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Efficiencies in the Use of Nanorobots in Targeted Drug Delivery for the Treatment of Cancers

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Abstract. Cancer has been one of the leading causes of death worldwide. Accurate diagnosis of these cancers often takes time and traditional treatments may cause harmful side effects on the patients. Nanotechnology has provided revolutionary breakthroughs in the diagnosis and treatment of cancers due to the biocompatibility, accessibility, control, and targeting characteristics of the nanoparticles. This research study focuses on the use of nanoparticles and nanorobots for targeted drug delivery specific to the tumor cells to minimize the adverse side effects of cancer treatment. There are various studies of nanoparticles that have been found to contribute to the drug delivery process. These include "Cornell Dots" (C Dots), bioadhesive nanoparticles, logic-gated nanorobots, and self-propelled autonomous nanorobots. Some of these nanoparticles, like C Dots, focus on the detection of the tumor and signifying the tumor location. Others, such as bioadhesive nanoparticles, are designed for the release of drug candidates once the tumor is detected. This research study aims to identify recommendations for improving upon drug delivery to target tumor cells using combined approaches from these studied uses of nanoparticles. One focus is the use of multi-gated aptamers to release drugs based on certain conditions being met, thus opening the nanostructure to release the drugs. Another option would be the controlled release of a drug using gated aptamers with bioadhesive properties. If these recommendations can be successfully evaluated in laboratory research then it will significantly reduce the need for high doses of chemotherapy, increase the treatment efficiency, and also minimize the side effects of these anti-cancer drugs on the patient.

Keywords: nanoparticles, nanorobots, drug delivery, cancer treatment, aptamers

1. Introduction

Cancer is caused by the proliferation of mutated body cells that may become malignant and metastasize to other parts of the body. Since cancerous tumors are not strictly localized to any one particular area of the body, treatment for cancer without significant side effects can be difficult. The cause for these side effects is mainly due to high dosage of drugs that are required to be administered to a human body in order to reach the targeted tumor sites. Current common treatments like chemotherapy are able to contain the proliferation of cells by killing cancer cells. Other unharmful rapidly dividing cells, however, are also affected by the chemotherapy drugs, causing side effects like hair loss and nausea. One of the goals in the recent research in the drug delivery arena has been to

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derive innovative treatments that are not only precise in targeting the cancer cells but also steering clear of the healthy surrounding cells.

The development of nanoparticles and nanorobots for drug delivery is a potential solution to the problem. With targeted drug delivery of anticancer drugs, cancerous tumors can be treated and minimized without the harmful effects on healthy human body cells. The developments of the C Dots, sticky nanoparticles, logic-gated nanorobots, and self-propelled nanorobots are some of the breakthroughs that have been made in nanorobotics use for drug delivery. These nanoparticles are able to aid in the development of nanoparticles that may be able to treat cancerous tumors with widespread use. This research study analyzes some of these novel nanotechnology innovations with emphasis on areas of new opportunities to enhance the use and efficacy of these nanorobots.

2. Analysis

2.1. Fluorescent nanoparticles

The "Cornell Dots", also known as C Dots, developed by Dr. Ulrich Wiesner serves as a biomarker with the purpose of identifying and locating tumors in the body [1]**.** The benefit of these nanoparticles is that they are "silica-encased fluorescent nanoparticles" [1] which allow experimenters to see the location of the tumors based on the fluorescence of the C Dots [2]. Inside the silica shell of the C Dots, there are fluorescent dye molecules that lead to the detection of the C Dots within the body. When there is a high density of these dye molecules when exposed to near-infrared light, it is indicative of the cancer tumor being present in that area as the C Dots stick to the tumor cells through molecules that bind to tumor cells (Figure 1). By use of fluorescence indicators, examiners can also visualize if the tumor has become metastatic and spread to other organ systems, which would be indicated by multiple clusters of fluorescent C Dots being displayed. In the current human trials of these nanoparticles, the fluorescence of radioactive iodine will be visible through PET scans. The C Dots are able to locate the tumors through tracking cancer markers, with a new iteration being able to track multiple cancer markers in tumors [3].These dots have the capabilities to also function as nanocarriers and deliver drugs to the tumor sites which they have identified. With this, C Dots can be used as a dual agent to both visualize the tumor as an examiner as well as treat the tumor with the necessary anticancer drugs required [4]. The fluorescent property of the nanoparticles will also allow for monitoring of the tumor to assess the rate with which it is being treated, thus providing information on the necessary doses. In addition, the C Dots are able to be cleared from the body due to their small size of 5-6 nm in diameter leading to easy clearance by the kidneys (Figure 1). This further strengthens the benefit of C Dots as they do not cause side effects in other parts of the body when not in use or if the tumor is not properly located.

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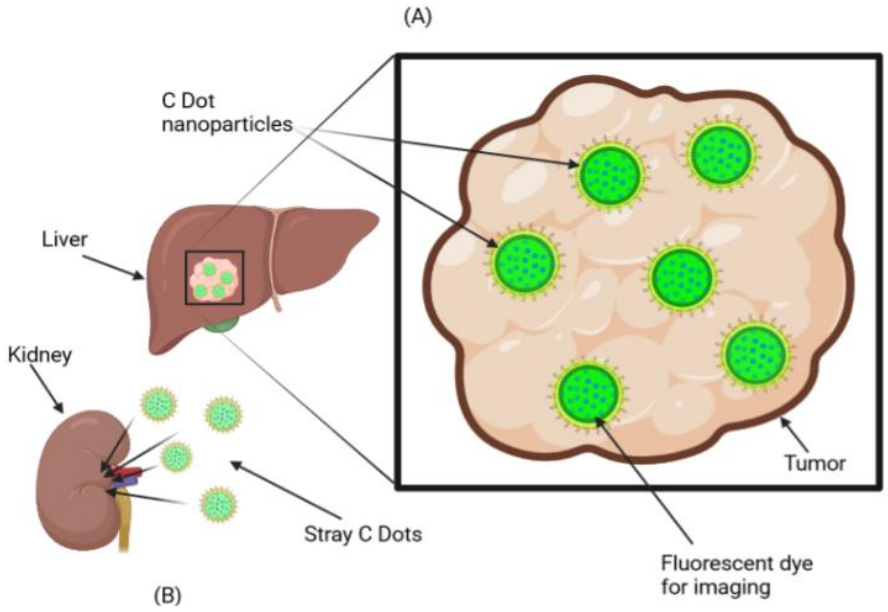

Figure 1. (A) C Dots with fluorescent dye for imaging are able to enter the tumor due to their ultra small size of 5 nm to 6 nm. This accumulation of C Dots allows for the visualization of the location of the tumor. (B) Stray C Dot nanoparticles are cleared from the body through the kidneys, limiting the side effects of accumulation of stray nanoparticles in the body.

2.2. Bioadhesive nanoparticles

Bioadhesive nanoparticles or sticky nanoparticles are nanocarriers which are loaded with chemotherapy drugs to be released at the tumor site [5]. In the research conducted by Dr. Mark Saltzman and Dr. Alessandro Santin, the sticky nanoparticles were targeted toward the treatment of gynecological cancer [5]. Though anti-cancer drugs have high toxicity, the encasement of these drugs in nanoparticles substantially reduces the toxicity of the drug to the body. In addition, the direct release of the drug at the tumor site contributes to the reduction of side effects. This study, however, determined that nanoparticles typically have a short time span to remain at the tumor site and does not allow for the most effective release of anticancer drugs. Through the addition of aldehyde groups, to which the bioadhesiveness of the nanoparticles is attributed, the nanoparticles can attach to the tumor cells. When comparing the adhesiveness of nanoparticles, sticky nanoparticles are shown to be more effective than non-adhesive nanoparticles. The bioadhesive nanoparticle was able to stay attached for a minimum of 24 hours whereas the non-adhesive nanoparticles could only stay attached for five minutes. The drastic change in adhesivity between these two displays the importance of bioadhesive properties for drug carriers, especially those targeting tumors.

2.3. Logic-gated nanorobots

Logic-gated autonomous nanorobots are DNA nanorobots that are controlled by inputs on the cell surface [6] [7]. These nanostructures are made using single-stranded DNA that forms a hexagonal three-dimensional structure that encases the drug [6]. This structure is hinged on one side to allow for the opening of the nanorobot. The logic-gating of this structure is attained through the use of aptamers. These aptamers sequences are encoded to recognize certain stimuli when reacting with binding antigens. This programmability of the DNA nanostructure allows for the nanoparticle to respond to stimuli [8]. If the conditions of the aptamers are met, the DNA nanorobot will open to release the drug into the tumor. Additionally, if multiple sequences of inputs are required to satisfy the conditions of the aptamers, then both conditions must be met before the DNA nanorobot can open to release the drugs.

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2.4. Self-propelled nanorobots

Self-propelled nanorobots are driven by external fields as their form of navigation through the body [9]. These nanorobots can be propelled by various types of propulsion, including chemical, physical, light, propulsion [9][10]. These methods of propulsion allow for nanoparticles to be able to be remotely controlled to reach difficult areas of the body [11].One method of chemical propulsion, as described in the study conducted by Yinglei Zhang, is the reaction between the molecules on a nanoparticle and its surrounding environment [9]. In this study, the reaction of chemicals in the nanoparticle with H_2O_2 caused the creation of bubbles, thus propelling the nanorobot [12]. Though this situation works, the use of natural catalysts is needed to model the potential reactions that could occur in the human body. Physical propulsion of the nanorobots mainly occurs through responses to light, radiation, magnetic fields, or electrical fields. However, since many of these are unable to be used as physical stimuli for the nanorobots within human bodies, sonic waves have shown to be a promising option for controlling the nanorobots. Since sonic waves are able to travel through various states of matter, controlling the nanorobots from outside the human body would be possible. In addition, there are little to no adverse effects of sonic waves on the human body.

3. Recommendations

Significant advancements have been made in nanotechnology by using nanoparticles to deliver the therapeutic drugs for treating various types of cancers [13] [14]. Based on these various types of researched nanoparticle applications and structures, a few recommendations can be made for enhancing the effect and efficiency of the nanoparticles. Many of these nanoparticles and nanorobots have overlapping characteristics that are important to preserve for drug delivery. The encasement of molecules within the nanoparticles is also important as it contributes to decreasing the toxicity of the highly toxic drugs that are required to treat cancers. In addition, the use of fluorescent dyes as a way to track these nanoparticles is imperative in analyzing the progress and understanding the effectiveness of the treatments. One approach to combining multiple features of these nanoparticles is to utilize aspects of the logic-gated nanorobots in conjunction with bio-adhesive nanoparticles and C Dots. Though the DNA nanorobots that have aptamer-encoded logic gates are significantly larger, about 35nm x 35nm x 45nm, compared to other nanoparticles, the stimuli-based actions can be incorporated into the other types of nanoparticles [6]. The aptamer logic which required multiple conditions to be satisfied before the release of the drug would enhance the specificity of the C Dot nanoparticles. Modifying C Dots to incorporate this idea from the logic-gated nanorobots in addition to integrating bioadhesive properties on the surface of the nanoparticles could significantly increase the efficacy of the drug delivery and treatment of cancer. The basis of the C Dot nanoparticles in identifying the location and spread of the tumor will aid in analyzing whether these techniques increased the potency of the use of nanoparticles in treating cancer.

Another approach to combine these technologies would be to modify the logic-gated nanorobots to be compartmentalized and opened through multiple aptamer-encoded gates. This could allow for multiple drugs to be delivered through DNA nanorobot structure. This multiple-drug approach could be more effective in treating tumors as tumors in different patients have various differences making a multi-pronged approach more likely to target the components of that tumor [15]. Each compartment would have a release triggered by different sets of aptamers being stimulated. By doing so, the treatment for cancer could be tailored to the exact properties of the tumor. With tumors being specific to individuals, general anticancer drug treatment may not be universally effective from patient to patient. Another application of this concept could be to compartmentalize the DNA nanorobot structure to control the release of singular drug treatment. Depending on the aptamers that are stimulated by the tumor, the corresponding compartments of anticancer treatment would be opened in the nanorobot. These two approaches are recommended for further research in order to compare the efficacies of the various methods of drug delivery using nanobots.

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3.1. Multi-gated aptamers for enhanced drug delivery

Aptamers in recent years have proven to be classic therapeutic agents with robust capabilities to recognize various proteins on the cell surface. Many aptamers have been introduced for treatment of cancers such as AS1411 which has a high level of accuracy in recognizing the nucleolin protein normally found on the surface of cancer cells. Further research is recommended on use of multiple aptamers on a nanorobot to serve as AND condition logic gate so that underlying drug is only delivered to target cancer cells when multiple exposure criteria are met. This multi-gated approach can also be used to deliver chemotherapy drugs that usually take a heavy toll on human health by damaging the healthy tissues.

3.2. Controlled drug release by single nanobot with Bio-Adhesive and chain linked aptamers

Another aspect that can be researched further is whether nanorobots can be modified to store multiple dosages of drugs so that they can be released in a controlled manner once they are already bound to the target cell. This can be potentially achieved by having multiple aptamers that react to different types and levels of protein on the target cell surface thus opening the DNA structure to release drugs. The increased number of aptamers allows for a more secure release of the drugs as it is less sensitive to the environment (Figure 2). Binding to the target cell can be further enhanced using bio-adhesive aptamer. The bioadhesive ligands coating the outer surface of the structure leads the nanorobot to be able to release the drug for a longer amount of time, thus increasing the effectiveness of the treatment (Figure 2).

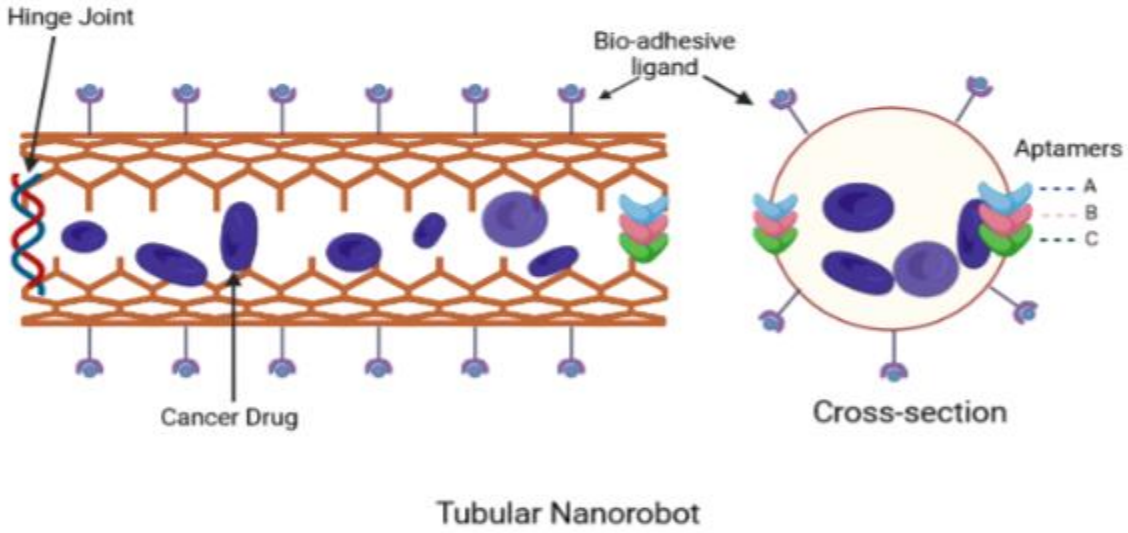

Figure 2. With a multiple-aptamer gated nanorobot, multiple conditions must be met in order for the high toxicity drug to be released from the tubular nanostructure.

4. Conclusion

This analysis of the various applications of nanoparticles in drug delivery shows that nanoparticle and nanorobot use in targeting cancerous tumors can be an effective measure of treating cancer tumors. Provided that these methods need reinforcement of their concepts through further research, the recommendations determined through combining principles of the several discussed nanoparticle application can increase the efficacy and efficiency of delivering the necessary drugs to the tumor sites. Though this is a novel field and many of these developments require additional research to solidify their use in clinical settings, the vast amount of current research in this field is contributing to its rapid growth. Incorporating nanoparticles in the treatment of cancers may significantly reduce the side effects that patients experience from cancer treatment.

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