

Research progress and clinical application of stimuli-responsive hydrogels in cervical cancer

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Abstract. Cervical cancer is the fourth most common malignancy in women worldwide and poses a great risk to women's health. There is an urgent need to develop a range of effective and innovative therapeutic options to overcome the shortcomings of conventional treatments: poor efficacy and toxic side effects. As an alternative therapy, a number of advances have been made in hydrogel-based drug delivery systems that enable targeted and localized therapy, as well as controlled release of drugs at the tumor site. These advantages can effectively increase drug concentration and reduce damage to normal sites caused by chemical drug toxicity. This paper reviews the progress of research applications of stimuli-responsive hydrogels in cervical cancer. The response mechanisms of hydrogels and the principles of enhanced drug efficacy are discussed in focus. These include thermal-responsive hydrogels, pH-responsive hydrogels, light-responsive hydrogels, enzyme-responsive hydrogels, and dual-responsive hydrogels. It is also argued that through the increasing understanding of hydrogels, it can be used clinically as an effective and durable therapeutic tool.

Keywords: hydrogel; breast cancer; stimuli responsiveness

1. Introduction

Cervical cancer is the fourth most common malignancy among women worldwide. Each year, more than 500,000 women worldwide are diagnosed with cervical cancer, and the disease causes nearly 270,000 deaths worldwide. The overall survival of cervical cancer patients has been extended due to extensive screening programs and an increase in the proportion of patients with early diagnosis of the lesion. However, the prognosis for late-stage cancer remains poor. The 3- to 5-year survival rate for cervical cancer in many underdeveloped countries is less than 50% [1]. Currently, the main treatments for cervical cancer are chemotherapy, radiotherapy, surgery, immunotherapy, targeted therapy, and gene therapy [2]. Among them, chemotherapy as the most common postoperative adjuvant therapy kills tumor cells with its drug toxicity, thus achieving tumor control and preventing recurrence [3]. However, chemotherapy also has some unacceptable drawbacks such as dose-related toxicity, low specificity, and tumor recurrence in patients due to proliferation of drug-resistant cells, with a recurrence rate of up to 80% in intermediate to advanced cervical cancer [3]. In addition, long-term exposure to conventional chemotherapy can cause much harm to patients with cervical cancer, including nausea and vomiting, hair loss, bone marrow suppression, nephropathy, peripheral neuropathy, and damage to various vital organs [4-6]. Therefore, there is an urgent need to develop a new drug delivery system to achieve increased efficacy and reduced toxicity. The advantage of excellent compatibility of hydrogels for regional concentration offers the possibility to achieve this goal.

Hydrogels are three-dimensional network structures formed by physical or chemical cross-linking and dissolve in water to thermodynamic equilibrium [7, 8]. Patient compliance can be improved due to the high water absorption of hydrogels, soft and moist surfaces, and low irritation to the body [9, 10]. Stimulus-responsive hydrogels, also called smart hydrogels, can improve regional drug concentration and reduce systemic drug toxicity by responding to external or internal stimuli. It can also serve as an effective drug carrier and reservoir to provide local drug delivery [11]. Stimuli can be classified as physical, chemical, or biological (Figure 1). Smart hydrogels may be affected by pH [12], temperature [13], and photoelectricity [14], resulting in changes in gel volume and properties. Based on this characteristic, many drug-carrying gels have been developed to target cancers such as

cervical cancer to achieve increased efficacy and reduced toxicity. For example, gel-based dual drug delivery systems (PEG-PCL-PEG/cisplatin + MPEG-PCL/paclitaxel, or PDMP) have been shown to induce G1 phase block, increase apoptosis, and reduce toxicity in cervical cancer cells [15]. HeLa cell lines exhibit more optimal drug uptake to DOX-doped polymer hydrogels, facilitating drug action in cancer cells [16].

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Although drug delivery by hydrogel systems has been gradually developed and perfected, few reviews have been conducted for a specific cancer species. This paper focuses on recent advances in research applications in the specific area of cervical cancer, discusses multiple response modalities including response to pH, temperature, light, and redox reactions and discusses recent advances in the treatment of cervical cancer.

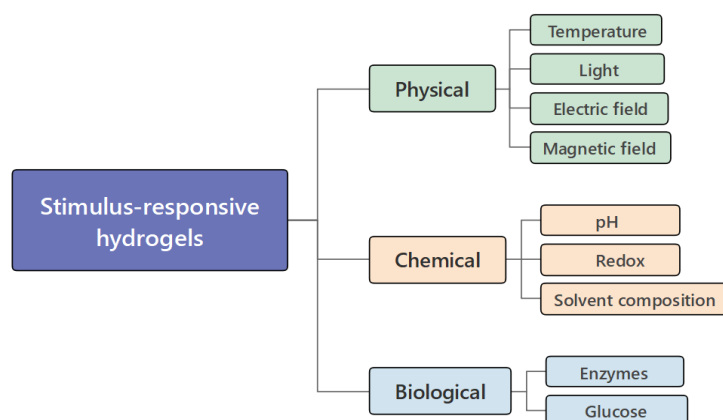


Figure 1. Classification of smart hydrogels can be classified as physical, chemical and biological according to the type of stimulus

2. Thermal-responsive Hydrogel

Thermal-responsive hydrogels change their morphology in response to changes in ambient temperature. The change in temperature affects the hydrophobic interactions and non-covalent forces such as hydrogen bonding to change the gel structure [17]. The solvation properties of hydrogels undergo even discontinuous abrupt changes in gel volume with small changes in temperature near a certain critical temperature, i.e., a volumetric phase transition. The temperature at which the volume changes is referred as lower critical solution temperature (LCST) [18]. When the temperature is below LCST, the thermal-responsive hydrogel is in a dissolved transparent state. When the temperature continues to increase above the LCST, the hydrogel shrinks and transforms into an opaque state of deswelling [19]. With this property, thermal-responsive polymers with LCST near the physiological temperature were developed and drugs were loaded onto the polymers at low temperatures. After injection into the body, the colloidal state is formed under the effect of body temperature. This technique has played an important role in continuous drug delivery, cell therapy and tissue regeneration [20-21]. As a result, many temperature-responsive complexes have been continuously developed. Currently, temperature-responsive polyethylene glycol/polycaprolactone (PEG/PCL) copolymers have been approved by the FDA for clinical use [22].

Thermal-responsive gel formulations for intravaginal drug delivery are increasingly being considered for cervical cancer treatment. Especially when LCGT approaches 37 °C, thermal-responsive polymers can flow through the needle or applicator and form a mucoadhesive gel directly in contact with the vaginal wall thereby enabling localized treatment [15]. Among many thermal-responsive gel polymers, poloxamers such as Pluronics are the most widely used [23]. They are the most widely used in drug delivery. Among them, Pluronic F127 (PF127) is listed as a gelling agent

for vaginal preparations in both the US and European pharmacopoeias. (Compendium of Pharmaceutical Excipients for Vaginal Formulations. Pharm. Technol.)

Wang et al. studied the hydrogel of poloxamer containing carboplatin and found that when mice were vaginally infused with poloxamer solution with an LCST of about 36°C, the solution could be rapidly converted into a mucoadhesive gel within 0.25 min to achieve topical treatment with the drug, and the tumor suppression rate in the experimental group of mice was as high as 68.3%, which was 6.8 times higher than that in the controlled group [24].

Li et al. found that a novel thermal-responsive hydrogel polymer ethylene glycol chitosan rapidly converted from solution to gel at physiological temperature, and the loaded anticancer drug DOX could be released continuously for 13 days with a maximum cumulative release of 86.4 %, allowing for the long-lasting control of cervical cancer [25].

In recent years, many studies have developed thermal-responsive hydrogels with multiple inhibitory effects. On the one hand, thermal-responsive hydrogels act in combination with other drug delivery systems. For example, Xu et al. developed PDMP hydrogel complexes, i.e., an antitumor formulation combining a thermal-responsive hydrogel containing cisplatin (DDP) and polymeric micelles containing paclitaxel (PTX), which could achieve a slow release (more than 14 days) of the drug at physiological temperature (37°C), and the survival of PDMP group mice could reach 55 days, effectively inhibiting tumor growth [15]. On the other hand, temperature-responsive hydrogels carry dual/multi-drug and all of them work together to improve efficacy by controlling the sequence of drug release. For example, Wei et al. developed a topical sequential delivery system of peptide hydrogels that integrated vascular disrupting drugs (CA4) and cytotoxic agents (DOX) in one platform. At physiological temperature, the aqueous solution is transformed into a hydrogel and degraded, and then the two drugs are released sequentially to act synergistically for the treatment of Hela cell transplantation tumors. Experimental results showed that the conversion of the cryogenic aqueous solution of the peptide into a hydrogel at body temperature resulted in sustained drug release for up to 28 days. In addition, staining of tumor sections showed that 83.9% of the tumor sections treated with the co-loaded gel had complete regional apoptosis, which was a significant tumor suppression effect. [27]. Haile et al. synthesized a poly(d,l-propyleneglycol)-poly(ethylene glycol)-poly(d, l-propyleneglycol) hydrogel loaded with bevacizumab (BVZ) and adriamycin (DOX). BVZ was released first to exert anti-angiogenic effects and recovered the tumor vascular system to create a favorable environment. Then DOX was subsequently released to exert synergistic anti-tumor effects. Experimental results showed that hydrogels applied to the test group of HeLa xenografts in nude mice at physiological temperature exhibited the highest tumor suppression effect (mean tumor suppression rate up to $80.03 \pm 3.07\%$) within 36 days [28].

Thermal-responsive hydrogels can also be applied in the fluoroscopic diagnosis of cancerous cells such as cervical cancer. Vaagn Andikyan et al [29] proposed a targeted hydrogel based on 5-aminolevulinic acid (5-ALA) mediation for the diagnosis of cervical intraepithelial neoplasia. The fluorescence intensity of the fluoro-diagnostic agent porphyrin reached a maximum after 4-6 h of incubation in 10% 5-ALA thermogels with a high selectivity (tumor: normal tissue selection = 3.5). It shows that the signal has some diagnostic reliability. Thermal-responsive hydrogels play an important role in the diagnosis as well as in the treatment of cervical cancer.

3. pH-responsive hydrogel

The pH-responsive hydrogel is one of the smart polymer gels, whose volume changes with the pH and ionic strength of the external environment [30, 31]. The pH-responsive behavior of this hydrogel is determined by the ionizable groups in the polymer backbone. When exposed to an aqueous solution with the appropriate pH and ionic strength, these groups will ionize, eventually leading to gel swelling due to electrostatic repulsion or changes in internal and external concentrations [32]. At the same time, the dissociation of the group will break the hydrogen bond within the gel and also cause the gel to swell. [33]. pH-responsive gels are divided into two types: anionic and cationic hydrogels. Anionic

hydrogels ionize at $\text{pH} > \text{pK}_a$, and the ionic concentration increases, producing an osmotic pressure difference that swells the gel. Conversely, cationic hydrogel swells at $\text{pH} < \text{pK}_a$. The most common pH-responsive materials include acrylic acid [34] (AA), methacrylic acid (MAA) [35, 36], dimethylaminoethyl methacrylate (DMAEMA) [37, 38], the natural biopolymer chitosan [39], and dextran [40]. Due to the weakly acidic tumor microenvironment, cationic hydrogels are more commonly used in antitumor applications. Table 1 demonstrates the pH of the tumor microenvironment in different regions of tumor and the corresponding responsive structures.

Table 1. Summary of pH-responsive structures. pH-responsive gels have responsiveness mainly assigned by pH-responsive groups or pH-responsive chemical bonds.

pH of tumor microenvironment		pH-sensitive structures	
		pH-sensitive groups	pH-sensitive bonds
Extracellular pH of the tumor	pH6.5~7.2	Poly(L-histidine) (pHis)	Imine bond ($\text{pH} < 5 \sim 7$)
		polysulfonamide	Dimethyl maleate bond ($\text{pH} < 6.8$)
PH in tumor cells	endosome: pH5.0~6.5 lysosome: pH4.5~5.0	Poly(beta-amino ester) (PAE)	
		poly(N,N-diethyl acrylamide) (PDEA)	
		Maleic acid derivative	Hydrazone bond ($\text{pH} < 5$)
		Carboxylated polyglycidyl	Acyl hydrazone bond ($\text{pH} < 5$)
		Acrylic acid derivative	Orthoester bond ($\text{pH} < 5$)
			Oxime bond ($\text{pH} < 5$)
			Acetal/ Ketal bond ($\text{pH} < 4 \sim 5$)

The pH-responsive hydrogel is loaded with antitumor drugs to address the weakly acidic ($\text{pH} < 6.5$) tumor microenvironment. As the pH in the tumor microenvironment decreases, the hydrogel gradually dissolves. Then the internal drug is gradually released and maintained above the effective concentration to provide precise targeted tumor therapy, improving drug delivery efficiency and therapeutic efficacy in general [41-43]. G Deepa et al [44] prepared polyethylene glycol cross-linked acrylic acid polymers by reverse phase emulsion polymerization and investigated the loading and release of the anticancer drug curcumin. The experimental results show that polyacrylic acid increases the swelling behavior from 16.4 ± 0.72 (g/g) to 36.6 ± 0.82 (g/g) when the pH is changed from 2.2 to 7.4. The release rate depends on the pH value of the release medium. In addition, toxicity tests demonstrated that 1% curcumin nanogel induced 24.7% G2/M blockage in Hela cells, which has a good tumor suppressive effect and is expected to be applied in the treatment of cervical cancer.

The pH responsiveness of hydrogels is important for the treatment of cervical cancer. Therefore, a number of scientists have conducted in vitro release studies for this purpose and plotted in vitro release curves to reflect the sensitivity of hydrogels to pH response.

Dextran phosphate hydrogels (DP-Pr hydrogels) loaded with Prospidine were tested for drug release at different pH levels ($\text{pH} = 7.4, 6.8, 4.0$, and 1.2) and it was found that the release rate as well as the release content of Pr was significantly higher in low pH environments than in neutral environments. This is due to the presence of phosphate and carbamate groups that make DP responsive to the acidic environment. Also, the results of in vivo anti-tumor efficiency tests showed that the use of DP-Pr hydrogels played an important role in increasing the anti-tumor activity and prolonging the therapeutic effect compared to Pr aqueous solutions, which could significantly increase the survival rate of animals [45]. Using the same method, Pillai et al. synthesized folic acid conjugated PEG cross-linked acrylic acid polymer (FA-CLAP) hydrogels and loaded with curcumin. The curcumin-encapsulated FA-CLAP had a good in vitro release profile compared to free curcumin. Besides, confocal microscopy observations indicated that the curcumin-loaded FA-CLAP hydrogel exhibited better cellular uptake. The ability of curcumin to induce apoptosis in HeLa cells was assessed by AO/EB staining, and the number of apoptotic cells was found to be 40%, which was approximately twice as high as that of the free curcumin group [46]. This shows that the above two hydrogels have significant anti-tumor effects.

In addition, some innovative hydrogel formulations are gradually being developed. Kozlovskaya et al. synthesized a pH-responsive hydrogel cube of doxorubicin (PMAA hydrogel). It was prepared

on a mesoporous manganese oxide template in cubic geometry based on the LbL template synthesis method. The PMAA hydrogel was found to have good pH responsiveness and stability while maintaining the cubic shape with long-term residence time. In addition, cytotoxicity assays showed that drugs loaded in the hydrogel cubes could be efficiently delivered to the interior of cells and resulted in the death of about 40% of Hela cells within 72 hours with good antitumor activity [47]. Zhang et al. prepared bionic multilayer hydrogel capsules by the ionic cross-linking method. The cumulative percentage release at pH 4.0 and 7.4 was 83.5% and 6.1%, respectively, within 12 h. The difference reflected the good pH responsiveness of the hydrogel and also solved the problems such as sudden drug release. In addition, the introduction of HA promotes the adhesion of cancer cells (Hela cells) to the hydrogel, which facilitates the local delivery of DOX [48]. Chitosan (CS)/polyvinyl alcohol (PVA) hydrogels were used as injectable drug carriers loaded with fluorouracil (5-FU). The final cumulative release of the drug at pH 5.0 reached 84.8%, with a significantly higher release rate and cumulative release than pH 7.0. Furthermore, it was observed using fluorescence microscopy to have better adhesion to Hela cells, which helped prevent drug diffusion to normal tissues and ensured a high concentration of drug at the lesion site, thus enhancing the antitumor effect [49]. These highly innovative ideas provide great help for local treatment of tumors.

4. Light-responsive hydrogels

Light-responsive hydrogels can be divided into two categories according to their molecular mechanisms: one is bring light-responsive functional groups into the system, and different functional groups will trigger different light reactions (including cleavage, addition, exchange and isomerization), which will lead to changes in the internal structure of the gel; the other is the addition of a photothermal agent, which converts light energy into thermal energy and causes the internal temperature of the gel to reach the phase change temperature and undergo reversible phase change [50], which is shown in Figure 2. Common photothermal agents include gold nanoparticles [51], reduced graphene oxide [52], black phosphorus quantum dots [53], and indocyanine green [54].

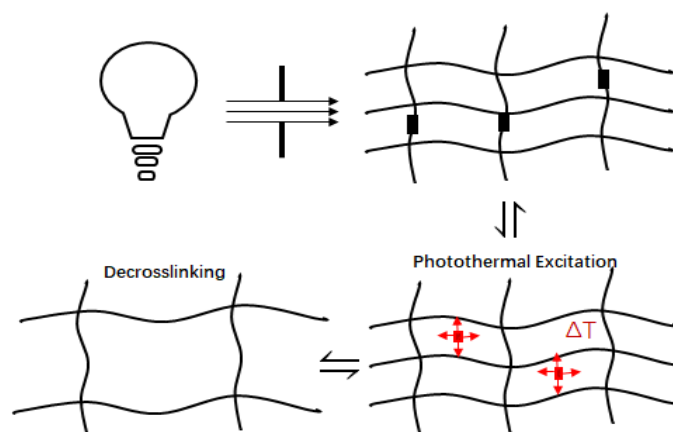


Figure 2. Sol-gel-sol transition of hydrogel in photothermal therapy Converting light energy into thermal energy to cause reversible phase change by raising the internal temperature of the gel to the phase change temperature

Photodynamic therapy (PDT) is a novel technique that has been rapidly developed in the last few years for various types and sites of cancer. When light irradiates a photosensitizer, it produces highly reactive singlet oxygen in the presence of oxygen and destroys target cells [55]. Currently, 5-aminolevulinic acid (5-ALA)-mediated photodynamic therapy has been proposed as an alternative cervical retention therapy for cervical intraepithelial neoplasia (CIN) [56]. Another study found that the survival rate of Hela cells cultured with 30 mg-mL⁻¹ SOLE/PEGDA decreased from 72.3% to 41.7% under NIR irradiation in poly(ethylene glycol) bisacrylate (PEGDA) composite hydrogels loaded with spinach extract (SOLE, a natural photosensitizer). It indicates that SOLE/PEGDA hydrogels are antitumor active in PDT treatment [57].

In addition to PTD, photothermal therapy (PTT) has been proposed for the treatment of cervical cancer. It was demonstrated that Pluronic F127-alginate hydrogel system can be applied as a vaginal membrane treatment tool. 47% of gold nanoparticles (AuNPs) can be used as photothermal agents in photothermal therapy) accumulated in the mucosa in 42 hours. The accumulation of photothermal agents opens up new possibilities for the application of photothermal therapy in oncology [58].

Photothermal therapy can also work synergistically in combination with chemotherapy or radiotherapy. An injectable and near-infrared (NIR) photoresponsive hybrid system was developed by incorporating photoresponsive mesoporous silica nanoparticles (MSN) as doxorubicin (DOX) carriers into a network of IR820/methylcellulose hydrogels for chemophototherapeutic applications. The obtained hydrogel, under NIR radiation, rapidly increased the temperature in the tumor region from 34.7 °C to 56.2 °C, and the cumulative DOX release increased from 28.89% to 76.43%. It reduced the cancer cell survival rate to 1.41% [59]. Another study developed cisplatin and gold nanoparticles (AuNPs) co-loaded into alginate hydrogel networks to form ACA nanocomplexes. AuNPs have a large photoelectric absorption cross-section, which increases the probability of secondary radiation emission and free radical formation under X-ray irradiation. Cisplatin, as a radiosensitizer, can enhance radiation-induced damage. Therefore, the two exert a synergistic effect, inhibiting up to 95% of tumor growth under X-ray radiation and increasing the antitumor activity by 51% compared to standard radiotherapy, with a significant tumor suppressive effect [60]. Mehri Mirrahimi et al. developed a multifunctional nanoplateform which is an alginate hydrogel co-loaded with cisplatin and gold nanoparticles (AuNPs) (referred to as ACA) in a triple combination of thermal-chemo-radiotherapy. Mice in the triple treatment group had an extended survival of up to 32 days compared to mice in the ACA treatment group [61]. In addition, Curry et al. synthesized a hydrogel system containing polyacrylamide-based nanoparticles and a covalently linked bright blue G dye matrix for the photothermal treatment of cervical cancer, using a reverse micellar microemulsion polymerization method. The developed system was found to be effective in inducing pyrolysis in cervical cancer (HeLa) cell lines, because more than 90% cell death was observed in cells incubated with 1.2 mg/ml CB-PAA NPs after 1.5 h of light treatment [62]. Therefore it is expected to be of value in the treatment of cervical cancer and other cancers. These results also validate that combination therapies have great potential in oncology treatment.

5. Enzyme-responsive hydrogels

Enzyme-responsive hydrogels are based on changes in their own morphology and structure triggered by enzymatic reactions [63]. Enzyme-responsive hydrogels have their unique advantages. On the one hand, enzyme-catalyzed reactions can be carried out in the mild conditions and have higher selectivity as well as substrate specificity. On the other hand, enzyme-catalyzed reactions can be carried out in vitro.

Enzyme-catalyzed reactions can be performed in vitro. This means that it is possible to realize simulated organismal environments and construct artificial systems for cascade reactions [64]. Currently, enzyme-responsive hydrogels are also applied in the eradication of cervical cancer cells by inhibition.

Currently, MMP-2 has been found to be overexpressed by human cervical cancer cell lines such as HeLa cells [65]. This implies that hydrogel materials sensitive to this enzyme can be targeted and developed for specific response. Indeed, a number of studies have been performed targeting this enzyme line. Magnetic iron oxide nanoparticles were coated with integrin-targeting and matrix metalloproteinase (MMP) responsive PEG hydrogel scaffolds for DOX targeted delivery into tumor tissues. The basic principle is that high concentration of MMP in the cancer cell environment can effectively cleave the MMP-responsive structural domains within the coating thereby allowing for the specific release of DOX loaded from the coating to the cancer cells. The hydrogel is used to load and trigger the intracellular release of the cancer therapeutic agent adriamycin (DOX). The DOX-loaded targeted nanocarriers were shown to achieve the highest uptake of DOX by HeLa cells and a

50% reduction in the viability of HeLa cells [66]. Based on the same principle, Ac-I 3 SLKG-NH 2 hydrogel encapsulating the anticancer peptide G(IKK) 3 I-NH 2 (G3) was developed. Due to HeLa cells overexpressing MMP, the self-assembled nanofiber network was disrupted thereby releasing the anticancer peptide. The survival rate of the experimental group decreased by 0.8 compared to the control group, demonstrating its considerable anticancer activity [67].

6. Dual-responsive Hydrogels

In order to meet the growing demand for the accuracy of controlled drug release, a series of dual or even multiple response hydrogels have been developed, including temperature-pH responsive hydrogels, thermal-magnetic responsive hydrogels, pH-redox responsive hydrogels, etc.

Temperature-pH responsive hydrogel is the most common one at present. It is made by mixing temperature- and pH-responsive polymers or by combining temperature-responsive polymers into their structures through pH-responsive bonds [68, 69]. Recently, pH- and temperature-responsive nanogels (SMGO/P(NIPAM-co-AA) NGs) based on saiep-modified graphene oxide (SMGO) of N-isopropylacrylamide (NIPAM) and acrylic acid (AA) have been reported. After loading DOX, the hydrogels released twice as much DOX at pH = 5.0 compared to pH=7.4. In addition, it was shown that DOX was released more rapidly at 42°C than at 37°C. These two responses together enhanced cytotoxicity to HeLa cells [70]. Jaiswal et al [71] developed a pH-temperature responsive nanogel based on poly-(N-isopropylacrylamide)-chitosan and combined with Fe₃O₄ magnetic nanoparticles to achieve a magnetically triggered thermal response. Doxorubicin was subsequently loaded to study drug release and cytotoxicity in vitro and to assess the drug delivery and antitumor potential of the formulation. The developed system showed a good response to both stimulus in terms of adriamycin release. The combined effect of thermochemotherapy resulted in an 85% increase in HeLa cell death which proves the potential to treat cervical cancer.

Redox hydrogels are not used alone, but are usually made in combination with pH-responsive materials to form dual-responsive hydrogels. Some experiments have shown that pH-redox dual-responsive hydrogels can be designed with a graded response by pH-responsive materials as well as redox reactions triggered by added glutathione. Lin et al [72] designed pH and redox dual-responsive nanocarriers for the delivery of doxorubicin (Dox) and phosphorylated curcumin (p-Cur). The polyethylene glycol acts as a shell that can be cut due to pH sensing to an acidic environment and then exposes a cationic hydrogel coating. At the same time, the cross-linked disulfide bonds are cleaved and the drug is released with the help of a redox reaction catalyzed by GSH in vivo. The graded release of p-Cur and DOX leads to synergistic effects and effective apoptosis of cancer cells.

Elena Pérez and colleagues [73] formulated pH-glutathione dual-responsive nanogels based on poly-N-isopropylacrylamide (NIPA), 2-acrylamide ethylcarbamate (2AAECM) and N-hydroxyethylacrylamide (HEAA) loaded with PTX by a microemulsion polymerization method. N-Cystamine bisacrylamide (CBA) was used as a cross-linking agent. Cellular uptake assays and cytotoxicity assays were performed using coumarin 6. The results showed that the nanogels loaded with coumarin 6 were rapidly absorbed within 2 h and accumulated intracellularly after 48 h, causing G2/M cell arrest. It was demonstrated that the gel could be used as a nanocarrier for novel anticancer drugs.

7. Conclusion

This paper reviews the application of smart hydrogels in the diagnosis and treatment of cervical cancer. The characteristics and working principles of temperature-responsive hydrogels, pH-responsive hydrogels, light-responsive hydrogels, enzyme-responsive hydrogels and dual-responsive hydrogels as well as the current research progress in the direction of cervical cancer are analyzed. The polymer materials of hydrogel as well as the types of anti-cancer drugs and their preparation methods are introduced.

The current research on smart hydrogels is mainly focused on the following aspects: (1) Optimization and modification on the structure of known polymers. That is, structural modification of polymers, including the addition of environmentally responsive functional groups, or the use of multiple polymers in combination, etc. (2) Addition of other substances to give new functions to hydrogels. An example is the addition of photothermal agents to temperature-responsive hydrogels. After forming a stable structure, the hydrogel can achieve a dual response of light and thermal energy. Another example is the addition of fluorescent nano ions to make it fluorescence in a specific environment and facilitate the diagnosis of lesion sites. (3) Development of non-spherical hydrogels. Particle shape affects cellular uptake, vascular dynamics and circulation which is critical for drug delivery. (4) Breakthrough of traditional processes and development of novel hydrogels. Such as supramolecular hydrogels, topological hydrogels, etc. These above, focus on improving the sensitivity of hydrogel response and its performance. In addition, there are also studies focusing on hydrogels loaded with multiple drugs, and by controlling the specific sequence of drug release, trying to play a synergistic role of drugs, thus obtaining the most effective tumor suppression effect. For successful antitumor therapy, multifunctional smart hydrogel systems must be able to be combined with physiological specificities to ensure precise drug targeting. Indeed, the ability to achieve the assessment of toxicity and bioavailability of therapeutic/diagnostic hydrogels under physiological conditions is essential and should be considered in view of the practicality of using the designed cancer therapeutic/diagnostic agent. This requires the joint development and continuous in-depth systematization of chemistry, materials science, pathology, biology, clinical medicine, and nanotechnology.

At this stage, although many innovative technological solutions for smart hydrogels have been developed and published, unfortunately, most of them are still in the basic development stage and few of them have completed preclinical studies to conduct clinical trials because of the limitations of polymeric material sensitivity and the lack of cervical cancer-specific targets. To date, few stimuli-responsive hydrogels for cervical cancer have been marketed. This may be because the corresponding sensitivity of hydrogels is not yet up to the requirements for in vivo treatment. In the case of enzyme-responsive type, for example, there are intricate enzyme systems present in the human body, which interferes with the response behavior of enzyme-responsive hydrogels. In addition, from the perspective of in vivo kinetics, the distribution of hydrogel drugs in vivo is somewhat undirected and may not bind to specific enzymes for catalytic reactions. Other responsive types also have more or less of these two conditions, namely nonspecificity of the signal and physiological interference. In addition, the preparation technology of hydrogels is not mature enough at present, and there are difficulties in scaling up production in factories. All of the above have led to the limitations of clinical application of hydrogels in cervical cancer. Although the development and production technology of smart hydrogel is still in the development stage, these questions will eventually be addressed as more research is done on drugs and hydrogels in vivo. It is believed that hydrogels will provide more possibilities for cervical cancer patients to survive in the near future.

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