Nanocarriers Based Approaches for the Management of Colorectal Cancer: A Systematic Review

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Abstract

Colon/rectal carcinoma is among the most commonly diagnosed cancers, and is one of the leading causes of mortality. It seems to have a remarkably higher incidence of metastasis, which is one of the primary causes of CRC fatalities. The efficacy of conventional chemotherapeutic treatments is limited by ineffectual drug content at the target site and toxic effects due to peripheral targeting. Nanocarriers based systems have shown remarkable promise and have the potential to improve distribution of drug, enhance half-life, and reduce toxicity. In recent years, nanoparticles have been the focus of research as a new promising material for cancer treatment. Although many chemotherapeutic agents are available for cancer care, their potential toxicity is the main source of concern. The conventional chemotherapeutic approach, on the other hand, is not very effective in colorectal cancer (CRC) because the drug molecule does not reach the target site in an effective concentration. To address this issue, scientists are attempting to use nanoparticles to directly target cancer cells, resulting in more effective treatment with lower toxicity. Oncology treatment through nanotechnology-based system is a fast growing in the field of science, is one of the new strategies being developed to address these issues. Over the last few decades, there has been a surge in interest in using nanoparticles and nanotechnology in cancer medicine. Nanomedicine has been proposed as a novel approach to improving CRC diagnosis.
Colon/bowel carcinogenesis, that develops from the internal surface of the epithelium of large intestine, has been the third most abundant cancerous growth and is associated with serious cause of demise worldwide [1]. Colorectal originated in the intestinal region in the form of small polyps, which may broaden significantly over time. Then it spreads to certain other tissues by invading the muscle fibers and lymph nodes. Some of the signs and symptoms include fatigue, abdominal discomfort, indigestion, stomach cramps, and loss of weight [2]. Existing diagnostic tools for CRC diagnosis are effective, but they have several flaws. Invasive procedures such as sigmoidoscopy, colonoscopy, incisional biopsies, and barium enemas are painful for the patient [3]. Most examinations also do not allow for a detailed analysis of the complete bowel. Furthermore, they are incapable of detecting early neoplasia or short lesions. The ability to diagnose using these techniques is dependent on knowledge. It requires the physician’s skill and judgment, as well as time. Organic dyes and radioactive compounds are used in imaging techniques. They have deficiencies such as low hydrophilicity and photostability, low quantum yields, insufficient biological system stability, and low detection sensitivity, all of which contribute to low efficiency [4]. The use of radioactive compounds carries significant biological risk as well. As a result, new and improved diagnostic tools for CRC detection are critical. During medication, curative quantities of a chemotherapeutic agents in cancerous cells are regularly quantified in terms of massive contamination of the surrounding tissue. This lack of specificity causes some toxicological issues that result in side effects and drug resistance, which are the main concerns and primary reasons for chemotherapy failure [5]. Polymeric system, dendrimers, lipids-based compounds and carbon-based materials, have been used as carrier systems in colorectal cancer therapy to overcome these challenges (figure 1). By leveraging the pathophysiology of the tumor microenvironment, Nano carrier based technologies had also allowed for the appropriate delivery of therapeutics into tumours, providing better immunology treatment effect [6]. The development of nanomaterials for use in biomedical imaging techniques has recently received a lot of attention. These nano-sized carriers benefit from favorable surface properties that allow them to be functionalized to target the desired site of action [7]. Lower accumulation rates in healthy tissues, combined with higher accumulation and retention rates in tumor tissues, explain the increased efficacy and low side effects. The nanocarriers’ pliable surface properties are also advantageous for cancer diagnostics, as they enable the development of new enhanced techniques for specificity in molecular imaging [8].

Introduction

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**Liposomes**

Liposomes are sphere-shaped vesicles made up of one or more phospholipid layers. Phospholipids, cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long-chain fatty acids, and even membrane proteins are used to make them. Liposomal drug delivery is distinguished by slow and delayed-release, passive targeting via the EPR effect, and high drug loading, which leads to dose reduction [9]. Liposomes have gained a great deal of interest in biomedical research in recent decades, notably as a drug carrier for cancer chemotherapy. They illustrated several advantages over traditional systems, including, but not limited to, enhanced therapeutic agents, protective measures of the effective dose from natural conditions, optimised product quality, prohibiting initial deterioration of the encapsulated drug, premium formulations of expensive drugs, and values attached with lowered cytotoxicity.

**Illustration 1: Nanocarriers for colorectal cancer**

**Nanocarriers Based Approaches for Colorectal Cancer**

**Liposomes**

Furthermore, drugs associated with liposomes have significantly different pharmacokinetic properties than free drugs in solution [10]. Stealth liposomes provide better half-life in systemic circulation via polymer coating such as PEG, pegylation etc. X. Hou et al. created and characterized HA-modified, lipid-coated PLGA nanoparticles that were loaded with mRIP3-pDNA [11]. Nanoparticles encased with lipid layer provide better therapeutic effect in target region. While used within conjunction with structurally administered chloroquine, the tumor inhibition rate in the CT26 mouse model was more than 80%. Merging therapeutic agents and fundamental gene therapies to activate multiple interdependent PCD pathways resulted in this effective CRC treatment. Ruttala and Ko created and tested PEG-based nanoliposomes containing curcumin and paclitaxel. The average particle size was 108.21nm, with a PDI of 0.2 and a negative surface charge of 2.65, according to the DLS experiment. Curcumin had an encapsulation efficiency (EE) of 99.9 percent and a loading capacity of 9.09 percent, while paclitaxel had an EE of 99.9 percent and a loading capacity of 5.9 percent, respectively. TEM images revealed a distinct spherical morphology. The drug release kinetics of the nanoliposomes were sustained in vitro for three days at pH 7.4. Curcumin and paclitaxel were released sequentially, with curcumin being released faster than paclitaxel. Within 24 hrs curcumin was released about 35%, whereas paclitaxel shows 20% release at the same time. In vitro cellular analysis provokes that the drug-loaded nanoliposomes outperformed the free drugs and individual free drugs in cytotoxicity against MCF-7 and B16F10. Both drugs’ sustained release profiles from nanoliposomes contributed to their significant cytotoxic effects in vitro [12].

Dendrimers

Dendrimers are a type of polymer nanoparticle. They are made up of globular molecules with branched layers (generations). Dendrimers are large, productive nanoscopic macromolecules that are three-dimensional (normally 5000-500,000g/mol), have a low polydispersity index, and have proven to play an important role in the growing field of nanomedicine. The name is derived from the Greek word “Dendron,” which means “tree,” and reflects their unique tree-like branching design. Dendrimers can also be referred to as “cascade molecules,” though this term is not as commonly used as dendrimers [13]. Monodisperse compounds are the natural consequence of a concise synthesis. Dendrimers can be designed with different organic compounds on their external layer, such as COOH, COONa, NH2, or OH. Dendrimers emit insightful nanomaterials designed to transport substances into key locations thereby evaluating the state of tissues invaded by macrophages and the advancement of the curative phase as a result of quite straightforward modification. They can assist in limiting the arrival of anti-cancer medications to specific objectives, thus also avoiding several of the effects of chemotherapy. Xie et al. used multiple Sialyl Lewis X antibodies (aSlex) conjugated with PAMAM dendrimers to specifically bind and capture colon cancer HT29 cells. The conjugating improved HT29 cell intercept in a frequency circumstance, with a highest sensitivity of 77.88 percent acquired upon 1 hour of susceptibility [14]. Ghaffari and colleagues formulated dendrimers of polyamidoamine (PAMAM) for the simultaneous delivery of curcumin and Bcl-2 siRNA to HeLa cancer cells. The particle size was found to be 180 nm and zeta potential of 48 mV. The curcumin was released in vitro at pH 5.4 (mimicking tumor environment) and 7.4 (mimicking physiological conditions). At both pH levels, less than 5% of the drug was release out from polymer matrix over a 10-hour period, accompanied by a controlled delivery at pH 5.4 with 40% drug release in three days. In seven days at pH 7.4, only 10% of the drug was released. PAMAM dendrimers
were found to have higher drug internalization in *in vitro* cellular uptake studies of co-encapsulated dendrimers into HeLa cells using fluorescent microscopy. In HeLa cells curcumin loaded dendrimers shows inhibition of cancerous tissue in time-dependent-manner. Curcumin and Bcl-2 siRNA co-delivery resulted in increased cellular drug uptake [15].

**Mesoporous Silica Nanoparticles**

Mesoporous silica nanoparticles (MSNs) are solid materials that have pores. In MSNs, the term mesoporous referred to pore size. Porous materials are classified as microporous, mesoporous, or macroporous by the IUPAC. Porous diameters lesser than 2, between 2 and 50 nm, and greater than 50 nm are classified as microporous, mesoporous, and macroporous. MSNs seem to be very prevalent in a range of contexts due to their properties including controllable particle and pore size, excellent durability and rigorous structure, massive surface area and high pore volume. There are three basic components in the synthesis of MSNs: the template, typically a surfactant, which will act as the agent to create the pores, the silica source to make up the walls surrounding the pores, and an acid or base to aid in the formation. Hwang and colleagues created MSNs using polyethylene glycol (PEG) and sodium silicate as the template and silica source. The synthesis was carried out at a pH of neutral, with acetic acid serving as a pH adjuster. They were successful in obtaining MSNs with spherical morphology and a surface area of 685 m²g⁻¹ [16]. Tian *et al.* created poly (N-isopropylacrylamideco-methacrylic acid) [P(NIPAM-co-MAA)] coated magnetic mesoporous silica nanoparticles (MMSNs) with particle sizes of 255 ± 28 nm and pore sizes of 2.6 nm for chemomagnetic therapy. Under the influence of an alternating magnetic field (AMF) with a frequency of 409 kHz and a magnetic field strength of 180 Gauss, the MMSNs generated enough heat to raise the cell temperature to 64.2°C in 15 minutes, inducing hyperthermia as well as the controlled release of loaded DOX. A CCK-8 assay revealed that the cell viability of Hela cells after treatment with the synthesized DOX-MMSN@P (NIPAMco-MAA) nanoparticles was only 23%, significantly lower than that of cells treated with DOX (76%) or AMF (42%). This demonstrates the powerful synergistic therapeutic effect of chemo-magnetic hyperthermia therapy and establishes a promising platform for combined chemotherapy [17].

**Carbon Nanotubes**

Carbon nanotubes (CNTs) are carbon allotropes with a cylindrical size. They are composed of cylindrical carbon molecules with remarkable properties [18]. CNTs are categorized depending on their composition: single-walled nanotubes (SWNTs), that are made up of a single graphite sheet encased into a hollow cylinder, and multi-walled nanotubes (MWNTs), that are made up of an array of such nanotubes axially enclosed around each other, much like the rings of a tree trunk. CNTs have been used as a nano-system to deliver chemo-preventive agents, genes, and proteins for cancer treatment through appropriate functionalization. Tripisciano *et al.* enclosed irinotecan, a more water-soluble semisynthetic analog of CPT, within MWCNTs. According to the results of the experiment, a greater internal diameter tube filled with more irinotecan than a smaller one, and loading efficiency of 32% was acquired. Because irinotecan’s stability and hydrophilicity increase in acidic conditions, rapid and complete release (pH 6.0 vs 7.0) was observed in a mildly acidic environment. However, no *in vitro* studies on colorectal cancer cells were carried out using this complex [19]. Yang *et al.* recently loaded the anticancer molecule gemcitabine into magnetic MWNTs and found high activity against lymph node metastasis when the formulation was injected subcutaneously into mice [20]. Another study found that the poorly water-soluble anticancer camptothecin loaded into polyvinyl alcohol-functionalized MWNTs could be effective in the
treatment of breast and skin cancers [21]. Using a solvothermal method, Wu et al created MWCNTs/ cobalt ferrite (CoFe2O4) magnetic hybrids. Following the intracellular release of DOX, DOX-loaded magnetic hybrids demonstrated significant cytotoxicity in HeLa cancer cells. In aqueous solutions, the magnetic hybrids demonstrated a high T2 relaxivity of 152.8 Fe mM⁻¹ s⁻¹ and significant negative contrast enhancement [22].

**Gold Nanoparticles**

For many years, gold (Au) has been used in the biomedical field. It is utilised in bioimaging and the treatment of arthritis/inflammation since the early twentieth century. Because gold salts have anti-inflammatory properties, they have been included in disease-modifying antirheumatic drugs (DMARDs), which are one of the drug classes used to treat rheumatoid arthritis. However, gold salts as DMARDs have been phased out and replaced by others, most likely due to gold’s affinity for DNA and thus interference with cell function. A study by Qiu et al. found that acute and chronic AuNP exposure disrupts gene expression. The USFDA has yet to approve any gold-based nanomedicines [23]. Because of their simple production process and functioning, and lesser side effect in preliminary assays, AuNPs have been described as “promising nanocarriers for therapeutics.” The interrelationships of nanomaterials with lipid membrane are chiefly determined by the chemical features encapsulated on the substrates of the nanoparticles, as well as their physical characteristics. Functionalization of AuNPs, in particular, is an essential characteristic that impacts their efficacy in therapeutic agents. As per Pissuwan et al., surface properties for AuNPs are mandated in targeted drug delivery to lengthen the residence of the AuNP conjugates in circulation, avert RES clearance, enable accurate connection of the preferred target specific molecules, improve AuNP consistency by prohibiting aggregation, and ultimately, neutralise the potential cytotoxicity caused by stabilising surfactant. For example, the outer layer of AuNPs may be encapsulated with neutrally charged groups such as PEG or zwitterionic ligands, or charged chemical bonds that seem to be anionic positive/negative to avoid rapid clearance via non-specific utilisation by the RES and to provide effective nanomaterials interrelations with cells [24]. Libutti et al discovered that in contrast to native TNF-α, TNF conjugated to a colloidal gold platform interspersed with thiol-derivatized PEG was more effective in reducing tumor burden in a colon cancer xenograft model without causing animal death. A Phase 1 clinical trial of the PEGylated colloidal gold TNF construct (CYT-6091) in patients with advanced-stage solid cancers revealed promising results [25].

**Conclusion**

Nanoplatforms are gaining popularity as a research methodology to diagnostic and therapeutic applications. Nanoplatforms are valuable drug delivery systems that have been shown to improve both diagnostic accuracy and therapeutic effectiveness in CRCs. Cancer nanomedicine is a rapidly evolving interdisciplinary research field that has the potential to transform diagnostic accuracy, toxicity, and drug delivery in rectal cancer. The combination of drug molecules with nanocarriers can protect them from degradation while also allowing for targeting and controlled release. Nanoparticle platforms have enabled the development of techniques in drug conjugation and nanomaterials engineering for improved therapeutic regimens. So far, promising results revealed that polymeric nano-system have the potential to improve chemotherapy drugs in contradiction of colorectal cancer.

**Bibliography**


