The Use of Folate Receptor Alpha-targeted Nanotechnology in Ovarian Cancer Diagnosis and Treatment

Briny Yu Xin Ya Xiao

The Henrietta Barnet School, London, United Kingdom
Email: Brineyxiao1@gmail.com

***Abstract*—Ovarian cancer is a major gynecological disease that has poor survival outcomes due to its frequent diagnosis at late stages of malignancy. As ovarian carcinomas overexpress the folate receptor alpha, FR*α* can be used as a target for improved diagnosis and therapeutic effects. This review examines recent studies on FR*α*-targeted nanotechnological approaches to improve ovarian cancer diagnosis through enhanced imaging contrast and treatment through controlled drug delivery. Specifically, diagnostic approaches include FA-PEG-FePt nanoliposomes and SPIONs, which enhance MRI contrast, and antibody-functionalized protein nanoparticles, which improve fluorescence imaging. In contrast, therapeutic approaches include FA-PEG-FePt/DDP nanoliposomes, folate-engineered chitosan nanoparticles, and extracellular vesicles, which provide high specificity in drug delivery, improved bioavailability, and reduced drug resistance. Nanomedicine is a promising approach to improving outcomes for patients with ovarian cancer, as it enhances diagnostic sensitivity, reduces toxicity, and improves the effectiveness of chemotherapeutic agents. However, clinical applications of nanotechnology are limited by off-target effects, immunogenicity, and tumor heterogeneity, suggesting that FR*α*-targeted nanotechnology has a promising but largely uncertain potential in ovarian cancer treatment. Ultimately, FR*α*-targeted nanotechnology provides a powerful platform for ovarian cancer diagnosis and treatment, yet scientists must resolve critical challenges in toxicity to ensure effective patient outcomes.**

***Keywords*—nanotechnology, ovarian cancer, folate receptor alpha, drug delivery, theragnostic**

I. Introduction

Ovarian cancer is one of the leading causes of death from gynecological diseases, affecting over 324,000 people and causing over 206,000 deaths in 2022 [1]. The general public's lack of awareness of ovarian cancer and frequent diagnosis at late stages of malignancy have contributed to the alarming mortality rates, highlighting ovarian cancer as a significant health challenge for women.

Ovarian cancer occurs when groups of cells grow uncontrollably in the ovary, fallopian tubes, and peritoneum. While there can be a combination of inherited and environmental factors that contribute to ovarian cancer, approximately 20% of cases are familial, resulting from inherited mutations [2]. Age and lifestyle factors such as obesity and smoking are all associated with an increased risk of ovarian cancer [3]. Conventional treatment relies on surgery and chemotherapy, but toxicity and drug resistance remain significant challenges [4].

Nanotechnology is defined as the creation and use of materials at the molecular and atomic level, specifically particles between 1 nm and 100 nm [5]. Nanomedicine is a subset of nanotechnology and a branch of medicine that uses nanoparticles to prevent and treat disease. Although nanotechnology has demonstrated potential in cancer diagnosis and treatment, research in FR*α*-targeted nanotechnology remains insufficient. As a result, this review asks: What is the potential of FR*α*-targeted nanotechnology in improving ovarian cancer treatment and diagnosis, and what challenges limit its clinical application? Answering this question may clarify how FR*α*-targeted nanotechnology could improve diagnostic sensitivity, therapeutic efficacy, and patient outcomes.

II. Folate Receptor Alpha Targeting Therapy

Folate Receptor Alpha (FR*α*) is a glycosylphosphatidylinositol-anchored glycoprotein encoded by the *FOLR1* gene, which binds and transports vitamin B9 (folate) into cells [6]. It is a vital surface protein that has a high affinity for folic acid and mediates cellular processes, including cell division, proliferation, and tissue growth [7]. FRα has a preferred substrate concentration of 1–10 nm and transports folates via receptor-mediated endocytosis. When folates bind to FRs on the cell surface, the receptors invaginate and bud off to form endosomes, where they acidify. Folates are then released from the receptors and exit the intact vesicle into the cell cytoplasm [8]. While FR*α* is found at low levels in healthy tissues such as the kidneys, it is frequently overexpressed in epithelial malignancies such as high-grade serous

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ovarian carcinomas. Up to 90% of epithelial ovarian cancers overexpress FRα [7], making FRα a crucial therapeutic target that can be utilized to identify cancerous cells.

III. Applications of Folate Receptor Alpha-Targeted Nanotechnology in Ovarian Cancer

A. Nanotechnology in Ovarian Cancer Diagnosis

While the majority of ovarian cancer patients experience symptoms such as postmenopausal bleeding and persistent pelvic and abdominal pain, these symptoms are often downplayed due to the general public's lack of awareness of the disease [9]. Moreover, existing diagnostic techniques such as magnetic resonance imaging, ultrasound, and tumour markers are not always sensitive enough to detect ovarian cancer at early stages (stages I and II) when the disease is still localised and has not spread to distant parts of the body [10, 11]. As a result, the majority of ovarian serous carcinomas are diagnosed at stage III (51%) and stage IV (29%), when the cancerous cells have metastasised to adjacent tissue and the 5-year survival rates are 42% and 26%, respectively [11]. This highlights the urgent need for improved diagnostic techniques for the early detection of ovarian carcinomas.

One extensively researched type of nanoparticle drug carrier is nanoliposomes, which are lipid vesicles used for the delivery of bioactive agents [12]. For example, scientists coupled Folate (FA) with Polyethene Glycol (PEG)-coated ferroplatinum nanoparticles, and then encapsulated cisplatin (DDP) into the FA-FePt-NPs to form FA-PEG-FePt/DDP nanoliposomes [13]. Folic acid guides the nanoparticle to folate receptor alpha, PEG improves stability and circulation time in the bloodstream, while cisplatin is the chemotherapeutic agent that is slowly released once inside tumor cells [13]. T2-weighted MRI detects differences in the Transverse relaxation (T2) times of tissues, and FePt nanoparticles create local magnetic field disturbances that shorten the T2 relaxation time [14]. Studies have shown that both FA-FePt NPs and FA-FePt/DDP nanoliposomes significantly suppress T2-weighted MRI signals, indicating their potential as folate receptor-targeted MRI contrast agents for ovarian cancer diagnosis [13].

Another promising type of nanoparticle drug carrier is Superparamagnetic Iron Oxide Nanoparticles (SPIONs). SPIONs are small synthetic γ-Fe_2O_3 (maghemite) or Fe_3O_4 (magnetite) particles coated with biocompatible polymers for the delivery of therapeutic agents [15]. These nanoparticles have unique magnetic properties that give them promising applications in ovarian cancer diagnosis, specifically through Magnetic Resonance Imaging (MRI) enhancement. MRI sensitivity relies on the relaxivity values of contrast agents, and SPIONs are especially effective because they have an r_2 relaxivity value that can exceed 200 $mm^{-1} \cdot s^{-1}$. SPIONs also increase the relaxation rate of water protons surrounding tumours, which enhances the visibility of target regions by creating darkened areas [16]. When Folic Acid (FA) was covalently linked to the coating copolymer and expressed on the surface of the SPIONs, physicochemical characterisation, *in vitro* biocompatibility study, and MRI in mice demonstrated improved targeting and imaging properties of the FA-SPIONs [17]. This highlights the effectiveness of FA-SPIONs as efficient contrast agents in conventional MRI.

The third type of folate receptor α-targeted nanoparticle drug carrier is protein nanoparticles. Protein nanoparticles are formed through the self-assembly of protein subunits, and they have numerous properties such as biocompatibility, biodegradability, and an optimal size for endocytosis, all of which make them ideal for drug delivery [18]. They are promising platforms for ovarian cancer diagnosis because they combine biocompatibility with the ability to carry fluorescent imaging agents. Scientists encapsulated a phthalocyanine dye within biocompatible protein nanoparticles and functionalized their surfaces with an anti-folate receptor antibody. They tested the targeting ability of the nanoparticles on A2780 ovarian cancer cells. Fluorescence Lifetime Imaging Microscopy (FLIM) revealed distinct fluorescence lifetimes between functionalized and non-functionalized nanoparticles, suggesting different intracellular uptake mechanisms, while demonstrating a highly sensitive method of detecting ovarian cancers [19]. These findings suggest the potential of antibody-functionalized protein nanoparticles in enabling early detection of ovarian cancer through synergistic deep red fluorescence imaging.

B. Nanotechnology in Ovarian Cancer Treatment

Traditionally, ovarian cancer treatment includes cytoreductive surgery or chemotherapy using drugs such as carboplatin and paclitaxel, depending on the size and type of the tumour and the stage of the disease. After treatment, early-stage ovarian cancer has a 5-year overall survival rate of 70% to 95%, while advanced-stage ovarian cancer has a 5-year overall survival rate of 10% to 40% [20]. The low specificity, high toxicity, poor bioavailability, and high rates of drug resistance associated with conventional therapies pose major challenges to treatment efficacy [21]. Compared to conventional methods, nanomedicine provides a targeted drug delivery system that minimizes harmful side effects while maximizing specificity and effectiveness.

Nanoliposomes act as effective drug delivery agents because of their biocompatibility, biodegradability, nanoscale size, and their ability to enhance the performance of bioactive agents by improving their solubility and stability while preventing unwanted interactions with other molecules. The high specificity of nanoliposomes coated with folic acid minimizes harmful side effects on healthy cells and tissues while allowing cancerous cells to receive drug concentrations required for optimum therapeutic efficacy [21]. In vitro and in vivo experiments showed that FA-FePt/DDP-NPs could effectively inhibit the growth of ovarian cancer by inhibiting cancer cell proliferation, invasion, and migration, and inducing cancer cell apoptosis [14]. Molecularly, E-cadherin proteins govern cell adhesion and are downregulated in ovarian cancer cells to facilitate cell detachment and migration [22], while Bax proteins control apoptosis and are suppressed in ovarian

cancer cells to evade cell destruction [23]. However, FA-FePt/DDP-NPs significantly increased E-cadherin and Bax protein levels in ovarian cancer cells, while inhibiting N-cadherin, Vimentin, and Bcl-2 proteins, proteins associated with cell survival and metastasis, thereby effectively inhibiting the malignant progression of ovarian cancer [14]. In addition, in an alternating magnetic field, FA-FePt/DDP nanoliposomes can rapidly reach 42–44 °C and efficiently kill tumour cells [14]. This highlights the potential of FA-FePt/DDP-NPs as useful agents in theranostic nanomedicine as well as magnetic hyperthermia.

Another important nanoparticle drug carrier is polymeric nanoparticles, which are particles ranging from 1 to 1000 nm in size, loaded with active compounds entrapped within or surface-adsorbed onto the polymeric core [24]. One example of such polymeric nanoparticles is folate-engineered chitosan nanoparticles. These particles can enclose hydrophobic anticancer molecules, thereby enhancing their solubility, permeability, and bioavailability [25]. Chitosan is also a versatile polymer because of its biodegradability and ability to provide controlled drug release, in which its hydroxyl groups form hydrogen bonds and its amines form bonds with acidic medications [26]. This suggests the potential of chitosan to create new possibilities for innovative drug delivery systems. In addition, chitosan improves the uptake of poorly soluble and poorly permeable drugs into tumour cells and can even enhance the absorption of oral medicines, allowing lower doses to be used over longer periods while maintaining their effectiveness [27]. These findings suggest the effectiveness of folate-engineered chitosan nanoparticles as a highly specific drug carrier in ovarian cancer treatment.

A more recent approach in ovarian cancer treatment is Extracellular Vesicles (EVs), which are lipid bilayer membrane-bound structures that mediate cell-to-cell signaling [28]. Extracellular vesicles can be divided into exosomes, ectosomes, apoptotic bodies, large oncosomes, and miscellaneous EV subsets [29]. These vesicles are naturally produced by healthy cells, making them highly biocompatible and less likely to trigger an immune response [28]. EVs shield large biological molecules from degradation by enzymes and have the ability to overcome biological barriers in the tumour microenvironment to transport functional gene therapies to specific locations. This highlights the role of EVs as promising drug delivery vehicles, as they help overcome problems such as non-targeted delivery, immunogenicity, and off-tumour toxicity associated with traditional nanoparticle drug delivery systems [29]. In a recent study, vesicles carrying the chemotherapy drug doxorubicin were also loaded with siRNA to block the production of P-glycoprotein, a protein responsible for pumping chemotherapy out of cancer cells. When combined with folic acid targeting, this strategy helped overcome drug resistance and enhanced the cytotoxic effects of doxorubicin on the tumour cells, which, in turn, increased tumour cell death and prevented tumour cell migration [30].

IV. Conclusion

In conclusion, nanoparticles such as FA-FePt-NPs, SPIONs, and antibody-functionalized protein nanoparticles enhance ovarian cancer diagnosis by acting as contrast agents in imaging. In addition, nanoparticle drug delivery systems including FA-PEG-FePt/DDP nanoliposomes, folate-engineered chitosan nanoparticles, and doxorubicin-loaded extracellular vesicles carry folic acid to target folate receptor alpha, reverse drug resistance, and improve drug bioavailability. These nanoparticles provide promising solutions for early ovarian cancer detection and treatment, potentially improving women's health in the future by making ovarian cancer treatment more effective and personalised.

However, various challenges impede the clinical application of nanotechnological solutions to ovarian cancer. Major issues with nanoparticles include toxicity and immunogenicity. Moreover, the heterogeneity of ovarian cancer tumours presents severe complications, as the tumour microenvironment often differs significantly from preclinical models.

Despite these challenges, a combination of folate receptor alpha-targeted nanoparticle drug delivery systems and patient-derived organoids offers innovative solutions to ovarian cancer treatment in the future. Patient-derived ovarian cancer organoids retain many of the genetic characteristics, FRα expression levels, and drug resistance mechanisms of the original tumour, and this personalised method of treatment could potentially improve treatment efficacy while reducing unnecessary toxicity.

Therefore, while FRα-targeted nanoparticle drug delivery systems demonstrate promising potential in improving ovarian cancer diagnosis and treatment, their clinical application remains limited by concerns regarding toxicity, highlighting the importance of integration with individualised models such as patient-derived organoids to bridge the gap.

Conflict of Interest

The author declares no conflict of interest.

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