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Ultrasound-Mediated Drug Delivery in Ovarian Cancer

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Abstract. Ovarian carcinoma is the most common type of ovarian cancer, comprising over 90% of all ovarian cancer cases. In this review, we aim to discuss strategies used for enhancing drug delivery in ovarian cancer treatment and to explore how these methods can improve therapeutic efficacy, with specifically focus on nanotechnology and ultrasound - mediated drug delivery. Nanoparticles can be designed to improve drug stability, penetration, and targeted delivery on tumor sides, which addresses major problems while treating epithelial ovarian cancer. Furthermore, ultrasound- mediated drug delivery utilizes microbubbles that can temporarily increase vascular and cellular permeability. This enhances localized release and uptake of drugs. These methods hold promise for advancing treatment and can lead to considerable increase in therapeutic efficacy.

Keywords: ultrasound-mediated drug delivery, ovarian cancer, nanoparticles

1. Introduction

Globally, ovarian cancer is the major contributor to cancer deaths in female population. Latest comprehensive data from 2022 shows 324,603 new cases of ovarian cancer [1,2]. Modern ovarian cancer management includes advanced treatment modalities such as hormone therapy and targeted therapy, but still survival rate of ovarian cancer is relatively low. Therapy to tumor present challenges including drug delivery paths, specific targeting to reduce toxicity and continuous treatment. Thus, a creative solution is needed.

1.1. Structure of ovarian tumor

Ovarian cancer is a formidable disease characterized by the abnormal growth of cells in the ovaries [3]. It can arise when different type cells in ovary become abnormal. Epithelial ovarian cancer is the most common form of OC. It has 5 subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC). These subtypes of epithelial ovarian cancer (EOC) behave differently during cancer treatment.

High-grade serous carcinoma (HGSC)

HGSC is a typical type II neoplasm which constitutes the majority of OC. This means that HGSC is more aggressive compares to type 1 category, usually grows rapidly and can spread to a wide area, which cause the low survival rate. Regardless, HGSC is known as being sensitive to platinum- based chemotherapy [4].

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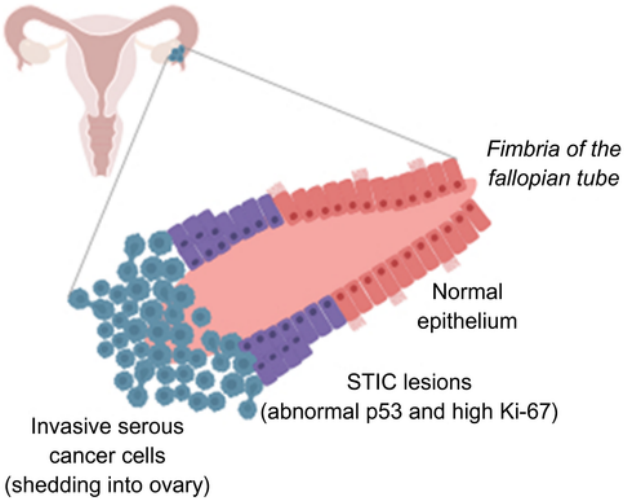

Figure 1. Development of HGSC

Low-grade Serous Carcinoma (LGSC)

The research of LGSC is limited as it's an infrequent subtype of ovarian cancer. LGSC is featured with relatively chemo resistant and indolent clinical course [5]. The histology LGSC is defined by a papillary growth pattern composed of cells with low mitotic activity and nuclear uniformity. Given its indolent clinical course and unique molecular profile, targeted therapeutic strategies is needed.

Clear Cell Carcinoma (CCC)

Clear cell carcinoma is known for poor sensitivity to chemotherapeutic agents and a worse prognosis than two serous carcinomas. It occurs when the clear cells present.

Endometrioid Carcinoma (EC)

Endometrioid carcinoma occurs when there's tissue similar to lining of the uterus developed outside the uterine cavity. Significant diagnostic challenges arise because the disease may be developed from a small, atypical epithelial spot inside the endometrioma, making it hard to recognized by sonography at an early stage.

Mucinous Carcinoma (MC)

MC is a rare type of epithelial ovarian cancer. MCs are characterized by glandular architecture and stratified columnar cells with basally located nuclei and pale-staining mucin in the apical cytoplasm [6]. Its high mucin content creates a physical barrier, hindering drug penetration.

1.2. Challenges in ovarian cancer therapy

Currently epithelial ovarian cancer presents several challenges in treatment due to its high recurrence rate, aggressive nature and propensity for develop drug resistance. What's more, the dense extracellular matrix and fibrotic stroma in ovarian cancer present a major physical obstacle to effective drug delivery [7].

1.3. Advantages of nanotechnology

Nanotechnology is a pressing method addressing those problems, according to its unique properties, including ease of production, biocompatibility, high therapeutic efficacy relative to free drug, non-toxicity, biodegradability, and off-target side effects [8]. Firstly, nanoparticles allowed for modulation of their chemical and physical properties, which enhance its stability and increasing

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therapeutic efficacy. Secondly, they can be designed to combine with specific mediation method to increase ability of penetrate the tumor, such like ultrasound, radiation, or hyperthermia. This enables for accumulation and uptake of drug at tumor side. Finally, surface modification techniques allow for the conjugation of targeting ligands. Recognition to ovarian cancer cells will thereby more specific, thus can improve cellular uptake.

2. Discussion

2.1. Nanotechnology in ovarian cancer therapy

Nanoparticles have emerged as a dominant antitumor therapeutic approach owing to their favorable biocompatibility, precise targeting, drug loading efficacy and stability, underscoring their considerable potential for further clinical applications. Study [9]have suggested that when using APRPG (Ala-Pro-Arg-Pro-Gly) peptide as targeting angiogenesis, peptide-modified poly (ethylene glycol)–poly (lactic acid) (PEG–PLA) nanoparticles (NP-APRPG) as carrier materials that encapsulates inhibitors of angiogenesis (TNP-470) (TNP-470-NP-APRPG), efficacy of drug can be enhanced by presence of nanoparticles.

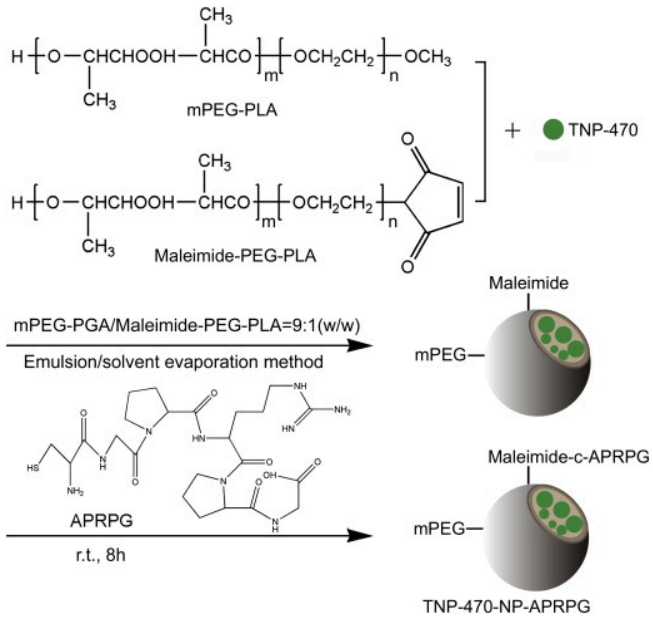

Figure 2. TNP-470-NP-APRPG [9] prepared sketch

The therapeutic potential of TNP-470 is hampered by its low aqueous stability and rapid hydrolysis in physiological environments. Consequently, advancing its use necessitates a delivery system based on non-cytotoxic nanocarriers, functionalized with specific targeting moieties and guided by a precise strategy to ensure effective drug delivery.

Researchers modulate nanoparticles' surface with APRPG and establish tumor model in female mice, following by imaging and antitumor efficiency experiments performed 2 weeks later.

The final tumor volume in the TNP-470-NP-APRPG group was 75.07 ± 38.19 mm^3, which was significantly smaller than that of the control groups, demonstrating the formulation's potent antitumor efficacy. Furthermore, mice treated with TNP-470-NP-APRPG showed no significant changes in body weight or evidence of tissue damage, comparable to the saline control group, indicating negligible systemic toxicity at the administered dose. Overall, TNP-470-NP-APRPG

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exhibits high antitumor efficacy, and the use of a low drug dose successfully mitigates toxicity. These results underscore the strong potential for the clinical translation of TNP-470-NP-APRPG.

2.2. Ultrasound- mediated drug delivery

In ultrasound-mediated drug delivery, microbubbles (MBs)—1–5 μm gas cores stabilized by phospholipid, polymer, or protein shells—function as contrast agents and drug carriers. Encapsulation within targeted MBs reduces degradation and prolongs circulation. Under insonation, MBs oscillate and, at suitable acoustic pressures, undergo stable or inertial cavitation; the latter generates microjets, shock waves, and transient membrane pores that increase local permeability and enable therapeutics to enter tumor tissue and cells. Clinically used MBs like SonoVue, Optison, and Definity typically contain inert gases such as SF_6 or C_3F_8; shell composition and PEGylation tune diameter, stability, and circulatory half-life. The diameter of microbubbles generally ranges from 1 to 5 μm, and microbubbles of different sizes respond differently to ultrasound. Under ultrasound irradiation, microbubbles expand and contract with the changing acoustic pressure, thereby magnifying cavitation locally.

2.3. Modification of microbubbles and drug carriers

By modifying microbubbles with ligands on their surfaces, they can selectively bind to receptors on tumor cells or on the endothelium of tumor vessels. Such modifications increase the accumulation of microbubbles near the target tissue, thereby improving therapeutic precision, enhancing drug-delivery efficiency and reducing adverse effects. Conventional chemotherapeutic drugs distribute widely in the body and often lead to bone-marrow suppression, hair loss and gastrointestinal reactions. In contrast, ultrasound-targeted microbubbles deliver drugs concentrated at the lesion and “explode” on demand under ultrasound, reducing damage to normal tissues.

2.4. Principles of ultrasound enhancement

When ultrasound interacts with microbubbles, two regimes of cavitation occur. Stable cavitation involves low-amplitude oscillations that generate microstreaming and reversible increases in membrane permeability without tissue injury [10,11]. At higher acoustic pressures, inertial cavitation occurs, where bubbles expand and violently collapse, producing microjets and shock waves that transiently perforate cell membranes to permit drug entry but risk tissue damage if the pressure is excessive (Fan et al., 2014). Voltage-clamp and imaging studies show that sonoporation transiently forms nanopores with mean radii of ~110 nm, which reseal within seconds to minutes [12]. Key ultrasound parameters such as acoustic pressure, pulse duration and frequency dictate whether stable or inertial cavitation predominates; high pressures (~0.4 MPa) and short pulses (≈8 μs) promote efficient drug delivery yet must balance safety (Fan et al., 2014)

2.5. Acoustic responses, ultrasound parameters and common enhancement methods

In general, three drug delivery enhancement methods can be applied on. First, non-drug-loaded microbubbles + ultrasound + free drug: bubbles act as cavitation nuclei; timed insonation transiently opens endothelium and cell membranes to raise uptake. Second, Drug-loaded microbubbles + ultrasound: the shell or surface carries the payload as a small 'reservoir'; insonation triggers on-site release and facilitates transvascular and transmembrane transport. And the third, physical modulation with non-drug-loaded bubbles: controlled cavitation and acoustic radiation force can

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push carriers to vessel walls, boost permeability, temporarily open barriers, or at higher intensities cause mechanical ablation—often used to pre-condition the tumor microenvironment for subsequent therapies.

Acoustic parameters such as frequency, acoustic-pressure amplitude, duty cycle and exposure time directly determine the response of microbubbles. Low-frequency ultrasound (< 1 MHz) has a longer wavelength and more easily drives microbubbles of several micrometres in diameter to oscillate at resonance, favoring the maintenance of stable cavitation; high acoustic pressures and short pulses (e.g. 0.4 MPa, 8 μs) readily induce inertial cavitation. In clinical contrast-imaging applications the mechanical index (MI) is typically kept below 0.3 to avoid microbubble rupture, but to enhance drug-delivery efficiency it is necessary to increase MI appropriately within safe limits so that microbubbles break under control. The following summarizes several common ultrasound enhancement strategies, categorized by whether the microbubble carries a drug and by the physical mechanism employed.

Beyond carrying drugs or genes, the physical effects generated by microbubbles under ultrasound can themselves serve as therapeutic mechanisms. For example, using high-intensity focused ultrasound to induce inertial cavitation of microbubbles can create pores in the tumor vascular endothelium and increase the permeability of nanoparticles or immune cells; alternatively, the microjets and shock waves produced when microbubbles collapse can directly damage tumor cells, resulting in mechanical ablation. Acoustic radiation forces can also push microbubbles towards the vessel wall, enhancing local deposition of drugs or nanoparticles. These “non-drug-loaded” strategies emphasize modulating the local vascular and cellular mechanical environment—for instance, improving tumor perfusion, temporarily opening the blood–brain barrier or enhancing immune-cell infiltration—to prepare the site for subsequent therapies.

In ovarian-cancer models, targeted luteinizing hormone-releasing hormone agonist (LHRHa)-decorated microbubbles loaded with triptolide suppressed proliferation by more than 70 % under 300 kHz, 0.5 W/cm² ultrasound [13]. Microbubble-mediated delivery of miR-let-7b to $CD133^{+}$ ovarian cancer stem cells enhanced transfection efficiency and induced apoptosis [14]. Resveratrol-loaded microbubbles combined with low-frequency ultrasound inhibited OVCAR-3 cells and modulated apoptosis-related proteins [15]. Achieving translational success requires optimizing ultrasound doses and microbubble formulations to maximise delivery efficiency while minimizing tissue injury. Future work should address tumour heterogeneity, cavitation localization and clinical monitoring, and explore combinations with chemotherapy, immunotherapy and other modalities. With interdisciplinary collaboration and rigorous clinical trials, ultrasound-microbubble technology could progress from preclinical studies to clinical cancer therapy.

3. Conclusion

Ovarian cancer causes significant harm among woman while present survival rate of OC is relatively low under hormone therapy and targeted therapy. Dense extracellular matrix and fibrotic stroma create a physical barrier to drug delivery, nanotechnology can be a considerable method to solve these problems by its performance drug loading and drug delivery capacity. Ultrasound mediated drug delivery offers a coherent engineering strategy to overcome the transport barriers and pharmacokinetics on current ovarian cancer therapeutics. Coupling widely used clinical microbubbles with adjustable acoustic fields can convert acoustic energy into controllable biophysical effects- Stability/inertial cavitation, marginalization due to microflow and radiation, and transient membrane porosity – thereby improving the efficiency of trans endothelial transport and intracellular delivery of drugs at the organ and cell scales. In general, UMDD it integrates acoustics,

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materials science, and tumor biology into a calibratable “engineering prescription.” With the three safeguards of standardized dosimetry, subtype-based patient stratification, and a robust quality-management system in place, UMDD is poised to advance from solid preclinical evidence to an image-guided precision-therapy strategy, offering a safe, reproducible, and combinatorically extensible clinical pathway for epithelial ovarian cancer.

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