HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2020 September 30.

Published in final edited form as:

Gynecol Oncol. 2018 November ; 151(2): 381–389. doi:10.1016/j.ygyno.2018.09.001.

Genomics to immunotherapy of ovarian clear cell carcinoma: Unique opportunities for management

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Abstract

Ovarian clear cell carcinoma (OCCC) is distinctive from other histological types of epithelial ovarian cancer, with genetic/epigenetic alterations, a specific immune-related molecular profile, and epidemiologic associations with ethnicity and endometriosis. These findings allow for the exploration of unique and specific treatments for OCCC. Two major mutated genes in OCCC are *PIK3CA* and *ARID1A*, which are frequently coexistent with each other. Other genes' alterations also contribute to activation of the PI3K (e.g. *PIK3R1* and *PTEN*) and dysregulation of the chromatin remodeling complex (e.g. *ARID1B*, and *SMARKA4*). Although the number of focal copy number variations is small in OCCC, amplification is recurrently detected at chromosome 20q13.2 (including *ZNF217*), 8q, and 17q. Both expression and methylation profiling highlight the significance of adjustments to oxidative stress and inflammation. In particular, up-regulation of HNF-1β resulting from hypomethylation contributes to the switch from anaerobic to aerobic glucose metabolism. Additionally, up-regulation of HNF-1β activates STAT3 and NF-κB

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Author contributions

K.O. wrote a manuscript (mainly Sections 1, 2, 3, 6), and organized the manuscript as one of corresponding authors; J.H. wrote a manuscript (mainly Section 4), and organized the manuscript as one of corresponding authors; K.M. generated the study concept and arranged the content, and checked and revised all the contents; and. K.H. wrote a manuscript (mainly Sections 4.4, 4.6 and 5).

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Disclosure statement

K.O. received research grant from Daiichi-Sankyo Co., Ltd., lecture fee from Chugai Pharmaceutical Co., Ltd.; J.H. received research grant from MSD, Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd. and Dainihon-Sumitomo; K.H. received research grant from Pfizer Inc., Yakult Honsha Co., Ltd., OncoThreapy Science Inc., honoraria from Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Eisai Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Bayer Yakuhin Ltd., advisory role for Merck Sharp and Dohme K. K. None for others.

signaling, and leads to immune suppression via production of IL-6 and IL-8. Immune suppression may also be induced by the increased expression of PD-1, Tim-3 and LAG3. Mismatch repair deficient (microsatellite instable) tumors as found in Lynch syndrome also induce immune suppression in some OCCC. In a recent phase II clinical trial in heavily-treated platinum-resistant ovarian cancer, two out of twenty cases with a complete response to the anti-PD-1 antibody, nivolumab, were OCCC subtypes. Thus, the immune-suppressive state resulting from both genetic alterations and the unique tumor microenvironment may be associated with sensitivity to immune checkpoint inhibitors in OCCC. In this review, we highlight recent update and progress in OCCC from both the genomic and immunologic points of view, addressing the future candidate therapeutic options.

Keywords

Ovarian clear cell carcinoma; Genomics; Neoantigen; Immune checkpoint; Immunotherapy; Oncogenesis

1. Background

Ovarian clear cell carcinoma (OCCC) is a relatively rare histological type of epithelial ovarian carcinoma (EOC) with a unique distribution pattern across ethnicity [1]. While OCCC accounts for <10% of EOC in North America and Europe, in Japan, it may be up to 25% [2,3]. The increased incidence of endometriosis in Japan may be associated with an increased incidence of OCCC, as the histologic subtypes of ovarian cancers associated with endometriosis are predominantly OCCC and endometrioid ovarian carcinoma (EMOC) [4].

Recently, it has been proposed that EOC be classified as either type I or type II [5]. OCCC, EMOC, mucinous ovarian carcinoma, and low-grade serous ovarian carcinoma are categorized as type I, while type II tumors are represented by high-grade serous ovarian carcinoma (HGSOC). The type II tumors are considered to arise from the distal fallopian tube, and show distinct genetic profiling as compared to OCCC [5,6]. For example, *TP53* mutations are found in <10% of OCCC, while they occur in over 96% of HGSOC [7,8]. In addition, *BRCA* mutations (both germline and somatic) are mainly observed in type II tumors [9,10].

Even among type I tumors, OCCC showed a significantly distinct molecular profiling pattern from other histologic types. Therefore, highlighting genetic, genomic and immunologic profiling of OCCC will assist in the development of precise therapeutics for these tumors. In this review, we focus on molecular subtypes of OCCC highlighting recent findings from both genomic and immunologic profiling.

2. Oncogenesis of OCCC

Although various histology-specific characterizations of OCCC have been unveiled, its oncogenic process is not fully understood. Although both OCCC and EMOC are well-known to be endometriosis-associated, it is still unclear how these tumors differentiate into this distinct morphology (and biology) [5,11]. The cellular origin of OCCC is also

controversial. Proposed sources include (i) endometrium, (ii) endometrial cysts (endometriosis-derived epithelial cells), (iii) ovarian surface epithelia, and (iv) fallopian tube-derived cells [3,5,11-14]. Of note, most of these same characteristics in OCCC have been observed in endometriotic cysts without malignancy.

Oxidative stress has been implicated in the pathophysiology of endometriosis, which causes a particular inflammatory microenvironment (Fig. 1). Dysregulation of immune cells have also been reported in endometriotic lesions [15]. Epigenetic modifications induced by oxidative stress have also been suggested to exist in endometriosis [16]. Moreover, common mutations in OCCC, including *ARID1A*, *PIK3CA*, *KRAS*, and *PPP2R1A*, have been frequently identified in endometriosis without cancer (Fig. 1) [17].

Loss of BAF250a (*ARID1A* gene) is also frequent in atypical endometriosis, suggesting its early contribution to the carcinogenesis [18]. Therefore, the majority of genomic/immunologic alterations may already exist before the transformation to OCCC. Overexpression of PD-L1 has not been reported yet in endometriosis, and copy number variations (CNVs) were rarely observed in endometriotic lesions [17], suggesting that acquisition of these biological characteristics may contribute to the transformation from non-invasive precursor lesion to OCCC (Fig. 1).

3. Genomic profiling of OCCC

3.1 Mutation profile of OCCC

Key molecules, pathways and molecular-targeted drugs are schematically summarized in Fig. 2. Two major mutated genes in OCCC are *PIK3CA* and *ARID1A* [19-21]. Oncogenic *PIK3CA* mutations activate the phosphatidylinositol 3-kinase (PI3K), whereas loss of function mutations in *ARID1A*, a component of the switch/sucrose non-fermentable (SWI/SNF) complex, results in dysregulation of chromatin remodeling [22,23]. The frequency of these mutations in OCCC is 40–62% for *ARID1A* and 33–51% for *PIK3CA* [24-26]. OCCC and EMOC showed a high frequency of mutations in PI3K, including *PIK3CA* and *PTEN*. *PTEN* mutations are less frequently observed in OCCC (~5%) than in EMOC (20%), whereas *PIK3CA* mutations are more commonly observed in OCCC than in EMOC (20%) [19,25,27]. Taken together with the high mutation frequency of *ARID1A* in EMOC (30%) [21], alterations in the PI3K pathway and the SWI/SNF complex are commonly shared in endometriosis-associated ovarian carcinomas.

Mutational analysis by whole-exome sequencing in OCCC revealed other genetic mutations in the PI3K pathway and the SWI/SNF complex, such as *ARID1B* (10%), *PIK3R1* (7–8%), and *SMARKA4* (encoding ATP-dependent chromatic modeler BRG1) (5%) [24,25]. The other genes mutated in OCCC, which were also confirmed by whole-exome sequencing or targeted multiple gene panel testing, included *PPP2R1A* (encoding serine/threonine protein phosphatase 2 scaffold subunit alpha) (10–20%), KRAS (9–17%), TP53 (5–15%), and *CTNNB1* (encoding betacatenin) (5–10%) [24-26,28,29].

3.2. Copy number variations of OCCC

Profiles of chromosomal CNVs in OCCC are also distinct from other histological subtypes [30,31]. Copy number analysis by single nucleotide polymorphism arrays revealed that the frequency of CNVs was significantly fewer in OCCC compared with that in HGSOC [32]. In contrast, the ratio of whole-arm CNVs among all CNVs (47%) in OCCC was significantly higher than that in HGSOC (21.6%). Thus, focal CNVs at the loci of specific genes were less frequent in OCCC than in HGSOC [32]. As whole-arm CNVs are associated with mitotic instability, each CNV might be less associated with the aberrant expression of cancer related genes in OCCC.

However, recurrent CNVs were identified at various loci [6,30,31]. At chromosome 20q13.2, including the *ZNF217* (Zinc finger protein 217) locus, they were frequently amplified in OCCC (~36%). Amplification of chromosome 8 (8p11.21-q11.23 and 8q22.1-q24.13) was detected in 52% of OCCC [32]. Increased copy numbers of *MET* (chr7q31) (31%) and *AKT2* (chr19q13.2) (24%) were also reported in OCCC (Fig. 2). Copy number loss (loss of heterozygosity or homozygous deletion) was detected at the loci of *CDKN2A/2B* (Cyclin-Dependent Kinase Inhibitor 2A/2B) (9p21.3) (17%) [33,34]. CNVs, evaluated by whole-exome sequencing, identified amplification at chr17q (46%) and deletion at chr13q (28%), 9q (21%) and 18q (21%) [25]. Although amplification of MET and AKT2 are potential candidate molecular targets, fewer CNVs at specific loci suggest that CNV-based targeted therapies may be limited in OCCC.

3.3. Expression signatures of OCCC

The gene expression profile of OCCC is also distinct from other histologic subtypes, especially as compared to HGSOC [32,35]. Expression arrays of OCCC and non-OCCC cell lines revealed that hepatocyte nuclear factor-1beta (HNF-1β) was the most abundantly up-regulated transcription factor in OCCC (Fig. 2) [35]. Overexpression of HNF-1β was also observed in 40% of endometriotic cysts without a malignancy [36]. Additional significantly up-regulated genes were identified in multiple microarray datasets, included versican (*VCAN*) and other genes related to oxidative stress [35]. Both oxidative stress-related and coagulation-related gene sets were up-regulated in OCCC, which is consistent with the increased frequency of endometriosis and venous thromboembolism in OCCC patients [37,38].

A set of 66 up-regulated genes was identified as a pathway network in OCCC. These genes included *HNF-1β*, *HIF-1α*, *IL-6*, *p21*, and *Signal transducer and activator of transcription 3* (*STAT3*), highlighting the significance of the IL-6-STAT3-HIF pathway (Fig. 2) [35]. Glycogenrelated pathways were also enriched in this pathway network [35]. In endometriotic cysts, exposure to high concentrations of free iron induces persistent oxidative stress and may promote carcinogenesis [39]. The response to this persistent oxidative stress and inflammation may be reflected in the altered gene expression profile of OCCC.

Clear cell carcinoma is also a major histologic subtype in renal cell carcinoma (RCC). Hierarchical clustering by microarray data sets with various cancer types (merged data for the OCCC cell lines and NCI60 cell lines) discriminate a specific cluster enriched within

both OCCC and RCC related to activation of HNF-1β and its downstream target genes [40]. Indeed, up-regulation of HIF-1α (by *VHL* mutations in RCC), amplification of *VCAN*, and a hypoxia-like mRNA expression signature are commonly observed in both OCCC and RCC [41-43]. Therefore, certain molecular targeted therapies against RCC that have not been tested in ovarian cancers or that have not demonstrated therapeutic benefit in unselected ovarian cancers may have efficacy if tested specifically for OCCC.

3.4. Epigenetic profiling of OCCC

Epigenetic alterations of OCCC are specific to histologic type. Hypo-methylation of HNF-1β is significantly detected in OCCC, suggesting that epigenetic silencing is one of the mechanisms of its overexpression [35,44]. Several other genes (*14-3-3 sigma*, *TMS1/ASC*, *WT1*, *RASSF1A*, *CDH13*, *CACNA1A*, *HIN*-1, and *sFRP5*) have also been reported as aberrantly methylated in OCCC [45-47]. Consensus clustering of DNA methylation profiles in ovarian cancer cell lines identified an OCCC-specific cluster, distinct from other histologic types [48]. In clinical samples, HGSOC was classified as a distinct cluster from non-HGSOC (type I). Sub-clustering of type I identified a specific methylation profile of OCCC, distinct from that of mucinous ovarian carcinoma and EMOC [48]. In OCCC, HNF-1 pathway genes (*HNF-1A*, *HNF-1B*, *PAX8*, and *SGK2*) were significantly hypomethylated, and the ER-α network genes were hypermethylated [48].

Unmethylated genes in OCCC ($n = 22$) were enriched for stress response-related gene ontology terms, while hyper-methylated genes in OCCC ($n = 276$) included “response to oxidative stress” gene ontology terms [48]. These data suggest that the expression profile of OCCC is closely associated with epigenetic regulation, possibly due to persistent oxidative stress. This unique epigenetic signature may lead to novel therapeutic strategies in OCCC.

3.5. Metabolic characteristics of OCCC

The Warburg effect is a phenomenon whereby tumor tissues tend to metabolize glucose to lactate, to a much greater degree than is seen in non-tumor cells (metabolization of glucose by glycolysis rather than oxidative phosphorylation) [49,50]. This is seen even under aerobic conditions. Although the mechanism of the Warburg effect in various cancer cells has not been fully clarified, there is growing evidence that high expression of HNF-1β plays an essential role in glucose metabolism [51]. Knocking down HNF-1β in OCCC cells significantly reduces the production of lactic acid (produced by anaerobic glycolysis) and increases that of citric acid (the first metabolite of the TCA cycle) indicating a switch from anaerobic to aerobic glucose metabolism [52].

Under hypoxic conditions, parental OCCC cells (with high HNF-1β) showed significant survival advantage, compared with HNF-1β-knockdown OCCC cells [52]. Overexpression of HNF-1β is also shown to reduce reactive oxygen species and contribute to protection of the cancer cells from the internal oxidative stress caused by the drastic changes in their cellular metabolism [50]. Thus, HNF-1β may be pivotal for cancer cell survival due to anti-stress effects, rather than increased proliferative potential. It is proposed that sustained high expression of HNF-1β cells may be associated with chemo-resistance in OCCC (Fig. 2)

[50]. This can potentially be overcome, if aerobic glucose metabolism can be induced, or if HNF-1β-mediated anti-oxidative stress can be counteracted in these cancer cells.

3.6. Candidate molecular targets in OCCC

Based on the genetic and epigenetic alterations in OCCC, candidate molecular targets and possible molecular-targeted drugs are listed in Table 1. The PI3K pathway inhibitors may be considered for *PIK3CA* mutated (or *PTEN* mutated or *PIK3R1* mutated) tumors, although clinical application of PI3K inhibitors has thus far been limited [53]. Copanlisib is a highly selective, pan-class I PI3K inhibitor, which preferentially inhibits p110α and p110δ isoforms, rather than the p110β and p110γ isoforms [54]. In 2017, copanlisib was approved for relapsed follicular lymphoma, in patients who have received at least two prior systemic therapies as a second FDA-approved PI3K Inhibitor [55]. As p110α is encoded by *PIK3CA* itself, this inhibitor may be a candidate drug for *PIK3CA* mutant OCCCs. Indeed, one endometrial cancer patient with coexistent mutations of *PIK3CA* and *PTEN* showed complete response to copanlisib [56].

We previously reported that a PI3K/mTOR dual inhibitor, DS-7423, showed anti-tumor activity in OCCC cell lines [57]. Therefore, the PI3K pathway remains a promising therapeutic target in OCCC. Inhibiting enhancer of zeste homolog 2 (EZH2) methyltransferase activity was reported to induce epigenetically synthetic lethality in *ARID1A*-mutated cancers by targeting of EZH2 methyltransferase activity in *ARID1A*-mutated cancers [58]. PIK3IP1 was found to be up-regulated by EZH2 inhibition as a direct target of ARID1A and EZH2, and it contributed to lethality through inhibition of PI3K signaling [58]. As several clinical trials with EZH2 inhibitors are ongoing for B-cell Lymphomas, as well as solid tumors [59], OCCC may be a good candidate of EZH2 inhibitors (Fig. 2).

MDM2 is a ubiquitin ligase, which degrades wild-type TP53 via proteasome-mediated ubiquitination [57]. We previously reported that the expression level of MDM2 in OCCC is significantly higher than that in HGSOC by expression arrays [60]. In addition, a MDM2 inhibitor, RG7112, showed anti-tumor effect and induced apoptosis of OCCC cells via TP53 activation [60]. MDM2 is known to be phosphorylated and activated by AKT (PI3K) signaling, and we showed that the PI3K pathway inhibition by DS-7423 dephosphorylated MDM2 and induced TP53-mediated apoptosis in OCCC cells [57]. Taken together, TP53 activation via suppression of MDM2 may be a possible therapeutic strategy against OCCC (Fig. 2), as clinical trials of MDM2 inhibitors are currently ongoing for solid tumors [61]. Immune checkpoint inhibitors are also promising in OCCC and are discussed in the following section.

4. Immunological aspects of OCCC

4.1. Immunobiology of OCCC

Several reports demonstrate that activation of oncogenes (*MYC*, *RAS*, *PI3K*) or inactivation of tumor suppressor genes (*p53*, *PTEN*, *STAT3*) induces an immune-suppressive state in the tumor microenvironment [62-66]. HNF-1β is preferentially activated in OCCC and has been

reported to contribute to various malignant features including metastases, altered glucose metabolism and immune suppression via production of IL-6 and IL-8 through activated STAT-3 signaling as well as via NF-κB dependent pathways (Fig. 3) 67,68]. High levels of IL-6, IL-8, and overexpression of NF-κB related signaling in both serum and cancer ascites have been associated with a poor clinical outcome in ovarian cancer [67]. In all ovarian cancer including OCCC [69], NF-κB signal can also induce programmed death ligand 1 (PD-L1 and B7-H1), an inhibitory costimulating B7 family molecule (see Section 4.5 for the detail) (Fig. 3). These findings show that OCCC has a unique immune microenvironment, and thus, immunotherapy may be an attractive strategy for its treatment.

4.2. Immune-related expression gene profile of OCCC

The gene expression profile signature of OCCC in a previous report identified up-regulation of IL-6, STAT3 related genes, as well as other inflammatory cytokines and immune-related genes which is suggestive of an immune-suppressive microenvironment [35]. Another report of the OCCC gene expression profile demonstrated that effector memory CD8+ T cell phenotype were overexpressed in tumors in stage I-II OCCC, as were cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), PD-1, T cell immunoglobulin and mucin-domain containing-3 (Tim-3), and lymphocyte-activation gene-3 (LAG3) genes [70]. At the same time, expression of human leukocyte antigens (HLA) -A, -B, and -C were decreased. These changes result in an immune-suppressive microenvironment which may serve as a promising therapeutic target in OCCC.

4.3. Cancer antigen and application of cancer vaccine in OCCC

Several antigens have been identified in ovarian cancers which might allow for the development of a cancer vaccine therapy; however OCCC has yet been to be included in this spectrum. Glypican-3 (GPC3), a member of the glypican family of heparan sulfate proteoglycansone, is a potentially useful carcinoembryonic antigen for cancer vaccine immunotherapy and is overexpressed in both hepatocellular carcinoma and OCCC [71]. HLA-A24-restricted GPC3298-306 (EYILSLEEL) and HLAA2-restricted GPC3144–152 (FVGEFFTDV) peptides, are able to induce GPC3-reactive cytotoxic T cells without inducing autoimmunity [72]. In a small study, OCCC patients were treated with a GPC3-derived peptide vaccine, and the overall response rate was reported as 9.4% (2 partial response [PR] and 1 stable disease [SD]) with the disease control rate 17.9% in 32 patients [73].

4.4. Neoantigens in OCCC

With the success of immune checkpoint blockade therapy, increased attention has been paid to neoantigens. Neoantigens are derived from tumor-specific mutations, and because they are foreign to the host immune system, they can be potential targets for anti-tumor immunotherapy. Recent data has shown that these neoantigens make up a large part of the functional targets of immune checkpoint blockade therapy [74]. Very few reports are currently available regarding immune-targeting of neoantigens in OCCC. Matsushita and his colleagues assessed the neoantigen load, the depletion of expected antigenic mutations and immune signatures in 74 cases of OCCC using data from exome sequencing and expression arrays [70]. They found that the number of predicted neoantigens assessed in the tumor did

not correlate with clinical outcomes, but the number of neoantigens per missense mutation did correlate with clinical outcomes.

Those with a lower number of neoantigens per missense mutation showed better clinical outcomes and demonstrated a phenotype consistent with T cell-mediated inflammation. This suggests that the cellular immune response functioned to eliminate neoantigen expressing subclones in tumors with a lower number of neoantigens per missense mutation. In contrast, decreased HLA class I expression as well as increased ratios of PD-1, Tim-3 and LAG3 were observed in tumors with higher number of neoantigens per missense mutation and worse clinical outcomes [70].

4.5. Immune checkpoint signals and DNA mismatch repair deficiency in OCCC

Although several immunological mechanisms contribute to immune suppression in the tumor microenvironment, the immune checkpoint signal PD-1/PD-L1 plays a central role in many cancer types [75,76]. The success of PD-1/PD-L1 inhibitors in various types of malignancies (such as RCC) has led to the expectation that they will be useful immunotherapy targets for gynecologic tumors including OCCC [77-80]. Some reports have identified the expression of PD-1 or/and PD-L1 on tumor cells and tumor-infiltrating lymphocytes (TILs) in OCCC and a correlation between these and clinical outcome [81,82].

Microsatellite instability (MSI) high tumors are associated with an enriched tumor mutation burden and a highly immunogenic phenotype. These tumors, including colorectal and endometrial cancer, which are also characterized as MSI high or mismatch repair deficient, are highly responsive to anti-tumor checkpoint inhibitors [83]. Women with Lynch syndrome, and a germline mutation of the mismatch repair genes (i.e. *MLH1*, *MSH2*, *MSH6*, and *PMS2*), have an increased life-time risk of colorectal, endometrial and ovarian cancer [84]. Lynch syndrome-associated ovarian cancer includes OCCC as well as EMOC [85]. Therefore, Lynch syndrome should also be taken into consideration with OCCC patients, especially with a Lynch syndromerelated family history. In a previous clinical sample analysis, PD-L1 expression was found in 43% of OCCC tumors, including 67% of OCCC with mismatch repair defects (Fig. 2) [86]. PD-L1 expression is common in mismatch repair proficient tumors and there is no correlation between PD-L1 expression and mismatch repair status in OCCC. Nevertheless, PD-L1 expression is prevalent in mismatch repair-intact OCCC [86].

Finally, OCCC with MSI exhibited a high number of CD8+ TILs and higher PD-1 expressing TILs compared with microsatellite stable (MSS) OCCC. PD-L1 expression in tumor cells or immune cells was also noted in all cases of OCCCs with MSI. MSI in specific subsets of OCCC was associated with endometriosis and ARID1A/BAF250A loss [82]. These observations may indicate an alternative therapeutic option for a subpopulation of the patients with OCCC.

4.6. Clinical response of immune checkpoint blockade for OCCC

In a recent phase II trial of pembrolizumab for recurrent ovarian cancer (KEYNOTE-100), anti–PD-1 antibody pembrolizumab for recurrent ovarian cancer (>300 patients) demonstrated that while the overall response rate of all cohorts was low (~8%), the response

rate of clear cell histology was 15.8% [87]. Another phase II clinical trial of the anti-PD-1 antibody nivolumab for heavily-treated platinum-resistant recurrent ovarian cancer, included 10% with a complete response (CR) demonstrating a durable antitumor effect (2 out of 20) [88,89]. One of these CR patients had OCCC histologic subtype and another was diagnosed as having an OCCC-like phenotype following additional gene expression profile analysis of the tumor. Further experiments revealed that these two CR patients exhibited MSS by immunohistochemistry and wild-type ARID1A by exome sequencing (unpublished data).

In an anti-PD-1 antibody trial with pembrolizumab, an exceptional complete responder with chemo-/radiation-resistant OCCC was reported, and genomic analysis revealed a PD-L1-genetic rearrangement in the tumor sample [90]. In a phase I study of the anti-PD-L1 antibody avelumab in recurrent ovarian cancer, both patients with OCCC exhibited a PR [91]. In a phase I study of the anti-PD-L1 antibody durvalumab in combination with the poly (ADP-ribose) polymerase inhibitor olaparib for recurrent ovarian cancer, only one patient with OCCC was enrolled and exhibited a PR [92]. While the sample size of OCCC in these clinical trials was small and further verification is needed, anti-PD-1 or -PD-L1 antibodies appear to be a powerful new therapeutic agent for patients with OCCC [93].

A phase II/III trial of nivolumab for recurrent ovarian cancer (NINJA trial, JapicCTI-153004; target accrual, $n = 300$) is ongoing, and this study may directly validate the antitumor effect of anti-PD-1 therapy specific for OCCC in the near future [89].

5. Clinical trials in OCCC

5.1. Non-immunotherapeutic approaches

Salient trials related to OCCC are outlined in Table 2. Not surprisingly, OCCC-focused clinical trials have thus far been very limited. A randomized phase III study, which compared the efficacy and safety of irinotecan plus cisplatin to standard paclitaxel plus carboplatin in patients with stage I-IV OCCC, was conducted by JGOG as an international inter-group trial (JGOG-3017), and the combination chemotherapy regimen with irinotecan and cisplatin did not show superiority to standard regimen with paclitaxel and carboplatin in those patients [94].

The mTOR-AKT pathway in OCCC is a candidate for therapeutic targeting, and Farley et al., reported the results of phase II study (GOG-268) in the 2016 ASCO meeting [95]. This study evaluated temsirolimus in combination with carboplatin and paclitaxel followed by temsirolimus consolidation as the first-line therapy in the treatment of stage III-IV OCCC. Nearly half (54%) of those with optimal debulking had a progression-free survival (PFS) longer than 12 months, however, this was not statistically significantly increased as compared to historical controls [95].

Multiple targeted tyrosine kinase inhibitors (TKI) have also been tested in OCCC. GOG-254, was a phase II trial of SU11248 (sunitinib), an oral multi-targeted tyrosine kinase inhibitor. This agent was studied for its efficacy and tolerability in persistent or recurrent OCCC (NCT00979992). The results were published recently and showed that the median PFS and overall survival (OS) was 2.7 and 12.8 months, respectively [96]. Sunitinib

demonstrated minimal activity in those patients. Another TKI, BIBF1120 (nintedanib) is currently being tested in patients with relapsed OCCC (NCT02866370).

Cabozantinib, a MET, VRGFR2 and RET TKI, was also evaluated recently in patients with recurrent OCCC (NRG-GY001). No objective responses were observed. The median PFS and OS were 3.6 and 8.1 months, respectively. Cabozantinib showed minimal clinical activity in those patients [97]. ENMD-2076, an oral active kinase inhibitor, targeting the mitotic kinase Aurora A, VEGFRs, and FGFRs, was investigated in recurrent OCCC (NCT01914510). Somatic mutations in ARID1A, a key component of the SWI/SNF chromatin remodeling complex, may result in up-regulation and overexpression of Aurora A. Lheureux et al. presented the efficacy of ENMD-2076 at the 2017 ASCO meeting which showed that the median PFS was 3.7 months, and 6-months PFS rate was 20% for the evaluable patients (31% in ARID1A loss and 12% in ARID1A positive patients) [98].

T cell immunoglobulin mucin-1 (TIM-1) expression is up-regulated in several human cancers, most notably in RCC and OCCC but has minimum expression in normal tissues. A dose escalation trial of an antibody-drug conjugate, CDX-014 that targets TIM-1 and is linked to a potent cytotoxic, monomethyl auristatin E (NCT02837991), is currently under investigation in patients with advanced or metastatic RCC and OCCC.

5.2. Immunotherapeutic approaches

In a recent list of clinical trials for ovarian cancers including OCCC, over 50 are related to immunotherapies including immune checkpoint inhibitors, immune-modulating drugs, and T cell-engineered therapies either as a single agent or in combination with a traditional chemotherapeutic or a different immunotherapy. OCCC-specific clinical trials with immunotherapies are also listed in Table 2, including durvalumab (NCT03405454), a combination treatment of nivolumab and the anti-CTLA4 antibody ipilimumab (NCT03355976). Further studies characterizing the immunological, molecular, and genetic make-up of OCCC holds promise to open the door for more personalized treatment using specifically targeted immunotherapies.

6. Conclusion

OCCC is a distinct type of tumor from other histologic types of EOC. The compiled information regarding genetic/epigenetic disorders, expression profiling, glycolytic modification, and identified alterations in the immune-related response may shed light on the novel therapeutic options in OCCC. It may be categorized as one of rare tumors with an ethnicity-related distribution, however, candidate molecular targets generally overlap with various types of tumors from other organs (especially with RCC). This should allow for the testing of diverse molecular-targeted drugs in basket clinical trials. Additionally, clinical sequencing in OCCC may identify various types of actionable mutations and prove helpful in the development of precision medicine against ovarian cancer.

Acknowledgement

We thank Brendan H. Grubbs, MD, for his scientific input for this manuscript.

Funding support

Grants-in-Aid for Scientific Research (C) 18K09249 (K.O.), and 16K11152 (K.H.). Ensign Endowment for Gynecologic Cancer Research (K.M.).

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HIGHLIGHTS

- OCCC is distinct from other ovarian cancers in its genetic, epigenetic, metabolomic and immunologic profile.
- Epigenetic/metabolomic modifications contribute to cell survival against oxidative stress.
- A unique immune microenvironment causes immune-suppressive state in OCCC.
- Genetic, epigenetic, metabolomic and immunologic differences of OCCC can be used to design treatments specific to OCCC

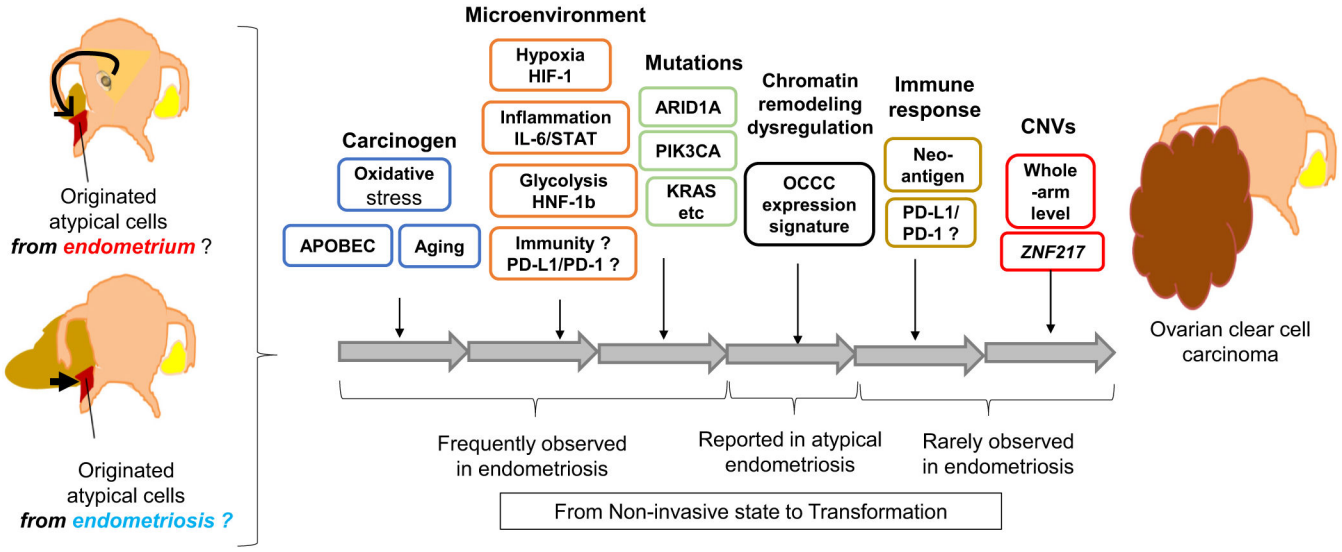

Fig. 1.

Proposed schema for oncogenesis of OCCC related to endometriosis. Various types of CCCC-specific microenvironment and genetic/epigenetic alterations may contribute to oncogenesis from the originated atypical cells (endometrium and/or possible endometriotic cells) to OCCC Exposure to the specific OCCC-related microenvironment such as oxidative stress, inflammation, glycolysis, and immune-suppressive state, possibly occurs before the malignant transformation. Genetic mutations may appear even in endometriotic cysts. The resultant gene disorders (induced by oncogenic activation of the PI3K, chromatin remodeling dysregulation, neoantigens, and etc.) and copy number variations (CNVs) may accelerate the cells to proceed to the malignant (invasive) state.

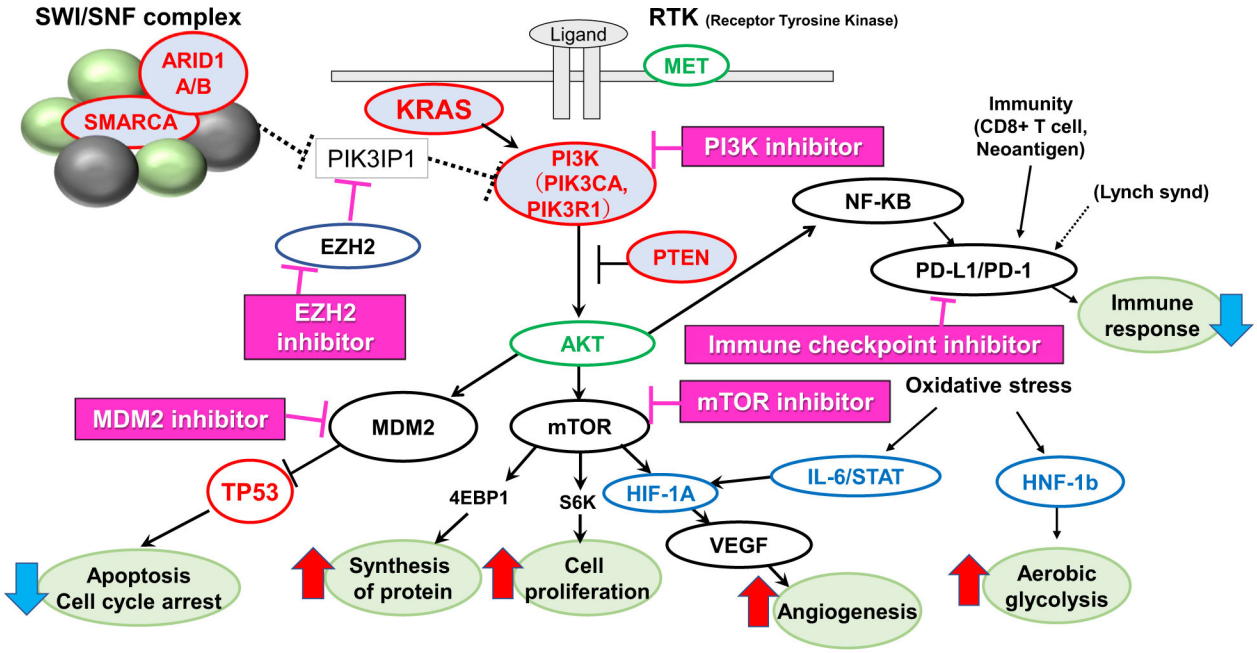

Fig. 2.

Candidate molecular targets and key pathways on basis of genomic characterization in OCCC. Frequently mutated genes (marked in red), frequently amplified genes (marked in green), and frequently up-regulated genes (marked in blue) cooperate to promote a unique cell survival advantage in OCCC. Genomic and/or immunologic-based candidate molecular targeted drugs are listed, which have been already approved or under clinical trials for other cancer types.

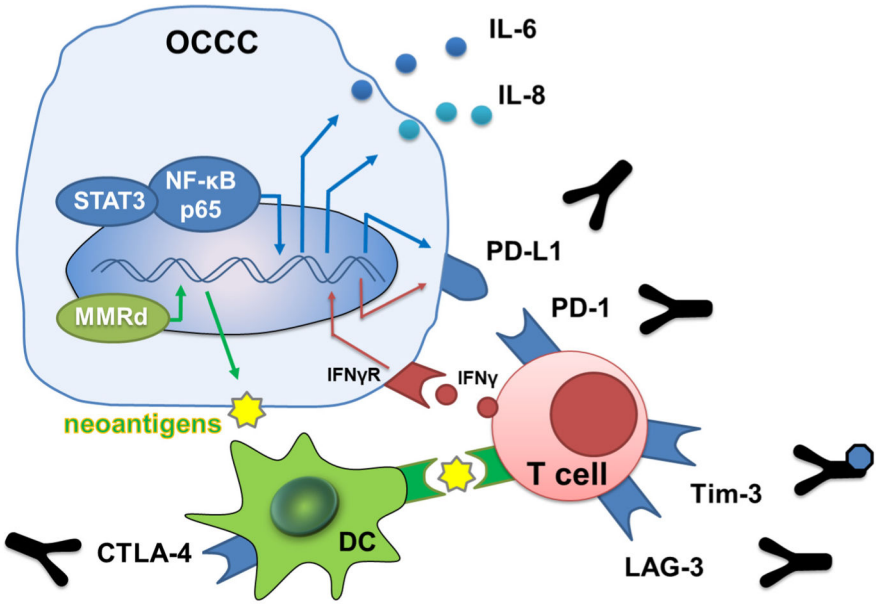

Fig. 3.

Immunobiology and target in OCCC. NF-κB and STAT3 induce immunosuppressive cytokine IL-6 and IL-8. NF-κB also induces PD-L1 on tumor cells. DNA mismatch repair deficient state increases the number of tumor mutation burden and neoantigen, and then dendritic cells and T cells recognize neoantigen and attack cancer cells. Activated immune cells produce IFN-γ and express PD-1, and then tumor cells express PD-L1 via IFN-γ/STAT1 signal. *DC, dendritic cell; MMR, DNA mismatch repair deficient; IFN-γ, interferon gamma; and IFN-γR, interferon gamma receptor. Y-shape figure indicates antibody.

Table 1

Types of gene alterations and possible molecular targets in ovarian clear cell carcinoma.

Genes	Type of alterations	Freq. (%)	Targeted pathway/molecule(s)	Drug availability	FDA approval (or clinical trials)	Reference
PIK3CA	Mutation	51%	PI3K/mTOR	PI3K inhibitor (e.g., copanlisib)	Follicular lymphoma	[55]
PTEN	Mutation	5%				
PIK3R1	Mutation	8%		mTORinhibitor (e.g., everolimus)	RCC and others	[99]
ARID1A	Mutation Copy number loss	60%	EZH2	EZH2 inhibitor (e.g., Tazemetostat)	Phase I/II (solid tumors/B-cell lymphomas)	NCT01897571
ARID1B	Mutation	10%				
HNF-1beta	Hypo-methylation Overexpression	>80%	Glucose metabolism?	Anti-diabetic?	N/A	N/A
HIF-1alpha	High expression	-	VEGF?	Bevacizumab	Ovarian cancer	[100]
MDM2	High expression	-	MDM2-TP53 interaction	MDM2 inhibitor (RG-7112, DS-7423 etc.)	Phase I/II (solid tumors)	NCT03362723, NCT01877382
NF-kB		-			N/A	N/A
PD-1/PD-L1	Mutation (Lynch synd.)	2–3%	MSI-high, MMR-deficient	Checkpoint inhibitor (e.g., pembrolizumab)	MSI-high/MMR-deficient solid tumor	[101]
PD-1/PD-L1	High expression	-	PD-1/PD-L1	Checkpoint inhibitor (e.g., nivolumab)	RCC, melanoma, lung cancer, gastric cancer	NCT03405454 NCT03355976

Frequently altered genes, their relevant molecules and pathways, candidate molecular-targeted drugs and their availability are listed. Multiple types of alterations may exist in a single gene with their correlation (i.e. mutation and copy number loss, hypo-methylation and overexpression).

Table 2

Clinical trials in OCCC.

Drug/combination	Molecular targets	Study name	RCT	Phase	Status	Summary	Reference
Combination chemotherapy							
Irinotecan + cisplatin	-	JGOG3017	Yes	III	Completed	Non-taxane combination chemotherapy was not superior to standard paclitaxel + carboplatin	[94]
Targeted therapy							
Temsirolimus + paclitaxel + carboplatin	mTOR	GOG268	No	II	Completed	Temsirolimus + paclitaxel + carboplatin followed by temsirolimus consolidation was not superior to historical controls	[95]
Sunitinib	VEGFR, PDGFR	GOG254	No	II	Completed	Minimal clinical activity	[96]
Nintedanib	VEGFR, PDGFR, FGFR	NiCCC (ENGOT-GYN1)	Yes	II	Ongoing	Nintedanib vs physician's choice chemotherapy	NCT02866370
Cabozantinib	MET, RET, VEGFR2	NRG-GY001	No	II	Completed	Minimal clinical activity	[97]
ENMD-2076	Aurora A, VEGFR, FGFR	-	No	II	Completed	Median PFS 3.7 months. Loss of ARID1A was correlated with better PFS	[98]
CDX-014	TIM-1	-	No	I	Ongoing	A dose-escalation safety and activity study	NCT02837991
Immunotherapy							
Durvalumab	PD-L1	MOCCA	Yes	II	Ongoing	Durvalumab vs physician's choice chemotherapy	NCT03405454
Nivolumab ± ipilimumab	PD-1, CTLA4	BrUOG 354	Yes	II	Ongoing	Nivolumab vs nivolumab + ipilimumab	NCT03355976