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Cancer Cell Survival in Human and Mouse

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Abstract

The vast majority of women diagnosed with ovarian cancer present with widely disseminated metastatic disease at diagnosis because there are no specific symptoms and no effective ways to detect the disease early. The overall survival rate for the most common type of ovarian cancer, high-grade serous ovarian carcinoma, has not significantly improved in over 40 years and remains below 30%, despite the efforts of dedicated doctors and scientists. Cytoreductive surgery and systemic chemotherapy are the standard methods of treating ovarian cancer in order to eradicate any remaining tumor cells and achieve clinical remission. High-grade serous ovarian carcinoma can go into remission in about 80% of patients, but the majority of these patients recur due to the presence of cancer cells that are resistant to chemotherapy. Various checkpoint inhibitors alone or in combination with standard treatment for ovarian cancer have failed recent clinical trials. As a result, effective alternative treatments are required right away.

Keywords: Ovarian cancer • Histone deacetylase inhibitor • Glycogen synthase kinase • Beta inhibitor • Chemotherapy resistance • HDAC • GSK3B

Introduction

Targeting multiple cellular pathways simultaneously to prevent the development of drug resistance in cancer cells, which is the primary challenge for standard chemotherapy, is a promising strategy for the development of more effective treatments for ovarian cancer. Several solid tumors, including ovarian cancer, are characterized by epigenetic dysregulation and modifications in metabolic pathways. In ovarian cancer cells, the glycogen metabolism enzyme glycogen synthase kinase kinase-3 beta (GSK3B) upregulates NF-B activity, a key driver of proliferation and survival. Inhibition of GSK3B caused tumor shrinkage in mice. In addition, recent research demonstrated that inhibiting histone deacetylases (HDACs) inhibited PAX8, an essential ovarian cancer oncogene, inhibited ovarian cancer growth and metastasis. In order to overcome chemoresistance in ovarian cancer. Ovarian cancer cells express stem cell markers less when APCS-540 is used. We also looked into whether APCS-540 had any effect on cancer stemness, a key mediator of drug resistance. In OVCA420 and BR-Luc cancer cells treated with 0.6 M APCS-540, the expression levels of the stemness markers CD133, Oct4, and Nanog, as well as the pro-tumorigenic marker YAP, were significantly decreased. In a similar vein, Oct4 and Nanog produced significant results in A2780 and A2780cis cancer cells. The reversal of chemoresistance and these results suggest that APCS-540 is a promising anti-tumor agent for ovarian cancer treatment.we hypothesized that dual targeting of the metabolic (GSK3B) and epigenetic (HDACs) pathways could significantly enhance anti-tumor treatment. A recent study found that a small molecule called 9ING41 significantly increased apoptosis in SKOV3 and OVCA432 ovarian cancer cell lines and decreased in vivo tumor growth in mice when GSK3B was inhibited [1].

Literature Review

Metavert, a novel dual GSK3B and HDACs inhibitor, was designed, synthesized, and tested by us previously for the treatment of pancreatic adenocarcinoma. The Metavert analog APCS-540 was found to be the most effective compound against ovarian cancer in comparison to other Metavert analogs in this study, which examined the anti-tumor effects of several dual inhibitors of HDACs and GSK3B on ovarian cancer cell proliferation, migration, and invasion in vitro in human and mouse ovarian cancer cell lines. In addition, we investigated the efficacy of APCS-540 in overcoming chemoresistance and tested its antitumor activity in human ovarian cancer cells (A2780cis) that are resistant to cisplatin. In this way, we analyzed the impact of APCS-540 in vivo on illness movement in a syngeneic ovarian malignant growth mouse model. We wanted to evaluate the anti-tumor activity of APCS-540 in the cisplatin-sensitive human ovarian cancer cell line A2780 and its cisplatin-resistant derivative A2780cis alone or in combination with cisplatin (10 M) because chemoresistance is one of the main factors in tumor recurrence and worse prognosis. Treatment with 0.6 M APCS-540 significantly inhibited the HDAC and GSK3B pathways in both A2780 and A2780cis cancer cells in comparison to the control when acetylated histone 3 lysine 9 (Ac-H3K9) and beta-catenin, which is the direct target of GSK3B, protein levels were re-probed for glyceraldehyde 3- S2A) [2].

Discussion

Amazingly, APCS-540 reduced cancer cell viability at a low concentration of 0.6 M in both A2780 and A2780cis cancer cells. In both cell lines, APCS-540 had a greater cytotoxic effect when administered in combination with cisplatin. Ovarian cancer cells' responses to chemotherapy can be synergistically enhanced and chemoresistance reversed by APCS-540, according to these findings. Ovarian cancer, which remains the most fatal gynecologic malignancy in the United States, has not seen a significant improvement in treatment in spite of remarkable advances in the treatment of several hematological cancers and solid tumors. In ovarian cancer, debulking surgery and platinum/taxane-based chemotherapy are the standard of care. However, despite these aggressive treatments, approximately 80% of patients experience tumor recurrence. An increasing number of studies on the evolution of cancer have shown that the primary cause of tumor recurrence is evolving tumor clones that acquire chemoresistance. As a result, developing an effective ovarian cancer treatment requires overcoming chemoresistance. Taxanes and platinum analogs, two common chemotherapeutics used to treat ovarian cancer, focus primarily on cell division rather than genomic integrity. However, in response to various cellular stresses, such as chemotoxicity, cancer cells can undergo extensive molecular changes at the genetic, epigenetic, and metabolic activity levels [3].

They can also adapt to the environment by utilizing alternative cellular pathways, resulting in increased cellular plasticity and chemoresistance. Targeting multiple key oncogenic pathways simultaneously presents a promising strategy for overcoming chemoresistance. Combinations of drugs that target

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various cellular pathways, such as the metabolic and epigenetic pathways, may result in more effective treatments for cancer because resistance to a single target is almost always present. Multiple agents may have an additive effect on the killing of cancer cells when combined; However, drug toxicity and drug-drug interactions can also result in potential side effects. As a result, a single drug with multiple targets can have better pharmacokinetics and pharmacodynamics while having fewer side effects. On the basis of this information, we developed a novel drug that simultaneously targets metabolic (GSK3B) and epigenetic (HDAC) oncogenic pathways. This is the first known case of using a dual GSK3B/HDAC inhibitor to treat ovarian cancer, according to our knowledge. GSK3B is a glycogen metabolism enzyme and a serine/threonine kinase that is involved in several NF-B signaling pathways. Due to its crucial roles in tumor proliferation and resistance to apoptosis, it has been proposed as a new therapeutic target for a variety of cancers [4].

However, it should be noted that inhibiting GSK3B on its own can also promote cancer by promoting the transition from epithelial to mesenchymal (EMT; cancer stemness (a measure of resistance to chemotherapy) and metastatic potential. Therefore, in order to overcome these negative effects, a single inhibition of GSK3B is ineffective and requires a complementary approach. By encouraging cancer stemness and EMT, epigenetic modulators known as histone deacetylases (HDACs) play a crucial role in carcinogenesis. It has been demonstrated that HDACs interact with EMT transcription factors, which promotes EMT in cancer cells. Clinical trials and FDA-approved treatments for a variety of cancers, including advanced lymphoma and metastatic cancers were ultimately made possible by the successful outcomes of using HDAC inhibitors. By suppressing oncogene PAX8 expression in a mouse model, HDAC inhibitors were found to be effective in killing ovarian cancer cells and reducing tumor growth. Given this background, we hypothesized that inhibiting EMT and its impact on metastasis and chemoresistance would prevent cancer cell growth simultaneously with inhibiting GSK3B and HDACs [5].

Conclusion

In this study, we looked into how first-in-class dual GSK3B and HDACs inhibitors affected ovarian cancer treatment. In human and mouse ovarian cancer cell lines, our findings demonstrated that simultaneous inhibition of HDACs and GSK3B significantly reduced cancer cell survival. APCS-540 demonstrated the highest anti-tumor activity of the developed dual inhibitors. Additionally, in vitro tests on human and mouse ovarian cancer cell lines demonstrated that APCS-540 effectively inhibits metastasis by significantly reducing cancer cell migration and invasion. In addition, when combined with cisplatin, APCS-540 remarkably reversed chemoresistance in cisplatin-resistant ovarian cancer cells, demonstrating significant cytotoxic activity. APCS-540 significantly increased survival by 66% in an immunocompetent syngeneic mouse model. Additionally, our initial in vitro results with cervical and endometrial adenocarcinoma cell lines demonstrated that APCS-540 may be effective in a wider range of gynecologic cancers. In conclusion, in preclinical cancer models, our simultaneous targeting of the cancer epigenome and metabolism demonstrated significant efficacy. Ovarian cancer, including platinum-resistant disease, may benefit from APCS-540, according to our findings.

Acknowledgement

None.

Conflict of Interest

None.

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