Harnessing Hydrogels for Precise Cancer Therapy: Innovations and Applications

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Abstract. Hydrogels, characterized by hydrophilic networks and ECM-like structures, serve as versatile platforms for drug delivery and tumor microenvironment (TME) modeling. They enable precise drug administration, minimize side effects, and enhance therapeutic efficacy. Intratumoral delivery strategies using smart hydrogels offer targeted drug release, while in vitro TME models replicate complex interactions. Additionally, an innovative injectable hydrogel strategy reshapes the adenosinergic axis, converting immunosuppressive adenosine to immune-enhancing inosine. The S@ABD hydrogel demonstrates remarkable potential in reversing the axis, amplifying Adenosine triphosphate (ATP) release, and reshaping the TME, promising effective cancer therapy. In summary, this review highlights the transformative role of hydrogels in cancer treatment, hydrogels redefine cancer research and therapy paradigms, holding the key to personalized and potent treatments.

Keywords: Hydrogels; cancer treatment; drug delivery; Intratumoral delivery; adenosinergic axis; immunosuppression.

1. Introduction

Hydrogels are versatile materials with a crucial role in modern cancer treatment strategies. These three-dimensional networks of water-absorbing polymers closely mimic the body's natural extracellular matrix, fostering an environment conducive to cell growth and interaction. In this review, we explore the principles, preparation methods, and applications of hydrogels in cancer therapy, particularly their ability to replicate the tumor microenvironment (TME) and reshape the adenosinergic axis for more effective treatment.

Hydrogels' unique properties make them invaluable for constructing TME models in vitro. Their structural similarity to the extracellular matrix (ECM) enables the study of complex cancer-stroma interactions and therapeutic responses. Additionally, hydrogels serve as efficient carriers for controlled drug delivery, minimizing side effects while maximizing drug efficacy. Intriguingly, smart hydrogels offer precise drug delivery through intratumoral administration. By strategically reshaping the adenosinergic axis, an injectable hydrogel strategy transforms immunosuppressive adenosine into an immune-enhancing agent, inosine. This novel approach holds promise for boosting immune responses against tumors [1].

Through this review, we delve into the diverse applications of hydrogels in cancer treatment, illustrating their potential to revolutionize therapeutic strategies and improve patient outcomes.

2. Principles of Hydrogels In Cancer Treatment

2.1. Definition and structure of hydrogels

Hydrogels stand as versatile materials with a significant role in advancing cancer treatment strategies [1]. These three-dimensional networks, composed of polymers, are imbued with an exceptional capacity to retain water and form a gel-like structure. The structural framework of hydrogels mirrors the ECM found in natural tissues, fostering a conducive environment for cellular interaction and growth [2].

2.1.1. Unique hydrophilic network

At their core, hydrogels are hydrophilic networks woven from polymer chains, demonstrating an intrinsic propensity to absorb substantial amounts of water [3]. This exceptional water-retention capability, akin to the body's native ECM, not only endows hydrogels with a biomimetic quality but also underpins their suitability for various biomedical applications, including cancer treatment.

2.1.2. Mimicking the ECM

The architecture of hydrogels remarkably resembles the ECM, which plays a crucial role in regulating cell behavior and functions. This structural similarity is pivotal for creating in vitro models that mimic the TME and facilitate the study of cancer-stroma interactions, invasion, and therapeutic responses [4]. By replicating the ECM, hydrogels offer a unique platform to dissect complex cellular processes that drive cancer progression [2].

2.2. Preparation Methods of Hydrogels

The intricate design and fabrication of hydrogels for cancer treatment hinge on a range of preparation methods, each tailored to confer specific biophysical and mechanical properties essential for mimicking the TME and facilitating therapeutic interventions [5].

2.2.1. Controlled gelation process

The formation of hydrogels hinges on a gelation process that harnesses both physical and chemical interactions. Parameters like temperature, pH, and ionic strength are meticulously controlled to enable self-assembly of molecules and crosslinking agents. For example, thermosensitive poly (lactic acid)-poly (ethylene glycol)-poly (lactic acid) (PLGA-PEG-PLGA) undergoes a sol-gel transition around 32°C and is a promising material for intramuscular vaccines. Among temperature-responsive polymers, poly (N-isopropylacrylamide) (abbreviated as pNIPA) is widely known. The crosslinked pNIPA network undergoes a bulk phase transition at about 32°C. The pNIPA network is a very efficient, efficient, and stable material, and it can be used in a variety of applications [6]. Through this process, hydrogels achieve the desired structural integrity and porosity, allowing for efficient nutrient diffusion, cell encapsulation, and growth [3].

2.2.2. Tailoring mechanical properties

Manipulating the mechanical properties of hydrogels holds immense significance in cancer treatment. Various strategies, such as the integration of natural materials and chemical modifications, contribute to controlling the stiffness and resilience of hydrogels. By enhancing stiffness using light-mediated crosslinking, for instance, hydrogels can more accurately mimic the mechanical cues present within the TME [3]. As a typical example, photo-crosslinked hydrogels can be manufactured using dextran modified with 2-isocyanatoethyl methacrylate and N-isopropylacrylamide. Photoinitiators, in particular irgacure 2959 from CIBA, are used in this process [7].

2.2.3. Advancing 3D structural architecture

The three-dimensional (3D) architecture of hydrogels holds profound implications for cancer research and treatment. By utilizing techniques like 3D bioprinting and layer-by-layer self-assembly, complex scaffold structures are engineered to support cell growth and provide a physiological environment. One of them is 3-D printing methods have begun to facilitate simpler, faster, and more cost-effective fabrication of millimeter-fluidic devices with resolutions up to 100-200 mm. This technique is valuable for fabricating complex and diverse tissues using PEGDA composite gels. By combining image-guided 3D tissue printing with focused light cross-linking techniques, complex and heterogeneous tissues can be fabricated [3]. These innovative approach enables the fabrication of intricate tissue analogues, fostering a potent tool for tissue engineering, drug screening, and the development of cancer models.

In summary, hydrogels represent a dynamic frontier in cancer therapy utilizing their unique hydrophilic network and ECM-like structure. Precise preparation methods including controlled

gelation processes, mechanical property tailoring, DN hydrogels, and advanced 3D structural approaches make hydrogels a sophisticated platform for studying the complexity of the TME and developing innovative therapeutic strategies.

3. Applications Of Various Hydrogels In Tumor Targeted Therapy

3.1. Drug carriers

A groundbreaking transformation in cancer therapy has been catalyzed by the innovative drug delivery systems rooted in hydrogels. These adaptable platforms excel in precise and controlled drug administration, curtailing widespread side effects while maximizing therapeutic potency. Within this framework, hydrogels emerge as efficient conveyors for a diverse array of therapeutic agents, augmenting their targeted delivery to malignant sites [8].

3.1.1. Localized dispensation of drugs

Central to achieving localized drug release in cancer therapy is the pivotal role played by hydrogels. By encapsulating chemotherapeutic compounds within hydrogel matrices, the release of drugs can be meticulously calibrated and synchronized with the intricate tumor microenvironment. This strategic approach ensures the maintenance of therapeutic concentrations at the tumor locus, simultaneously minimizing exposure to healthy tissues. Thus, the incorporation of hydrogel-based drug carriers contributes substantively to bolstered treatment outcomes and a reduction in toxicity [9].

3.1.2. Responsive to stimuli hydrogels

The propulsion of cancer therapy has been significantly advanced by the integration of stimuli-responsive hydrogels. These ingenious hydrogels react selectively to specific cues within the confines of the tumor microenvironment, engendering a precisely controlled liberation of drugs. Xiao et al. documented bilayer hydrogels that respond to salt, featuring a pseudo-double network structure driven by the interplay between polyelectrolyte and anti-polyelectrolyte influences [10]. Temperature, pH levels, and enzymatic activity are among the stimuli adroitly harnessed. Such adaptive responsiveness culminates in the provision of spatiotemporally precise drug release, optimizing therapeutic impact and mitigating untoward effects [8].

3.1.3. Fusion of nanoparticles and hydrogels

The synergistic amalgamation of nanoparticles with hydrogels has emerged as a potent strategy in cancer therapy drug delivery. These nanoparticles, embedded within the matrix of hydrogels, confer heightened drug encapsulation capability and facilitate a prolonged release profile. Notably, these nanoparticles can be meticulously engineered for targeted action, augmenting their accumulation and uptake within tumors. The concerted impact of nanoparticle-hydrogel composites underscores a more efficacious and streamlined approach to cancer treatment, such as poly (acrylic acid) (PAA) nanogels has been shown to be useful for anti-tumor therapies [11].

These hydrogel-based carriers not only facilitate the local distribution of drugs, but also exploit the synergistic effects of reactive behavior and nanoparticles. As cancer therapy continues to evolve, hydrogel-based drug delivery systems will redefine therapeutic approaches and hold the promise of improved efficacy and enhanced patient welfare.

3.2. Targeting strategies for intratumoral delivery and local administration

Smart hydrogels have emerged as innovative platforms, advancing tumor-targeted therapy through intratumoral delivery and local administration. These adaptable materials respond to specific triggers within the tumor microenvironment, enabling precise and controlled drug release. In this discussion, we delve into strategies employed for intratumoral delivery and local administration using smart hydrogels, highlighting their potential applications and impact on cancer treatment [12].

3.2.1. Advantages of intratumoral Delivery

The intratumoral administration approach offers a strategic method for directly delivering therapeutic agents to tumor sites. By bypassing systemic circulation, this technique achieves concentrated drug exposure at the target cells, reducing necessary dosage and minimizing off-target effects. Furthermore, intratumoral delivery reaches regions with compromised vasculature, often overlooked by systemic administration [13]. As a case in point, PEG–PLA hydrogel enables localized rhIL-2 delivery, achieving 50% release in 16 days. In vivo, intratumoral injection in mice effectively reduces tumor size over 1–2 weeks, surpassing free drug's impact. This approach concentrates treatment, minimizing off-target effects [14].

3.2.2. Injectable biodegradable hydrogels

Injectable biodegradable gels provide a minimally invasive means of drug delivery with exceptional adaptability to tumor geometry. These gels can be customized to possess shear-thinning properties, allowing injection through narrow needles followed by a return to gel-like consistency at the tumor site. Alternatively, in situ-gelling systems transition from liquid to gel upon injection, forming drug depots for sustained release. Such gels hold promise for effective drug retention and controlled release, while their biodegradable nature ensures compatibility and reduces the need for subsequent interventions [15].

3.2.3. Responsive hydrogels

The ability of stimuli-responsive hydrogels to adjust their structure and behavior in response to specific cues within the TME is a transformative feature. These hydrogels encompass diverse categories (Fig. 1) [15]:

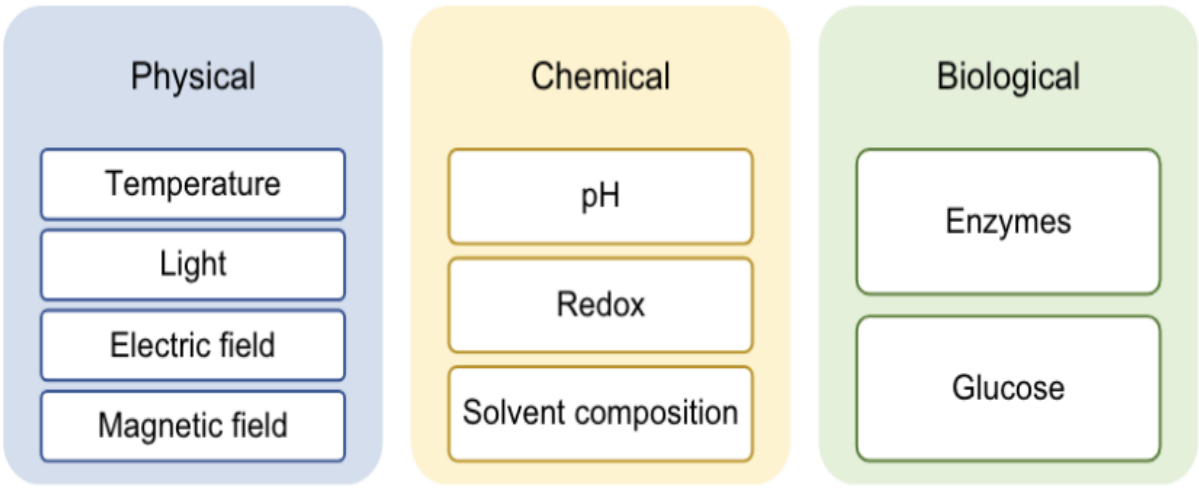


Fig 1. Classification of stimulation modalities to which the hydrogel will respond.

Smart hydrogels: These hydrogels offer versatile platforms for precise drug delivery in cancer therapy. Thermoresponsive hydrogels undergo phase transitions in response to temperature changes, enabling localized drug release at elevated tumor temperatures. Photo-responsive hydrogels utilize light-triggered structural changes for on-demand drug release, achieving precise control with photoreactive components. pH-responsive hydrogels swell or contract in tumor-specific pH environments, enhancing drug release kinetics. Redox-responsive hydrogels respond to the oxidative tumor environment, allowing selective drug release. Enzyme-responsive hydrogels degrade in response to over-expressed tumor enzymes, offering targeted and responsive drug delivery. These strategies empower tailored and effective therapeutic interventions in cancer treatment [1, 15].

Dual and Multiple Stimuli-Responsive Hydrogels: Combination of multiple stimuli-responsive mechanisms empowers hydrogels with enhanced responsiveness and adaptability to complex TME (Table 1) [16].

Table 1. List of dual and Multiple Stimuli-Responsive Hydrogels.

Stimuli	Composition	Highlights
Temperature; pH	PDMAEMA, DOX, ^{131}I-BSA	PDMAEMA solutions transformed into nanogels at 37 °C At pH 5.8, electrostatic repulsion within polymer network led to swelling and fast *in vitro* release of DOX
	CS-*g*-(mPEG-*b*-PCL), DOX, Curcumin	Sol–gel phase transition occurred at pH 6.9 and physiological temperature CS-*g*-(mPEG-*b*-PCL) hydrogels released both hydrophilic and hydrophobic drugs in sustained manner for up to 2 weeks
	P(NIPAM-*co*-IA), CS/β-GP, DOX	Incorporation of hydrophilic moiety (IA) elevated LCST of PNIPAM toward body temperature Swollen state of cationic hydrogel quickened release of DOX
pH; enzyme; light; temperature	Gela NP, PDA NP, DOX	GdL-induced acidification caused charge reversal of Gela NP to form colloidal Gela/PDA hydrogel Degradation of Gela NP by proteases anticipated responsiveness to MMP-2/9 and enzymatic promotion of DOX release PDA NP converted NIR light into heat, eliciting gel–sol transition and increased release of DOX
pH; ROS; GSH; light; temperature	HSF, Cy7, DOX	HSF molecules self-assembled into hydrogel via physical forces Acidity and ROS damaged β-sheet structure, whereas GSH cleaved intra- and intermolecular disulfide bonds in HSF molecules Hyperthermia generated by Cy7 upon NIR irradiation enhanced molecular thermal motion, disrupting physical interactions within hydrogel HSF hydrogels responded to multiple stimuli that together increased release rate of DOX

In conclusion, smart hydrogels mark a paradigm shift in tumor-targeted therapy. The versatility of stimuli-responsive hydrogels and their intratumoral delivery capabilities hold great potential for personalized and effective cancer therapy. As research progresses, these hydrogel-based strategies may revolutionize our approach to cancer treatment and bring new hope to patients and clinicians.

4. Hydrogels For Constructing The Tumor Microenvironment In Vitro

4.1. Overview of the tumor microenvironment

The TME consists of cancer cells and their surrounding stroma, including fibroblasts, endothelial cells, immune cells, and ECM (Fig. 2) [17]. Characteristics of the TME include high levels of ECM deposition, abnormal vascular structures, and the role of immune cells. Tumor cells influence drug response and tumor progression by interacting with the matrix. Tumor cells interact through ECM remodeling, angiogenesis, and immune cells, which together contribute to tumor progression [17].

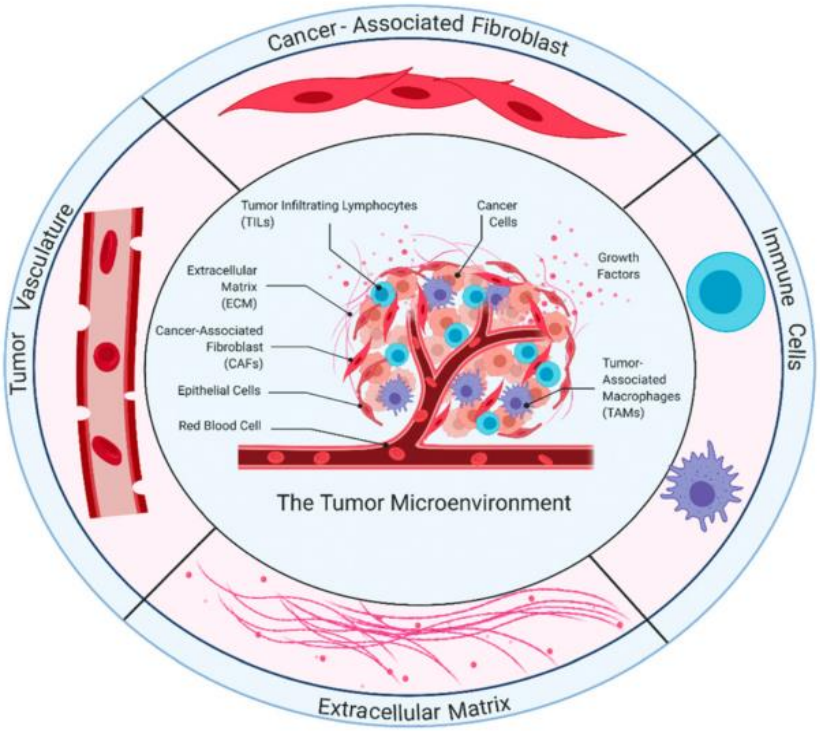


Fig 2. Composition and structure of TME.

4.2. Importance of studying the in vitro TME

The study of TME within in vitro models is gaining paramount importance in cancer research. This recognition stems from the realization that a comprehensive understanding of cancer biology necessitates the integration of TME elements. Here, we emphasize the significance of investigating the in vitro TME using hydrogel-based systems [17].

To faithfully replicate the intricate interactions between cancer cells, stromal components, and the ECM, researchers have embraced innovative strategies, with hydrogels emerging as a versatile tool. Hydrogels, characterized by three-dimensional networks of hydrophilic polymers cross-linked through physical or chemical means, provide an exclusive platform to mirror essential biophysical and biochemical features of the tumor ECM, thus fostering an environment conducive to both cancer and stromal cell cultures [5].

The success of in vitro tumor models hinges upon their capacity to accurately mimic the diverse characteristics of the TME. Hydrogels address this challenge by enabling meticulous engineering of their biochemical and biophysical properties, encompassing porosity, stiffness, and composition. This versatility arises from the categorization of hydrogels into natural, synthetic, or hybrid types, each offering distinct advantages in recapitulating the intricate complexity of the TME [18]. Mollica et al.'s study develops biomimetic 3D culture systems for improved cancer research. It utilizes rat and human mammary ECMs and introduces decellularized mammary glands as substrates. This innovative approach offers insights into cell-microenvironment interactions and enhances our understanding of cancer progression and treatment responses [18].

In summary, the integration of hydrogel-based systems to study the in vitro TME provides a transformative avenue for advancing cancer research. As the importance of the TME becomes increasingly apparent, the precise engineering of hydrogels allows for meticulous replication of its key elements. By bridging the gap between in vivo complexity and in vitro performance, these systems have the potential to reshape drug development strategies, guide personalized therapies, and facilitate a comprehensive understanding of the complex dynamics driving cancer progression. The journey to unlock the full potential of hydrogel models represents a promising step toward the ultimate goal of conquering cancer.

5. Reshaping The Adenosine Axis Through Injectable Hydrogel Strategies For Potent Cancer Therapy

5.1. Background of the adenosine axis and its role in the TME

Adenosine triphosphate (ATP), a crucial intracellular metabolite, transforms into a potent extracellular messenger upon release, engaging in diverse biological functions. Within the TME, extracellular ATP assumes a pivotal role in initiating precise immune responses by elevating tumor immunogenicity [19]. Nonetheless, the TME harbors an inherent negative feedback mechanism—the adenosinergic axis—converting ATP into immunosuppressive adenosine. This axis impedes immune reactions and fosters an immunosuppressive TME. Traditional methods indirectly target the adenosinergic axis, while an innovative approach involves enzymatically converting adenosine into an immunopotentiator, inosine. Our groundbreaking injectable hydrogel strategy introduces a novel paradigm, reshaping the adenosinergic axis by metabolizing adenosine into inosine [20]. Through this distinctive approach, our objective is to dismantle immunosuppression and invigorate the immune response, exhibiting promising prospects for potent cancer therapy.

5.2. Negative feedback mechanism mediated by CD39 and CD73 in adenosine conversion

The complexities of the TME introduce a notable challenge through the operation of the adenosinergic axis, an inherent mechanism that provides negative feedback. This axis revolves around the actions of CD39 and CD73 enzymes, which work together to convert extracellular ATP into adenosine, known for its immunosuppressive effects [21]. Consequently, adenosine regulates the

behavior of effector T cells, curbing their multiplication and cytotoxicity, while simultaneously encouraging the growth of regulatory T cells. The binding of the A2A adenosine receptor (A2AR) further contributes to immune suppression within the TME, thus dampening the immune response against tumors [19, 21].

Although conventional methods have indirectly addressed the adenosinergic axis, an innovative approach has emerged. By enzymatically converting adenosine into inosine, a substance that enhances immune response, a revolutionary concept has the potential to counteract immunosuppression and rejuvenate the immune reaction. A novel injectable hydrogel strategy that spearheads this idea, aiming to reshape the adenosinergic axis and foster a robust anti-tumor immune response. The integration of CD73 and CD39 inhibition with this strategy holds promise in breaking the negative feedback loop and bolstering the potential for effective cancer treatment [22-23].

The coordinated approach of the S@ABD hydrogel, which will be explained in 4.4, in cancer therapy arises from its significant impact on the adenosinergic axis, with a specific emphasis on the negative feedback orchestrated by CD39 and CD73. Experiments conducted within a melanoma model have provided substantial evidence of the remarkable therapeutic effectiveness of the S@ABD hydrogel [24].

Zhao et al.'s study presents a novel hydrogel strategy combining DOX and BTC to induce autophagy, ensuring ATP supply for a robust immune response. ADA within the hydrogel reconfigures the adenosinergic axis, converting immunosuppressive adenosine to immune-enhancing inosine, enhancing immunotherapy potential. Histopathological analysis confirms S@ABD hydrogel's significant impact on tumor tissue, disrupting adenosinergic axis via ADA-induced inosine conversion. This approach enhances immunotherapeutic response against tumors by countering CD73 expression and overcoming immunosuppression, offering innovative insights for effective cancer therapy [24].

5.3. Challenges of adenosine-induced immunosuppressive TME in tumor elimination

The TME created by the adenosinergic axis hinders anti-tumor immune responses. Adenosine, produced from extracellular ATP by CD73 and CD39 enzymes, suppresses immune activity [21]. A novel solution involves an injectable hydrogel designed to reshape the adenosinergic axis within the TME. This hydrogel includes adenosine deaminase (ADA) to convert adenosine into immunopotentiator inosine. When injected into tumors, the hydrogel triggers autophagy, releasing ATP and promoting immune response. ADA catalyzes adenosine-to-inosine conversion, dismantling immunosuppression and enhancing T cell proliferation and activity [21]. In vivo experiments with melanoma models confirm the hydrogel's effectiveness in inhibiting tumor growth, attributed to axis remodeling and immune-promoting TME [24].

In conclusion, this new strategy deftly addresses the problem of adenosine-induced immunosuppression by remodeling the TME through the ingenious application of an injectable hydrogel. This hydrogel disrupts the adenosinergic axis while promoting Teff proliferation via inosine synthesis, thus opening a promising path for potent and effective cancer therapy. By overcoming the obstacles posed by adenosine-mediated immunosuppression, this innovation is expected to change the landscape of cancer immunotherapy.

5.4. The potential of S@ABD Hydrogel in reshaping the adenosinergic axis and enhancing cancer immunotherapy

The adenosinergic axis holds a crucial role within the TME by converting extracellular ATP into immunosuppressive adenosine. This pathway impedes the immune response against tumors by fostering adenosine buildup and dampening immune cell function. To counteract this suppression, a novel approach has emerged using an injectable hydrogel platform (S@ABD) [24].

The S@ABD hydrogel amalgamates various elements: adenosine deaminase (ADA), an enzyme that transforms adenosine into the immunopotentiator inosine; an autophagy inducer (BTC) and a chemotherapeutic drug (DOX) that synergistically boost ATP release; and sodium alginate (SA) that

forms the injectable hydrogel. This intricate combination tackles the hurdles posed by the adenosinergic axis and the degradation of extracellular ATP in the TME.

This hydrogel-based strategy yields several pivotal outcomes:

Reversing the adenosinergic axis: By infusing ADA into the hydrogel, the adverse feedback loop of the adenosinergic axis is disrupted [21]. This culminates in the conversion of immunosuppressive adenosine into the immunopotentiator inosine. This conversion intensifies the immune response against tumors and spurs T cell activation [20, 24].

Amplified ATP Release: The interaction between DOX and BTC within the hydrogel triggers autophagy, fostering ATP release from apoptotic tumor cells [20]. This ATP serves as fuel for immune cell activation, further bolstering the immune response [24].

Reshaping the TME: The hydrogel shapes an immunogenic microenvironment within the TME. It reshuffles the TME by curbing the conversion of ATP to adenosine and augmenting the presence of inosine and ATP. This shift from an immunosuppressive to an immunogenic setting bolsters immune cell action against tumors.

In Vivo Anti-Tumor Effectiveness: In a live melanoma model, the S@ABD hydrogel exhibits robust anti-tumor effects. It markedly suppresses tumor growth both locally and in distant sites (abscopal tumors), outperforming other hydrogel formulations. This underscores the therapeutic potential of the hydrogel approach [24].

In summary, S@ABD hydrogels have set a precedent for remodeling the adenosinergic axis within TME. By simultaneously addressing both adenosine conversion and ATP supply, this approach overrides the immunosuppressive outcome of this axis and improves the immune response to tumors. Hydrogel-based approaches offer a promising avenue for effective cancer therapy by effectively remodeling the TME and enhancing immunogenicity.

6. Conclusion

Hydrogels have emerged as dynamic tools with immense potential to reshape cancer treatment strategies. Their unique ability to mimic the ECM and create intricate TME models in vitro opens new avenues for cancer research and therapy. By precisely tailoring their biophysical and biochemical properties, hydrogels facilitate the study of complex cancer-stroma interactions and enable the development of innovative drug delivery systems. Smart hydrogels, responsive to specific triggers within the TME, hold promise for targeted drug release and enhanced therapeutic efficacy. Moreover, the novel approach of reshaping the adenosinergic axis using injectable hydrogels demonstrates the potential to overcome immunosuppression and bolster anti-tumor immune responses. As research progresses, hydrogel-based strategies are poised to revolutionize cancer treatment, guiding personalized therapies and advancing our understanding of the complex dynamics driving cancer progression.

While the translation of hydrogel-based therapies from bench to bedside requires overcoming challenges related to scalability, standardization, and regulatory approval. Achieving precise control over hydrogel properties, such as stiffness and degradation rates, remains a technical challenge. Furthermore, hydrogel-based therapies must navigate the complexities of individual patient responses and potential adverse effects. Future research efforts should focus on refining hydrogel fabrication techniques, optimizing drug release kinetics, and conducting rigorous clinical trials to validate their safety and efficacy in human patients. By addressing these limitations, hydrogels can fully harness their potential to transform cancer treatment and significantly improve patient outcomes.

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