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The Potential Molecular Therapeutic Approach in Targeting Ovarian Clear Cell Carcinoma

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Abstract

Ovarian Clear Cell Carcinoma (OCCC) is a distinctive subtype of Epithelial Ovarian Cancer (EOC). Compared with other subtypes of EOC, CCC has relatively poor in prognosis and bad outcome in current clinical management using maximal cytoreduction and platinum plus paclitaxel–based combined chemotherapy. Therefore, the investigation of molecular therapeutic approaches targeting at signaling pathways associated with chemoresistance is needed. This review describes some recent potential signaling pathway targets and also suggests putative small molecule kinase inhibitors as well as natural anti-cancer agents in combating this disease.

Keywords: GRB7; ERK; FOXM1; Ovarian cancer; High-grade tumor

Ovarian cancer is the most lethal disease among all gynaecological malignancies. It can be categorized into three major groups according to the origins of the ovarian tumors: (1) epithelial tumors, (2) stromal tumors and (3) germ cell tumors. Among these three groups, Epithelial Ovarian Cancer (EOC) accounts for approximately 90% of ovarian malignancies and can be divided into four major histological subtypes based on morphological and appearance criteria: serous, mucinous, endometrioid and clear cell carcinoma. Each of these histologic subtypes is further subdivided into benign, borderline and malignant according to their malignant potential [1-3].

Ovarian Clear Cell Carcinoma (OCCC) is distinct histopathologically and clinically from the other EOC subtypes. This tumor has a high incidence at stage I and usually present as a large pelvic mass, rarely exist bilaterally, associated with endometriosis, hypercalcemia as well as thromboembolic vascular complications [4,5]. While the incidence of OCCC is not high and accounts 3.7-12.1% of all EOC [4,6,7], patients with OCCC have a poorer prognosis and higher recurrences than patients with other EOC subtypes [8]. The recent clinical management of advanced EOC includes maximal cytoreduction and platinum plus paclitaxel–based combined chemotherapy. However, the survival rates of OCCC patients are much lower than other advanced EOC such as endometrial subtype [9,10]. The poor response of OCCC to platinum-based regimens may be due to the intrinsic chemo-resistance. Therefore, novel treatment approaches such as molecular-targeted therapies plus more effective combinations of new chemotherapeutic agents should be investigated in a prospective clinical trial in OCCC.

Although the underlying mechanisms of chemo-resistance in OCCC remain unclear, a growing body of reports has indicated that several signaling cascades aberrantly activated by genetic alteration are specifically targeting P13K/AKT/ERK/mTOR signaling axis. For examples, Raf265 (Novartis), PLX4032 (Roche), AZD6244 (AstraZeneca), ARRY797 (Array BioPaherma) and Sorafenib (Bayer/Onyx) etc. targeting Raf/MEK/ERK signaling cascade have been tested in different phases of clinical trials in a decade ago [32,33]. Recently, Temsirolimus (Torisel®) (Wyeth) and Everolimus (Afinitor®) (Novartis) (Merck) have been approved to treat patients with advanced and aggressive tumors through inhibiting mTOR mediated cell growth [34-36]. Moreover, Avastin® (bevacizumab), Tarceva (erlotinib) and MK-2206 are approved by FDA in clinical trial for advanced ovarian cancer with failing standard chemotherapy [36-38]. However, the concerning issues include the toxicity or side effects versus potency, as well as the specific inhibition versus multiple targeting when using these small molecule kinase inhibitors.

Another approach is using the combination of current chemotherapeutic reagents and other anti-neoplastic agents which are specifically targeting P13K/ AKT/ERK/mTOR signaling axis. For examples, Mabuchi et al. [25] have recently reported that the anticancer substance, Trabectedin or ET743 extracted from the sea squirt Ecteinascidia turbinata, exhibits high efficiency in the treatment of OCCC when in combination with Everolimus [39-41]. The combined

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established a new avenue for treating ovarian cancer cells. The combined use of Metformin and taxanes in chemotherapy treatment provides a promising therapeutic approach for patients with this disease.

References


