Advancements in cancer imaging: receptor-targeted approaches for enhanced precision and therapy guidance

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Chapter 5

General discussion and future aspects

Summary of the thesis

This thesis explores the use of chitosan and PLGA polymeric NPs for breast cancer treatment and rectal cancer imaging, aiming to enhance payload delivery by encapsulating therapeutic and imaging agents within the NPs. To further improve tumor specificity, cancer cell membrane vesicles and peptide-based targeting moieties were incorporated, ensuring selective payload delivery to cancer cells while minimizing off-target effects on healthy tissues. This receptor-targeted approach advances precision in cancer imaging and therapy guidance. In **Chapter 2**, we developed redox-sensitive chitosan NPs (CS-NPs) coated with cancer cell membranes (CCMs), red blood cell membranes (RBCMs), and hybrid RBC-4T1 membranes to enhance DOX delivery to breast cancer cells. DOX-loaded CS-NPs (DOX/CS-NPs) demonstrated high loading capacity, while 4T1CM coating improved NP uptake and cytotoxicity. Optimizing the RBCMs:4T1CMs ratio enhanced homotypic targeting. *In vivo*, 4T1-coated DOX/CS-NPs (4T1@DOX/CS-NPs) most effectively suppressed tumor growth and metastasis. CM coating also reduced macrophage uptake and accelerated NP clearance, emphasizing the role of self-recognition in improving targeting and cytotoxicity. **Chapter 3** investigated gastrin-releasing peptide receptor (GRPR) as a key biomarker for rectal cancer targeting and imaging, confirming its significant overexpression in cancer cells and tissues. A novel GRPR-targeting peptide, gastrin-releasing peptide-derived peptide (GRP-DP), was designed and demonstrated strong in vitro targeting for rectal cancer imaging, aiding tumor resection. Additionally, indocyanine green (ICG)-loaded poly(lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) nanoparticles (NPs), functionalized with GRP-DP, exhibited controlled release, biocompatibility, and efficient cancer cell internalization, enhancing fluorescent tumor cell imaging. Finally, in **Chapter 4**, we investigated cholecystokinin 2 receptor (CCK2R) expression in rectal and colorectal cell lines and assessed its targeting using a PP-F11 Cy5-labeled peptide in both CCK2R-positive and CCK2R-negative cells. Immunohistochemical (IHC) staining of a tissue microarray (TMA) from human rectal tumor tissues revealed significant overexpression of CCK2R in both epithelial and stromal compartments of rectal cancer tissues compared to normal tissues. Clinicopathological characteristics and stromal CCK2R expression correlated with tumor differentiation and TNM stage, and were associated with tumor-stroma interactions and the tumor microenvironment. In contrast, epithelial CCK2R expression did not show a significant correlation with clinical outcomes, except for circumferential margin involvement. Additionally, the CCK2R binding peptide Cy5@PP-F11 was identified as a promising fluorescence probe for intraoperative imaging, enhancing CCK2R-targeted image-guided surgery. These findings support CCK2R as a viable target for tumor imaging and surgical guidance.

Polymeric Nanoparticles for cancer drug delivery and imaging

Polymeric nanoparticles enhance drug delivery by enabling targeted uptake, controlled release, and improved stability, bioavailability, and versatility while reducing side effects [1]. In this thesis, we used two kinds of polymeric nanoparticles, including chitosan and PLGA. Chitosan, being a natural polymer, is biocompatible and biodegradable, making it ideal for biomedical applications such as drug delivery. Chitosan nanoparticles (CSNPs) enable targeted medication transport, controlled release, and safe degradation into non-toxic byproducts, ensuring sustained therapeutic effects [2]. Poly(lactic-co-glycolic acid) (PLGA) is FDA and European Medicine Agency (EMA)-approved for drug delivery systems, available in various molecular weights and copolymer compositions. Its degradation time ranges from months to years. PLGA undergoes hydrolysis in the body, producing metabolites that are safely eliminated with minimal toxicity [3]. These properties of Chitosan and PLGA NPs encourage their use. Additionally, our previous experience with these nanoparticles in drug delivery, as demonstrated in prior publications from our group, has further increased our confidence in using them [4, 5].

In **Chapter 2**, natural polymer CS NPs loaded with doxorubicin (DOX) were developed to enhance chemotherapy efficacy in breast cancer *in vitro* and *in vivo*. To improve tumor specificity, drug bioavailability, and reduce systemic toxicity, lipoic acid was incorporated into the CS structure. This modification enabled tumor-specific DOX release, enhanced stability, and minimized toxicity. The modified NPs exhibited biocompatibility and triggered DOX release under acidic and redox conditions, mimicking the tumor microenvironment [6], with up to 80% drug release within the first 8 hours. Another type of synthetic polymeric NPs, PLGA, was utilized in **Chapter 3** for rectal tumor imaging and fluorescence-guided surgery. Indocyanine green (ICG) was encapsulated within PLGA-polyethylene glycol (ICG/PLGA-PEG) NPs, exhibiting favorable physicochemical properties, including a spherical shape, uniform size distribution, controlled ICG release kinetics, and biocompatibility. Data demonstrated that PLGA-PEG NPs, in addition to improving the self-quenching phenomenon of ICG loaded in PLGA NPs, released approximately 80% of ICG within 24 hours and achieved complete release by 192 hours.

In the chapters 2 and 3, polymeric NPs were utilized; however, despite their benefits, NP therapies face several challenges in technical development, biological compatibility, regulatory approval, and economic feasibility. Key technical hurdles include maintaining stability, preventing aggregation, and controlling synthesis parameters to ensure consistent quality [7].

CS-based NPs offer biocompatibility and biodegradability but struggle with membrane crossing, immune reactions, and issues like aggregation, stability, and scalability, limiting clinical application [7]. To overcome these challenges, innovative approaches such as surface modifications and polymeric coatings are essential to enhance stability and enable targeted delivery[7]. In **Chapter 2**, to address the low solubility of CS in neutral and alkaline pH [8], we used its water-soluble derivative, CS oligosaccharide (CSO). Additionally, we modified the surface of CSNPs cancer cell membranes (CCMs), red blood cell membranes (RBCMs) to enhance stability, immune reactions and enable targeted delivery.

CS-based nanocarriers challenges such as hemocompatibility issues, off-target drug distribution, rapid clearance, and variability in properties based on source and processing limit their clinical use. Modified chitosan formulations, while FDA-approved for oral delivery and wound healing, may pose toxicity risks [2]. Formulating chitosan into NPs adds complexity, requiring precise size control for optimal circulation. While chitosan demonstrates immunostimulatory activity, excessive inflammation remains a concern. Despite these obstacles, chitosan NPs have advanced in clinical trials and, with improved standardization, hold strong potential as a delivery vehicle for various therapies [10].

Despite the numerous advantages of PLGA NPs-based drug delivery systems, they also have limitations. Notably, their relatively low drug loading efficiency poses a significant challenge for clinical translation [9]. In **Chapter 3**, the encapsulation efficiency (%EE) of ICG in PLGA-PEG NPs was found to be 86.18 ± 1.4%, and the loading capacity (LC) was 4.52 ± 0.08%. Future research could focus on developing techniques to precisely enhance these values.

In addition to the successful application of PLGA NPs in preclinical studies, several formulations have also demonstrated clinical translational success. Notably, products such as Lupron Depot® (leuprolide acetate) for prostate cancer and endometriosis, and Sandostatin Lar® (octreotide acetate) for acromegaly, have successfully transitioned from the laboratory to the clinic. These formulations utilize PLGA microspheres for sustained drug release, offering improved patient compliance and more controlled therapeutic effects [11].

Preclinical framework for receptor-targeted cancer approaches using Nanoparticles

Cancer arises from complex molecular interactions that drive abnormal cellular behavior. Surface receptors, which regulate functions like signal transduction, cell adhesion, and immune responses, play a crucial role in these processes, making their study essential for understanding cancer progression [12, 13]. However, in many cancers, these receptors become overexpressed, mutated, or dysregulated, contributing to uncontrolled cell proliferation, metastasis, and resistance to therapy. Targeting these aberrant receptors is a crucial strategy in cancer treatment, as they influence key biological processes like cell growth, differentiation, and survival [13]. Unlike passive targeting, which relies on the Enhanced Permeability and Retention (EPR) effect, active targeting involves the attachment of targeting molecules (ligands) to the NPs surface [14]. Ligand-receptor interactions enable targeted drug delivery by facilitating nanocarrier uptake in cancer cells, enhancing drug accumulation and treatment efficacy.

In **Chapter 2,** CS NPs were functionalized with cancer cell membranes (CCMs), red blood cell membranes (RBCMs), and hybrid erythrocyte-cancer membranes (RBC-4T1CMs) to create cell-membrane-coated biomimetic nanoparticles. These modifications aimed to enhance circulation time, enable immune evasion, and leverage homotypic targeting, allowing them to perform complex functions in dynamic biological environments through specific proteins and unique properties. The data demonstrated active versus passive targeting both *in vitro* and *in vivo*, revealing the efficacy of receptor-targeted DOX delivery for breast cancer treatment. The two key properties of biomimetic NPs homotypic targeting and immune escape mechanisms [15] were studied *in vitro* for CCMs-coated DOX/CS NPs, highlighting their potential benefits in targeted drug delivery. Homotypic targeting data confirm the self-recognition ability of CCMs-coated CS NPs for targeted breast cancer therapy, while CD47 on CM-coated DOX/CS NPs aids immune escape by reducing macrophage uptake. Further analysis using the 4T1 orthotopic mammary tumor metastasis model evaluated the *in vivo* anti-tumor effects of the NP formulations. All DOX-loaded CS NPs coated with 4T1CMs or RBCMs, along with free DOX and DOX/CS NPs, significantly inhibited tumor growth compared to the saline group. Notably, complete tumor regression was observed in one mouse treated with 4T1@DOX/CS NPs. Our study shows that NP formulations, particularly those coated with 4T1 cell membranes (4T1CMs), hold promise for targeted drug delivery in cancer therapy. These NPs enhance tumor targeting and reduce toxicity, as observed in our findings. Future studies should focus on optimizing their design, evaluating long-term safety and efficacy in clinical trials, and exploring their potential in combination therapies to improve anti-tumor efficacy and minimize side effects.

Another study on receptor-targeted approaches was conducted in **Chapters 3**. In **Chapter 3**, PLGA-PEG NPs were functionalized with peptide ligands for targeted rectal cancer imaging. Peptide ligands, bridging small molecules and antibodies, offer high affinity, specificity, and effective drug delivery. They provide advantages like better tissue penetration, low immunogenicity, and cost-effective synthesis, with versatile chemical properties for modification [16]. In addition to PEG functionalization, which reduces opsonization and prolongs circulation time, these NPs were conjugated with the peptide ligand gastrin-releasing peptide- derived peptide (GRP-DP). This ligand specifically binds to the gastrin-releasing peptide (GRP) receptor, enhancing tumor targeting, penetration, and accumulation. The potential of GRP-DP, both as a standalone agent and in combination with PLGA-PEG NPs, was investigated to enhance cellular uptake. *In vitro* data showed that the uptake of GRP-DP-functionalized PLGA-PEG NPs (GRP-DP@ PLGA-PEG NPs) was significantly higher compared to non-targeted NPs, demonstrating enhanced internalization in GRPR-expressing cancer cells. Additionally, the specificity of FITC labeled GRP-DP was assessed by comparing its uptake in both cancerous and normal cells, revealing a markedly greater accumulation in GRPR-positive cancer cells.

Given the promising data in **Chapter 2** (*in vitro* and *in vivo*) and **Chapters 3** (*in vitro*), receptor-targeted strategies using NP show potential in cancer therapy and imaging. Their success depends on receptor expression, ligand affinity, tumor microenvironment, and resistance mechanisms. Challenges persist in translating receptor-targeted NPs, like GRP-DP coated PLGA-PEG and CS NPs functionalized with cancer cell membranes, into clinical applications. For CCM-coated DOX/CS NPs in **chapter 2**, while CCM-coated NPs (CCMNPs) show promise, they face challenges before commercialization. Patient education is essential, as some may be hesitant to receive cancer-derived materials, particularly for preventive use. Additionally, strict testing is required to ensure membrane purity and safety [17]. Before clinical application, key challenges include also ensuring the correct membrane orientation on nanoparticles, large-scale production, and long-term biocompatibility. The membrane's surface proteins must remain correctly positioned for functionality, requiring optimized coating methods. Additionally, sourcing cell membranes, especially from tumor cells, is complex and costly, necessitating alternative approaches for scalable production [17-19]. Future research should focus on (1) long-term stability and safety, assessing degradation and accumulation risks; (2) immune interactions, studying immunogenicity and long-term effects; (3) clinical translation, developing guidelines for safety, efficacy, and regulatory approval; (4) targeting precision, optimizing therapeutic effectiveness and reducing off-target effects; and (5) multifunctional CCMNPs, integrating them with other therapies for enhanced treatment outcomes [20]. Even though GRP-DP@PLGA-PEG NPs demonstrated promising *in vitro* specificity in **Chapter 3**, the scalability of peptide-conjugated NPs remains a challenge due to production inconsistencies, stability issues, and high costs. Future advancements, including automated synthesis, microfluidics, and self-assembling peptide strategies, can improve efficiency, uniformity, and large-scale production feasibility [21].

Peptide-based strategies for targeted tumor imaging

The peptide tracers and peptide ligands used in **Chapters 3 and 4** for image-guided surgery purposes in rectal cancer are closer to clinical application. Both tracers, GRP-DP and PP-F11, demonstrated promising results, though they function in different affinity ranges, µM and nM respectively. The dissociation constant (Kd) of the GRP-DP tracer was determined to be 4 µM, whereas PP-F11, a known peptide with modifications introduced in our study, exhibited Kd values in the nM range. Notably, this study represents the first application of PP-F11 in fluorescent imaging. Labeling peptide tracers with appropriate fluorophores can enhance imaging contrast and reduce background signal. In **Chapter 3**, GRP-DP was labeled with fluorescein isothiocyanate (FITC); however, autofluorescence posed a significant challenge. The natural emission of light by biological structures upon excitation at specific wavelengths can interfere with fluorescence imaging, particularly when using FITC, which has an emission spectrum that overlaps with endogenous fluorophores. This interference often leads to a reduced signal-to-noise ratio, making it difficult to accurately detect specific signals [22]. However, FITC labeling was used as a model system. Future studies will use near-infrared dyes, which have low tissue autofluorescence and reduce interference. In **Chapter 4**, PP-F11 was labeled with Cyanine 5 (Cy5), a far-red fluorophore with a longer excitation wavelength, significantly reducing autofluorescence and improving imaging quality [23]. Additionally, selecting the appropriate labeling for peptide tracers is crucial in preclinical research. In our experience , FITC labeling not only exhibited autofluorescence but also showed strong adhesion to assay plates in various experiments, whereas Cy5 did not.

Future research should focus on improving the stability of GRP-DP and PP-F11 and optimizing their labeling with near-infrared dyes. However, these tracers have not yet been tested *in vivo*. For effective clinical application of peptide-drug conjugates or other peptide-based agents, tumor-targeting peptides must demonstrate high on-target affinity, permeability (cell/tumor penetrating peptides), plasma stability, and retention [24]. GRP-DP and PP-F11 can be labeled with IRDye 800CW, Cy7, Alexa Fluor 750, DyLight 800, or Indocyanine Green (ICG) to enhance *in vivo* and clinical applications by reducing autofluorescence and improving tissue penetration. Peptides conjugated to IRDye 800CW [25] and labeled with Cy7 have demonstrated effective tumor targeting [26], while ICG is clinically approved for deep-tissue imaging [27].

Expression and clinical significance of receptor markers in rectal cancer

This research provided two novel markers which are overexpressed in rectal cancer. This study investigated the expression and clinical significance of gastrin-releasing peptide receptor (GRPR) and cholecystokinin-2 receptor (CCK2R) in rectal cancer, with a particular focus on their potential for image-guided surgery (IGS). **Chapter 3** examined GRPR expression in a limited cohort of rectal cancer patients. While correlation analysis with clinical outcomes and survival was theoretically possible, the small sample size limited its statistical reliability, so it was not performed.

GRPR expression has varied clinical implications across cancers. In breast cancer, it predicts tamoxifen response in ER-positive patients but does not impact overall or disease-free survival in lymph node-negative cases [28]. In prostate cancer, it improves PSA recurrence-free survival in high AR or Cyclin D1 cases but lacks independent prognostic value [29] . In Lung adenocarcinoma (LUAD), high GRPR levels worsen survival by promoting metastasis, making it a prognostic marker for poor clinical outcome and a therapeutic target [30]. In colon cancer, GRPR enhances survival, reduces metastasis, and recruits immune cells, highlighting its protective role and therapeutic potential [31].

Chapter 4 of this study identified significant CCK2R overexpression in both the epithelial and stromal compartments of rectal cancer, expanding beyond previous research that focused on epithelial expression. While epithelial CCK2R significantly correlated only with circumferential margin status, stromal CCK2R was significantly associated with tumor grade, TNM stage, and increased lymphoid infiltration. The present study found that epithelial CCK2R had no clinical prognostic impact, while higher stromal expression correlated with better patient survival. In contrast, a previous study [32] analyzed total CCK2R expression, where higher levels correlated with worse DFS. This suggests that combining both tumor compartments (stroma and epithelium) may mask opposing prognostic effects, highlighting the present study's refined insight into CCK2R's role in rectal cancer prognosis.

Future research should include GRP, as its co-expression with GRPR has demonstrated significant relevance in colorectal cancer [31]. The functional interplay between GRPR and CCK2R in rectal cancer should be further investigated, particularly to determine whether their co-expression affects tumor progression and therapeutic response. Given their distinct expression patterns, dual-targeted imaging strategies may enhance image-guided surgery by improving tumor localization. Additionally, research should determine whether GRPR and CCK2R expression correlates with treatment response, particularly to chemoradiotherapy, and explore their potential as targets for receptor-based therapies. Lastly stromal *versus* epithelial expression of GRPR would be of interest to determine its distinct role in the tumor microenvironment. Given the findings on CCK2R, further validation in larger cohorts is needed to confirm the clinical significance of these compartment-specific expression patterns. Finally, multicenter validation studies are essential to establish GRPR and CCK2R as reliable biomarkers and therapeutic targets in rectal cancer.

In conclusion, this body of work contributes valuable insights into the design and application of receptor-targeted nanoparticles for both therapy and imaging. It underscores the importance of understanding the tumor microenvironment and molecular receptor expression in developing next-generation cancer diagnostics and therapeutics. The integration of molecular profiling with functional nanomaterials opens new opportunities for personalized, precise, and effective cancer treatment strategies.

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