New perspectives on molecular targeted therapy in ovarian clear cell carcinoma

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Ovarian clear cell carcinomas (OCCCs) account for about 5–13% of all epithelial ovarian carcinomas in Western populations. It is characterised by resistance to conventional platinum-based chemotherapy, and new therapeutic strategies are urgently required. This article will focus on how recent discoveries have enhanced our understanding of the molecular pathogenesis of OCCCs, leading to new therapeutic opportunities. These include mutations in *ARID1A*, which provides a link to endometriosis, upregulation of the phosphatidylinositol 3-kinase/AKT pathway, particularly through mutations of *PIK3CA* and inactivation of PTEN, and increased activity of pathways involved in angiogenesis. Targeting HER2, apoptotic escape mechanisms and mismatch repair defects offer additional opportunities for treating this enigmatic tumour subtype.

There is now compelling evidence to suggest that epithelial ovarian cancers (EOCs) represent a heterogeneous group of tumours with distinct subtypes having different tissues of origin, molecular characteristics and outcome (Kurman and Shih, 2010). In Western populations, ovarian clear cell carcinomas (OCCCs) account for about 5–13% of all EOCs (Chan *et al*, 2008; McCluggage, 2008), whereas in Japan, its prevalence rises to 15–25% (Sugiyama *et al*, 2000; Itamochi *et al*, 2008) of all EOCs. It is currently unclear why OCCCs are more common in women of oriental descent, but, regardless of ethnicity, OCCCs have been shown to be associated with a poorer prognosis and are relatively resistant to conventional platinum-based chemotherapy when compared with other EOC subtypes (Tan and Kaye, 2007).

In a large retrospective analysis of 1411 (795 Stage I, 47 Stage II, 295 Stage III, 166 Stage IV) cases of OCCCs (Chan *et al*, 2008), OCCCs were associated with a poorer prognosis across all stages compared with other EOC subtypes. Interestingly, there are also data from smaller studies suggesting that early-stage OCCCs may actually have an equivalent or better prognosis than early-stage serous EOC (Kennedy *et al*, 1989; Köbel *et al*, 2010). However, in the setting of advanced disease, studies have consistently demonstrated a significantly poorer prognosis in advanced OCCC when compared with serous EOC (Chan *et al*, 2008; Mackay *et al*, 2010). Furthermore, in patients with platinum-sensitive or -resistant (i.e., >6 months or <6 months of platinum-free interval, respectively) relapsed OCCCs,

reported response rates to second line chemotherapy are only between 0 and 8% (Pather and Quinn, 2005; Takano *et al*, 2008). Consequently, OCCCs present a considerable clinical challenge and there is a need to optimise currently available treatments and develop new therapeutic strategies in the management of this disease.

Increasingly, a greater understanding of the molecular pathogenesis and heterogeneity of cancer has led to the development of more effective treatment strategies in various tumour types. In this article, the recent advances in our understanding of the molecular characteristics and pathogenesis of OCCCs and how they may facilitate the development of targeted therapeutic strategies in this enigmatic EOC subtype are reviewed.

OVARIAN CLEAR CELL CARCINOMA IS A HETEROGENEOUS DISEASE

From a histopathological perspective, OCCCs have conventionally been considered a uniform entity and are usually classified as high-grade carcinomas (McCluggage, 2008). Early gene expression analyses (Schwartz *et al*, 2002; Zorn *et al*, 2005) of OCCCs also suggested that they appear to represent a distinct and possibly homogenous subtype of EOCs at the molecular level (Zorn *et al*, 2005).

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Evidence for the molecular genetic and phenotypic heterogeneity of OCCCs can be seen, however, in early conventional comparative genomic hybridisation studies of these tumours, where distinct DNA copy number abnormalities were observed in subsets of OCCCs (Suehiro et al, 2000) and specific copy number gains could be correlated with overall survival (Hirasawa et al, 2003). In a study by Tan et al (2011), 50 archival OCCCs were subjected to high-resolution microarray-based comparative genomic hybridisation analysis to determine whether distinct genomic subgroups of OCCCs existed. The study revealed that OCCCs are genetically heterogeneous (Tan et al, 2011) and can be further subdivided into distinct patterns of copy number aberration. Moreover, by performing unsupervised hierarchical clustering analysis based on the genomic copy aberrations, two distinct genomic subgroups of OCCCs (cluster-1 and cluster-2) that did not significantly differ in terms of their clinicopathological and histological features were identified. Subsequent survival analysis revealed that patients from cluster-1 had a significantly shorter median progression-free survival (PFS) than those from cluster-2 (11 vs 65 months, $P = 0.009$) and subsequent multivariate analysis revealed that genomic cluster was an independent prognostic factor for PFS.

These data suggest that OCCCs are genomically heterogeneous and that the pattern and complexity of genome-wide copy number aberrations are not only of taxonomic interest, but may also underpin the phenotypic differences in OCCCs with regard to clinical outcome. Indeed, it would appear that subgroups of OCCCs may harbour specific copy number changes that render them more chemoresistant than other OCCCs (Tan et al, 2011). This heterogeneity has now been extended to include patterns of gene mutations and aberrations in signalling pathways that have emerged on the molecular landscape of OCCCs in recent years (Anglesio et al, 2011a) and are now providing us with a framework (Table 1) for the development of targeted therapeutic approaches.

TARGETING THE EMERGING MOLECULAR LANDSCAPE OF OCCC

ARID1A **mutations in OCCCs: therapeutic implications.** Unlike serous EOC, which is thought to originate in the distal fallopian tube (Lee et al, 2007), the association of OCCCs with endometriosis up to 58% of cases (Jenison et al, 1989) and the identification of similar somatic mutations found in both OCCCs and adjacent atypical endometriosis (Wiegand et al, 2010) has led to the suggestion that OCCCs do not originate from the ovarian epithelium, but represent transformed neoplastic cells from displaced endometriotic tissue (Anglesio et al, 2011a). Recent studies have identified putative driver genes and aberrant pathways present in endometriotic lesions that may be essential for malignant transformation and the development of OCCC (Wiegand et al, 2010; Yamamoto et al, 2011). Endometriotic cysts have also been found to contain a high concentration of free iron that may promote carcinogenesis by iron-induced persistent oxidative stress (Yamaguchi et al, 2008) and induction of an 'OCCC genomic signature' has been reported in immortalised ovarian surface epithelial cells when exposed to the contents of endometriotic cysts (Yamaguchi et al, 2010). Hence, early differentiation into the clear cell lineage may take place in ovarian endometriosis, with subsequent carcinogenesis being influenced by the microenvironment of the endometriotic cysts, thus leading to its frequent association with OCCC.

Wiegand et al (2010) identified somatic mutations in *ARID1A* (the AT-rich interactive domain 1A (SWI-like) gene, which encodes BAF250a, a key component of the SWI-SNF chromatin remodelling complex) in 46% of OCCCs (55 out of 119) and found

mutation status was associated with loss of ARID1A (BAF250a) protein expression. *ARID1A* mutations and loss of protein expression were also evident in contiguous atypical endometriosis associated with two OCCCs harbouring mutations (Wiegand et al, 2010). Subsequent studies have confirmed *ARID1A* mutations in 57% of primary OCCCs using exome sequencing (Jones et al, 2010). Loss of ARID1A expression has been correlated with shorter PFS and overall survival in patients with OCCCs following platinum-based chemotherapy (Katagiri et al, 2011).

ARID1A is a component of the SWI/SNF chromatin-remodelling complex, which alters chromatin structure by ATP-dependent disruption of histone–DNA interaction (Reisman et al, 2009). The complex has a major role in the repair of DNA lesions directly by facilitating DNA accessibility on the chromatin or indirectly by facilitating the functions of DNA repair proteins, such as p53, BRCA1, GADD45 and Fanconi Anemia proteins (Reisman et al, 2009). By altering the accessibility of chromatin, it also regulates many cellular processes, including development, differentiation and proliferation (Nagl et al, 2005; Gao et al, 2008; Reisman et al, 2009). The SWI/SNF complex is increasingly being recognised as a *bona fida* tumour-suppressor complex with mutations in a number of subunits identified in a variety of malignancies (Gui et al, 2011; Wilson and Roberts, 2011; Mamo et al, 2012; Shain et al, 2012). The exact mechanisms by which mutations in this complex-drive tumourigenesis are unclear. However, ARID1A has recently been demonstrated, albeit in a small number of models, to act as a negative regulator of the cell cycle through interaction with p53 (Guan et al, 2011). Ovarian clear cell carcinomas with mutations in the *ARID1A* subunit frequently lack genomic instability (Wiegand et al, 2010) and it has been suggested that perturbations in the regulation of chromatin remodelling may be able to substitute for genomic instability in OCCC tumourigenesis (Wilson and Roberts, 2011). The multifaceted role of the SWI/SNF complex provides a tantalising hint to the potential utility of targeted approaches in signalling pathways that are transcriptionally dysregulated by loss of SWI/SNF function (Wilson and Roberts, 2011). These include downregulation of cyclin-dependent kinase inhibitor p16[INK4A] expression (Wilson and Roberts, 2011), overexpression of the polycomb group protein EZH2, which has been implicated in the pathogenesis of ovarian and renal carcinomas (Wilson and Roberts, 2011), increased expression of the oncogenic proteins cyclin D1 and MYC (Wilson and Roberts, 2011), aberrant activation of the Hedgehog signalling pathway (Wilson and Roberts, 2011) and aberrant regulation of pro-motility proteins involved in invasion and metastasis such as increased activity of the Ras homolog gene family member A GTPase and RHO-associated protein kinase 1 which regulate the actin cytoskeleton and promote cell migration (Wilson and Roberts, 2011). It can therefore be envisaged that once the constitutional defects of the cellular functions caused by *ARID1A* mutation in OCCCs are accurately catalogued, they can be explored for the development of novel targeted therapies.

Targeting the phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway. The PI3K pathway is thought to have an important role in the pathogenesis of OCCC (Kuo et al, 2009). Mutations of *PIK3CA* (which encodes p110α, the catalytic subunit) have been identified in 33% of OCCC patients (Kuo et al, 2009) and are present in the endometriosis of patients with OCCC harbouring PIK3CA mutations (Yamamoto et al, 2011). A broad range of functions related to cancer progression are associated with PI3K activity, including proliferation, cell adhesion, apoptosis and transformation (Engelman, 2009). It has been shown that PI3K regulates G1 cell cycle progression and cyclin expression through activation of Akt/ mTOR/p70S6K1 signalling pathway in ovarian cancer cells (Engelman, 2009) and promotes cell survival through a variety of

Table 1. Molecular characteristics of ovarian clear cell carcinomas and their cellular effects Abbreviations: ARID1A = AT-rich interactive domain 1A; ATM = ataxia-telangiectasia mutated; MSI = microsatellite instability; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; PPP2R1A = protein phosphatase 2 regulatory subunit A.

Molecular characteristic	Frequency	Cellular effect
ARID1A mutation (Jones et al, 2010; Wiegand et al, 2010)	40–57%	• Loss of BAF250a, a key component of the SWI–SNF chromatin remodelling complex
IL6-STAT3-HIF upregulation (Anglesio et al, 2011b)	IL-6 expression in 49%	• Angiogenesis
HNF-1β upregulation (Kato et al, 2006; Yamaguchi et al, 2010)	Almost 100%	• Apoptotic escape
TMS/1/ASC methylation (Terasawa et al, 2004)	69%	• Apoptotic escape
PI3K/AKT/mTOR pathway activation by PTEN loss (Hashiguchi et al, 2006)/PIK3CA mutation (Kuo et al, 2009)/AKT2 amplification (Tan et al, 2011)	PTEN loss in 40% PIK3CA mutation in 33% AKT2 amplification 14%	• Activation of cell cycle progression • Inhibition of apoptosis • Increased cell motility • Impaired homologous recombination
HER2 amplification and overexpression (Tan et al, 2011)	14%	• Activation of PI3K, MAPK, STAT signalling pathways • Promotes cellular proliferation • Inhibition of apoptosis
PPM1D amplification (Tan et al, 2009)	10%	• Negative regulation of p53, Chk2 and ATM
Loss of mismatch repair genes (hMLH1 and hMSH2; Cai et al, 2004; Pal et al, 2008; Ketabi et al, 2011)	7–18%	• MSI
PPP2R1A mutations (Jones et al, 2010)	7%	Impaired PP2A function leading to uncontrolled cell growth
KRAS mutations (Jones et al, 2010)	4.7%	Activation of RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways

mechanisms, including phosphorylation and inactivation of proapoptotic proteins Bad and caspase-9 (Khwaja, 1999; Neve et al, 2006).

Loss of PTEN expression, which is a key negative regulator of the PI3K pathway has been noted in 40% of early-stage OCCC, suggesting that PTEN inactivation may be an early event in OCCC development (Hashiguchi et al, 2006). In another study, Mabuchi et al (2009) performed immunohistochemical (IHC) analysis of phospho-mTOR expression in a tissue microarray of 98 primary ovarian cancers and showed that mTOR was more frequently activated in OCCC than in serous carcinomas (86.6% vs 50%). AKT2 amplification has also recently been described in a subgroup of OCCCs that are associated with a shorter PFS (Tan et al, 2011).

Given that the PI3K/AKT/mTOR signalling pathway is more frequently activated in OCCCs (Mabuchi et al, 2009), it would appear a potential therapeutic pathway that can be utilised for a targeted approach to treatment. Mabuchi et al (2009) recently showed that cell growth was markedly inhibited in both cisplatin-sensitive parental and cisplatin-resistant human OCCC cell lines following treatment with the mTOR inhibitor everolimus, and a variety of additional candidate compounds targeting this pathway, for example, the AKT inhibitor MK2206 (Yap et al, 2011), are now available. The majority of the agents targeting the PI3K pathway are in early-phase clinical trials and, to date, there is no evidence that support their use in the management of OCCCs, furthermore, there is a move towards combination strategies to improve efficacy. A single-arm phase II study is currently underway examining the combination of the mTOR inhibitor temsirolimus with carboplatin and paclitaxel for the first-line treatment of patients with advanced OCCC (http://clinicaltrials.gov/ct2/show/NCT01196429).

Recent evidence also suggests that PTEN is involved in the maintenance of genomic stability and that loss of PTEN function results in defective homologous recombination-mediated repair of DNA double-strand breaks, thus sensitising cells to inhibition of the poly (adenosine diphosphate ribose) polymerase (Dedes et al, 2010). Hence, PTEN-deficient OCCCs may also be sensitive to poly(adenosine diphosphate ribose) polymerase inhibitors like olaparib (Dedes et al, 2010).

Targeting angiogenesis in OCCCs. Vascular endothelial growth factor (VEGF) has several known activities pertinent to tumour growth and progression (Campos and Ghosh, 2010). In ovarian cancer, increased levels of VEGF have been associated with a poorer prognosis and platinum resistance in EOCs (Siddiqui et al, 2011). Recent randomised phase III trials involving the combination of chemotherapy with the anti-VEGF agent bevacizumab in both the adjuvant and relapsed settings of EOC demonstrated improved response rates and prolonged PFS with the addition of bevacizumab, although response rates in specific histological subgroups were not examined (Heitz et al, 2012).

Mabuchi et al (2010) demonstrated that VEGF was strongly expressed both in early- and advanced-stage OCCCs, and that early-stage OCCCs with high levels of VEGF had significantly shorter survival than those with lower levels of VEGF expression. Furthermore, expression of VEGF in vitro was found to be significantly higher in cisplatin-refractory human OCCC cells when compared with the cisplatin-sensitive parental cells (Mabuchi et al, 2010). Recently, Anglesio et al (2011b) demonstrated specific overexpression of the pro-angiogenic IL6-STAT3-HIF (interleukin-6 signal transducer and activator of transcription-3 hypoxia-induced factor) pathway in OCCC tumours compared with

high-grade serous cancers and reported sustained clinical and functional imaging responses in two patients with chemotherapy-resistant OCCCs who were treated with sunitinib, a multi-targeted receptor tyrosine kinase inhibitor, which inhibits both platelet-derived growth factor receptor and the VEGF receptor. A National Cancer Institute of Canada funded phase II study (NCT01396408) investigating the efficacy of sunitinib in patients with advanced rare tumours, including recurrent OCCC, is currently ongoing (http://clinicaltrials.gov/ct2/show/NCT01396408). Similarly, increased activity of pathways involved in angiogenesis and hypoxic cell growth has been observed after whole-gene expression profiling of microdissected OCCCs, as well as marked inhibition of OCCC cell growth *in vitro* and *in vivo* following inhibition of HIF1-α and treatment with sunitinib (Stany *et al*, 2011). It remains to be seen, however, if the efficacy of anti-angiogenic therapy applies to all EOC subtypes or is particularly enhanced when used in patients with OCCCs.

HER2 as a therapeutic target in OCCCs. Amplification and overexpression of HER2 have been described in 14% of OCCCs (Tan *et al*, 2011). In a study by Schwartz *et al* (2002), a molecular signature that distinguished OCCC from other histological types of EOC identified a total of 73 genes with greater than two-fold higher expression in OCCC, including *HER2* (Schwartz *et al*, 2002). In addition, Trastuzumab, a humanised recombinant monoclonal antibody, against HER2 significantly and dose-dependently reduces the growth of the HER2-overexpressing OCCC cell line RMG-1 *in vitro* and *in vivo* and prolonged the survival of RMG-1 xenografted mice (Fujimura *et al*, 2002). Hence, there are data to suggest that HER2 may be an additional therapeutic target in OCCCs. In a previous phase II study of trastuzumab monotherapy in recurrent EOC (with HER2 over-expression documented by IHC), an overall response rate of only 7% was observed (Bookman *et al*, 2003). However, patient selection (41 patients of which 7 were OCCCs) was only based on HER2 IHC expression levels without assessment of *HER2* copy number status (Bookman *et al*, 2003). Future studies designed to assess the predictive value of *HER2* amplification and overexpression and response to trastuzumab or other anti-HER2 agents in OCCCs are warranted.

Targeting apoptotic escape mechanisms in OCCC. Mutations in p53 are a common event in tumourigenesis, being particularly common in serous ovarian carcinomas (∼96%; Hetland *et al*, 2011), but are remarkably uncommon in OCCC (9–10%; Tan and Kaye, 2007). This implies that other antiapoptotic mechanisms are likely to be involved in the development of OCCC. HNF-1β, an IHC marker for OCCCs (Kobel *et al*, 2009), has been implicated in mediating apoptotic escape in tumour cells and is upregulated and overexpressed in OCCC cell lines (Yamaguchi *et al*, 2010). Kato *et al* (2006) examined 30 OCCCs and found nuclear expression of HNF-1β in all OCCC tumours, whereas it was rarely expressed in other EOC subtypes. In addition, distinct nuclear immunostaining for HNF-1β was detected in endometriotic epithelia associated with OCCCs (Kato *et al*, 2006). Furthermore, 40% of endometriotic cysts without neoplastic changes also expressed HNF-1β, mainly in areas exhibiting inflammatory atypia (Kato *et al*, 2006). This indicates a mechanism for apoptotic escape in early OCCC tumour development, which may also have implications for drug resistance. Aberrant methylation resulting in transcriptional silencing of TMS1/ASC, a member of the caspase recruitment domain family of proapoptotic mediators, has also been frequently observed in OCCC tumours (Terasawa *et al*, 2004).

PPM1D (protein phosphatase magnesium-dependent 1 delta) encodes for a protein phosphatase with established oncogenic functions (Lu *et al*, 2008) that has been shown to negatively regulate the TP53 (Takekawa *et al*, 2000), Chk2 (Fujimoto *et al*, 2006) and ataxia-telangiectasia-mutated (ATM) kinase (Shreeram

et al, 2006), tumour-suppressor proteins. Amplification and overexpression of the *PPM1D* are present in ∼10% of OCCCs (Tan *et al*, 2009) and have been associated with a poorer outcome (Hirasawa *et al*, 2003). Inhibition of PPM1D in *PPM1D*-amplified OCCC cells results in reduced cell survival, suggesting this is a potential therapeutic target for a subset of OCCCs (Tan *et al*, 2009). The anti-apoptotic function of PPM1D may be particularly pertinent in driving the biology of tumours with wild-type *TP53* and the relevance of this hypothesis to OCCC is given further credence by the low prevalence of *TP53* mutations in OCCCs (Tan *et al*, 2009).

Reduced expression of the apoptotic activator BAX has been noted in patients with chemoresistant EOC (Spentzos *et al*, 2005), whereas high levels of BAX have been correlated with sensitivity to paclitaxel and improved survival in patients with EOC (Courjal *et al*, 1997). Among the IHC characteristics of OCCC is the notable overexpression of the proapoptotic protein BAX in stage I and II OCCC tumours (Skirnisdottir *et al*, 2005). In addition, the antiapoptotic protein Bcl-2, which inhibits BAX-mediated apoptosis, has been observed to be more highly expressed in metastatic deposits than primary OCCCs (Yoshida *et al*, 2001). A p53-mediated pathway has been implicated in the induction of cell death following DNA damage by platinum-based chemotherapeutic agents, which results in a decrease in the relative ratio of Bcl-2/BAX, thus favouring apoptosis (Sheikh-Hamad *et al*, 2004). Hence, the presence of a lower relative ratio of Bcl-2/BAX in early-stage OCCC tumours, and a higher relative ratio of Bcl-2/BAX in metastatic OCCC lesions, may account for the reported dichotomy in outcome observed in good prognosis early-stage OCCC tumours *vs* the relatively more platinum-resistant and poorer prognosis late-stage OCCC tumours. In this context, the potent, orally bioavailable Bcl-2 family inhibitor ABT-263 (Navitoclax) may be of potential interest in patients with high levels of Bcl-2 expression (Gandhi *et al*, 2011). Notably, *in vitro* data suggest that ovarian cell lines that express Bcl-2 family proteins exhibit strong synergy in terms of growth inhibition when navitoclax is combined with paclitaxel (Wong *et al*, 2012).

Targeting mismatch repair (MMR) defects in OCCCs. Microsatellite instability (MSI), caused by defects in the DNA MMR genes, has been observed at high levels (i.e., MSI-high) and low levels (i.e., MSI-low) in 14% and 7% of OCCCs, respectively, with a strong correlation between alterations in the expression of hMLH1 and hMSH2 and the presence of MSI in these tumours (Cai *et al*, 2004). Further evidence that a subset of OCCCs are associated with MMR defects was observed in a study of Swedish and Danish Lynch syndrome ovarian cancer patients of which 17% had OCCCs (Ketabi *et al*, 2011). A meta-analysis of various histological subtypes of MMR-deficient EOC has also reported that OCCCs represent about 18% of these tumours (Pal *et al*, 2008). The therapeutic relevance of MMR deficiency has recently been elucidated in a study demonstrating that methotrexate induces oxidative DNA damage and is selectively lethal to tumour cells with MMR defects via inhibition of dihydrofolate reductase (Martin *et al*, 2009).

Protein phosphatase 2 regulatory subunit A (PPP2R1A) and KRAS mutations. Presumed oncogenic mutations in *PPP2R1A*, which encodes a constant regulatory subunit of the serine/threonine protein phosphatase PP2A that is involved in the control of cell growth and division, have been reported in 7% of OCCCs (Jones *et al*, 2010). Although its role in the pathogenesis of OCCCs is unclear, impaired PP2A activity has also been observed in haematological malignancies and is a potentially druggable target (Perrotti and Neviani, 2008). Mutations of *KRAS* have also been reported in 4.7% of OCCCs (Jones *et al*, 2010), which suggests that therapeutic strategies using drugs that inhibit signal transduction downstream of RAS (Dienstmann *et al*, 2012), such

as MEK and PI3K/AKT/mTOR inhibitors, may be worth exploring in this subset of OCCCs as well.

EXPERIMENTAL MODELS OF OCCCS

In order to further understand OCCCs and develop novel therapeutics, appropriate preclinical models are required. Human cancer cell lines and xenograft models are traditionally used for the identification of molecular aberrations and drug sensitivities. Although relatively few OCCC cell lines exist compared with other EOC subtypes, they appear to reflect the mutational pattern seen in patients with 50% of cell lines harbouring *ARID1A* mutations (4 out of 8) and one-third with *PIK3CA* (3 out of 9) mutations, as well as lower frequencies of *KRAS* (1 out of 9) and *BRAF* (1 out of 9) mutations, and *PPM1D* amplification (1 out of 12; Tan *et al*, 2009; Guan *et al*, 2011; Rahman *et al*, 2012). Xenografts of human cancer cell lines into immunodeficient mice are used to examine the efficacy of therapeutic compounds and the tumourogenicity of cells, and OCCC xenografts have been successful using subcutaneous, intraperitoneal and orthotopic transplantation (Shaw *et al*, 2004). To our knowledge animal models in which *de novo* OCCC develop do not exist. However, patient-derived human xenografts are increasingly being used for oncology drug development (Tentler *et al*, 2012) and OCCC tumours have been successfully established to mimic patient tumour biology and heterogenetity (Dobbin *et al*, 2012). It is essential that as we gain an increased understanding of the molecular landscape of OCCCs, appropiate models are developed alongside to assist with the development of novel therapeutic approaches.

FUTURE PERSPECTIVES AND CONCLUSION

In recent years, it has also become increasingly clear that unlike high-grade serous ovarian cancer, which is characterised by *TP53* mutations (Ahmed *et al*, 2010) and frequent mutations or defects in BRCA1 or BRCA2 pathway (Gross *et al*, 2010; Kurman and Shih, 2010), OCCCs appear to harbour a different pattern of molecular events such as activating mutations in *PIK3CA* and loss of *PTEN* (Tan and Kaye, 2007) and *ARID1A* (Wiegand *et al*, 2010). The precursor lesion for OCCC remains unknown but current evidence suggests that a proportion of OCCCs may have developed from endometriotic precursor lesions (Wiegand *et al*, 2010). The distinct molecular features of OCCC and serous ovarian cancer serve to emphasise the need to develop subtype-specific therapeutic approaches in the management of EOC. Furthermore, despite displaying histologically uniform features, OCCCs do not constitute a single entity and may be classified into distinct molecular genetic subtypes that also appear to be associated with clinical outcome (Tan *et al*, 2011). Additionally, a question which remains unanswered is whether OCCCs observed in Asian and Western populations are molecularly distinct entities, which might require different therapeutic approaches.

It is envisaged that further elucidation of the underlying genetic mechanisms driving the development of OCCCs will provide a foundation for future studies exploring novel therapeutic approaches. Currently, there is insufficient evidence to recommend specific treatment for patients with OCCC, although we believe they are best treated in centres with OCCC-specific trials. Ultimately, it is our hope that these studies will eventually enable clinicians to offer an individualised treatment plan for patients with OCCC that will allow for differences in behaviour and therapeutic responses to be addressed early, rather than a 'one size fits all' treatment approach, thus fulfilling the promise of personalised medicine.

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