HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 3 (2024)

Analysis of Specific Nanoparticles in Colorectal Cancer Therapeutics and Diagnostic Techniques

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ABSTRACT

Colorectal cancer (CRC) is a form of cancer that commonly develops in the sigmoid colon, leading directly to the rectum. CRC is the 2nd leading cancer in terms of death globally and the risk of development increases with age. In terms of detection of the disease, many patients with CRC are diagnosed in either stage 3 or 4, leading their treatment options to be fairly limited. Currently, a few options for diagnosis exist, such as the fecal occult blood test (FOBT), however, there are limitations to these techniques such as FOBT lacking the sensitivity to identify precancerous polyps that haven't caused significant bleeding and endoscopy being very invasive and expensive. There are also certain trade offs present within current treatments for CRC, such as colectomy, however, it's highly invasive and risky due to the removal of the colon partially or completely. (Lavy et al., 2015) Additionally, chemotherapy drugs such as irinotecan are utilized in combating CRC, however, though they are effective they are highly non-specific and emit toxicity to non-cancerous cells too. For this reason, nanotechnology and nanoparticles are significant to consider and study further as they allow for more accurate diagnosis and more specific chemotherapy, allowing for less excessive toxicity. Nanoparticles have been researched globally by various researchers and utilized in colorectal cancer treatment as well. (Gogoi et al., 2022) This review covers the implementation of specific nanoparticles as diagnostic devices and therapeutic enhancers for CRC and its specific implications for specific patients. (Duan et al., 2022)

Introduction

Colorectal cancer has been traced to the late 19th and early 20th centuries, when surgical techniques led to significant advancements in leveraging novel forms of surgeries, diagnosis and treatment that led scientists to inch closer towards early detection and diagnosis, with advanced screening programs. (Jeevenandam et al., 2018) However, it can also be traced back to the Egyptian era of the 200-400 CE, where Dr. Warthin, an American pathologist, had unveiled and suspected his family member to have hereditary colorectal cancer, rooted in his family history. Since then, in an effort to introduce new forms of colonoscopy and colonoscopic polypectomy, scientists have been able to trace certain lifestyle factors and risk factors that have led to appropriate medical diagnostics and medical interventions. (Haroon et al., 2022) Since the late 20th century, nanotechnology has become identified as a form of drug delivery system that researchers have utilized to better evaluate treatment efficacy and breakthroughs beyond drug delivery. For instance, in the 2010s, nanomaterials had officially entered the clinical trials, whereby nanoparticle-based therapies became tested for addressing cancer management with a broad range of potential.

Adaptation of Nanoparticles for Targeted Therapeutics for Colorectal Cancer

Nanoparticles enter the human body through three main mechanisms: inhalation, oral consumption, or injection. They work through the lymphatic system, where they are primarily absorbed into the lymphatic system during fluid recovery where the lymphatic system returns excess fluid and protein into circulation allowing the nanoparticle drug carrier and its respective drug to be taken in. (Rizvi et al., 2018)

The system continues to accumulate foreign cells and chemicals from the bodily tissue and the nanoparticle carrier with its respective drug binds to the cancerous colorectal cells utilizing its ligand and by opsonizing the cancerous cells or through some other indication system to indicate to the immune system that this cell is toxic. The fluids are then filtered by the lymphatic system and the nodes detect the marked cancerous cells, triggering macrophages to engulf them and eradicate them from the body. Nanoparticles are immensely valuable for targeted therapeutics in colorectal cancer because of their controlled release of drugs and small size allowing them to cross the blood-brain barrier and other systems. To be adapted into drugs, they are incredibly small, roughly 100-500 nm allowing for effective drug release due to higher binding efficacy. (Rizvi et al., 2018)

Additionally, they are adapted with ligands by being coated with molecules such as Biotin and folic acid for accurate delivery. They are further adapted with coatings such as Polyethylene Glycol (PEG) to achieve drug encapsulation and protect the protein and nucleic acids of colorectal cancer drugs from degradation, and to avoid recognition by the immune system. PEG, much like other coating substances, is additionally able to prolong circulation time and ensure accuracy in identifying the majority of cancerous cells in the body through its hydrophilic nature. (Rizvi et al., 2018)

In conjunction with this, other researchers and scientists have examined the components and features of nanoparticles that have enabled the microbiological perspective of drug resistance. For instance, Jain et al., proposed that nanoparticles can be loaded with siRNA to silence genes involved in drug resistance within colorectal cancer cells which is of major concern. (Jain et al., 2023)

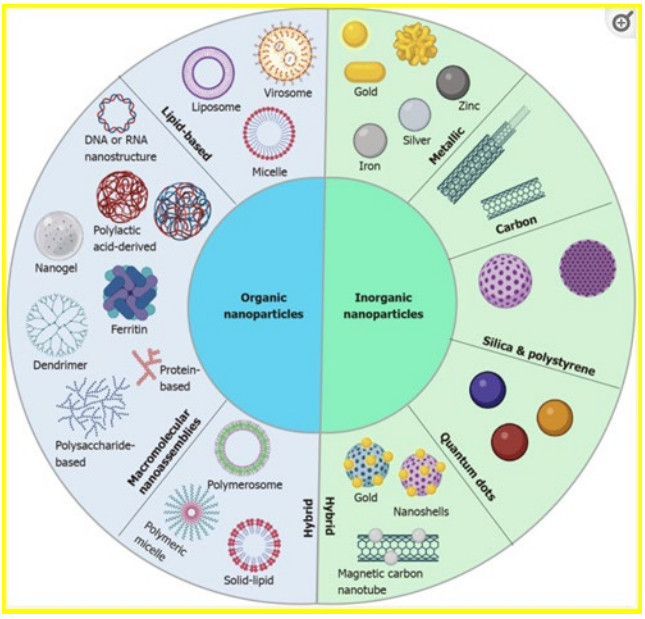

Figure 1. Graphic Illustration of various types of nanoparticles implemented in detecting and treating Colorectal Cancer grouped by chemical properties

Comprehensive Comparison Between Advancements in Immunotherapy, Cancer Diagnostics for Colorectal Cancer and Nanoparticle-Based Treatments

In recent medical advancements, nanotechnology has presented radical implications and applications towards identifying novel solutions entailing the prominent cancer-related mortality in the United States. Intrinsically, researchers have identified a new form of nanotechnology that can bind to the "diarrheagenic bacterial heat-stable peptide enterotoxin ST" which can create positive clinical management of the disease. (Fortina et al., 2007) Such nanoparticles have been identified as meaningful forms of diagnostics by analyzing the diagnostic tests on blood serum to identify the assays that make it easier for clinicians to create "non-invasive imaging in the detection, staging and overall management of patients with cancer." (Fortina et al., 2007) As colon cancer has been an emerging disease that is in need of improved diagnostic capabilities as well as increased sensitivity to address the management of colon cancer patients, unique forms of "targeted strategies" that can have specific identification of target molecules may be necessary. Other argues have echoed this idea, by discussing how nanoparticles can help promote drug targeting, solubility and bioavailability, thus, significantly revitalizing the ways in which drugs and cells interact, which can lead to a positive implementation of nanoparticles in the treatment of colorectal cancer. (Naeimi et al., 2022) For instance, through the forms of nanotechnology, there can be better facilitation of drug delivery, which can have significant consequences in the CRC diagnosis and treatment for years to come.

Development of Nanoparticles for Colorectal Cancer Imaging

Nanoparticles have positive implications specifically for biomedical imaging and its properties. For instance, researchers have been plunging into the Near Infrared (NIR) fluorescent nanoparticles that have been identified to be of usage for clinical use, in creating new bonds that can bind to LS174T human color tumors and the surrounding area, without having to target the molecule. (Tivony et al., 2014) Recent studies and advancements have highlighted how non-invasive imaging tools, like endoscopy that is utilized by cancers can be bonded with fluorescence imaging capability, which can increase higher precision for testing its compliance. In comparison to other forms like MRI and PET scans, fluorescence imaging can help better detect the content within the tissue as well as designing active tumor targeting to evaluate the small molecules and tumors surrounding it in the microenvironment. (Tivony et al., 2014) Nanoparticles consist of a particular blocking protein that has not endured any chemical modifications, and through its high-absorption value, these nanoparticles that have the adsorbed ICG are able to culminate in a precise and solid imaging that can help detect colon tumors. (Tivony et al., 2014)

By having the absorption measures incorporated, researchers have witnessed how these nanoparticles have enabled the binding process of colorectal tumors, which have enabled them to examine the particular tumor that can now be excised and scanned in precision.

Interventions of Nanoparticle Graphene Oxide to treat Colorectal Cancer

Graphene oxide (GO) is the water-soluble form of graphene and has demonstrated great capabilities in increasing the half-life and treatment efficacy of current drugs such as curcumin and as a drug carrier for aromatic, water-insoluble drugs. Graphene oxide can easily bond with molecules such as epoxide hydroxyl, carboxyl, and hydroxyl which allows it to easily bind with protein, DNA, and RNA. Graphene oxide has numerous benefits as a drug carrier such as a large and easily modifiable surface because of its oxygen functional groups, its high

loading efficiency, low cytotoxicity to non-cancerous cells, and water solubility and its eco-friendly materials involved in the synthesis of reduced graphene oxide (rGO). GO is compatible with many forms of colorectal cancer treatment such as gene therapy, chemotherapy, and photothermal and photodynamic systems. Additionally, it is a valuable nanoparticle in transporting drugs in colorectal cancer because of its tumor specificity, ability to prevent tumor metastasis, and ability to carry multiple drugs at once. The uptake of graphene oxide results in breakage in the DNA strands and inhibition of the electron transport chain in mitochondria, leading to decreased ATP synthesis as the drug induces cytotoxicity. It has proved effective as a carrier in two drugs: curcumin and SN38. In 2020, it was found that curcumin AuNP-reduced GO produced and successfully killed drug-resistant colon cancer cells, whilst also increasing the half-life of the drug and specific cytotoxicity of the curcumin, proving its efficacy. (Krasteva et al., 2022) Additionally, GO has proven effective as a carrier for SN38, a chemotherapy drug that exerts anti-cancer effects by inhibiting the enzyme topoisomerase which is responsible for DNA replication and repair. Before the integration with GO, its clinical use was highly limited because of its inherent poor solubility and fast metabolism, however, GO greatly increased its therapeutic efficacy. (Liu et al., 2022)

Examination of Dendrimer Nanoparticles to Activate CRC Immunotherapy

Dendrimers are radially symmetric macromolecules with branches around a polymer core. They are highly diverse, with polyionic dendrimers allowing for change in size, shape, flexibility and the branch end groups can be functionalized greatly to treat CRC. (Abbasi et al., 2014) Specifically, polyamidoamine dendrimers (PAMAM) have been found to be very versatile and effective in drug-delivery for CRC. The drug is placed within the dendrimer either through encapsulation which encloses the drug within the cavities or the drug can be placed on the surface, preventing degradation. Dendrimers can easily penetrate through the plasma membrane, alleviating the issue of drug-resistance and ensuring direct delivery. (Bober et al., 2022) PAMAMG3 modified with biotin and exposed to irradiation was found to create reactive oxygen species which can induce cell death, illustrating the efficacy of dendrimers. Additionally, dendrimers can solubilize hydrophobic drugs, allowing for greater biodiversity. PEGylated-G4 PAMAM covalently linked to mercaptohexadecanoic acid functionalized with a gold nanorod and DOX was found highly effective for CRC over singular molecule treatments. Alibolandi and their colleagues found that a PAMAM dendrimer with PEGylated amine-terminated tetrachloroaurate ions created a structure that could load CUR. CUR on its own is limited in its bioavailability and efficacy because of its fast metabolism and poor solubility, but through encapsulation, it was found that this molecule was effectively taken by colon cancer cells and induced less cytotoxicity to non-cancerous cells. (Rai et al., 2023) Dendrimer particles have also been found to be effective contrast agents for MRI scans. Traditional agents such as GD3+ and DTPA are highly toxic, and accumulate in the liver and bones, whereas PPI dendrimers conjugated with DTPA and Gd(III) have been found highly effective in detecting colorectal cancer because they can easily be functionalized with fluorophores or contrast agents. (Cruz et al., 2023)

Analysis of Carbon Nanotubes and Their Optical Features to Detect Biomarkers as Well as Potential Tumors

Carbon nanotubes are highly valuable in colorectal cancer therapeutics because of their high surface area, flexibility in contact with CRC drugs, efficient loading, and targeted drug release due to their nanoneedle morphology because they can penetrate cell membranes. Single-walled carbon nanotubes (SWCNT) are roughly 0.2 - 2 nm in diameter and are made from a graphene sheet folded into a hollow tube. Loaded SWCNTs enter the plasma membrane through clathrin-mediated endocytosis and function by binding to nuclear DNA and impairing telomeric i-motif genetic material which enhances the expression of CRC tumor-suppressing genes and

inducing cell death. They further block cellular division by carrying polynucleotide molecules that bind to entities involved in mitosis such as antisense agents. Their high surface area and enhanced water solubility allow them to selectively and easily enter cancerous cells through the plasma membrane. Multi-wall carbon nanotubes (MWCNTs) are much larger than SCWCNTs, roughly 5-700 nm, and function through mimicking microtubules in the cell responsible for cell migration, proliferation, and intracellular transport. Disguised, the drug can bind to the tubulins within the cells and cause nucleation which changes microtubule assembly and creates abnormalities in the mitotic spindle which destabilizes the cytoskeleton and prevents CRC cell migration and proliferation effectively. Carbon nanotubes are additionally greatly compatible with biological systems, at a pH of 7.4, matching internal physiology pH, allowing for easy release. SWCNTs coated with PEG and carboxylic acid proved effective in killing colorectal adenocarcinoma Caco-2 cells, however, demonstrated some cytotoxicity towards healthy cells, which is a limitation currently being further studied. Carbon nanoparticles (CNPs) are additionally immensely beneficial in identifying cancerous lymph nodes after colonic polypectomy which is performed to remove precancerous lesions. CNPs combined with titanium clips were found to be effective in identifying cancerous polyps when injected into the submucosal layer causing minimal side effects and leading to a higher rate of accurate cancerous lymph node removal. (Ma et al., 2023)

Analysis of Liposomes and Their Delivery Properties to Detect CRC Biomarkers

Liposome drug carriers are lipid vesicles with 1 or more aqueous bilayer compartments formed in a honeycomb structure. Unilamellar vesicles with a singular bilayer are roughly 30 - 100 nm and multilamellar vesicles are roughly 30 nm - 1 μm. Liposome drug carriers are prescribed through oral, nasal, and pulmonary methods and 14 liposomal products have been authorized by the FDA. (Liu et al., 2022) Some examples of these are Doxil ™ , DaunoXome ™ , Marqibo ™ , and Thermodox ™ which is a thermo-sensitive liposome used in treating colorectal cancer directly. (Allen et al., 2012) Liposome carriers work by entering the large porous capillaries in colorectal cancer tissue by crossing over the neovasculature vessel walls and are detained through binding affinity. From here, they enter CRC cells through endocytosis where the liposomes are engulfed. They are optimized for drug-carrying through binding with saturated cholesterol for tighter membrane packaging and high drug retention, allowing for the drug cytotoxicity to be effectively transferred to the cancerous cells. Additionally, the liposomes are modified with ligands to effectively bind to overexpressed CRC receptors with substances such as folic acid, iRGD peptides, and galactolipids for specific binding. Liposomes are also treated with MethoxyPEG which covalently binds to DSPE allowing for stealth. This benefits in longer circulation and durg performance time, protecting liposomes from unwanted binding serum proteins and preventing liposomes from aggregating. Additionally, the intrinsic change from gel-like to liquid-crystal phase membrane allows for the liposome and its respective drug to be effectively carried into the CRC cells and bind effectively to chemotherapeutic drugs for CRC such as 5-fluorouracil and oxaliplatin. Liposome drug-carrying like Doxil comes with additional benefits, such as being unable to cross the endothelial junctions of major drug vessels due to circulating liposome particles versus traditional drugs like doxorubicin and it has been reported that DaunoXome, a liposomal drug carrier increases drug-delivery by 10 times the standard daunorubicin. (Liu et al, 2022)

Examination of Gold Nanoparticles in CRC Therapeutics

Gold nanoparticles (AuNPs) have emerged as a promising platform for the detection and treatment of colorectal cancer (CRC) due to their unique physicochemical properties (Siddique et al., 2020). These nanoparticles, typ-

ically below 100 nm in size, exhibit a high surface area-to-volume ratio, enabling increased loading and interaction with biomolecules like proteins, DNA, and ions on their surface (Siddique et al., 2020). This property allows AuNPs to be used for sensitive detection and sensing applications.

The binding of analytes, such as proteins, DNA, and ions, to AuNPs can alter their physicochemical properties, including charge, conductivity, and redox behavior (Siddique et al., 2020). These changes can be leveraged for the development of colorimetric assays and surface-enhanced Raman scattering (SERS) techniques, enabling highly sensitive detection of CRC biomarkers (Siddique et al., 2020). For example, the binding of analytes can cause aggregation or dispersion of AuNPs, leading to a visible color change that can be used to quantify the presence of the target biomolecule (Siddique et al., 2020).

Furthermore, AuNPs possess the remarkable ability to absorb light, particularly in the near-infrared (NIR) region, and convert it into localized heat (Siddique et al., 2020; Costantini et al., 2021). Costantini and colleagues synthesized branched gold nanoparticles (BGNPs) that exhibited efficient light-to-heat conversion and were able to rapidly induce hyperthermia-mediated eradication of colon cancer cells (Costantini et al., 2021). The heat generation and photothermal conversion efficiency of AuNPs are highly dependent on their size, shape, and surface properties (Siddique et al., 2020).

In addition to photothermal therapy, AuNPs can also act as photosensitizers, generating reactive oxygen species (ROS) when exposed to light (Siddique et al., 2020). These ROS can induce oxidative stress and apoptosis in cancer cells, leading to their destruction, making AuNPs a promising platform for photodynamic therapy of CRC (Siddique et al., 2020).

Beyond their diagnostic and therapeutic applications, AuNPs can also serve as drug delivery vehicles for CRC treatment (Siddique et al., 2020). Their high surface area allows for the attachment of various therapeutic agents, such as chemotherapeutics, improving their solubility, stability, and targeted delivery (Siddique et al., 2020; Brar et al., 2021). Safwat and colleagues demonstrated that 5-fluorouracil (5-FU) loaded onto glutathione-functionalized AuNPs (5-FU/GSH-GNPs) exhibited a two-fold higher anticancer efficacy compared to free 5-FU (Brar et al., 2021).

The ability to precisely control the size, shape, and surface functionalization of AuNPs further enhances their specificity and efficacy, offering promising avenues for improving CRC management.

Exploration of Interdisciplinary Combination Treatments (Through the Synergy of Traditional Chemotherapy, Radiation and Nanoparticle-Based Gene Therapy)

Nanomaterials on their own, within the context of cancer therapeutics are typically used as drug-carriers and as such are at optimal performance and value when combined with other treatment techniques to deliver the cytotoxicity specifically and leave noncancerous cells minimally damaged. Particularly, nanoparticles are valuable when combined with chemotherapeutic drugs, whose main concern is killing vital cells such as platelets and white blood cells instead of CRC cells. Liposomes have been tested in this combinatorial treatment, and a study found that the liposome LE-SN38 in HT-29 mice with CRC had their tumors inhibited by 90% when prescribed 40 mg/kg, which is highly effective. (Cisterna et al., 2016) Additionally, Batist et al., found in another study that irinotecan, a drug used to prevent the uncoiling of DNA during replication when encapsulated within a liposome was highly effective in treating CRC tumors, leading 70% to cease growing during the treatment period. (VanDyke et al., 2016) This is mainly because nanomaterials are highly valuable in delivering cytotoxicity specifically and in effectively crossing the plasma membrane through disguising with MethoxyPEG, allowing for the prevention of drug-resistance and effective treatment. Nanomaterials have additionally been found useful in combination with radiotherapy. Radiotherapy is used to treat 50% of patients with cancer and effectively damages the DNA of the cell through ionization radiation concentrated through an external beam or

internal radiation source. Due to this, excited water molecules are produced leading to the production of free radicals which damage genetic material. However, there have been noted issues with this technique because of the heavy genomic damage it causes to noncancerous cells, and nanomaterials have been found useful due to their high surface area to volume ratio, deep tissue penetration and enhancing the cytotoxicity delivered to cancerous cells. Gold nanoparticles have been particularly studied for treating CRC due to their high photoelectric absorption, as have carbon nanotubes due to their optical properties. Once again, the specificity and bioavailability of nanoparticles allow them to be characterized through modification of functional groups, and catered to concentrate the beam as radiosensitizers. Nanomaterials have also been found valuable in photothermal therapy, where the process of hyperthermia heats CRC cells to induce apoptosis and the energy from the heat harms all surrounding cells. Nanoparticles and materials can be utilized to absorb the energy coming from the phototherapy to concentrate it. Goodrich et al., studied the efficacy of photothermal treatment in colon cancer through infusing tumors with PEGylated gold nanorods and radiating it and two months afterward, 44% of the treated mice survived and the tumors were destroyed. (Freitas et al., 2023)

Discussion, Ethics and Limitations

Whilst the findings derived from this publication are of optimal use in addressing the root cause of colorectal cancer, as well as the significant scientific breakthroughs in nanomaterials, that have become diversified for treating colorectal cancer in the form of therapeutics, it is notable to also consider some of its ethical implications and limitations. For instance, one significant limitation has to do with the limited clinical trials — since nanoparticles are claimed to have high potential in interacting negatively with humans' microbiological systems, it is important to ensure that these long-term negative consequences that nanoparticles may have on the human health are minimized as much as possible. Additionally, it is also important to ensure that proper informed consent and appropriate disclosure is provided to patients that are being tested in clinical trials with nanoparticle-based therapeutics, or diagnostic interventions. As nanoparticle research is still currently being fully governed by regulations and safety standards, it is also prominent to know that patients diagnosed with colorectal cancer from low-income demographics may have unequal accessibility to medical interventions that patients belonging to higher-income demographics would have access to.

Conclusion

In summary, nanotechnology and materials are promising prospects for cancer therapeutics and diagnosis, through their easy customization, bioavailability, and ability to concentrate cytotoxicity. Nanomaterials such as liposomes, carbon nanotubes, graphene oxide, and dendrimers will be highly valuable in enhancing the toxicity of chemotherapy drugs and radiation techniques by providing specificity, drug protection from degradation and deep penetration of cancerous cells, and greater patient outcomes and treatment time. Colorectal cancer is one of the predominant causes of death in the United States, and optimizing nanoparticles for screening to remove precancerous polyps and for minimally invasive cancer treatment is a priority in improving the lives of patients. However, as this technology develops, researchers must seek to address and acknowledge the limitations of this technology such as cytotoxicity found within MWCNTs and biocompatibility issues. In conclusion, the findings demonstrate a prospect of utilizing nanoparticles to improve CRC imaging and therapeutic techniques through drug-delivery through many nanoparticles with distinct properties that make them compatible with traditional cancer treatments.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

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