitation of mucosal barrier and carry out local intervention for oral, cervical, and bladder epithelial precancerous lesions to reduce the risk of toxic side effects caused by systemic medication.

In the direction of early diagnosis, microenvironment-responsive fluorescent and contrast probes achieve in situ imaging signal activation at the lesion. Marker-activated integrated prodrugs achieve lesion recognition and drug release simultaneously. Body fluid nanosensing technology relies on blood and urine to achieve non-invasive screening. From tissue imaging in situ and local intervention to large-scale sample screening in vitro, these approaches improve the efficiency of early tumor detection across multiple dimensions.

The dual-function integrated nano platform further integrates lesion identification and preventive intervention, constructs a closed loop of “intervention upon detection”, and solves the pain points of the separate implementation of detection and intervention in the traditional mode. However, the vast majority of the relevant research is still in the preclinical stage, and there are still many obstacles before large-scale clinical application: the potential safety hazards caused by individual heterogeneity of the tumor microenvironment; difficulties in scaling up the production of multi-component nano-preparations and insufficient storage stability; the lack of complete benefit evidence at the clinical level, the need to improve patient medication compliance, and an incomplete screening system for patients likely to benefit. These problems all need to be solved one by one.

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7. Outlook

Stimulus-responsive early prevention and early diagnosis preparations have shown good potential in preclinical studies, but before they are actually applied to clinical practice, multidisciplinary research in materials science, pharmacy and clinical oncology is needed, and continuous iterative optimization from material design, preparation process to clinical evaluation is needed [6].

The subsequent formulation design will gradually shift from a single stimulus response to a multi-signal "logic gate" recognition mode, and simultaneously sense a variety of lesion characteristics such as pH, ROS, protease and hypoxia, so as to minimize the non-specific activation in normal tissues and improve the specificity and safety of the formulation [13]. Artificial intelligence and machine learning will be deeply involved in drug preparation research and development, covering the whole process of carrier screening, sensitive chemical bond design and clinical sample data analysis, promoting research and development from trial and error mode to data-driven rational design [26]. The introduction of synthetic biology technology promotes the development of a new generation of systems such as engineered bacteria and gene-regulated intelligent carriers, which is expected to realize advanced functions such as dynamic sensing of carcinogenesis and adaptive drug release [3].

At the material level, degradable carriers with low immunogenicity should be preferentially developed, sensitive chemical bonds should be optimized, and both in vivo response sensitivity and storage stability should be taken into account to improve the short shelf life of preparations [27]. In the production process, microfluidic and continuous synthesis technologies are promoted, and a standardized quality control system is established to narrow the gap between small-scale laboratory trials and industrial production [4]. In the development of dosage forms, non-invasive preparations such as oral formulations and mucosal patches should be developed to simplify the administration scheme and improve the medication compliance of high-risk populations [19]. At the same time, the companion diagnostic strategy should be improved, the applicable population should be screened, and standardized clinical trials should be carried out to evaluate the clinical benefits and health economic value. In the long run, multi-disciplinary collaboration will be relied on to build a complete intelligent technical system covering high-risk population screening, precancerous lesion prevention, and early lesion intervention, which is expected to provide a new technical tool for domestic cancer prevention and control.

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Conflicts of Interest

The authors declare no conflict of interest.

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