Theranostic nanoplatforms for treatment and diagnosis of rectal and colon cancer: a brief review

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Abstract

Colorectal cancer (CRC) is a common health problem due to its high prevalence and high mortality rate. Adjuvant and neo-adjuvant strategies, chemotherapy and radiotherapy alone or in combination, have substantially improved survival and local recurrence rates. Their effectiveness remains limited due to the intrinsic build-up of resistance of cancer cells to chemotherapy drugs, dose-limiting toxicities and other major side effects. New strategies to overcome these issues are being developed, one of which is cancer nanomedicine, a rapidly developing interdisciplinary research field. The last few decades have seen a rapid growth of interest in utilising nanoparticles and nanotechnology in cancer medicine. This is mainly due to the suitable physical and chemical properties of nanoparticles for in vivo applications. Cancer nanomedicine for targeted drug delivery and imaging has been widely investigated preclinically and clinically. Nanomedicine has been considered as a novel solution to enhance CRC diagnosis and treatment, both separately and in combination using theranostic techniques. This review highlights the research, opportunities, and challenges for the development of nanoplatforms for diagnosing and treating CRC.

Keywords: Nanomedicine, colorectal cancer, nanoparticles

INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer in the world¹⁻³. In stage III rectal cancer surgical resection followed by adjuvant chemotherapy, and of late neo-adjuvant chemo-radiotherapy in locally advanced disease, survival rates up to 58% at 5 years³⁻⁴ have been reported. Recurrence, local
and/or distant, may occur in up to approximately 50% of patients, but 5-year survival if curative resection or R0 metastasectomy is achieved, may still be from 22%-49%. In primary CRC survival is very much stage dependent and varies from 90% 5-year survival rate in stage I rectal cancer to less than 10% of people diagnosed with distant metastatic cancer[6,9]. Lymph-node (LN) metastases are the most powerful predictor of survival and need for adjuvant treatment in all solid cancer and almost always follow a well-defined tumour-draining lymph node basin[10]. Due to their small size and poor vascularisation, LN metastases are difficult to detect with certainty using conventional imaging modalities. Given that chemotherapy and radiation in the (neo-) adjuvant setting have their specific adverse effects and limited efficacy profile, it is imperative to increase the diagnostic accuracy of LN metastases in the pre-operative setting[11]. Nanomedicine may offer an alternative and potentially may be more effective in diagnostics. In combination with therapeutics, it may offer a less toxic theranostic pathway[12-20]. The present paper highlights the current understanding of nanomedicine and its role in the management of CRC, and rectal cancer in particular. Nanomedicine is in its adolescence and is slowly transitioning from cell and animal studies towards human trials. To develop appropriate first-in-human trials it is important for clinicians to understand the variety of nano-platforms and particles currently available along with their specific features.

NANOMEDICINE

The ability to explore the structure and characteristics of materials at the nanoscale has made a great change in many fields of science such as medicine. In the comparison of nanoparticles to their bulk systems, the main properties of nanoparticles that make them fundamentally different in their behaviour are surface-related characteristics and quantum characteristics[21-25]. Efficient drug and medical radioisotopes loading (due to the highly reactive surfaces of nanoparticles) in combination with unique physical (e.g., magnetic) properties of nanoparticles have led to rapidly growing interest in nanoparticles for medical applications such as drug delivery and imaging[26-33]. Particles or molecules with 10-100 atoms (at least in one dimension) are normally regarded as nanoparticles[34-37][Figure 1]. Generally, nanoparticles are sized between 1-100 nanometers. Nanoparticles compared to their bulk system (e.g., microparticles) have high surface area-to-volume ratio. Therefore in a nanoparticle, the number of atoms at the surface is greater than those within their internal core and consequently they have a high number of interaction sites available at the surface which makes them chemically more reactive[38]. Moreover, at nano-scale where the size of particles (e.g., nanocrystal) is comparable to the de Broglie wavelength of an electron, the change in electronic energy levels become discretely discrete, a condition known as the quantum confinement of the electron wave function[39]. This effect is responsible for some of the unique behaviour (e.g., optical) of nanoparticles such as quantum dots. These unique properties (e.g., optical, magnetic, active surface) give nanoparticles the potential to be used as a diagnostic agent or carrier for delivering therapy and thus to be an ideal platform for developing theranostic nano-agents in medicine.

NANO-PLATFORMS FOR DRUG DELIVERY

Tumour tissues of different cancer types such as colon, breast, prostate and lung cancer are permeable to nano-molecules and nanoparticles[40-42]. This is due to their distinctive structural characteristics such as the hyper-permeable vasculature and impaired lymphatic drainage[40,43,44]. Nanoparticle and nano-molecule drug delivery mechanisms can be classified into active and passive targeting. Active targeting highly depends on the interaction between the target cell receptors and nanoparticles whereas passive targeting relies on a number of factors such as longer biological half-life, long-circulating time at tumour locations and the flow rate of nanoparticles to the impaired lymphatic system[45-49]. Moreover, the enhanced permeability and retention effects and nanoparticle clearance by the mononuclear phagocyte system play an important role in determining the effectiveness of the nano-platform drug delivery system[44,50]. The reticuloendothelial system (RES) effect is one of the most common problems among all different
types of nanoparticles. RES effect refers to the quick absorption of nanoparticles by macrophages which usually results in clearing nanoparticles from the circulation in vivo\[^{51-53}\]. Specific types of nanoparticle coating may prevent and minimise the RES effect. Nanoparticles with surfactants or covalent linkage of polyoxyethylene have shown to effectively minimise the RES effect\[^{54}\]. The size and shape of nanoparticles are the other two main factors that affect the delivery of conventional therapeutics to solid tumours. Nanoparticles larger than 500 nm are shown to be rapidly removed from the circulation in vivo\[^{44,55}\]. In addition, targeted nanoparticles as a drug delivery system based on monoclonal antibodies are currently one of the main approaches for CRC therapy under preclinical development\[^{56,57}\]. A list of these nanoplatforms is presented in Table 1.

### LIPOSOMES-BASED NANOPARTICLES

The first therapeutic nano-platform applied in medicine was introduced by Bangham et al.\[^{63}\] in 1961. This nano-platform was based on liposomes which were the first drug-delivery system approved by FDA for clinical practice. Liposome-based nanoparticles are one of the commonly used nanoparticles for delivering small peptides, nucleic acids, and proteins in nano-platform drug delivery\[^{64-66}\]. Nanoliposomes are non-toxic, spherical nano-carriers containing an aqueous core with phospholipid bilayer\[^{67,68}\]. Nanoliposomes are considered as one of the most effective drug delivery systems at a cellular level. This is mainly due to their size, ability to incorporate various substances and slow-releasing and targeting characteristics which also results in decreasing side effects\[^{69,70}\]. There are three main types of nanoliposomes: (1) stealth liposomes or long-circulating liposomes, which have a modified phospholipid bilayer structure and added gangliosides or a polyethylene glycol (PEG) to assist avoiding blood plasma opsonins proteins binding to the liposome surface and minimise the RES effect; (2) active nanoliposomes: this type of nanoparticle targets receptors, hormones, peptides and antibodies; and (3) sensitive nanoliposomes: they are special active nanoliposomes with unique properties such as pH-sensitive, thermo-sensitive and magnetic\[^{21,70,71}\].

Doxorubicin (Doxil\textsuperscript{®})-liposome is an example of FDA approved nanoliposome for chemotherapy for CRC\[^{72}\]. Doxil is approximately 100 nm and although it has much less gastrointestinal and cardiac toxicity, it causes other side effects such as redness and peeling of the skin\[^{72}\]. Marqibo\textsuperscript{®} is another recent nanoliposomal drug approved by FDA\[^{73-76}\]. Marqibo is approximately 100 nm and it is a cell cycle-dependent anticancer drug. Thermo-sensitive liposome doxorubicin (Thermodox\textsuperscript{®}) is another promising nanoliposomal drug for colorectal liver metastases in combination with radiofrequency ablation\[^{77}\]. Thermodox\textsuperscript{®} is a nanoliposomal with doxorubicin formulation which releases the drug upon a mild hyperthermic trigger\[^{77}\]. Thermodox can deliver 25 fold more doxorubicin into tumours than IV doxorubicin does\[^{77}\].

### CORE-SHELL NANOPARTICLES

There has been an increasing interest in developing and synthesizing core-shell nanoparticles\[^{78,79}\]. The core-shell nanoparticles are composed of two or more materials which can be synthesised with different
combinations of inorganic and organic materials. To enable efficient surface modification, increasing the functionality and stability, the core nanoparticles is coated. The core-shell has different applications in the medical field such as controlled drug delivery, multimodal-imaging, cell labelling and nuclear medicine therapy. Superparamagnetic iron oxide nanoparticles (SPIONs) are one of the most common core-shell nanoparticles that are used in medical imaging and therapy.

**SPIONS**

SPIONs are nanoparticles that have become the focus of nanomedicine research since 1980, and have evolved to include SPIONs with a biocompatible polymer coating and core surface modification specifically for nanomedicine and nuclear medicine applications. The key features of SPIONs include exhibiting magnetisation only in an applied magnetic field and the ability to load drugs and medical radioisotopes (due to their highly active surface). Over the past few decades, further developments in radiochemistry and radiation sciences have led to applying the field of nanomedicine to nuclear medicine for enabling multimodal medical imaging (radiolabelled nanoparticles with imaging isotopes) and radionuclide therapy (radiolabelled nanoparticles with therapeutic isotopes) of different types of cancer. This has significantly improved cancer diagnosis and therapy. Currently nanoparticle-based magnetic resonance imaging (MRI) is utilised in cancer medicine for enhancing the MR image contrast. There are key advantages of SPION drug delivery including longer circulation half-lives, improved pharmacokinetics, capability to carrying a large amount of drugs, reduction in side effects and targeting the drug to a specific location in the body.

Additionally, the doped gold-SPIONs have been developed for targeted photothermal therapy for destruction of CRC. The developed gold-SPIONs were also functionalised with a single chain antibody to enable active targeting of the A33 antigen, which is overexpressed in CRC cells. Results demonstrated that the internalisation of gold-SPIONs was five times faster for cells expressing the A33 antigen than cells not expressing the antigen. Furthermore, this study has shown that upon 6 min of laser radiation exposure (with an 800 nm laser at 5.1 W·cm⁻²), 53% A33-expressing cells died whereas only 5% of A33 non-expressing cells died. These results demonstrated an excellent selectivity for targeting and killing CRC.

Moreover, SPION-based MRI has emerged as a common approach in medical imaging specifically of lymph nodes in solid cancers, including CRC. This caused by a preferential uptake of SPIONs in lymph node as well as the ability of SPIONs to produce high contrast between cancerous and healthy tissues. Due to the physical and chemical properties (e.g., highly reactive surface and magnetisation) of SPIONs, they have attracted enormous attention in cancer diagnosis and therapy. SPIONs in vivo can perform actively (targeting a tissue or an organ) or passively. Peptide or antibody labelled SPIONs act as an active carrier for targeting the organ or tissue of interest. However, passive SPIONs mainly rely on the polymer type and particle size to achieve accumulation at the target site. Hydrophilic SPIONs with dextran and
PEG surfaces are able to evade the RES as well as resisting the opsonisation (destruction by an immune cell) which leads to the increase of their biological half-life (circulation time) and the probability of targeting a specific cell \[98-100\]. Moreover, SPIONs with a size of less than 30 nm can also slowly extravasate from vascular space to interstitial space, from where they can be taken up by immune cells (monocytes/macrophages) and delivered via lymphatic vessels to lymph nodes. These passive SPIONs can remain in normal nodal tissue and reduce MRI signal intensity, thereby enhancing contrast against any metastatic lesions in the node \[Figure 2\].

CONCLUSION AND FUTURE DEVELOPMENT
Nanoplatforms constitute valuable drug delivery systems that have been shown to serve the dual purpose of improving diagnostic accuracy and therapeutic effectiveness for CRCs. Cancer nanomedicine is a rapidly developing interdisciplinary research field that may have a transforming effect on diagnostic accuracy, toxicity and drug delivery specifically in rectal cancer. Finally, cancer nanomedicine for targeted drug delivery and enhanced imaging holds great promise and is moving from basic cell line research and subsequent animal studies work into the next stage of the translational pipeline: first-in-human trials.

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Authors’ contributions
Preparing the article: Gholami YH
Revising it critically for important intellectual content: Engel A

Availability of data and materials
Not applicable.

Figure 2. A: Following intravenous injection, SPIONs slowly extravasate from vascular space to interstitial space, from where they can be taken up by immune cells (monocytes/macrophages) and delivered via lymphatic vessels to lymph nodes. The SPIONs remain in normal nodal tissue and reduce MRI signal intensity, thereby enhancing contrast against any metastatic lesions in the node; B and C: demonstrating the mechanism of negative contrast agent, SPIONs in lymph node imaging; B: a conventional T2-weighted MR image of the lymph node showing the whole lymph node is associated with cancer metastases; C: the T2-weighted MR image of the lymph node with enhanced contrast produced by SPIONs showing only two small metastatic regions (e.g., hyper intense foci). The MR images in B and C were reproduced\[^96^\]. SPION: superparamagnetic iron oxide nanoparticle; MRI: magnetic resonance imaging
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Conflicts of interest

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Ethical approval and consent to participate

Not applicable.

Consent for publication

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