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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 associated with poor response to platinum-based regimens in human cancers [11-16]. Among these signaling pathways, PI3K/AKT/mTOR is the most well-known signaling cascade involved in cisplatin/paclitaxel chemo-resistance of EOC [15-20]. Our laboratory has previously found that loss of MKP3 led to aberrant activation of AKT/ERK1/2 activity [14], whereas overexpression of GRB7/GRB7v was remarkably associated with high-grade ovarian cancer including OCCC and increased AKT/ERK1/2 [21] signaling pathway. Moreover, activated AKT/ERK1/2 could upregulate the expression of crucial oncoprotein FOXM1 which was again significantly associated with high-grade tumors including OCCC [22]. Recent findings also indicated that the overexpressed Serine/Threonine Kinase PAK4 was also associated with OCCC and involved in a variety of tumorigenicity through activating c-Src and MEK1/ERK1/2 [23]. Furthermore, numerous studies have documented that mTOR, an essential modulator in cell proliferation, is frequently upregulated in human cancers including OCCC [24-29]. Therefore, this provides us an attractive target by exploring inhibitors in order to suppress its activity resulting in the elimination of cancer cells. Taken together, these reports have suggested that targeting PI3K/AKT/ERK/mTOR signaling cascade may be an effective novel therapeutic approach in OCCC.

Different from conventional anti-cancer drugs, the new trend of target-based therapeutics is the application of small molecule kinase inhibitors in inhibition of cancer cell growth and survival through de-regulating of the aberrant activation of signaling activities. To date, more than 10 small molecule kinase inhibitors have been approved by US Food and Drug Administration (FDA) for clinical trial [30,31]. For examples, Raf265 (Novartis), PLX4032 (Roche), AZD6244 (AstraZaneca), 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 chempotherapy [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 turbinate, exhibits high efficiency in the treatment of OCCC when in combination with Everolimus [39-41]. The combined

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application of these drugs was able to sensitize OCCC cells to cisplatin- or paclitaxel-induced cell apoptosis *in vitro* and *in vivo* through inhibition of AKT/mTOR activity [39]. Apart from Trabectedin, an oral antidiabetic drug Metformin has recently been shown to have potent anti-cancer effects against a variety of human cancers [42-44]. Metformin is the biguanide derivative which has been generally used as the first-line drug for Type 2 diabetes [45,46]. But recent evidences from clinical and preclinical studies have shown that Metformin has anti-cancer functions. Clinically, retrospective data have found that diabetic patients with breast cancer receiving Metformin have better response under neoadjuvant chemotherapy [47]. This function is particularly obvious in Her2+ breast cancer patients [48]. Moreover, the combinational use of Metformin and temozolomide (TMZ) is useful to treat Glioblastoma multiforme (GBM) [49]. Mechanistically, the inhibition of cancer cell growth by Metformin is associated with indirect and direct effects. The indirect effect exerted by metformin is linked to the inhibition of treanscriptional activities of key gluconeogenesis genes which in turn elevating insulin sensitivity and decreasing blood glucose and insulin levels [50,51]. The direct effects of Metformin are through activation of AMP-activated protein kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR) which is an effector governing protein synthesis and gluconeogenesis [52,53]. The overall reduction of protein synthesis through inhibition of mTOR is the main mechanism of Metformin action in the inhibition of cancer cell growth. However, most cancer cells have constitutive action of phosphoinositide 3 kinase (PI3K) activity which leads to increased cell survival under chemotherapy treatment. Therefore, the co-treatment of PI3K inhibitor (LY294002) with Metformin can synergistically enhance cisplatin-induced cell apoptosis in ovarian cancer cells [54]. Together, these reports suggest that the use of natural anti-cancer agents is the alternative therapeutic approach in supplement to the current chemotherapeutic regimens against OCCC.

In summary, although current treatment on OCCC always comes across of obstacles in clinical outcome, the exploration of molecular therapeutic approach using small molecular kinase inhibitors or even the intervention of natural anti-cancer agents will provide a new avenue in improving the efficiency of chemotherapy in this disease.

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