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Stimuli-responsive DNA-based hydrogels for controlled drug delivery applications

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Abstract

Adverse side effects from drugs being delivered to healthy tissue inside the body remain a persistent challenge within the medical field. Targeted drug delivery by use of stimuli-responsive DNA-based hydrogels emerge as a promising solution to this issue. These hydrogels can be used for a "smart" controlled drug delivery system that enables a drug to be delivered to a target location in a controlled amount by responding to an external stimulus. DNA hydrogels that respond to various non-biological and biological stimuli and their potential applications for targeted drug delivery are discussed in this paper.

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1. Introduction

Traditional drug delivery systems are associated with adverse side effects due to their nonspecific biodistribution, and uncontrollable drug release [1]. This can cause drugs to be released in an area with healthy tissue, which can be harmful, and waste the drug. Controlled, targeted drug delivery systems with the use of stimuli- responsive DNA-hydrogels emerge as a solution to this limitation. They can allow for the drug to be released in a controlled manner in a specific location. This increases the effectiveness of the drug while reducing the toxicity to the whole body by containing the drug one area instead of allowing it to spread to non-target sites where it may have a harmful effect.

There have been many recent developments in DNA-based hydrogels that show potential for use in targeted drug delivery systems. A hydrogel is a hydrophilic gel that is made up of crosslinked polymer chains, and it can often be crosslinked with another substance, such as DNA. DNA, a molecule composed of nucleic acids, contains genetic information in all living organisms. DNA is hydrophilic, biocompatible, and highly programmable, making it a material of choice for biomedical applications [2]. Furthermore, DNA as a molecule exhibits great mechanical rigidity and physicochemical stability, which makes it an ideal molecule to be cross-linked into a hydrogel.

DNA hydrogels can be stimuli-responsive, which means that they can change phase properties or crosslinking density in response to environmental changes or external stimuli [2]. Triggers are either biological or nonbiological. Biological triggers are biomolecules, including nucleic acids, antigens, enzymes, and adenosine triphosphate (ATP). Non-biological triggers include temperature, light, pH, and magnetic fields [3]. Interactions between the trigger and the hydrogel cause changes in the properties of the hydrogel, including capturing or releasing small molecules or macromolecules. This translates to drug delivery when a DNA-hydrogel is loaded with a drug, the drug can be released in a controlled manner by responding to the stimuli. Stimuli-responsive DNA-hydrogels have implications for targeted drug delivery systems as a target site in the body can have a specific stimulus which triggers a DNA-hydrogel to release a drug. This is known as a 'smart' controlled drug delivery system, which is aimed to achieve drug accumulation at disease sites, in order to reduce drug accumulation in undesirable locations and non-target locations. By focusing the drug accumulation in the target area of a biological system, this will thus reduce the overall toxicity. In comparison to traditional drug delivery methods, this approach to drug delivery has also been shown to reduce the frequency of drug dosages while maintaining a high

concentration of drug accumulation in target areas of the body for an extended period [1]. Furthermore, these hydrogels have been shown to be successful in targeting sites of tumors, infection, inflammation, and damaged tissue, which shows promise for uses in therapies including chemotherapy, immunotherapy, and gene therapy. Various DNA-hydrogels that respond to both biological and non-biological stimuli will be discussed in this report.

2. Non-Biological Stimuli

2.1. Temperature Responsive

Temperature may be used as a stimulus for DNA-hydrogels when a temperature higher than the DNA melting temperature is applied. The melting temperature of DNA depends on the length and composition of the DNA, but is typically between 50 and 100ºC [3]. In a DNA-hydrogel, when the critical DNA melting temperature is reached, the DNA duplex breaks and leads to a reversible phase transition from a gel into a solid [4]. Guo et al synthesized a DNA-hydrogel that undergoes a gel-solid transition at 32ºC, which is close to the ambient human temperature of 37ºC [5]. This temperature-dependent property of DNA hydrogels has implications for drug delivery, as specific hydrogels can be loaded with a drug in a solid phase, and upon contact with a target tissue site of lowered temperature (below 32ºC), the duplex transitions into a gel and releases the drug. This can allow for drugs to be localized to a target site when the DNA duplex breaks upon coming into contact with the temperature at the target and releases a drug in gel form.

2.2 Light Responsive

Light can also be used as a stimulus in DNA hydrogel and is favorable as it can be administered remotely and with high accuracy. In 2012, the Tan group designed a photo-responsive DNA-polymer hybrid hydrogel [6]. This research group cross-linked DNA with a hybrid acrylamide polymer hydrogel to create a molecule that is photosensitive and can isomerize depending on the wavelength of the light it is exposed to. They found that irradiation of visible light causes formation of DNA duplex-cross linkers, while irradiation of UV light causes the dissociation of DNA duplex cross-linkers [6]. This study shows the potential for light-stimulated DNA hydrogels loaded with drugs as treatments in the human body, with exposure to UV light being used to cause the DNA duplex to dissociate and release a drug to a target area. However, further research needs to be done before using UV light as a stimulus, as UV light have known harmful effects on the human body [6].

2.3 Magnetic Field Responsive

Magnetic fields are a third non-biological stimuli for DNA-based hydrogels. External magnetic fields can remotely control DNA hydrogel migration in time and space. This was described by Ma et. al, when they introduced magnetic nanoparticles into a DNA hydrogel [7]. This was formed with scaffolds and complementary linkage. The magnetic nanoparticles were encapsulated by DNA through hybridization in order to prevent the magnetic nanoparticles from leaking out of the DNA [7]. One of the benefits of adding a magnetic component to the hydrogels is that the gel can be molded into specific shapes that are desirable for drug delivery purposes. Furthermore, the magnetic response can be used to direct the movement of the DNA-hydrogels, and their contained drug(s), to a specific location by controlling an external magnetic field.

A successful application of this was done by Yao et. al, where they created a magnetic DNA nanogel using iron oxide magnetic nanoparticles as the core [8]. In this study, Doxorubicin, an anticancer drug was loaded into the nanogel, and an external magnetic field was used to guide the nanogel to the tumor site [8]. This study successfully demonstrated the ability of a magnetic-stimulated DNA hydrogel to locate a and transport a drug to a target site. Furthermore, they found that the nanogel that they created was not only stimulated by magnetic fields, but also pH and nuclease, which has potential to allow for both the location and time of a drug release to be controlled.

3. Biological Stimuli

3.1. pH Responsive

PH can be considered biological stimuli for DNA-based hydrogels, as all the conditions that trigger a shift in pH are biological. Most tumor, infection, inflammation, and tissue damage sites exhibit higher acidity than the healthy parts of the human body. Therefore, DNA-hydrogels that are stimulated by pH have shown potential for drug release to target these sites. This was successfully demonstrated by Liu et. al, who made a fast-acting pH responsive DNA hydrogel. At higher (basic) pH's, the DNA hydrogel keeps its isolated state [9]. However, when the pH lowered, the DNA became protonated, and the solid to gel switch occurred, allowing for the release of a drug. While this hydrogel is stable at basic conditions, more recently, Hu et al. discovered a method of creating a DNA-hydrogel that would be stable at neutral conditions that undergoes a solid to gel switch at a lower (more acidic) pH [10]. This hydrogel demonstrated promise for targeting sites of tissue damage within the body that exhibit lowered pH. However, there are limitations with these studies as the hydrogel has not successfully been delivered *in vivo*. Further research needs to be done on the amount of time for the solid to gel transition to occur as well as if this hydrogel is stable in physiological environments in order to this to extend this technology to human applications.

3.2 ATP Stimulated

Biologically-stimulated DNA-hydrogels also have potential for drug delivery. Recently, adenosine triphosphate (ATP) - aptamer cross-linked DNA-stabilized microcapsules were created by the Wilner group. The microcapsules were loaded with a drug, and when stimulated by the presence of ATP, aptamer-ATP complexes were formed, resulting in the dissociation of the DNA-microcapsules. Since ATP is

overexpressed in cancerous tumor cells, this ATP-stimulated hydrogel can boost the release of cargos in targeted areas with greater amounts of ATP compared to healthy tissue [11]. This would allow for drug distribution in target tissue while avoiding healthy tissue.

The Qi group also developed ATP-responsive DNA-hydrogels [12]. These hydrogels were created by grafting DNA strands onto polymer chains, which were hybridized by ATP aptamers to form a hydrogel with a shell core. They were able to load the hydrogel with Doxorubicin, an anticancer drug, resulting in a nanogel with a fairly large particle size. The system created by the Qi group utilized both pH and ATP responsiveness [12]. When the hydrogel was around a tumor with a lowered pH (6.4), the size of the gel was compressed, causing the drug to be released [12]. Furthermore, the ATP rich tumor sites further enabled the drug release [12]. The research done by this group was a successful example of a targeted drug delivery system promoted by two different stimuli.

3.3 Enzyme Stimulated

Enzyme-stimulated DNA-hydrogels also show great potential for drug delivery. A restriction enzyme is a protein that cleaves DNA at certain sites called restriction sites. The digestion of DNA duplexes at specific restriction sites can be enabled by these enzymes. These sites can be introduced in DNA monomers and used to build enzyme-stimulated DNA-hydrogels. The resulting hydrogels can be dissociated at the presence of a specific restriction enzyme [13]. This has promise for drug delivery as a target site in the human body may have a unique enzyme that could activate an enzyme-stimulated DNA-hydrogel to release the drug at the target site.

4. Conclusions

To conclude, the study of DNA-hydrogels is growing in the field of materials science and engineering. These novel drug delivery systems have capabilities to overcome shortcomings of conventional drug delivery systems. Specifically, stimuli-responsive DNA-hydrogels are very useful for drug delivery, as once they are activated by specific stimuli, they can target specific locations in the body to release the drug. This has the potential to both increase the efficiency of a drug and reduce the toxicity of the drug in the body by localizing the drug to a specific location and minimizing the chance of the drug going to non-target sites. This can be used in treatment of numerous health ailments, including cancer, where current treatments are invasive and non-specific. Furthermore, the use of targeted drug delivery systems can reduce drug dosage frequency and amounts, which could mean a lower financial cost to the patient.

Although there has been much research done on creating different types of DNA-based hydrogels, and the many applications of these gels, further research must be conducted to extend the applications of this novel technology. While DNA hydrogels have consistently demonstrated promise for drug delivery applications, they have limited stability, and there is a high cost associated with the production of these hydrogels [14]. In order to extend this technology out of the laboratory, further testing needs to be done on the stability of these hydrogels in physiological conditions. A more cost-effective method of synthesizing these hydrogels must be considered before extending these drug delivery systems to in-vivo applications.

Conflict of Interest

The author declares no conflict of interest.

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