

Ovarian Clear Cell Carcinoma

Subjects: **Obstetrics & Gynaecology**

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This entry summarizes the recent advances in the process and prevention of carcinogenesis, the characteristic nature of tumors, and the treatment of post-refractory ovarian clear cell carcinomas (OCCCs), which are highly linked to oxidative stress.

ovarian clear cell carcinoma

endometriosis

antioxidant

cancer stemness

1. Introduction

Ovarian clear cell carcinomas (OCCCs) are resistant to conventional anti-cancer drugs; moreover, the prognoses of advanced or recurrent patients are extremely poor. OCCCs often arise from endometriosis associated with strong oxidative stress. Of note, the stress involved in OCCCs can be divided into the following two categories: (a) carcinogenesis from endometriosis to OCCC and (b) factors related to treatment after carcinogenesis. Antioxidants can reduce the risk of OCCC formation by quenching reactive oxygen species (ROS); however, the oxidant stress-tolerant properties assist in the survival of OCCC cells when the malignant transformation has already occurred. Moreover, the acquisition of oxidative stress resistance is also involved in the cancer stemness of OCCC.

The removal of oxidative stress suppresses the development of OCCCs in endometriosis. Strong antioxidants, such as vitamin A, carotenoids, or flavonoids, may help prevent carcinogenesis of OCCCs. However, the stress tolerance properties of OCCCs induce therapeutic resistance, making their treatment difficult. Antioxidants display bidirectional effects toward endometriosis and OCCCs. Elimination of oxidative stress, including by uptake of antioxidants, is highly effective in preventing progression from endometriosis to OCCCs, but, antioxidants are not suitable for treatment of established OCCCs, in which oxidative stress tolerance has accrued, providing therapeutic resistance.

In OCCCs, downstream of receptor tyrosine kinases (RTKs), AT-rich interactive domain 1A (*ARID1A*)-related chromatin remodeling factors, and genomic instability, including MSI-H, are activated. These are currently being targeted.

In OCCC therapeutics, inhibition of oxidative stress tolerance molecules is essential. Therefore, other therapeutic strategies, such as nucleic acid-based drugs, RDH10, RECQL1, WRN, and HNF1B, should be targeted in the future to reduce cancer stemness, induce cancer-specific synthetic lethality, and reduce gluconeogenesis, together with a drug repositioning strategy against SOD2 anti-oxidative stress molecules.

2. Molecular Characteristics in OCCCs Related to Anti-Oxidative Pathway

As mentioned above, in OCCCs, which arise from endometriosis under massive oxidative stress, abnormalities are often detected in genes associated with the oxidative stress response and ROS metabolism. Several antioxidant molecules are involved in OCCC carcinogenesis. Among them, the overexpression of hepatocyte nuclear factor 1 homeobox B (HNF1B), a major homeobox-containing protein, also known as transcription factor-2, is highly important. Under hypoxia and acidosis, HNF1B can modify and adapt cancer cells to survive through a process between gluconeogenesis and glycolysis, commonly known as the Warburg effect. Tsuchiya et al. first reported HNF1B overexpression in OCCCs and showed that reduced HNF1B expression considerably increased the apoptosis rate in two OCCC cell lines. Overexpression of HNF1B was observed in endometrial tissues adjacent to OCCC tumors, suggesting that HNF1B overexpression is an early event in OCCC carcinogenesis. Kato et al. found that hypomethylation of the CpG island of HNF1B induced its overexpression in OCCCs, indicating that overexpression in OCCC was also caused by epigenetic changes rather than by mutations. Moreover, recent research has revealed that HNF1B promotes the dedifferentiation of cancer stem-like cells (CSCs) via activation of the Notch pathway and enhancing the invasive potential and epithelial–mesenchymal transition in cancer cells. Anti-oxidative pathways are deeply involved in carcinogenesis and therapeutic resistance in OCCCs. As oxidative stress tolerance represents therapeutic resistance, OCCCs usually exhibit poor and fatal prognoses, even during gradual progression. OCCC has low sensitivity to platinum- and taxane-based chemotherapy. Therefore, the prognosis of OCCCs is extremely poor, particularly in its advanced stages. Previous studies have revealed the role of HNF1B in driving the expression of several characteristic genes associated with OCCCs, stimulating metabolic changes to promote gluconeogenesis, glycogen accumulation, and aerobic glycolysis, inducing chemotherapeutic resistance by suppressing sulfatase-1 (Sulf-1), an extracellular sulfatase catalyzing the 6-O desulfation of heparan sulfate glycosaminoglycans, and reducing the activity of immunological checkpoints against tumors. Thus, HNF1B plays an important role in therapeutic resistance via oxidative stress tolerance in OCCCs (Figure 1).

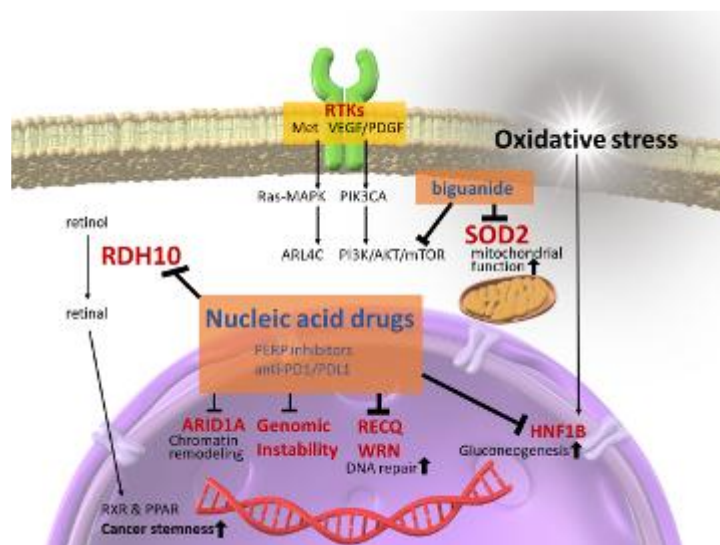


Figure 1. Activating pathways and targeting proposals in ovarian clear cell carcinomas. In ovarian clear cell carcinomas, downstream of receptor tyrosine kinases (RTKs), AT-rich interactive domain 1A (*ARID1A*)-related

chromatin remodeling factors, and genomic instability, including MSI-H, are activated. These are currently being targeted. However, other therapeutic strategies, such as nucleic acid-based drugs, RDH10, RECQL1, WRN, and HNF1B, should be targeted in the future to reduce cancer stemness, induce cancer-specific synthetic lethality, and reduce gluconeogenesis, together with a drug repositioning strategy against SOD2 anti-oxidative stress molecules.

Although therapeutic approaches should still be improved against OCCCs, multi-combinatorial treatments including nucleic acid-based drugs directed to the transcriptional profile of each OCCC are expected to improve the outcomes of patients.

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