

Application Exploration of Multifunctional Hydrogels in Local Drug Delivery and Anti Inflammatory Microenvironment Construction

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ABSTRACT

This paper examines the use of multi-functional hydrogels in local drug delivery and designs strategic anti-inflammatory microenvironments. Hydrogels are three-dimensional cross-linked polymeric networks with tunable properties that can serve as good biomaterials for spatiotemporal control of therapeutic agent release. At present, in terms of the main Design ideas of these biomaterials, emphasis is placed on stimuli-responsive architectures and injectable forms to achieve localised drug release at diseased tissues. In addition, this paper explores the way to integrate immunomodulatory drugs and functional nanomaterials more proactively into hydrogel carriers for treating local inflammation. Through organisation of macrophage polarisation, active remodelling of the pathological cellular niche can be achieved by the biomaterials, and they are thus transformed from passive delivery systems into dynamic therapeutic platforms. Synthesize relevant research papers to assess the effect of the above systems on chronic wound healing and tissue regeneration in solid tumour therapy. In addition, this paper will address the existing structural deficiencies and regulatory hurdles, as well as the future engineering optimisation directions required for the clinical translation of advanced hydrogel delivery systems. Standardisation of the manufacturing process and validation of long-term biological safety are still required for wider clinical application.

KEYWORDS

Multifunctional Hydrogels; Local Drug Delivery; Anti-Inflammatory Microenvironment; Stimuli-Responsive Polymers; Macrophage Polarization; Tissue Engineering

1. INTRODUCTION

Local diseases are generally not subject to the same side effects as drugs in the entire body. The conventional routes of drug administration, such as oral and intravenous routes, are prone to systemic toxicity and have relatively low concentrations at the diseased site. Conventional ways cannot keep the therapeutic concentration in a particular small area stable because they are rapidly broken down by metabolism and enzymes, and they do not distribute evenly throughout the body. Therefore, biomedical engineering and materials science have begun to focus on the development of specialised localised drug delivery systems. The first goal of the above-mentioned targeted systems is to deliver the therapeutic materials precisely to the place of injury, maximise treatment effectiveness and reduce damage to the body from other areas.

Hydrogels have gradually been applied in recent years to address the aforementioned difficult problems in drug delivery. Hydrogels are cross-linked three-dimensional networks of hydrophilic polymers that can absorb and hold a large amount of water or biological fluid naturally without losing their structure. Hydrogels have a high water content and a soft structure and texture; thus, they are

relatively close to those of natural biological tissues. The above structure is naturally compatible with the body; therefore, hydrogels can be used directly in vivo to avoid adverse effects such as severe foreign-body reactions or prolonged immune responses.

Now, research on materials has begun to focus on multifunctional hydrogels in an engineering manner. These complex polymeric systems are used to control the release rate of medicinal materials; at the same time, they can be triggered by specific signals from the body and change their properties dynamically in the presence of cells. A representative use of the above active biological interactions is the targeted creation of an anti-inflammatory microenvironment. An irreducible chronic inflammatory state is a common pathological feature of many debilitating diseases, such as delayed wound healing, severe autoimmune diseases, and the expansion of a local tumour microenvironment. Alteration of the physical and chemical properties of hydrogels can reduce harm caused by localised immune reactions and oxidative stress, and injured tissue in living cells can be repaired.

The purpose of this all-encompassing academic review is to study the application of multi-functional hydrogels in localised drug delivery and microenvironment modification. Section 2 will introduce the basic design Ideas and the physical phenomena of controlled drug release in polymer networks. Section 3: Application of stimuli-responsive hydrogels in targeted drug delivery. Section 4 introduces the active construction of anti-inflammatory local microenvironments and targeted immune regulation. Section 5 presents the latest clinical applications and current limitations of systemic manufacturing for tissue engineering and local tumour therapy. Section 6 is a summary section. Based on the above analysis, this paper will introduce the theoretical system and prospects of application in clinical practice for these new biomaterials. At present, many efforts are underway to integrate biomaterials into the body for various medical applications in research and development. To keep the cells alive and functioning normally over an extended period, the synthetic matrices need to be closely similar in structure to those in the natural extracellular matrix.

2. STRUCTURAL DESIGN AND DRUG RELEASE KINETICS

A hydrogel can serve as a carrier system for drugs to deliver them locally, and thus a controlled-release phenomenon will occur due to changes in the structure or other physical and chemical reasons. Hoffman's [1] first determined that various hydrogel types, from those that are simply physically intertwined to those with complex chemical cross-links, have different permeation and diffusion speeds for solutes in their swollen polymer networks. In light of the above structural basis, recent studies have explored how changes in hydrogel network characteristics and hydrogel-drug interactions can modify release profiles [2]. The size of the structural mesh is the distance separating individual polymer cross-links in the system; it serves as a physical obstruction to the outward diffusion of encapsulated drugs [1, 3]. A low initial polymer concentration can be employed to reduce the size of the mesh in a certain drug-releasing material and change its release characteristics.

Many kinds of high-end hydrogel systems have been developed to achieve accurate spatio-temporal control over non-Fickian diffusion. Zhang and Khademhosseini [3] showed that dynamic cross-linking strategies can be employed to degrade the polymer network in a controlled manner when cells are introduced. At the same time, the conventional continuous-release method uses hydrolytically cleavable chemical bonds embedded directly in the main chain of the polymer. As the structural network progressively disintegrates in the physiological environment, the trapped drug molecules are continuously released into the surrounding local tissues and thus maintain a prolonged therapeutic effect [2, 4]. A controlled-degradation method can be employed to reduce the amount of damaged tissue requiring surgery, and based on recent research in tissue engineering, it is now an available alternative.

Another problem is the actual state of the hydrogel before use in patients' bodies. Injectable Hydrogels can be used to avoid surgery and be injected. These highly specialised systems are in the form of low-

viscosity liquid precursor solutions that can be delivered to deep or irregularly shaped diseased tissue sites via a minimally invasive standard-syringe method. Contact with certain physiological stimuli causes the liquid precursor to rapidly undergo a sol-gel phase change and form a solid hydrogel matrix in situ at the site of injury [4]. This close fit of the anatomy will ensure that the biomaterial is in direct contact with the native tissue, thus enhancing the efficiency of drug delivery and localised anti-inflammatory effects [2, 4].

3. STIMULI-RESPONSIVE ARCHITECTURES FOR TARGETED ADMINISTRATION

A typical feature of new research in the field of hydrogels for local drug delivery is their stimuli-responsive, or "smart", polymeric structures. These high-tech materials will be affected by certain changes in the environment and release the cargo only under abnormal circumstances [5]. The tumor microenvironment generally has a low extracellular pH and a relatively high local temperature compared with healthy tissues [6]. Stimuli-responsive hydrogels can be developed that are triggered by the above specific physiological signals to prevent early drug leakage in healthy tissues. When these hydrogels reach an acidic lesion, the protonation of certain functional groups in the polymer network causes rapid swelling of the matrix and thus releases the encapsulated agents promptly.

To improve this targeting function, scholars have often been using enzyme-responsive degradation. Some pathological conditions, such as chronic inflammatory wounds and aggressive solid tumours, are associated with abnormal biochemical signals, including a low pH, oxidative stress and elevated enzyme activities [5, 6, 10]. Therefore, hydrogels can be engineered to have responsive chemical bonds or degradable linkers that respond to these pathological signals for localised and disease-associated drug release [5, 10]. As shown in recent reviews of oncology materials, the specific design can be used to release the drug cargo from the hydrogel at a speed related to the severity of the local disease. Directly connect the drug release kinetics with biological markers of disease severity, and thus create an autonomous, self-regulating drug-delivery system for responsive materials.

Multiple stimuli-responsive mechanisms are being incorporated into a single hydrogel matrix at present to construct a target-delivery system. Dual-responsive hydrogels need both an increase in temperature and a specific enzyme to be activated; thus, they have shown lower off-target toxicity [6, 10]. Therefore, several verification methods can be used to confirm that highly toxic chemotherapeutic drugs are stably bound to the polymer matrix in healthy tissues during circulation. At this point, when a multi-stimulus pathological niche is reached, a hydrogel rapidly changes its structure to release a high concentration of therapy precisely at that site to kill cancer cells or suppress severe localised infections [6, 11].

4. ACTIVE MODULATION OF THE LOCAL ANTI-INFLAMMATORY NICHE

Besides passive drug delivery, a new type of therapeutic effect for many-functional hydrogels is the active formation of an anti-inflammatory microenvironment. Chronic localised inflammation is generally a severe and destructive physiological state characterised by a high level of reactive oxygen species (ROS). To address the problem of oxidative stress, researchers have developed pathological microenvironment-responsive anti-inflammatory hydrogels [8]. Liu et al. [7] have presented injectable pathological microenvironment-responsive anti-inflammatory hydrogels that can respond to inflammatory pathological conditions and offer a biomaterial strategy for local anti-inflammatory regulation. Therefore, this focused method reduces local oxidative stress and offers support for cell repair at the same time [7, 8]. The hydrogel backbone is a free-radical scavenger that achieves dual therapy [10].

The construction of this good microenvironment will also need to change the type of immune cells, such as macrophages. The local microenvironment of the surrounding area is the primary reason for determining whether resident macrophages will be activated as M1 or M2 [9, 11]. Macrophage M1 cells are generally in an anti-inflammatory M2 state under normal conditions for tissue repair. Macrophages in chronic diabetic wounds or severe autoimmune lesions are frequently locked in the damaging M1 state and cannot switch to other states to prevent further tissue injury [8, 11]. Recently, multifunctional nanocomposite hydrogels have been designed to drive the required phenotypic conversion by force.

Add specific antioxidant components and strong immunomodulatory drugs to the hydrogel matrix directly, and it will actively inhibit harmful M1 activation [8]. Hydrogels release specific chemical cues and localized pharmacological gradients that stimulate the rapid recruitment and active polarisation of beneficial M2 macrophages. Chemically induced and significantly altered in the phylum level, chronic inflammation has thus been suppressed at the cellular level. Next, the newly formed M2-dominant area will promote the critical biological processes of new tissue regeneration, such as accelerated fibroblast migration and strong angiogenesis, to restore functional homeostasis of the damaged tissue [10, 11].

5. CLINICAL TRANSLATION, ONCOLOGY APPLICATIONS, AND MANUFACTURING BOTTLENECKS

Localisation of drug delivery and fine-tuning of the immune microenvironment have achieved excellent results in all areas of medicine, such as advanced tissue engineering and localised tumour therapy. A long-standing local inflammatory condition in the treatment of serious chronic wounds is unable to heal normally [8]. Multifunctional hydrogels address the above complex pathological problems simultaneously by encapsulating antimicrobial agents and specific anti-inflammatory drugs [3, 10]. These composite hydrogels continuously treat local bacterial infections and reduce the severity of the inflammatory response. A strong hydrogel matrix is a relatively moist and protecting material that helps to prevent severe dehydration of damaged tissue and promotes rapid re-epithelialization [3, 11].

Smart hydrogels have also introduced a new generation of localised oncology treatments by alleviating the problem of immunosuppression caused by solid tumours [9]. Specialised, injectable hydrogels that carry a high concentration of strong chemotherapy drugs can be used to deliver a large amount of toxic material directly to the site of a removed tumour in the middle of surgery [6, 11]. This way will not cause serious systemic toxicity. Modern hydrogel platforms can also be used to combine this localised chemotherapy with active immune microenvironment remodelling. These high-performance hydrogels release particular immunomodulatory factors to draw cytotoxic T lymphocytes directly to the site of damage and thus create a highly active immune area in an unresponsive tumour microenvironment [10-11].

Although there have been some impressive preclinical results, several serious structural, biological and regulatory problems have yet to be solved; thus, these multi-functional hydrogels have not yet entered general clinical use. The first engineering problem is how to balance the strength of the hydrogel in mechanics with its required biodegradability in the body [2, 3]. To improve the mechanical properties of the structure, increase the cross-linking density of the polymer, reduce the space for cell infiltration, and thereby slow down controlled degradation. Moreover, the excessively complicated production process for stable-stimulus-responsive nanocomposite hydrogels is also difficult to scale up in industry. Small fluctuations in the molecular weight of consecutive batches of polymer affect drug release [4]. Therefore, the development of standardisation and automation in manufacturing processes, along with all-encompassing and prolonged in vivo toxicity research, must be carried out before these advanced delivery systems can be applied widely in the clinic [10, 11].

6. CONCLUSION

Multi-functional hydrogels are being used in some fields of local drug delivery and the construction of anti-inflammatory microenvironments to achieve good results in modern biomedical engineering. Hydrogels have a good and versatile structure that can achieve the simultaneous spatially and temporally controlled release of strong medicinal substances and active regulation of surrounding cells. High-precision engineering of multi-stimuli-responsive polymer structures and various injectable formulations have been introduced to develop dynamic, intelligent biomaterials that can respond promptly and accurately to specific pathological signals.

These highly interactive systems have successfully broken the old model of passive drug carriers. Specifically reduce damaging localised oxidative stress to avoid serious bacterial infection and induce a pro-healing macrophage polarisation state at the basic level, thus actively resolving severe chronic inflammation via multi-functional hydrogels. Chemically induced modification of the microenvironment speeds up the complicated healing of chronic wounds and improves the high-specificity effect of localised tumour therapy. Hydrogels are now dynamic, active immunomodulatory environments that can deliver drugs for treating diseases rather than just serving as passive delivery systems.

However, the full extent of the above-mentioned clinical applications is constrained by the entire scientific community's inability to address the significant structural and regulatory barriers that have not yet been overcome. Strictly optimise the complex mechanical properties of hydrogels, establish perfectly reproducible large-scale production processes, guarantee absolute long-term biological safety through all-encompassing toxicity tests, and thus meet the conditions for successful clinical application. By continuously addressing these long-standing engineering and regulatory challenges with high-level interdisciplinary research, the biomedical community aims to help multi-functional hydrogels move from the lab to standard clinical practice to offer potent targeted therapeutic options for localized human diseases.

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