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Hydrogel in Cancer Research: Emerging Trends and Therapeutic Potential

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Abstract

Hydrogels, which are three-dimensional hydrophilic polymer networks capable of holding substantial amounts of water, have become a valuable tool in cancer research. Their excellent biocompatibility, adjustable physical characteristics, and capacity to replicate the extracellular matrix (ECM) render them highly suitable for diverse biomedical applications. This manuscript provides a thorough review of the current and emerging roles of hydrogels in cancer research, including tumour modelling, drug delivery, immunotherapy, and tissue engineering. The discussion includes key advancements, current challenges and potential future outlooks to elucidate the potential of hydrogels in transforming cancer diagnosis and treatment.

Keywords: Hydrogel; Cancer Research; Immunotherapy; Tissue Engineering; Tumour Modelling

1. Introduction

Cancer remains one of the foremost global health challenges, noted for its high incidence of morbidity and mortality. Conventional therapeutic approaches, such as surgery, chemotherapy, and radiotherapy, often face limitations such as systemic toxicity, non-specific targeting, and the emergence of multidrug resistance [1]. These challenges highlight the urgent need for innovative therapeutic approaches that improve treatment effectiveness while reducing adverse effects [2,3].

hydrogels, capable of retaining considerable amounts of water [4], have shown great promise in cancer therapy [5]. Their inherent properties biocompatibility, tuneable mechanical strength, and the ability to encapsulate a variety of therapeutic agents enable their use in localized and controlled drug delivery applications [6].

Recent advancements have given rise to stimulus-responsive hydrogels [1] that are able to release their therapeutic agents in response to certain internal or external signals, such as changes in pH levels, temperature variations, or enzymatic activity [7]. For instance, pH-responsive hydrogels exploit the acidic microenvironment of tumour tissues to achieve targeted drug release, thereby enhancing therapeutic outcomes while reducing systemic toxicity [8].

Moreover, the fusion of nanotechnology with hydrogel systems has facilitated the creation of multifunctional platforms capable of simultaneous diagnostics and therapy, known as theranostics [9]. Such advanced hydrogel systems can be tailored to react to various stimuli, enabling more precise control of drug release and improving the accuracy of cancer treatment [10].

In this paper, we delve into the recent developments in hydrogel-based systems for cancer treatment, exploring their design, functional mechanisms, and therapeutic applications. We also discuss the challenges associated with their clinical translation and potential future directions in this rapidly evolving field.

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2. Hydrogel Composition and Properties

The unique properties of hydrogels render them ideal for a versatile application, including biomedical [1-10], agricultural [11-13], and environmental fields [14,15]. Hydrogels are primarily composed of (a) Polymers, (b) Cross-linkers, (c) Water, and (d) Additives (Fig. 1). The backbone of hydrogel structures is made by polymers which can be natural (e.g., alginate, chitosan, gelatine) or synthetic (e.g., polyacrylamide, polyethylene glycol). Cross-linkers chemically bond polymer chains, forming a network that imparts structural integrity to the hydrogel. In this polymer network, water is absorbed giving hydrogels their characteristic swelling behaviour. Different compounds like nanoparticles, drugs, or other bioactive compounds can be incorporated as additives to enhance or impart specific functionalities.

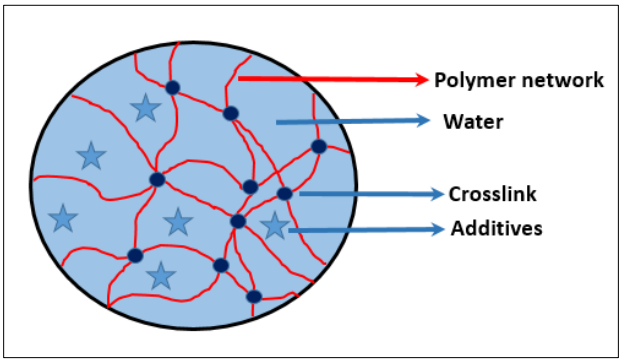

Figure 1 Simple structure of Hydrogels

Depending on their origin and composition, hydrogels can be grouped [16] into different categories: (i) Natural Polymers: Derived from renewable resources, these include polysaccharides (e.g., alginate, chitosan) and proteins (e.g., gelatine, collagen). Their compatibility with biological systems and ability to degrade naturally make them ideal for biomedical applications. Next class of hydrogels is (ii) Synthetic Polymers. These are the man-made polymers like polyacrylamide and polyethylene glycol offer tunable properties but may lack biodegradability. The third type of it is (iii) Nanocomposite Hydrogels which incorporate nanoparticles (e.g., cellulose, starch) into the polymer matrix to enhance mechanical strength and control drug release profiles.

Hydrogels can absorb significant amounts of water, leading to swelling. Natural polymers often exhibit higher swelling ratios due to their hydrophilic nature [17]. Higher crosslinking reduces swelling by limiting the mobility of polymer chains [18]. pH, ionic strength, and temperature can affect the swelling behaviour [17, 18]. The mechanical strength of hydrogels is crucial for their functionality in applications like tissue engineering. Factors affecting mechanical properties include crosslinking degree, polymer concentration, incorporation of nanoparticles. Higher crosslinking increases stiffness but may reduce flexibility [19] while higher concentrations lead to stronger gels [20]. On the other hand, Nanocomposite hydrogels exhibit enhanced mechanical properties due to the reinforcement provided by nanoparticles [21].

3. Applications in Tumour Modelling

Hydrogels have emerged as pivotal tools in tumour modelling, offering a biomimetic environment that closely resembles the natural extracellular matrix (ECM). Their versatility in composition, tuneable mechanical properties, and biocompatibility make them ideal for creating *in vitro* models that mimic the tumour microenvironment (TME). These models are instrumental in understanding tumour biology, drug responses, and therapeutic strategies (Fig. 2).

Compared to standard 2D cultures, 3D hydrogel cultures present a physiologically relevant platform. They promote interactions between cells and with the surrounding matrix, enhancing the simulation of in vivo environments. For instance, a study developed a hydrogel-based 3D glioblastoma model using a gelatin–sodium alginate hydrogel, demonstrating its utility in assessing the efficacy of CD73 inhibitors [22]. Similarly, a hydrogel composite incorporating nanofibers was designed to replicate the ECM's structural and mechanical properties. This composite facilitated the study of cancer stem cell behaviours and chemo-resistance in prostate cancer cells, highlighting the importance of mechanical cues in tumour progression [23].

Injectable hydrogels offer a dynamic approach to tumour modelling, allowing for the creation of models that can be easily administered and adapted. A notable example is the establishment of a hydrogel-based three-dimensional glioblastoma cell culture model for examining CD73 inhibitor responses [22]. Moreover, injectable hybrid hydrogels have been engineered to enhance combination chemotherapy and stimulate anti-tumour immunity. These hydrogels, loaded with therapeutic agents, can be precisely delivered to tumour sites, improving treatment efficacy and immune response [24].

The mechanical properties of tumour microenvironment significantly influence tumour cell behaviour. Hydrogels can be engineered to mimic these mechanical cues, providing insights into tumour mechanobiology. For example, hydrogel models of pancreatic adenocarcinoma have been utilized to study cell mechanosensing, revealing how changes in tissue stiffness affect tumour progression and chemo-resistance [25]. Additionally, 3D bioprinting techniques have been employed to create multicellular tumour spheroids within hydrogel matrices, allowing for the study of tumour cell interactions and drug responses in a controlled environment [26].

Furthermore, in situ chemo-immunotherapy hydrogels have been developed to elicit immunogenic cell death and stimulate efficient anti-tumour immune responses. These hydrogels release chemotherapeutic agents and immune adjuvants, promoting both direct tumour cell killing and activation of the immune system [27, 28].

Thus, hydrogels have revolutionized tumour modelling by providing versatile, biomimetic platforms that closely mimic the TME. Their applications span from 3D cell culture systems and injectable models to drug delivery and tissue preservation techniques. These advancements enhance our understanding of tumour biology and improve the efficacy of therapeutic strategies, paving the way for more personalized and effective cancer treatments.

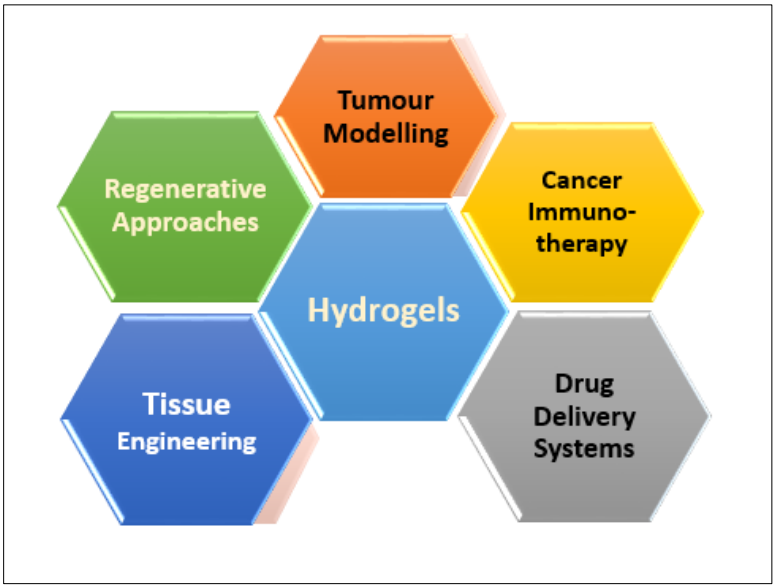

Figure 2 Applications of Hydrogel

4. Hydrogels in Drug Transport Systems

Hydrogels have emerged as useful materials in drug delivery systems (DDS), offering controlled release, biocompatibility, and responsiveness to various stimuli. Their hydrophilic nature and structural properties make them suitable for encapsulating and releasing therapeutic agents (Fig. 3). The design of hydrogels for DDS involves tailoring their composition and crosslinking to achieve desired release profiles and responsiveness. Hydrogels can encapsulate chemotherapeutic agents, protecting them from premature degradation and allowing controlled release. Targeted delivery can be achieved by functionalizing hydrogels with ligands or antibodies that recognize cancer-specific markers. This reduces systemic toxicity and enhances treatment efficacy.

Both natural and synthetic polymer-based hydrogels can act as drug reservoir and supply the drug at the targeted location. Among the natural polymers, cellulose nanocrystals (CNCs) and cellulose Nano-fibrils (CNFs) are utilized to create hydrogels with high surface area and biocompatibility [29, 30]. These hydrogels can be cross-linked physically or chemically and are responsive to stimuli such as pH and temperature. They are particularly effective in controlled

drug release applications. Chitosan, a biopolymer derived from chitin, forms hydrogels that are biodegradable and biocompatible. These hydrogels can be engineered for controlled release and are suitable for delivering proteins, peptides, and nucleic acids. Their muco-adhesive properties enhance drug absorption. Pectin, a natural polysaccharide, forms hydrogels that are responsive to environmental conditions. These hydrogels are used in oral and transdermal drug delivery, offering controlled release and potential applications in wound healing [31]. Among the synthetic polymer-based hydrogels, Poly(N-isopropylacrylamide) (PNIPAAm) hydrogels exhibit thermos-responsive behaviour, transitioning from hydrophilic to hydrophobic states at specific temperatures. This property allows for the controlled release of encapsulated drugs in response to temperature changes [32, 33].

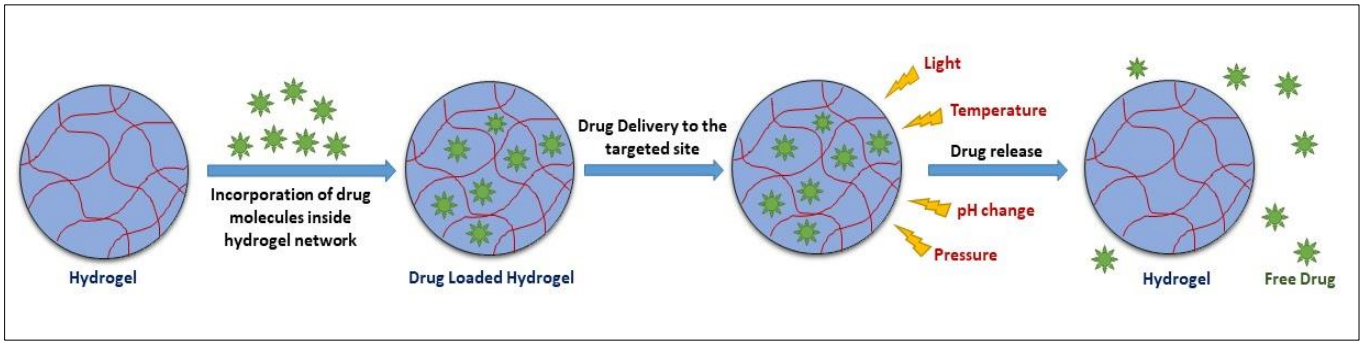

Figure 3 Drug loading and release from hydrogels

5. Role in Cancer Immunotherapy

Hydrogel-mediated immunotherapy represents a promising avenue in cancer therapy, enabling site-specific drug delivery, sustained release, and effective immune regulation. Recent advancements have focused on designing hydrogels that not only deliver therapeutic agents but also actively engage the immune system to combat tumours.

5.1. Role of Hydrogels in T Cell Infiltration and Tumour Immune Evasion

A study published in Nanoscale Horizons (2024) [9] introduced an injectable hydrogel composed of sodium alginate, linagliptin, and BMS-202. Linagliptin preserved the chemokine CXCL10, promoting T cell infiltration into the tumour microenvironment. Simultaneously, BMS-202 inhibited the PD-L1 checkpoint, countering immune evasion by tumour cells [24]. This dual-functional hydrogel demonstrated enhanced anti-tumour immunity and reduced metastasis in mouse models.

5.2. In Situ Chemo-immunotherapy Hydrogel

Qin Liu et. all. in the year 2024 [28] have developed a hydrogel incorporating nab-paclitaxel (Nab-PTX) and the TLR7 agonist R837. Upon peritumoral injection, the hydrogel induced immunogenic cell death, leading to increased infiltration of effector memory T cells and activation of immune responses. This approach showed significant tumour suppression in hepatocellular carcinoma and breast cancer models, with minimal systemic toxicity.

5.3. Dual-Functional Alginate-Collagen Hydrogel

Juyoung Hwang et. all., in the year 2022 presented a thermally responsive hydrogel made from alginate and collagen, loaded with poly (I:C) and indocyanine green [34]. Under near-infrared irradiation, the hydrogel facilitated photothermal therapy and induced a cancer-specific immune response. This strategy effectively treated primary tumors and prevented lung metastasis in murine models.

5.4. Combination Therapy with Oncolytic Adenovirus Silk Hydrogel

A silk hydrogel carrying a recombinant oncolytic adenovirus with a PD-L1 inhibitor was developed in the year 2024 by Wenqiang Zhang et. all [35]. This combination enhanced T cell infiltration and anti-tumor immunity in bladder cancer models, offering a promising strategy for overcoming immune suppression in the tumor microenvironment.

The integration of hydrogels in cancer immunotherapy holds significant promise for clinical applications. Their potential to ensure site-specific, sustained, and controlled drug release enhances therapeutic outcomes and reduces systemic toxicity. Ongoing research is focusing on optimizing hydrogel formulations, improving their biocompatibility,

and developing strategies for their clinical translation. Linking hydrogels with other therapeutic modalities, such as photothermal therapy or gene editing [36], may further augment their therapeutic potential.

6. Tissue Engineering and Regenerative Approaches

Hydrogels play a crucial role in advancing tissue engineering and regenerative medicine [37]. Their exclusive characteristics like biocompatibility, tuneable mechanical strength, and the ability to mimic the extracellular matrix—make them ideal candidates for supporting cell growth, tissue formation, and drug delivery [38]. Post-tumour resection, hydrogels can assist in tissue regeneration by providing scaffolds for cell attachment and proliferation. Incorporating bioactive molecules and stem cells within hydrogels can accelerate tissue healing and restore normal function [39].

The diverse applications of hydrogels in tissue-engineering is largely attributed to advanced fabrication techniques that allow for precise control over their structure and properties like ***3D Bioprinting:*** Facilitates the construction of intricate, patient-tailored tissue structures via sequential layering of hydrogel bioinks, allowing controlled integration of cells and growth factors [40, 41]; ***Electrospinning:*** Produces nano-fibrous scaffolds that closely resemble the native extracellular matrix, supporting cell attachment and growth [42, 43]; ***In Situ Gelation:*** Permits hydrogels to be delivered as liquids that post-injection converted into gel, precisely filling the defect site and offering immediate stabilization. These techniques enable the customization of hydrogel properties to meet the specific requirements of different tissue types.

Hydrogels have been applied in various tissue engineering applications, including cartilage and bone regeneration, cardiac repair, skin wound healing, neural tissue engineering etc [44]. Injectable hydrogels loaded with stem cells can deliver stem cells and growth factors directly to the site of injury, promoting tissue repair and regeneration [45]. It can be used to deliver therapeutic agents to the heart following myocardial infarction, aiding in tissue repair and reducing fibrosis [46]. Hydrogel dressings can maintain a moist environment, promote cell migration, and provide controlled release of antimicrobial agents, accelerating wound healing. It can also support the growth of neurons and glial cells, offering potential treatments for spinal cord injuries and neurodegenerative diseases [47, 48].

7. Preserving Human Tumour Tissues for Drug Testing

Innovative hydrogel formulations have been developed to preserve human tumour tissues outside the body, maintaining their structural and functional integrity. Researchers at the University of Manchester discovered a method to preserve breast tissue in a special gel solution, VitroGel, for at least a week [49, 50]. Kenny Zhuoran Wu et.al., reported a hyaluronan-based hydrogel system that preserves the original tumour microenvironment (morphology, tissue architecture, and composition) of patient-derived peritoneal metastasis samples, facilitating clinically meaningful drug testing [51]. Christabella Adine et.al., also reported that embedding patient-derived tumour slices in hydrogels preserved the original tumour's composition, including cancer cells, cancer-associated fibroblasts, and distinct immune cell subsets [52]. This advancement allows for more accurate drug testing and personalized treatment strategies, reducing the need for animal models.

8. Challenges and Future Perspectives

Despite favourable outcomes, the clinical implementation of hydrogel-based systems, including scalability, reproducibility, and regulatory hurdles still faces several challenges. Many hydrogels lack the mechanical robustness required for load-bearing tissues, necessitating the development of reinforced or nanocomposite hydrogels. The degradation rate of hydrogels must be synchronized with tissue formation to avoid premature loss of structural support or prolonged inflammation. Facilitating the development of functional blood vessels in tissue-engineered constructs is also crucial for their survival and function, requiring strategies to promote angiogenesis within hydrogel constructs. Apart from that standardization of hydrogel formulations and manufacturing processes is essential to meet regulatory requirements for clinical use. Future research is focusing on developing smart, environment-sensitive hydrogels that adjust to external stimuli, such as pH, temperature, or light, to provide dynamic control over tissue regeneration processes. Also, it should focus on developing smart hydrogels with multi-functional capabilities, integrating biosensors, and advancing personalized cancer therapy.

9. Conclusion

Hydrogels represent a transformative technology in cancer research, with vast potential to improve diagnostics, drug delivery, and therapeutic outcomes. Hydrogels have emerged as a versatile and promising foundation for tissue

engineering and regenerative therapies, offering customizable properties that can mimic the natural extracellular matrix. Ongoing advancements in hydrogel design and fabrication are paving the way for their clinical application in tissue repair and regeneration. Continued interdisciplinary efforts will be crucial in harnessing their full potential for clinical applications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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