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siRNA formulated with tumor targeting scfv modified lph nanoparticles as possible therapy for metastaic epithelial ovarian cancer

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Abstract

Each year, about 22,000 women in the United States are diagnosed with ovarian cancer. In theUnitedStates, ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer death, after lung and bronchus, breast, colorectal, and pancreatic cancers. Ovarian cancer causes more deaths than any other cancer of the female reproductive system, but it accounts for only about 3% of all cancers in women. Metastatic ovarian tumors are thought to account for 10–30% of malignant ovarian tumors; it is difficult to determine the precise incidence of ovarian metastasis.Most metastatic ovarian tumors originate from the gastrointestinal tract, breasts, and gynecologic organs. The pathway of cancer cell metastasis from no gynecologic cancer to the ovary remains unclear except for the case of direct dissemination. The 5-year survival after resection of metastaticovarian tumor is 19%.Besides primary ovarian malignancies, the ovaries are also a frequent location of metastasis from other malignant primary tumors. Most cases of metastases to the ovary originate from the gastrointestinal (GI) tract, breast, and other gynecologic organs. Management and treatment of metastatic ovarian cancer is a challenge.RNA-based therapeutics has been developed as a potentialtherapeutic agent to treat human diseases including cancer. RNA molecules such as siRNA and miRNA are highly effective therapies for cancer, as it silences the expression of cancer-related genes/ selectively regulate the pathways that are involved in the development and progression of cancer. It has been shown that, inhibition of c-Myc, MDM2, and VEGF protein expression by siRNA formulated with tumor-targeting scFv modified LPH nanoparticles markedly suppressed B16F10 metastatic tumor growth. Thiswas achieved by co-delivering of miRNA and siRNA in the LPH formulation, the combination strategy is effective to trigger an enhanced therapeutic effect. This methodology of the formulation modified with tumor-targeting scFv is highly effective for delivery of siRNA or miRNA into the affected body organ(s) in patients with ovarian cancer metastasis.scFv has several advantages over the conventional monoclonal antibody or small molecule as a target moiety for drug/gene delivery to cancer. They include profound penetration into the tumor site, high specificity, strong affinity, low toxicity, and weak induction of the unwanted immune response. Nanoparticles modified with GC4 scFv may be internalized by the cells through receptor-mediated endocytosis. miRNA, a potential therapeutic agent, regulates cellular behavior via specific targeting and downregulating mRNAs by nearly perfect base pairing. It has been reported that certain miRNAs are involved in the oncogenic and tumor suppressor networks and can potentially inhibit tumorgenesis. The miR-34a was found to suppress tumor proliferation and migration and cause apoptosis in cancer cells by activating p53 and downregulating c-Met and E2F3. In addition, it was shown that miR-34a induced apoptosis, suppressed the survivin expression and inactivated MAPK pathway in cancer cells. The LPH nanoparticle formulation for RNA-based metastatic ovarian cancer therapy is potentially suitable for clinical use due to its reduced toxicity. Moreover, the ability of the nanoparticles to target tumor site further increases the therapeutic value of the RNA therapeutics. It is noted, that the capacity to deliver siRNA and/or miRNA with a single formulation simultaneously targeting several different oncogenic pathways is an important advantage of the current approach. To conclude, this co-delivery of miRNA and siRNA has the potential of development therapeutic agent for metastatic ovarian cancer.