Chapter 7
Signaling and Drug Resistance

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Abstract Cervical cancer: Resistance to concurrent radiochemotherapy (CCRT) is strongly related to cancer stem cell (CSC) phenotype. Several pathways including Hedgehog, Wnt/β-catenin, and STAT3 pathways are involved in the acquisition or maintenance of the CSCs population.

Endometrial cancer: It has been reported that Estrogen receptors or growth hormones are involved in acquiring chemoresistance in Type-I Endometrial cancer. Although the involvement of the PIK3/Akt pathway is also well known, the therapeutic effect of the monotherapy of PIK3CK inhibitor is insufficient. However, it might be expected in the case of mutation in CTNNB1. The STAT1 pathway and phosphorylation of ser727 are involved in chemoresistance in Type-II endometrial cancer. EGFR pathway is also important because we have the clinically available drug. A combination of HER2-target therapy with PIK3CA inhibitor is expected.

Ovarian cancer: High-grade serous ovarian cancer (HGSOC) is famous for its diverse mechanism of acquisition of chemoresistance. Epithelial to mesenchymal transition (EMT) is closely related to CSC functions and plays an important role in the acquisition mechanism. Various pathways such as TGF-β, STAT3, Hedgehog, and Wnt/β-catenin pathways are involved in the enhancement of EMT. TLE2 might be an important factor that can regulate multiple EMT-related pathways in common. A clinically important issue is that the mesenchymal subtype of HGSOC is relatively sensitive to paclitaxel. Ovarian clear cell carcinoma (OCCC) is also famous as a subtype with strong resistance to chemotherapy. HNF1β is specifically expressed in OCCC and is greatly involved in the chemoresistance ability of OCCC through alteration of metabolic pathway and regulation of cystine transporter expression.

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7.1 Treatment Resistance in Cervical Cancer: Relationship with Cancer Stem Cell Phenotype

An important drug in the therapy for cervical cancer is cisplatin. Concurrent radiochemotherapy (CCRT), which combines cisplatin and radiation therapy, is a basic treatment strategy for advanced cervical cancer [1]. Sensitivity to both cisplatin and radiation is a factor that is greatly involved in the prognosis of cervical cancer patients.

The cancer stem cell (CSC) phenotype in cervical cancer has recently attracted attention as a factor related to treatment resistance. CSC is a theory originally proposed in hematological malignancies, in which a small population of cancer cells, known as CSCs, possesses several malignant phenotypes, including enhanced tumorigenicity and chemoresistance. Recently, it has been found that a CSC-like population exists in many kinds of solid tumors, including cervical cancer. Many researchers have also investigated specific markers to identify CSC-like cells. Thus far, several markers have been reported to identify CSCs, such as CD133-positive cells in Glioblastoma, LGR5-positive cells in colorectal cancer, and CD44-positive/CD24-negative cells in breast cancer. However, for cervical cancer, definitive CSC markers have not been detected. Therefore, studies have been conducted on markers that were reported in other carcinomas. CD133(+) cells, CD44(+)/CD24(–) cells, LGR5(+) cells, and SOX9(+) cells were recently reported as CSC-like cells possessing malignant potential in cervical cancer [2–6]. In addition, CSC usually possess high ALDH activity. Based on these aspects, we can consider ALDH-high populations as CSC-like fractions. Some researchers have investigated the role of these small populations in cervical cancer [7]. We summarize those reports in Table 7.1.

Thus, although we cannot define definitive CSC markers yet, there appears to be a small population of highly resistant therapeutic fractions for cervical cancer. In particular, such CSC-like fractions are either platinum-resistant or radiation-resistant. If we can elucidate the specific nature or signaling of those CSCs, we may be able to develop new treatment strategies to resolve resistance to platinum and radiation therapy. Several mechanisms have been related to controlling the CSC-like cell fraction. As for LGR5+-defined CSCs, inhibition of the Wnt/β-catenin pathway has been reported to control their malignant potential [2]. The Wnt/β--catenin pathway has also been reported to be involved in phosphorylation levels of eukaryotic translation initiation factor 4E (eIF4E) and controls the chemosensitivity of cervical cancer cells [20]. As for SOX9, cupper transporter protein 1 (CR1) has been reported to be regulated by the SOX9/miR-130a/CTR1 axis, controlling

Table 7.1 Summary of CSC-related reports in cervical cancer

Marker/ pathway	Main findings	References
LGR5 (marker)	Overexpression of LGR5 promotes CSC-like phenotype via Wnt/β-catenin pathway. LGR+ cells harbor multiple CSC characteristics including high in vivo tumorgenicity, asymmetrical division, and chemoresistance	[2]
SOX9 (marker)	SOX9 inversely regulates miR-130a through directly targeting the promoter of miR-130a, which regulates Copper transporter protein 1 (CTR1) and has a great influence on sensitivity to cisplatin	[3]
CD44+/ CD24− (marker)	Overexpression of cytosolic phospholipase A2α (cPLA2α) results in a CD44+/CD24− phenotype associated with mesenchymal traits, including increased invasive and migration abilities	[6]
	α-Actin-4 (ACTN4) knockdown suppresses sphere formation and CSC proliferation (CD44+/CD24− cell population). ACTN4-knockdown CSCs were sensitive to anticancer drugs, which was observed by the downregulation of the ABCG2 involved in drug resistance	[5]
SOX2, ALDH1A1 (marker)	Immunohistochemistry analyses reveal that low-$P16^{INK4A}$/high-SOX2 and low-$P16^{INK4A}$/high-ALDH1A1 groups had a worse prognosis. Depletion of $P16^{INK4A}$ promotes chemoresistance and radioresistance of cervical cancer cells, increased the expression of SOX2 and ALDH1A1, and exhibited higher self-renewal ability.	[4]
	Analyses using clinical samples show that increased expression of ALDH1 is related to poor response to NAC therapy	[7]
Hedgehog pathway (pathway)	Upregulation of the Hh pathway is observed in E-cadherin low cervical cancer cells, which is an in vitro EMT model. Inhibitors of the Hh pathway (cyclopamine and GANT58) inhibit invasiveness and apoptosis in E-cadherin low cervical cancer cells	[8]

cisplatin resistance [3]. As for CD44+/CD24-defined CSCs, cytosolic phospholipase A2a (cPLA2α) has been reported to control its fraction [6]. In addition, α-actin-4 (ACTN4), an actin-binding protein, is also involved in the fraction of CD44+/CD24− defined CSCs [5]. The sonic hedgehog pathway (sHh) is a famous pathway related to stemness and has been related to chemoresistance in cervical cancer. Inhibition of the sHh pathway, such as GANT58, may be potential strategies [8]. STAT3 pathway and Hippo pathway, which are well known to be related to CSC phenotype, are also reported to be related to CSCs in cervical cancer [21, 22]. However, identifying a novel important factor and developing a new treatment strategy are extremely difficult and time-consuming. Drugs that can be realistically considered as new treatment options are inhibitors of the PI3K/Akt and EGFR2 pathways.

The PI3K/Akt/mTOR signaling pathways are involved in HPV-related carcinogenesis in cervical cancer [23, 24]. From the viewpoint of cisplatin sensitivity, genetic variations in the PI3K/Akt pathway relate to chemotherapeutic sensitivity in squamous cell carcinoma, which is the most common subtype of cervical cancer [25]. Unfortunately, monotherapy with everolimus, a typical PI3K inhibitor, has not

improved prognosis thus far. However, when used in combination, it may enhance the sensitivity of cisplatin and further enhance the therapeutic effect. As for the EGFR pathway, there are several clinically available inhibitors. Erlotinib, an EGFR tyrosine kinase inhibitor (TKI), has been reported to overcome chemoresistance of MUC-1-positive cervical cancer [26]. Moreover, if HER2 amplification exists, TKI or antibody-HER2 may show some therapeutic effects. HER2 amplification can be found in approximately 5% of cervical cancers based on c-BioPortal analysis. Although HER2 amplification exists in only a few populations of cervical cancer, anti-HER2 therapies should be considered when present.

7.2 Chemoresistance and Signaling in Endometrial Cancer

Endometrial cancer is the most common gynecological malignancy in Japan. The number of patients has been increasing in recent years due to the influence of the spreading westernized diet. Endometrial cancer is generally classified into Type-I and Type-II based on pathological, molecular, and clinical backgrounds [27]. Type-I endometrial cancer is typically caused by long-term exposure to unopposed estrogen, sequentially developing via a precancerous condition known as atypical endometrial hyperplasia. Therefore, the carcinogenic process is strongly influenced by sex hormones, including estrogen and progesterone. Endometrioid adenocarcinoma Grade 1/2 is a typical pathological subtype. Type II, on the other hand, is not affected by unopposed estrogen and is said to develop de novo without a precancerous condition. Endometrioid adenocarcinoma Grade 3 and serous adenocarcinoma are typical pathological subtypes. It is also characteristic to possess a p53 mutation.

Type I accounts for approximately 80% of total endometrial cancers, and complete resection results in a good prognosis [27]. However, since chemosensitivity is relatively low, treatment is often difficult when surgery is no longer an option due to advanced stage or in case of recurrence. The estrogen receptor ERα controls the transcription of multiple genes and regulates the carcinogenesis and chemosensitivity of Type-I endometrial cancer. For example, the transcriptional coactivator NCOA6 plays an important role in ERα-activated growth-regulating estrogen receptor binding 1 (GREB1) activity [28]. This axis is involved in ERα-related carcinogenesis, and GREB1 status has been related to the chemoresistance of endometrial cancer. In addition, progesterone (P4) receptor membrane component 1 (PGRMC1) has been reported to be involved in cell growth and chemosensitivity [29]. Growth hormones can differentially modulate resistance to multiple chemotherapy, including doxorubicin, cisplatin, and paclitaxel in Type-I endometrial cancer cell lines [30].

The PIK3CA/mTOR pathway has also been associated with endometrial cancer because cross-regulation between ERα signaling and PI3K/Akt/mTOR pathways has been reported [31]. From this aspect, combination therapy using a PI3K inhibitor and hormonal therapy was conducted [32, 33]. Unfortunately, overall conclusions were negative, but there seem to be subpopulations where combination therapy might be effective in sub-analysis. Among recurrent cases of endometrioid

adenocarcinoma grade 1/2, the combination of everolimus and letrozole is effective for cases with CTNNB1 mutations. Although detailed mechanisms about the relationship between the CTNNB1 and PIK3CA pathways remain to be elucidated, PIK3CA inhibitors can be effective in some cases of endometrial cancer.

Type II accounts for approximately 20% of endometrial cancers [27]. They are known to have relatively high invasion/metastasis capacity, and their malignant potential is high compared to that of Type I. As the chemosensitivity is not high, the prognosis is even worse [34].

We have investigated detailed mechanisms of the malignant potential of uterus serous adenocarcinoma (USC), one of the major subtypes of Type-II endometrial cancer. Firstly, we found that the STAT1 pathway is highly involved in the malignant properties of USC, including platinum resistance [35]. Furthermore, among several phosphorylation sites in STAT1, we found that serine 727 is the most responsible phosphorylation site for platinum resistance [36]. Inhibition of its phosphorylation can resolve platinum resistance of USC. We are now trying to find a small molecule that can prevent phosphorylation of serine 727 in STAT1.

Other than the STAT1 pathway, the HER2-related pathway is interesting because we already have clinically available drugs, such as trastuzumab, anti-HER2 antibody, and lapatinib, an EGFR-TKI. Even though the frequency is low, HER2-positive populations can be found among tumors across many organs. From TCGA data analysis, HER2 amplification can be found in approximately 10% of type-II endometrial cancers. However, thus far, clinical trials using Lapatinib and Trastuzumab in HER2-positive endometrial cancer have not been very successful [37]. This may be because oncogenic pathways other than HER2 can coexist. For example, some reports have shown that the resistance to HER2-targeted therapy is caused by the coexistence of PIK3CA mutations, and the combination of PIK3CA inhibitors can confer this resistance [38, 39]. Although there are no clinical trials or case reports that use a combination of anti-HER2 therapy and other small molecule therapy at present, we expect future progress in this area.

7.3 Chemotherapy Is Particularly Important for Ovarian Cancer

Although there are fewer ovarian cancer patients than cervical and endometrial cancer patients, its prognosis is very poor. To improve its prognosis, we are seeking new treatment strategies. There are various histological types of ovarian cancer. Here, we discuss high-grade serous ovarian cancer (HGSOC) and ovarian clear cell carcinoma (OCCC).

HGSOC is the most common subtype of epithelial ovarian cancer in the world and in Japan [40, 41]. It is often found in advanced status, with multiple disseminations in the abdominal cavity at initial presentation [42]. For this reason, surgical treatment alone is often inadequate, and chemotherapy accounts for a very high proportion of treatments. Chemotherapy outcomes have improved since the advent

of platinum reagents, with most cases responding relatively well to initial chemotherapy with a combination of paclitaxel and carboplatin [43]. However, the tumor cannot be completely killed, and recurrence of the tumor occurs in many cases [44]. To make matters worse, as the recurrence is repeated, the resistance to chemotherapy increases. Tumors that have developed resistance to platinum are more likely to show resistance to other drugs simultaneously [43]. This acquisition mechanism is the main reason for the poor prognosis of HGSOC. Elucidation of the detailed acquisition mechanism is required because it can restore chemosensitivity and improve prognosis.

OCCC is the second most common ovarian cancer after HGSOC, especially in Asian countries [41]. OCCC is known to arise from endometriotic cells in endometriosis. From the viewpoint of chemotherapy, OCCC is characterized by its high resistance to chemotherapy, including platinum [45]. Therefore, especially in advanced stages, when chemotherapy is the main treatment, the prognosis is extremely poor [46, 47]. Recurrent tumors are more resistant to chemotherapy and are difficult to treat. OCCC clearly has limitations compared to HGSOC in current chemotherapy; thus, the elucidation of its resistance mechanism is a major goal.

7.4 Homologous Repair in HGSOC

When DNA damage occurs, there are several DNA repair mechanisms, one of which is homologous recombination repair (HR). BRCA1/2 is known to play an important role in HR and is known as a tumor suppressor. Thus, when there is a certain mutation or LOH in BRCA1/2, the risk of developing various malignant tumors is clearly high. HGSOC is one of those BRCA1/2-associated cancers [48]. Recently, it has been shown that BRCA-related cancers, including HGSOC, are selectively sensitive to the poly(ADP-ribose) polymerase (PARP) inhibitor PARPi [49–51].

PARP1, the major target of PARPi, is mainly involved in the repair of single-strand DNA breaks (SSBs). In the absence of BRCA1/2, SSBs caused by PARPi can be lethal. Recently, it has also been considered that PARPi may be sensitive to HR-defective cancers, even if BRCA1/2 is normal [52–55]. Clinical trials using the HR pathway as a marker for PARPi have begun. Unlike conventional anticancer agents, PARPi can be used as a maintenance therapy [49, 50]; thus, its clinical impact is very large.

However, from the perspective of chemoresistance, the role played by PARPi is limited. This is because the sensitivity to PARPi is usually positively correlated with that to platinum. That is, if the tumors become resistant to platinum, they are also resistant to PARPi [51]. Therefore, PARPi is considered refractory to tumors that have recurred repeatedly and become resistant to platinum [51, 56]. Conversely, PARPi could potentially be used if the mechanism for reversing resistance to platinum is elucidated. Therefore, it will be very useful to elucidate the key mechanisms of platinum resistance in HGSOC.

7.5 Role of Epithelial–Mesenchymal Transition in Malignant Potentials in HGSOC

A major feature of HGSOC is high copy number alterations [42]. As a result, morphological and genetic findings can differ greatly among samples. In 2011, the TCGA project announced for the first time that HGSOCs can be divided into four major subtypes: Immunoreactive (IR), proliferative (PG), differentiated (DG), and mesenchymal (MT) [57]. Clinically, the prognosis of the MT type was found to be particularly poor in comparison with the other three [58]. The MT type is a subtype characterized by activation of the epithelial–mesenchymal transition (EMT) pathway. The relationship between EMT and malignant potentials of cancer has been debated for a long time, and they are known to be closely related. Chemoresistance ability is also greatly related to EMT [59]. The chemotherapy regimen used in the first line of HGSOC is a combination therapy of paclitaxel (T) and carboplatin (C), well known as TC therapy. Among these, carboplatin, a type of platinum, is greatly involved in EMT. That is, tumors with elevated EMT are resistant to carboplatin [10, 60, 61]. Therefore, the elimination of EMT can restore the sensitivity to platinum. Thus, elucidating the factors controlling EMT in HGSOC is important.

In the era of single-cell sequencing, there are additional several reports that show an important role of EMT in HGSOC. Zhiyuan H et al. show that there is some heterogenicity in non-cancer fallopian tube epithelial cells [62]. Using the subtype molecular markers of non-cancer cells, they define a gene signature that robustly identifies a poor prognosis EMT–high subtype of HGSOC. They propose that they could make an accurate prediction of cancer behavior based on that signature. Tongtong Kan et al. investigated the relationship of disseminated cancer cells and their surrounding cells deeply using single-cell sequencing analysis [63]. They applied single-cell EMT-related transcriptional analysis and found that surrounding cells were heterogenous cellular units comprised of epithelial tumor cells, leukocytes, and cancer-associated fibroblasts. They also showed that cancer-associated fibroblasts induce EMT of tumor cells, resulting in the acquisition of malignant phenotype.

However, many pathways can cause EMT in HGSOC. We previously reported that TGF-β causes EMT via phosphorylation of Smad3C [64]. BMP2, a member of the TGF-β super-family, is also involved in the poor prognosis of ovarian cancer via phosphorylation of SMAD5 [65]. Recently, it was also reported that BMP2 is closely related to the proportion of CSC fractions characterized by ALDH-CD133+ and is associated with a poor prognosis [9]. STAT3 is also well known as an oncogenic transcription factor. It has been reported that, in HGSOC, the STAT3 pathway enhances EMT and is involved in various malignant factors, including acceleration of the cell cycle and chemoresistance, resulting in poor prognosis [60]. STAT3 is activated by stimulation with IL-6, which is a member of the interleukin family. Because IL-6 is also reported to be involved in platinum resistance in HGSOC by inducing CCL2 secretion in addition to the activation of STAT3 [66], anti-IL-6 antibody therapy might be effective. Recently, phase I clinical trials using IL-6 receptor

antibody have been conducted [67], and future progress is expected. Other than those pathways listed above, there are still other mechanisms reported to be involved in the malignant phenotypes of HGSOC, including the NF-κB pathway [10, 68]. Moreover, cancer stem cells (CSCs) are also known to be closely related to EMT [61]. There are also many pathways that are reported to be related to CSC in HGSOC including NFATC4 [69], ERK–RSK axis [70], and NAMPT [19]. We summarize several pathways recently reported to be related to EMT or CSC in HGSOC in Table 7.2.

Table 7.2 EMT- or CSC-related pathways reported in HGSOC

Pathway/ factor	Main findings	References
BMP2 pathway	BMP2 promotes ALDH+/CD133+ cell expansion while suppressing the proliferation of ALDH−/CD133− cells. BMP2 acts as a feedback mechanism promoting ovarian CSC expansion and suppressing progenitor proliferation	[9]
NF-κB pathway	Epithelial status exhibited higher resistance to cisplatin treatment. Pathway analysis revealed that activation of NF-κB downstream genes occurred by cisplatin	[10]
	HOTAIR, HOX transcript antisense RNA, expression results in sustained activation of DNA damage response after platinum treatment. Expression of HOTAIR induces NF-κB activation and includes acquisition of resistance to platinum	[11]
	Advanced ovarian cancers NF-κB signaling via RelB transcription factor supports tumor-initiating cell populations by directly regulating the cancer stem like associated enzyme ALDH	[12]
STAT3 pathway	High level of PBX1, a stem cell reprogramming factor, correlated with shorter survival in post-chemotherapy ovarian cancer patients. An analysis of genome-wide chromatin immunoprecipitation data indicated that PBX1 binds directly to the promoter of STAT3, positively regulating its transcription	[13]
	Deletion of STAT3 blocked cell proliferation and migration in vitro and suppressed tumor growth in mice. Deletion of STAT3 transcriptionally suppressed key genes involved in EMT	[14]
TGF-β pathway	Analyses using the microarray dataset show that TGF-β signaling pathway was activated in omental metastasis as compared to primary sites. A-83-01, an inhibitor of TGF-β signaling, has therapeutic effects in the mouse model of peritoneal dissemination	[15]
SOX9	Epigenome profiling of multiple cellular models of chemoresistance identified unique sets of distal enhancers, super-enhancers (Ses), and some EMT-related genes are involved in them	[16]
NFATC4	Nuclear factor of activated T cells cytoplasmic 4 (NFATC4) related to poor prognosis, associated with CSC in ovarian cancer	[17]
ERK1/2-RSK1/2 axis	Cisplatin and carboplatin induce ERK1/2-RSK1/2-EphA2-GPRC5A signaling. Inhibition of RSK1/2 prevented oncogenic EphA2-S897 phosphorylation and FphA2-GPRC5A co-regulation sensitized cisplatin-resistant ovarian cancer cells	[18]
NAMT	NAMPT inhibition suppresses senescence-associated cancer stem cells induced by platinum-based chemotherapy in ovarian cancer. A combination of the NAMPT inhibitor and cisplatin improved the survival in mice xenograft model	[19]

As shown, many factors are associated with chemoresistance in relation to EMT or CSC in HGSOC. This implies that the factors involved in EMT or CSC may differ from patient to patient. This is a clinically important issue. It may be possible to deal with each individual if markers can distinguish them easily and if inhibitors for each pathway are clinically available. However, at present, we do not have such methods or drugs. If some factors that affect several EMT-related pathways are shared, we can regard them as therapeutic targets that can act across multiple EMT-related pathways.

Therefore, we used functional screening using the shRNA library to identify such factors [71]. We conducted a functional screening focusing on CSC phenotype, which has been reported to be associated with EMT. In ovarian cancer, there is no consensus marker that defines the CSC-like population; thus, the side population (SP), which has high dye excretion ability, was used as a marker of CSC-like cells.

As a result, the expression of MSL3, ZN691, VPS45, ITGB3BP, TLE2, ZNF498 was closely related to the SP fraction individually. Downregulation of these six factors individually increased the SP fraction and vice versa. In addition to the proportion of SP fraction, it was greatly involved in the acquisition of resistance to multiple anticancer agents, including platinum and paclitaxel, the colony formation ability, and tumorgenicity in vivo. We then investigated the relationship between our six factors and the TGF-β, Wnt/β-catenin, Notch, and Hedgehog pathways, which have been reported to be closely related to EMT and stemness. We found that common alterations in the Hedgehog pathway occurred among all six factors. The specific mechanism by which these six factors are involved in the Hedgehog pathway remains unclear, but the Hedgehog pathway may be involved in a relatively large proportion of treatment resistance cases in HGSOC. In addition, among these six factors, TLE2 is a molecule of particular interest. Thus far, little is known about the functions of TLE2, other than as a corepressor of the Wnt/β-catenin pathway [72, 73]. In our study, when the expression of TLE2 was suppressed, the expression of more than 3000 genes was greatly altered, resulting in very large changes in cell function as well as morphology. Interestingly, deletions of TLE2 were found in more than 80% of HGSOC samples from TCGA data analysis. We believe that TLE2 clearly affects various pathways other than the Wnt/β-catenin and Hedgehog pathways and plays a very important role in HGSOC. In other cancer subtypes, N-myc downregulated gene 1 (NDRG1) has been reported to decrease TLE2 expression and is involved in the malignant phenotype [74]. It may be possible to establish strategies to increase TLE2 expression. Such treatments may possibly be novel therapeutic strategies for resolving chemoresistance in HGSOC.

7.6 Complementarity of Platinum Resistance and Paclitaxel Resistance

The above-described attempts to identify factors controlling EMT and search for therapeutic targets are inevitably time-consuming and cannot be clinically applied at present. Therefore, we searched for clinically available chemotherapies that were

particularly sensitive to MT type [75]. We analyzed multiple clinical data sets, including the reactivity to drugs, such as paclitaxel and carboplatin, and the comprehensive gene expression data of clinical samples, and we calculated the scores that can predict the drug sensitivity of each. As a result, the sensitivities of platinum and of paclitaxel had a complementary relationship; that is, the MT type had relatively low sensitivity to platinum, while the sensitivity to paclitaxel was maintained. As a clinical study, when comparing the effect of dose-dense TC (ddTC) therapy with increased paclitaxel dose and the effect of normal TC therapy in the MT type, ddTC contributed to the improvement of progression-free intervals [58]. In the present situation, where there is no specific therapeutic strategy for controlling EMT in HGSOC, the choice of ddTC for the MT subtype is a realistic method to improve its poor prognosis.

7.7 Various Mechanisms Relating to Acquisition of Chemoresistance in HGSOC

Various mechanisms other than EMT have been also reported to be involved in the acquisition of chemoresistance in HGSOC. For example, there are reports about focal adhesion kinase (FAK) and the acquisition of chemoresistance. Y397 phosphorylation of FAK has been observed in the process of chemoresistance acquisition, and this phosphorylation is related to β-catenin [76]. FAK inhibition sensitizes chemoresistant HGSOC cell lines to chemotherapy, and FAK inhibitors can be useful to sensitize chemoresistant HGSCO tumors.

In addition, several studies have evaluated the mechanism of tumor microenvironments and platinum resistance. It is known that tumors are exposed to a relatively hypoxic microenvironment, which favors the secretion of exosomes and chemokines. Under hypoxic conditions, it was found that cisplatin efflux via exosomes was significantly increased in HGSOCs [77]. Coculture of hypoxic ovarian cancer cell-derived exosomes (HEx) with tumor cells increased cell survival in response to cisplatin treatment. Hypoxic conditions also link invasion and immunosuppressive phenotypes, resulting in resistance to treatment. That is, improving hypoxia may be the key to resolving platinum resistance.

Intracellular metabolism is also involved in platinum sensitivity. Cellular metabolism is regulated by various enzymes and transporters, and metabolic reprogramming has been defined as a key hallmark of cancer cells. It was recently that subgroups of carbon resources show a preference for either aerobic glycolysis or oxidative phosphorylation (OXPHOS) [78]. HGSOC cells can also be divided into two groups: low-OXPHOS and high-OXPHOS. High-OXPHOS tumors are exposed to chronic oxidative stress and are sensitive to platinum. The PML-PGC-1α axis, which regulates OXPHOS metabolic processes in high-OXPHOS HGSOC, is greatly related to chemosensitivity via the production of oxidative stress.

Chromatin modification is also involved in platinum resistance. Bromodomain containing 4 (BRD4), a member of the bromodomain and extraterminal (BET) protein family, is involved in cancer cell proliferation and survival, including HGSOC. Inhibition of BRD4 is related to restored sensitivity to platinum via blocking HR [79]. Inhibition of BRD9, another member of the BET protein family, also inhibits HR via the RAD51–RAD54 axis and leads to sensitization of HGSOC to platinum [80].

There are also reports of fusion genes and acquisition of chemoresistance. In 2015, a study performed whole-genome sequencing of recurrent tumors and examined the process of drug resistance acquisition in detail [81]. According to the results, a fusion gene involving MDR1 occurred in recurrent tumors. This fusion gene was apparently associated with the acquisition of platinum resistance. MDR1 is an important transporter involved in drug excretion and is the cause of resistance to multiple chemotherapy, including platinum. The fusion gene relevant to MDR1 also plays some roles in the acquisition of chemoresistance in HGSOC.

Thus, various pathways are involved in platinum resistance in HGSOC, and the mechanism may differ from patient to patient. Rather than aiming to establish a novel treatment that can ubiquitously change platinum sensitivity in HGSOC, a personalized medicine-based approach may be an alternative way to search key drugs for chemoresistant tumors [82].

7.8 Chemoresistance in OCCC

Unlike HGSOC, OCCC is known to have low sensitivity to chemotherapy, including platinum and paclitaxel, from initial treatment [46, 47]. Accordingly, its prognosis is relatively poor compared to that of HGSOC [42, 45]. We are the first to find and report that there are several genes specifically related to OCCC, now referred to as the OCCC signature [83]. Among this signature, some famous oncogenic pathways, including the IL6-STAT3 axis, TAZ, and important members of the Hippo pathway, are included. In addition, there are several transcription factors that are strongly involved in cellular metabolism. Among them, we have focused on HNF1-β.

We previously revealed the role of HNF1-β in malignant characteristics of OCCC. Essentially, HNF1-β regulates the cellular metabolism of OCCC, and its downregulation changes metabolism from anaerobic glucose catabolism to aerobic glucose catabolism [84]. Aerobic glucose catabolism leads to activation of the TCA cycle and increases ROS production. At the same time, HNF1-β regulates the expression of rBAT, a cysteine transporter. Cystine is the source of glutathione that prevents ROS production. Suppression of HNF1-β decreased rBAT expression, resulting in increased ROS levels. Taken together, the production of ROS was significantly affected by alterations of HNF1-β expression.

Cisplatin can increase ROS production and results in cell death. In our research, suppression of HNF1-β increased sensitivity to platinum [84]. We believe that this

is caused by the acceleration of ROS levels via the downregulation of HNF1-β. Thus, HNF1-β seems to play an important role in platinum resistance in OCCC.

In OCCC, the loss of ARID1A, a member of the SWISS/Complex, a chromatin modifier, is also a common feature [85, 86]. The SWISS/Complex affects the activity of various pathways and also affects chemoresistance. For example, a reduction of ARID1A promotes the expression of SLC7A11, a cystine transporter, which increases glutathione production and contributes to platinum resistance by causing ROS resistance [87]. This can be another factor of chemoresistance in OCCC.

In OCCC, other than signaling pathways, cellular metabolism and cascades of ROS production are also key factors for chemoresistance [88]. We may therefore need to focus on factors other than signaling pathways to resolve chemoresistance in OCCC.

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