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Conjugation of Theranostic Nanoparticles and Immune-Enhancing Agents to Improve Cancer Treatment

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Abstract

Cancer is currently a leading cause of death, killing millions of people worldwide, but has yet to have a definitive cure. Although therapies such as chemotherapy, immunotherapy, and radiation therapy are commonly used, such therapies incur numerous downsides, especially for the health of the patients themselves. Because of this, theranostics were invented to combine the most precise imaging with the most targeted treatment methods. However, theranostics still fail to treat many cancers, its use being limited by the rapid evolution of cancer cells. This paper proposes a novel theranostic that involves conjugating nanoparticles with immune-enhancing agents. The therapy consists of iron-oxide nanoparticles conjugated to natural killer (NK) cell engagers and STING agonists. This allows for the ability to target a variety of distinct cancer cells through the adaptive and innate immune systems. If successful, this treatment could impact the lives of countless patients, potentially saving the lives of those with advanced and aggressive cancer.

Introduction

Cancer is a collection of related diseases, in which abnormal cells undergo uncontrolled growth and spread throughout the body. This disease can emerge from various causes, including genetic mutations, exposure to carcinogens, ultraviolet (UV) radiation, certain chemicals, infections such as HPV and hepatitis viruses, and a family history of cancer (Hobbs, 2010). Genetic mutations can occur spontaneously or be inherited, leading to the activation of oncogenes, inactivation of tumor suppressor genes, or the disruption of stability genes (Oncogenes, Tumor Suppressor Genes, and DNA Repair Genes, 2021), which are necessary for maintaining genetic material during cell division. UV radiation, for instance, can cause direct DNA damage in skin cells, leading to mutations that may cause cancer development (Does UV Radiation Cause Cancer?, 2024).

Mutations can facilitate the growth of cancer cells by allowing them to evade normal body regulatory mechanisms like apoptosis (DANDOTI, 2021), which is the programmed death of cells that prevents the accumulation of damaged cells. Because they can avoid such mechanisms, they tend to accumulate within a certain area of the body. These damaged cells can eventually replicate and spread elsewhere, leading to further proliferation of unhealthy, abnormal cells (Martin et al., 2017). This process is known as metastasis.

Each type of cancer has unique characteristics and stages. Cancers are often categorized by the tissue from which they arise, such as breast, lung, prostate, colorectal, and skin cancers (Hobbs, 2010). The progression of cancer is typically described in stages, ranging from Stage 0, where the tumor is confined to its original location and is often precancerous, to Stage IV, where cancer has metastasized to distant organs (Staging Cancer, 2015). The stage of cancer plays a crucial role in determining the treatments, as early-stage cancers may be treated with localized therapies such as surgery or radiation, while advanced-stage cancers often require more complex and multistep treatments.

Cancer typically includes the alteration of normal cellular metabolism. Tumor cells frequently exhibit an effect known as the Warburg effect, where they rely on glycolysis for ATP and NADPH production even in the presence of oxygen (Romero-Garcia et al., 2011). This change in metabolism supports the rapid growth and survival of cancer cells by providing large amounts of energy (ATP) and a foundation for further cell division. NADPH supports antioxidant defense and lipid and nucleotide biosynthesis, all of which are critical for tumor growth and survival. Additionally, tumor cells can reprogram their metabolism based on environmental conditions inside the body such as low oxygen levels or limited nutrient availability, further enhancing their ability to survive and proliferate (para. 4).

The tumor microenvironment, which includes other elements such as immune cells, blood vessels, fibroblasts, and the extracellular matrix, plays a critical role in supporting tumor growth and metastasis (Anderson & M. Celeste Simon, 2020). As cancer cells proliferate, they recruit these surrounding cells to create a microenvironment that facilitates their survival and spread (para. 1). Hypoxia, a common feature of solid tumors marked by low levels of oxygen in the body tissues, arises when the rapidly growing tumor outgrows its blood supply, leading to oxygen deficiency (Shi et al., 2021). Hypoxic conditions can allow for a plethora of negative effects, as seen in Figure 1. Notably, it can make tumors more aggressive and resistant to therapy (para. 1), as cancer cells adapt by altering their metabolism. Furthermore, hypoxia is closely associated with angiogenesis, the process by which tumors induce the formation of new blood vessels to supply oxygen and nutrients, thereby promoting further tumor growth and metastasis (para. 2).

Given cancer's ability to rapidly divide and spread throughout the body, it is necessary to employ adequate imaging techniques to accurately detect tumors as early as possible. This makes it feasible to treat or potentially cure patients, as well as accurately monitor disease progression.



Figure 1. The variety of effects of hypoxia on cancer cells. ROS refers to reactive oxygen species. DNA refers to deoxyribonucleic acid (Shi, 2021).

Imaging

Imaging techniques are crucial to diagnosing and treating cancer. Common imaging techniques are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). CT scans, which create three-dimensional images by compiling a series of X-ray images taken from various angles, are often used to visualize anatomical structures such as bones, organs, and tumors (Computed tomography (CT) scan, 2015). Despite their scans being quick — typically less than a minute — CT scans involve exposing the patient to ionizing radiation, raising concerns about potential DNA damage and the associated long-term risk of secondary cancers (para. 13).

In contrast to CT scans, MRI scans use strong magnetic fields and radio waves to produce high-resolution images of soft tissues, including the brain, joints, and internal organs (M~ Magnetic Resonance Imaging (MRI), 2022). This technique is especially beneficial for detecting soft tissue abnormalities, such as brain tumors, and does not involve ionizing radiation, making it a safer alternative for patients requiring multiple scans (para. 4). However, MRI procedures are more time-intensive, often requiring 20 to 50 minutes, during which patients must remain still, presenting challenges for certain individuals, such as those with claustrophobia or severe discomfort (para. 7). Additionally, patients who have magnetic material, such as dental implants or surgical screws, in their bodies are ineligible for an MRI scan (para. 7).

PET scans offer a different approach by assessing the metabolic activity within tissues. By using radiotracers such as fluorodeoxyglucose (FDG), PET scans highlight areas of increased glucose uptake, which are indicative of cancerous activity due to the heightened metabolic rate of tumor cells (Kapoor & Kasi, 2022). The integration of PET with CT (PET/CT) also provides a comprehensive view by combining metabolic activity with anatomical detail, thereby improving the accuracy of tumor detection, staging, and treatment monitoring (Fallahpoor et al., 2024). However, even using PET scans alone offers risks. Using radiotracers has downsides, particularly because the half-life of FDG is less than two hours (Ashraf & Goyal, 2023), meaning that FDG will degrade quickly and will not be usable. This poses a requirement of high levels of clinical coordination due to the fact that FDG must be synthesized fresh for each patient. Any manufacturing failure would be costly and could impact the patient as well.

The integration of nanoparticles, a particle with a diameter of 1-100 nm (“Nanoparticle | Definition, Size Range, & Applications | Britannica,” 2024), into these imaging techniques has furthered their diagnostic capabilities. In CT imaging, nanoparticles with high atomic numbers, such as gold and bismuth, are utilized to improve contrast by enhancing X-ray scattering, thereby providing a very high contrast between healthy and abnormal tissues (Sim & Wong, 2021). Similarly, in MRI, superparamagnetic nanoparticles, particularly iron oxide-based, interact with the magnetic field to shorten the relaxation times of nearby hydrogen atoms in tissues (Xiao et al., 2016), leading to clearer and more detailed images, which are crucial for identifying small or early-stage tumors (Jin et al., 2014). Additionally, such particles have been proven to have longer blood circulation times as opposed to contrast agents such as FDG (para. 2).

Treatment

Surgical removal of tumors is often effective for localized cancers but may be insufficient due to microscopic spread, inaccessible locations, or the nature of some cancers. Additionally, factors like patient health, aggressive tumor behavior and the need for adjunct therapies often necessitate combining surgery with other treatments. Chemotherapy is a commonly used cancer treatment that involves drugs designed to target and kill dividing cancer cells. This treatment can be

administered orally, intravenously, or through other methods depending on the type and location of the cancer (Chemotherapy to Treat Cancer, 2022). There are several types of chemotherapy, the most popular including cytotoxic and targeted therapies. Cytotoxic chemotherapy is the most common form and works by disrupting the cell division process, thus preventing cancer cell growth (Amjad et al., 2023). Drugs such as doxorubicin, cisplatin, and paclitaxel fall into this category (para. 11-22). These drugs operate by inserting themselves between DNA base pairs, causing DNA strand breakage and inhibiting the creation of DNA and RNA (para. 9).

Despite its effectiveness and wide usage, chemotherapy is associated with significant downsides, including nausea, vomiting, fatigue, hair loss, anemia, and a weakened immune system, making patients more susceptible to infections (Chemotherapy Side Effects, 2019). A notable risk is the potential for some cancer cells to develop resistance, reducing the overall effectiveness of the chemotherapy. Additionally, chemotherapy drugs can harm healthy cells, leading to adverse effects throughout the body. Some patients may develop secondary malignancies due to damage to healthy cells (para. 3).

To address these issues, targeted therapy has emerged as a more specific approach, using drugs that target particular proteins or pathways involved in cancer growth (Targeted therapy, 2015). For example, imatinib is used for chronic myeloid leukemia (Deininger et al., 2004), and trastuzumab targets HER2-positive breast cancer cells specifically (Kreutzfeldt et al., 2020). While targeted therapy is more likely to avoid secondary malignancies than chemotherapies, they still occur occasionally. Long-term use of imatinib has been associated with an increased risk of secondary cancers. Specifically, studies have shown that patients treated with imatinib may have a slightly higher risk of developing secondary cancer (Mughal, 2010).

Immunotherapy is a cancer treatment that uses the body’s immune system to target and destroy cancer cells (Immunotherapy for Cancer, 2019). It consists of several distinct treatments, such as checkpoint inhibitors, monoclonal antibodies, CAR-T cell therapy and oncolytic viruses. Checkpoint inhibitors block proteins from sending inhibitory signals to T cells, allowing them to attack cancer cells (para. 3). Monoclonal antibodies are lab-created proteins designed to target specific antigens on cancer cells, either marking them for destruction or delivering toxic substances directly (para. 3). CAR-T cell therapy involves genetically modifying a patient's T cells to express receptors targeting specific cancer cell antigens (para. 3). Oncolytic viruses are engineered to infect and kill cancer cells while stimulating the immune system (Rahman & McFadden, 2021). Finally, cancer vaccines are designed to boost an immune response against cancer-specific antigens (Immunotherapy for Cancer, 2019).

While immunotherapy can be highly effective, its success is often limited by the tumor microenvironment, which can suppress immune function, genetic mutations that reduce antigen recognition, and the potential for tumors to increase checkpoint proteins to counteract the therapy. Side effects can include inflammation of various organs and long-term risks, with some patients experiencing immune-related adverse effects (para. 3).

Radiation therapy, or radiotherapy, is a localized cancer treatment that uses X-rays or other forms of radiation to target and destroy or shrink cancer cells (Radiation Therapy for Cancer, 2019). The most common type is external beam radiation,

where a machine directs radiation at the tumor from outside the body (para. 3). Another approach, internal radiation or brachytherapy, involves placing a radioactive source directly inside or close to the tumor, allowing for precise delivery of radiation (para. 3). Proton therapy uses protons instead of X-rays and is advantageous in minimizing damage to surrounding healthy tissues, as doctors have better control over a photon bean's pathway (Proton Therapy - Mayo Clinic, 2023). However, it comes with high costs due to the equipment needed, and thus is not widely available (para. 1). Photon therapy involves X-rays that penetrate beyond the tumor, potentially affecting healthy tissues and increasing the risk of secondary malignancies (para. 3). Electron therapy, while less commonly used due to its limited penetration ability, is effective for treating superficial tumors (External Beam Radiation Therapy for Cancer, 2018).

Radiation works by damaging the DNA of rapidly dividing cancer cells, which disrupts their growth and division, leading to cell death (Radiation Therapy for Cancer, 2019). This therapy, due to its ability to shrink tumors, is often used in combination with surgery or chemotherapy to eliminate residual disease and prevent the cancer from coming back (Radiation therapy, 2015). New advancements include biology-guided radiation therapy or SCINTIX, which uses tracers to target tumors in real-time, and recent research revealing that free electrons in water form bubble structures upon radiation, potentially impacting treatment models (Conger, 2023). Despite its effectiveness, radiation therapy can cause side effects such as fatigue, skin changes, and radiation-induced fibrosis (Radiation Therapy Side Effects, 2022), and carries the risk of secondary cancers due to its potential to damage healthy tissues.

Nanoparticles are extremely small particles that provide a myriad of applications in cancer diagnosis, imaging, drug delivery, and therapy. As discussed in this paper previously, they can enhance cancer diagnosis by acting as imaging agents, such as contrast agents or fluorescent dyes, which improve the visibility of tumors in techniques like MRI, CT, or fluorescence imaging (Lan et al., 2023). Nanoparticles such as quantum dots and iron oxide nanoparticles are utilized for their unique optical properties and extended circulation time, assisting in better lesion detection in tissues and reduced toxicity (Jin et al., 2014). However, it should be noted that the use of contrast agents can pose risks, including allergic reactions and thyroid dysfunction (Andreucci et al., 2014).

In drug delivery, nanoparticles are designed to transport drugs specifically to cancer cells, reducing damage to healthy tissues and enhancing the effectiveness of treatments (Yoo et al., 2024). This includes the development of targeted therapies like photothermal and photodynamic therapies, where nanoparticles either convert light into heat to destroy cancer cells or generate reactive oxygen species to induce cell death (Overchuk et al., 2023). Other recent advancements involve integrating nanoparticles with imaging technologies, such as radiolabeled nanomaterials for theranostics (Najdian et al., 2024), and using techniques like ion irradiation to control nanoparticle properties (Thomson, 2023). Additionally, nanoparticles can be engineered for gene therapy delivery, including the targeted delivery of therapeutic genes or genome editing tools like CRISPR-Cas9, offering the potential for correcting the genetic mutations associated with cancer (Duan et al., 2021). Their versatility extends further to immunotherapy, where nanoparticles have shown promise in various cases in activating immune responses against tumors by delivering antigens or immune modulators. Collectively, these advancements highlight nanoparticles' impact across diagnostics and medicine, addressing challenges like off-target effects and enhancing the precision of cancer treatments.

Theranostics is a technique that integrates diagnostics and therapy through nanotechnology, using the various functions of nanoparticles to both identify and treat tumors (Arda Könik et al., 2021). This strategy often uses one type of drug for diagnostic purposes, such as detecting tumor presence, and another for therapeutic actions, specifically targeting and eliminating cancer cells. An example of a diagnostic nanoparticle is the use of iron oxide-based nanoparticles (IONPs) in magnetic resonance imaging (MRI), where they serve as agents to enhance image quality and improve the detection of abnormal tissues (Zhu et al., 2016). Normally, when IONPs are synthesized, they exhibit superparamagnetic properties, where they are weakly attracted to magnets (Fernández-Barahona et al., 2020). However, these nanoparticles generate strong local magnetic fields when placed in an external magnetic field (para. 2) — in this case, the MRI magnetic field. When administered, these nanoparticles will accumulate in tumor tissue due to the enhanced permeability and retention effect (Nichols & You Han Bae, 2014). Such an effect allows molecules of a certain size to accumulate in tumor tissue more than in normal tissues (Wu, 2021). When analyzing images from the MRI, areas with darker spots will appear due to IONP accumulation and MRI signal suppression (Fernández-Barahona et al., 2020), providing an evident contrast in scans.

Another example of theranostics is a method that involves attaching a radioactive element to a protein that binds to specific receptors on tumor cells, thereby ensuring that the radionuclide damages the tumor's DNA with minimal impact on healthy cells (Marin et al. 2020). These theranostics include the drug Ga-68 DOTATOC, which targets somatostatin receptors (SSTR2) on tumor cell membranes, making these tumors visible on PET scans (FDA approves new diagnostic imaging agent to detect rare neuroendocrine tumors, 2016). Additionally, theranostic agents like Y-90-DOTATOC or Lu-177-DOTATATE can target and destroy tumors expressing SSTR2 (Nisa et al., 2010). Another notable technique is Peptide Receptor Radionuclide Therapy (PRRT), which uses a targeted approach to treat neuroendocrine tumors by delivering a small amount of radioactivity directly to cancer cells through their peptide receptors (Peptide Receptor Radionuclide Therapy (PRRT), 2022). While these techniques demonstrate significant potential, they are not without limitations. For example, Ga-68 DOTATOC and related agents are highly effective in identifying and treating tumors with overexpressed somatostatin receptors, but their reliance on the presence of specific biomarkers limits their applicability to certain patient cases. Similarly, theranostic agents like Y-90-DOTATOC and Lu-177-DOTATATE have been praised for their ability to reduce tumor burden and improve progression-free survival in neuroendocrine tumor patients, yet they can cause side effects such as nephrotoxicity and myelosuppression due to off-target radiation (Nisa et al., 2010). Additionally, logistical challenges such as the short half-life of radionuclides and the need for specialized facilities to produce and administer these agents limit their usage in many countries. However, advancements in theranostics continue to refine these techniques, aiming for greater precision and broader applicability in cancer care.

Novel Therapy Proposal

Based on the limitations of past therapeutics, a more optimal theranostic cancer therapy strategy would be using iron oxide nanoparticles (IONPs) reversibly conjugated with NK cell engagers and STING agonists. IONPs have magnetic properties that enhance MRI contrast and they exploit the enhanced permeability and retention (EPR) effect, allowing them to accumulate selectively in tumor tissues. This selective accumulation distinguishes cancer sites from healthy

tissue, providing high contrast in MRI imaging. The NK cell engager, which is only cleaved off of the nanoparticle within the acidic tumor microenvironment, would enhance innate immune responses and induce tumor cell killing. The STING agonist would further strengthen this immune response by recruiting and activating adaptive immune cells such as T cells. The targeted nature of this therapy means that a larger dose can be given to a patient without causing the side effects associated with systemic delivery of NK cell engagers or STING agonists.

A custom manufacturing approach is required to produce this novel therapeutic. Firstly, the IONPs will be synthesized. In this process, aqueous solutions containing ferrous, Fe^{2+}, and Fe^{3+}, ferric, salts must be used (Besenhard et al., 2020). Under moderate temperatures of <100°C, a base such as ammonium hydroxide must then be added (para. 1). The reaction induces the simultaneous precipitation of iron oxide nanoparticles. In this reaction, several parameters must be controlled. The pH of the final solution must be maintained at a neutral pH, to ensure the complete precipitation of iron oxides while preventing the formation of unwanted side products (para. 1). This pH control also helps to prevent the agglomeration of nanoparticles, holding their small size and high surface area (para. 1). Temperature must also be kept within an optimal range to produce uniform nanoparticles without excessive growth or aggregation. Thirdly, the ionic strength of the solution is controlled by adjusting the concentration of salts in the reaction medium, which influences the stability and size of the nanoparticles (para. 1). Higher ionic strength can lead to larger particles due to increased accumulation. Lastly, stabilizing agents, such as polyethylene glycol (PEG) must be added to the reaction mixture to coat the nanoparticles, which prevents agglomeration, allows for the functionalization of these nanoparticles, and reduces toxicity (Boyer et al., 2010).

The PEG chains coating the nanoparticles can be end-functionalized with hydrazone linkers, which are stable under neutral conditions but cleave in the acidic microenvironment of tumors (pH ~5-6) (Sonawane et al., 2017). The process begins with the activation of the terminal hydroxyl groups on PEG chains. This is commonly achieved by converting these groups into aldehyde or ketone functionalities (para. 3), which are reactive towards hydrazide groups. This conversion can be carried out using reagents such as succinic anhydride or glutaraldehyde (Banerjee et al., 2012), resulting in PEG chains with terminal aldehyde or ketone groups. These activated PEG chains can then be mixed with hydrazides to form stable hydrazone bonds. The NK cell engagers will be conjugated to these hydrazone linkers, enabling targeted delivery to the tumor site and pH-sensitive cleaving.

The final step of the nanoparticle synthesis is conjugating STING agonists to the NK cell engagers. This conjugation can be achieved by using STING agonists that contain maleimide in their linker. This was proven in a recent paper written by Malli Cetinbas et al. where a method is provided to conjugate STING agonists to antibodies. The maleimide will bind to cysteines on the engager after a reduction step (Malli Cetinbas et al., 2024). If STING agonists are added to the nanoparticles in high molar excess, several will bind to each engager (para. 5). This reaction can then be quenched and will result in a solution containing IONPs coated with reversibly conjugated STING-engager complexes, which will be shed when the nanoparticle enters the tumor (para. 5)

This therapy is intended to be administered intravenously to patients, particularly as a last-line treatment option. Once in the bloodstream, due to the enhanced permeability and retention (EPR) effect, the IONPs will naturally accumulate in the

tumor tissue. The patient would return to the clinic after 24 hours for MRI imaging. The effects of this treatment could be monitored monthly, ensuring no harmful side effects. After the first month, the therapy can be administered again if it is tolerated well and the patient can be imaged the following day. If the imaging shows signs of tumor shrinkage, the therapy would then be administered for the next several months or until surgeons decide that the tumor should be removed.

Discussion

Through addressing the limitations of chemotherapy, immunotherapy, and radiation therapy, this paper presents a novel theranostic approach involving iron oxide nanoparticles (IONPs) conjugated with NK cell engagers and STING agonists offers a potential solution for enhancing both cancer imaging and treatment. The integration of these components allows for the selective accumulation of IONPs in tumors due to the enhanced permeability and retention (EPR) effect, MRI imaging to be enhanced and the conjugated NK cell engager and STING agonist to cleave directly in the tumor environment. After being cleaved, the NK cell engagers activate an innate immune response, while the STING agonists amplify this effect by recruiting adaptive immune cells. This therapy not only minimizes the side effects commonly associated with traditional therapies but offers a more flexible and adaptive approach to cancer therapy.

Before human deployment, however, assessing safety through preclinical testing using mice with human tumor xenografts would be crucial, as well as tracking the accumulation of IONPs through MRIs. Literature supports individual components of this strategy. Studies on IONPs demonstrate their imaging and drug delivery capabilities in terms of cancer therapy, while STING agonists (Afsaneh Amouzegar et al., 2021) and NK cell-based therapies (Chu et al., 2022) both show an upward trend in investigation as potential cancer therapeutics in preclinical and clinical settings. However, there are controversies to this approach, including concerns about the potential immunotoxicity of IONPs (Shah & Dobrovolskaia, 2018), which may accumulate in healthy tissues and cause unintended side effects. Additionally, immunogenicity is a concern, as overstimulation of the immune system could lead to adverse inflammatory responses.

Furthermore, gaps in knowledge lie in the literature that supports conjugated therapy. Although such components are shown to function well individually, their conjugated function remains unknown. Therefore, future research should focus on real-world clinical trials and addressing challenges and controversies based on immunotoxicity and immunogenicity. Ultimately, although further clinical studies are crucial, this research lays the foundation for a future cancer therapy that is both highly precise and minimally invasive, aiming to improve the quality of life for millions of cancer patients worldwide.

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