Chapter 9
Molecular Landscape in Ovarian Clear Cell Carcinoma

Nozomu Yanaihara and Aikou Okamoto

Abstract Ovarian clear cell carcinoma (OCCC), one of five major histological subtypes of epithelial ovarian cancer (EOC), has unique clinical and molecular features. There is no specific targeted therapy for OCCC, and studies on translational genomics underlying OCCC pathogenesis are still ongoing. This chapter focuses on the molecular landscape in the OCCC tumor and its microenvironment. Our findings will help in the stratification of OCCC patients who may benefit from precision medicine for this unique histological subtype of EOC.

Keywords Clinical trial · Ovarian clear cell carcinoma · Molecular landscape Targeted therapy

9.1 Introduction

Ovarian clear cell carcinoma (OCCC) is one of five major histotypes of epithelial ovarian cancer (EOC). The clinicopathological and biological features of OCCC include hypercalcemia, thromboembolism, a close association with endometriosis, and a higher prevalence in Eastern Asian women [1, 2]. In addition, compared to other histological subtypes, OCCC patients present at a relatively younger age and an early stage [3]. The 5-year survival rate for stage I OCCC is ~90%, with differences depending on the substage: patients with stage IA or IC1 OCCC have a favorable clinical outcome, while patients with stage IC2 or IC3 have a statistically poorer prognosis [4–6]. In addition, advanced-stage OCCC is resistant to conventional platinum-based front-line chemotherapy, resulting in poor prognosis [6, 7].

N. Yanaihara (✉) · A. Okamoto
Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Minato-ku, Tokyo, Japan
e-mail: yanazou@jikei.ac.jp

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Because of the low prevalence of OCCC in Western countries, there is a lack of large randomized controlled clinical trials targeting OCCC with chemotherapy including molecular medicine. The current standard treatment is a one-size-fits-all approach, which includes debulking surgery with platinum agent + paclitaxel combination chemotherapy. A randomized phase III clinical trial conducted by the Japanese Gynecologic Oncology Group compared irinotecan and cisplatin (CPT-P) with paclitaxel plus carboplatin (TC) in stage I–IV OCCC patients. The authors reported no significant survival benefit in the CPT-P group [8]. In addition, studies on translational genomics underlying OCCC pathogenesis are ongoing [1, 9–12]. These findings highlight that other therapeutic approaches might improve survival in OCCC patients.

In this chapter, we reviewed recent advances in molecular profiling related to carcinogenesis and molecular targets of OCCC.

9.2 Mutational Landscape

Several studies on large-scale genome-wide gene profiling for OCCC have reported actionable gene alterations that could lead to the development of a target therapy for OCCC (Table 9.1) [13–20]. Both *AT-rich interactive domain 1A* (*ARID1A*) and

Table 9.1 Genetic alterations in OCCC

Alteration	Frequency (%)	Affected pathway	Reference
Somatic mutation			
ARID1A	40–70	SWI/SNF chromatin remodeling complex	[13–19]
PIK3CA	40–50	PI3K/Akt/mTOR	[14–16, 18–20]
PPP2R1A	10–20	Akt/MAPK	[16–19]
KRAS	5–20	Akt/MAPK	[14–16, 18, 19]
TP53	5–15	P53 pathway	[15, 17–20]
PTEN	5–10	PI3K/Akt/mTOR	[15, 16, 19]
Germline mutation			
BRCA1/2	2–6	DNA repair	[21, 22]
Copy number alteration			
ZNF217 (20q13.2 Amplification)	20–40	ZNF217	[23, 24]
MET (7q31.31 Amplification)	30	Akt/MAPK	[25]
AKT2 (19q3.2 Amplification)	20	Akt/mTOR	[25]
HER2 (17q12-q21 Amplification)	14	HER	[26]
PPM1D (17q23.2 Amplification)	10	P53 mediated apoptosis	[27]
CDKN2A/2B (9q21.3 Deletion)	9	CDK inhibitors (p15/p16)	[24]

phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit α (*PIK3CA*) are most frequently mutated and often coexist in OCCC [19]. The coexistence of these mutations initiated OCCC tumor formation in a genetically engineered mouse model [28]. Since cancer cells are vulnerable to ARID1A deficiency, synthetic lethal approaches to *ARID1A* mutation in OCCC are of considerable clinical interest [1, 12]. *PIK3CA* and *phosphatase and tensin homolog deleted from chromosome 10* (*PTEN*) mutations highly activate the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signal [14–16, 18–20]. In addition, *KRAS* and *protein phosphatase 2 scaffold subunit A alpha* (*PPP2R1A*) mutations have been found in 5–20% and 10–20% of OCCC patients, respectively [14–16, 18, 19]. Notably, mutations of these genes, where the mitogen-activated protein kinase (MAPK) signal could be a target candidate, also often coexist [18]. Compared to high-grade serous ovarian cancer (HGSOC), the most common form of EOC, germline mutations of *germline breast cancer susceptibility 1* (*BRCA1*) and *BRCA2* are infrequent and are found in 2–6% of OCCC patients [21, 22], indicating that only a small percentage of OCCC patients might benefit from a newly innovated treatment strategy using poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors.

9.3 Copy Number Landscape

Several molecular technologies, including single-nucleotide polymorphism (SNP) array, comparative genomic hybridization (CGH) array, and exome sequencing, have revealed copy number alterations (CNAs) in OCCC. Frequent amplification has been observed in chr8q, chr17q, and chr20q loci, while deletion has been observed in chr9q, chr13q, chr18q, and chr19p loci [16, 23, 29]. Notably, the whole-arm-CNA ratio is higher in OCCC compared to HGSOC, although fewer CNAs are found in OCCC patients [29]. Interestingly, whole chr8q and chr20q13.2 amplification, including *zinc finger protein 217* (*ZNF217*), is more prevalent in Japanese OCCC patients compared to Korean or German OCCC patients [23]. Amplification or deletion of certain loci that contain several cancer-related genes might affect intracellular signals as potential therapeutic targets (Table 9.1).

9.4 Signaling Pathway Landscape

9.4.1 IL6/STAT3 Pathway

OCCC-specific expression signatures have been obtained using global gene expression assays. Compared to HGSOC, OCCC shows an enhanced interleukin 6 (IL6)/signal transducer and activator of transcription 3 (STAT3) pathway [30–32]. In addition, high tumor and serum IL6 levels are significantly correlated with poor

prognosis in OCCC patients [5, 31]. IL6 is a pleiotropic pro-inflammatory cytokine that mediates critical processes, including cell proliferation, angiogenesis, and chemoresistance. IL6 signal inhibition has antitumor effects in OCCC, indicating that this pathway is a promising therapeutic target [33]. Although anti-IL6 antibody (siltuximab) has shown clinical activity in a phase II clinical trial of 18 patients with platinum-resistant ovarian cancer (1 OCCC patient) [34], no clinical trials specific for OCCC-targeting IL6/STAT3 signals have been conducted.

9.4.2 Angiogenesis

Intertumoral hypoxia with high hypoxia-inducible factor 1-alpha (HIF-1α) expression, in which a malignant tumor commonly develops, leads to an increase in the activity of various angiogenesis-related signals. In OCCC, increased HIF-1α expression increases the intracellular glycogen content, causing cell chemoresistance [35]. In addition, in OCCC, IL6 signals via STAT3 activates the expression of downstream genes, including *HIF1A* [31]. Therefore, vascular endothelial growth factor (VEGF), induced by HIF-1α, is overexpressed in >90% of OCCC patients, and VEGF expression is correlated with the patient's survival [36]. Notably, bevacizumab, a monoclonal human VEGF antibody, has antitumor effects in OCCC both in vitro and in vivo.

On the basis of the findings that OCCC and renal CCC have similar gene expression profiles, one of which is characterized by the activated HIF pathway [37], researchers have focused on anti-angiogenetic therapy for OCCC (Table 9.2). The GOG-254 phase II study on sunitinib, which targets vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), for recurrent or persistent OCCC treatment reported a median progression-free survival (PFS) and overall survival (OS) of 2.7 and 12.8 months, respectively [38]. The NRG-GY001 phase II study on cabozantinib, which targets VEGFR, MET, and RET, for recurrent or persistent OCCC reported that a single administration of cabozantinib leads to a median PFS and OS of 3.6 and 8.1 months, respectively [39]. In addition, a phase II study on ENMD-2076, which targets Aurora A and VEGFR, for recurrent OCCC reported a median PFS of 3.7 months, and 22% of evaluable patients had a 6-month PFS, which did not meet the preset bar for efficacy [40]. Most of these trials showed limited efficacy. A randomized phase II international NiCCC (ENGOT-GYN1) study on nintedanib (BIBF 1120), which targets VEGFR, PDFGR, and fibroblast growth factor receptor (FGFR), versus chemotherapy in recurrent or persistent OCCC is ongoing (NCT02866370) [41].

9.4.3 PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway plays a crucial role in the malignancy of human tumors and is involved in OCCC pathogenesis via frequent genetic alterations [14–16, 18–20]. Notably, comprehensive genomic profiling of OCCC shows that ~70% of

Table 9.2 Clinical trials based on the molecular landscape in OCCC

Title	Drug	Targets	Condition	RCT	Phase	Trials identifier	Reference
Anti-angiogenesis							
GOG-254	Sunitinib	VEGFR, PDGFR	Recurrent or persistent	No	II	NCT00979992	[38]
NRG-GY001	Cabozantinib	VEGFR2, MET, RET	Recurrent or persistent	No	II	NCT02315430	[39]
A Study of ENMD-2076 in OCCC	ENMD-2076	VEGFR, Aurora A	Recurrent	No	II	NCT01104675	[40]
NiCCC (ENGOT-GYN1)	Nintedanib	VEGFR, PDGFR, FGFR	Recurrent or persistent	Yes	II	NCT02866370	[41]
Anti-PI3K/Akt/mTOR pathway							
GOG-268	Temsirolimus	mTOR	Stage III or IV	No	II	NCT01196429	[42]
Synthetic lethal approaches for ARID1A							
GOG-283	Dasatinib	Abl, Src, c-Kit	Recurrent or persistent	No	II	NCT02059265	[43]
Immune checkpoint blockade							
MOCCA	Durvalumab	PD-L1	Recurrent or persistent	Yes	II	NCT03405454	[44]
BrUOG 354	Nivolumab Ipilimumab	PD-1 CTLA4	Recurrent or persistent	Yes	II	NCT03355976	[45]

samples harbor mutations in at least one component of the PI3K/Akt/mTOR pathway [46]. In addition, inhibitors of the PI3K/Akt/mTOR pathway shows antitumor effects in OCCC cells with high pathway activity [47]. These findings indicate the potential benefits of therapies targeting the PI3K/Akt/mTOR pathway in OCCC patients.

The GOG-268 phase II study on temsirolimus, which targets mTOR complex 1, in combination with paclitaxel and carboplatin, followed by temsirolimus, as a first-line therapy in stage III–IV OCCC patients did not show an improved PFS compared to historical controls (Table 9.2; NCT01196429) [42].

9.4.4 HNF-1β Pathway

Hepatocyte nuclear factor 1β (HNF-1β), a transcription factor, is commonly expressed in OCCC and is therefore used as an OCCC diagnostic marker [1, 9, 11, 12]. A decrease in HNF-1β expression is associated with a favorable clinical

outcome in OCCC patients [48]. Epigenetic silencing via hypomethylation is one of the mechanisms underlying high HNF-1β expression [30]. In OCCC, HNF-1β plays an important role in cancer cell survival and chemoresistance by modulating glucose metabolism and internal oxidative stress [49, 50].

9.5 Synthetic Lethal Approaches for *ARID1A*

As mentioned before, cancer cells are vulnerable to ARID1A deficiency. Therefore, synthetic lethal approaches to targeting this vulnerability of OCCC cells are being developed. The small-molecule inhibitor of the enhancer of zeste homolog 2 (EZH2) methyltransferase (GSK126) inhibits growth in *ARID1A*-mutated ovarian cancer cells because ARID1A and EZH2 have an antagonistic association with regard to *PI3K-interacting protein 1* (*PIK3IP1*) expression that promotes apoptosis via negative PI3K/Akt signaling regulation [51]. As another epigenetic concept of ARID1A deficiency, modulation of histone deacetylase 6 (HDAC6) activity using the HDAC6 inhibitor (ACY1215) has a therapeutic effect in *ARID1A*-mutated tumors [52]. ARID1A transcriptionally represses *HDAC6*, so *ARID1A* mutation inactivates the apoptosis-promoting function of P53 via HADC6 upregulation. Notably, high HDAC6 expression, as shown by immunohistochemistry (IHC) assay, is correlated with unfavorable prognosis in OCCC with ARID1A loss [53]. In addition, HDAC6 inhibition can synergize with anti-programmed death-ligand 1 (PD-L1) immune checkpoint blockade in an ARID1A-inactivated genetic OCCC mouse model [54].

ARID1A-deficient tumors show therapeutic vulnerability to PARP inhibitors [55]. ARID1A is recruited to the site of double-stranded DNA breaks (DNA DSBs) via interaction with ataxia–telangiectasia and RAD3-related protein (ATR), in addition to facilitating DNA DSB end processing and sustaining ATR activation for DNA damage signaling. Therefore, impaired DNA damage checkpoint regulation in ARID1A-deficient tumors sensitizes cancer cells to PARP inhibitors. In addition, high-throughput RNA interference (RNAi) chemosensitization screening shows that ARID1A is a synthetic lethal partner of the ATR inhibitor [56]. ARID1A deficiency delays the cell cycle because of the inability to recruit topoisomerase II to chromatin, increasing dependency on ATR checkpoint activity. Therefore, ATR inhibition in ARID1A-deficient tumors induces premature mitosis, triggering genomic instability and cancer cell death.

A high-throughput drug screen targeting *ARID1A* synthetic lethal effects revealed dasatinib, a multitarget kinase inhibitor, as a clinically used selective drug for *ARID1A*-mutated OCCC cell lines [57]. The sensitivity of dasatinib in *ARID1A*-mutated cancer cells is characterized by G1 cell cycle arrest, followed by p21- and Rb-associated apoptosis. Studies focusing on cellular metabolism as a new concept of synthetic lethal approaches have shown that ARID1A-deficient tumors are vulnerable to glutathione (GSH) metabolism [58]. ARID1A maintains GSH homeostasis by modulating SLC7A11 expression (a transporter of cysteine, a key source for

GSH) and therefore maintains an intricate balance between GSH and reactive oxygen species (ROS). Inhibition of the GSH metabolic pathway using either APR-246 or buthionine sulfoximine (BSO, a rate-limiting enzyme in GSH synthesis) in ARID1A-deficient tumors collapses the GSH-ROS balance, followed by apoptosis by ROS.

The ARID1A deficiency status is used for OCCC patient stratification in both clinical settings and trials. OCCC with *ARID1A* mutation shows selective sensitivity to gemcitabine, although the underlying molecular mechanism is unclear [59]. Gemcitabine is commonly available for EOC treatment, so this finding might directly contribute to precision medicine for OCCC. In addition, a phase II retrospective study on dasatinib for recurrent or persistent ovarian and endometrial clear cell carcinoma to evaluate antitumor effects with regard to the ARID1A expression status is ongoing (NCT02059265) [43].

9.6 Immunological Landscape

Pembrolizumab is a humanized monoclonal antibody against programmed death-1 (PD-1) and is approved for any unresectable or metastatic solid tumor with microsatellite instability (MSI). MSI with a high tumor mutation burden arises from mismatch repair (MMR) deficiency caused by either germline mutations in MMR gene components in Lynch syndrome patients or somatic hypermethylation of the *MLH1* promoter region in tumors. Histological subtypes of EOC associated with Lynch syndrome include endometrioid carcinoma and OCCC [60]. The frequency of aberrant MMR expression, as assayed by IHC, is 6–13% in OCCC [61–63], and MMR expression and MSI status are correlated [63, 64].

In the KEYNOTE-100 phase II study on pembrolizumab in 376 recurrent EOC patients, the objective response rate (ORR) of OCCC was 15.8%, although the overall ORR was 8% [65]. Importantly, this study also showed that higher PD-L1 expression in tumors is correlated with a higher ORR; ~50% of OCCC patients showed positive PD-L1 expression regardless of the MMR status [62, 63], indicating that a large percentage of OCCC patients might benefit from this new therapeutic approach of immune checkpoint blockade. ARID1A deficiency induced impaired MMR via interaction with MSH2, followed by increased PD-L1 expression, in a syngeneic ovarian cancer mouse model [66]. In another phase II study on the anti-PD-1 antibody nivolumab in 20 platinum-resistant EOC patients, 2 patients (one with OCCC) showed a durable complete response [67]. Other ongoing clinical trials targeting immune checkpoint blockade for OCCC include the MOCCA phase II randomized study on durvalumab, which targets PD-L1, versus chemotherapy (NCT03405454) [44] and the BrUOG 354 phase II randomized study on nivolumab plus ipilimumab, which target CTLA4, versus only nivolumab (NCT03355976) [44] (Table 9.2).

9.7 Conclusion

The clinical need for OCCC treatment is still unmet. Alternative therapeutic strategies using targeted therapies based on the molecular characteristics of OCCC might significantly affect the clinical outcome in OCCC patients. Given its low prevalence, the proof-of-concept via adequately designed clinical trials with international collaboration on the basis of the OCCC molecular landscapes are required in order to develop precision medicine for OCCC.

Conflict of Interest Statement None of the authors have any conflict of interest to disclose.

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