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Targeting the tumour microenvironment in platinum-resistant ovarian cancer

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Abstract

Ovarian cancer typically presents at an advanced stage, and although the majority of cases initially respond well to platinum-based therapies, chemoresistance almost always occurs leading to a poor long-term prognosis. While various cellular autonomous mechanisms contribute to intrinsic or acquired platinum resistance, the tumour microenvironment (TME) plays a central role in resistance to therapy and disease progression by providing cancer stem cell niches, promoting tumour cell metabolic reprogramming, reducing chemotherapy drug perfusion and promoting an immunosuppressive environment. As such, the TME is an attractive therapeutic target which has been the focus of intense research in recent years. This review provides an overview of the unique ovarian cancer TME and its role in disease progression and therapy resistance, highlighting some of the latest preclinical and clinical data on TME-targeted therapies. In particular, it focuses on strategies targeting cancer-associated fibroblasts, tumour-associated macrophages, cancer stem cells and cancer cell metabolic vulnerabilities.

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy, accounting for 4,100 deaths per year in the UK alone. While the introduction of platinum-based chemotherapy has led to a near doubling of survival rates over the last 40 years, the long-term outlook remains poor, with only 35% of patients surviving 10 years or more in the UK [1]. EOCs are a heterogeneous group in terms of origin, histology, molecular characteristics and response to therapy [2, 3]; Table 1. The commonest type (~70% cases) is high grade serous carcinoma (HGSC). These tumours are almost always *TP53* mutated [4], are genomically unstable, evolve rapidly, have no associated precursor ovarian lesion, and are frequently diagnosed at a late stage. By contrast, the other molecular subtypes of EOC, which include low grade serous carcinomas (LGSCs), clear cell (CCOC), mucinous and endometrioid carcinomas, are found in association with ovarian precursor cystic lesions, and less commonly harbour *TP53* mutations. It is now increasingly accepted that most ovarian epithelial malignancies do not originate in the ovary [5]. Both endometrioid and CCOC subtypes are believed to arise from endometriotic cysts implanted in the ovary [6, 7], whereas HGSCs are thought to originate in the distal fallopian tube as serous tubal intraepithelial carcinoma (STIC) [8]. Finally, LGSCs have been postulated to develop from ovarian inclusion cysts of benign tubal epithelia or papillary tubal hyperplasia, whereas some mucinous tumours are hypothesised to arise at the tuboperitoneal junction [9].

The mainstay of EOC treatment is cytoreductive surgery and combination chemotherapy with a platinum-based agent plus a taxane. While most patients achieve a complete response to first-line chemotherapy, some tumours will relapse within 6 months as platinum-resistant recurrences. Unfortunately, the majority of patients who initially respond will also relapse within 3 years (defined as platinum-sensitive recurrences), at which point treatment is switched to palliative intent. Eventually, these patients cease responding to platinum therapy due to acquired resistance [10-13]. As such, platinum resistance (whether intrinsic or acquired) is a

significant obstacle to improving EOC survival rates. While much progress has been made in understanding the cellular mechanisms underlying platinum resistance, it clear that these are complex and multifactorial. An added layer of complexity is the influence of the TME on platinum resistance. However, the TME also offers novel therapeutic targets for the management of platinum resistant EOC. This is particularly relevant for the treatment of HGSC, since it is characterised by genomic instability rather than recurrent targetable mutations.

This review will provide an overview of the current concepts regarding the cellular mechanisms of platinum resistance, the role of EOC TME factors in the modulation of chemosensitivity and current pre-clinical and clinical research on microenvironment-targeted therapies in EOC.

	HGSC	**Endometrioid**	**CCOC**	**Mucinous**	**LGSC**
Percent of cases	~70%	~10%	~10%	<5%	<5%
Proposed origin	Fallopian tubal epithelium (STIC)	Endometriosis	Endometriosis	Uncertain (transitional epithelium at tuboperitoneal junction/ transformation of mature teratoma)	Uncertain (fallopian tube epithelium - benign tubal epithelium/ papillary tubal hyperplasia)
Association with precursor borderline ovarian tumour	No	Yes (rare) (endometrioid borderline ovarian tumour)	Yes (rare) (clear cell borderline ovarian tumour)	Yes (mucinous borderline ovarian tumours)	Yes (serous borderline ovarian tumour/ micropapillary variant)
Associated hereditary predisposition	*BRCA1/2* germline mutations	Lynch syndrome	Lynch syndrome	None identified	None identified
Somatic mutations/ genetic abnormalities	*TP53* mutations (>95%); *BRCA1/2* mutations; *NF1,* *RB1* and *PTEN* loss; *EMSY* and *CCNE1* amplification; genomic instability [4]	*PIK3CA, ARID1A, KRAS, TP53, CTNNB1, PTEN* and *PIK3R1* mutations; MSI (MMR deficiency) ~30% [14]	*ARID1A, PIK3CA, PPP2R1A, TP53, PIK3R1, KRAS* and *PTEN* mutations [14]; *ZNF217, PPM1D, AKT2* and *MET* amplification [15]; MSI: 0% [14] ~10% [16]	*KRAS, TP53* and *PIK3CA* mutations; *MYC* and *ERBB2* amplification; *CDKN2A/B* loss [17]	*KRAS, BRAF* and *NRAS* mutations [18]
Typical stage at presentation	Late	Early	Early	Early	Late
Response to chemotherapy	Good	Good	Poor	Poor	Poor
% Survival (FIGO I)	84 (80-87)	87 (84-90)	82 (76-86)	83 (79-86)	93 (87-97)
% Survival (FIGO II)	68 (65-69)	84 (79-88)	69 (63-74)	66 (64-75)	83 (72-89)
% Survival	32 (31-33)	45 (37-52)	22 (18-27)	14 (11-17)	54 (47-60)

(FIGO III-IV)					

Table 1: Characteristics of epithelial ovarian cancer histotypes
EOC subtypes differ in their origin, aetiology, molecular characteristics and outlook [19, 20]. Associated gene mutations (in approximate order of frequency) are indicated for the different subtypes, together with other genetic abnormalities (gains, losses, genomic instability). FIGO stage-specific five-year overall survival rates for the different histotypes are also indicated; % survival (95% confidence interval) [21]. Abbreviations: HGSC: high grade serous ovarian carcinoma, CCOC: clear cell ovarian carcinoma, LGSC: low grade serous ovarian carcinoma, STIC: serous tubal intraepithelial carcinoma, MSI: microsatellite instability, MMR: mismatch repair, FIGO: International Federation of Gynaecology and Obstetrics.

2. Platinum-based chemotherapy and mechanisms of disease resistance

2.1. General mechanisms of cellular resistance to platinum therapy

The primary target of platinum-based drugs (cisplatin, carboplatin, oxaliplatin) is genomic DNA, where associated lesions include mono-adducts and both intra- and inter-strand crosslinks (ICLs). When unrepaired, these lesions exert their cytotoxicity by blocking RNA synthesis and DNA replication, eliciting the apoptotic cascade. However, platinum drugs also contribute to cytotoxicity through cytoplasmic actions, such as their ability to bind cysteine and methionine residues, to promote oxidative stress via sequestration of reduced glutathione (GSH) and generation of reactive oxygen species (ROS), and to cause mitochondrial DNA damage [22, 23]. Known cellular resistance mechanisms fall into three main categories (reviewed in [22]):

(i) those governing intracellular platinum levels/activity, such as reduced influx via the copper transporter CTR1 [24], increased efflux via ATP-binding cassette (ABC) transporters and copper exporters, as well as increased sequestration via metallothionines and detoxification via glutathione-S-transferases, which conjugate electrophiles such as cisplatin to GSH for export;

(ii) those involving DNA repair pathways including homologous recombination repair (HRR), non-homologous end-joining (NHEJ), nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and translesional DNA synthesis [25, 26];

(iii) those controlling DNA damage-induced cell death, including members of the Bcl-2 and BAX families, cIAP proteins [27], survivin (BIRC5) [28] and the mitochondrial permeability transition pore regulator, VDAC1, which is itself a cisplatin target [23].

2.2. Molecular heterogeneity of ovarian cancer and response to platinum therapy

Reflecting their aetiological and molecular heterogeneity, EOC subtypes also differ in their response to platinum-based therapy. While the majority of HGSCs respond well to first-line chemotherapy, LGSCs, CCOCs and mucinous carcinomas are relatively chemoresistant [29, 30]. Inherent differences in DNA repair competencies may explain some of the variations in response to platinum therapy. Over 50% of HGSCs have identified defects in the HRR machinery, which is necessary for the repair of ICL-induced double strand breaks (DSBs). The majority of these defects are associated with *BRCA1* or *BRCA2* germline or somatic mutations/promoter methylation [4, 31]. Conversely, about 20% of HGSCs harbour *CCNE1* amplifications, which appear to be mutually exclusive to *BRCA1/2* mutations and are associated with primary resistance to platinum therapy [32]. As well as being sensitive to platinum drugs, HRR deficient EOCs are hypersensitive to poly (ADP-ribose) polymerase

(PARP) inhibitors, which induce DSBs by inhibiting single strand break repair (an example of synthetic lethality) [31, 33-35]. Following success in clinical trials, PARP inhibitors have been given EMA and FDA approval for the treatment of platinum sensitive EOC recurrences [34]. In particular, a history of platinum-sensitive relapse remains the best predictor of PARP inhibitor efficacy in the maintenance setting [20]. Thus, the mechanisms leading to intrinsic/acquired platinum therapy resistance remains a significant clinical question.

By studying the genomic consequences (structural and single nucleotide variants) of defective DNA repair in ovarian cancers, Wang and co-workers [14] were able to stratify HGSCs, CCOCs and endometrioid cancer subtypes. This study confirmed the association of defective HRR with HGSCs and identified a potential role for microhomology end-joining (MHEJ, a form of NHEJ) for platinum resistance in HSGCs. However, differences in DNA repair defects likely only partially explain different intrinsic sensitivities to platinum amongst EOC subtypes. For example, endometrioid ovarian cancers are generally HRR proficient and yet respond well to platinum-based therapy [36]. Similarly, while mismatch repair (MMR) deficiency is associated with platinum resistance *in vitro*, it is inconsistently associated with clinical resistance and may require larger, histotype-specific studies [37]. Likewise, the role of NER in platinum resistant EOC is unclear and evidence for the most widely studied NER protein, ERCC1, is conflicting [25]. Owing to its comparative rarity, molecular drivers of chemoresistance in CCOC remain to be elucidated. While loss of ARID1A expression has been associated with adverse outcome/chemoresistance in this subtype, overall findings are contradictory [38, 39]. A recent study on a cohort of immunohistochemically validated CCOCs failed to identify recurrent mutations/genetic aberrations associated with treatment response, although lack of HNF-1β expression was associated with good outcome [39]. Mucinous and LGSCs are rarer still, and while mechanisms driving platinum resistance in mucinous EOCs are poorly understood, the relatively indolent nature of LGSCs is thought to be a factor in their inherent resistance to chemotherapy [30].

2.3 Genetic mechanisms of acquired resistance to platinum chemotherapy in ovarian cancer

Since surgery is infrequently carried out on recurrent disease, there have been comparatively few sequencing studies focussing on the mechanisms of acquired platinum resistance in the clinical setting. However, frequent reversion of *BRCA1/BRCA2* germline mutations have been identified in both platinum and PARP inhibitor resistant recurrent HGSCs [32, 40, 41]. Genomic sequencing of therapy resistant recurrent HGSCs has also revealed promoter fusions leading to increased ABCB1 (multidrug resistant (MDR1)) expression and inactivation by gene breakage of *RAD51B, RB1*, *NF1*, and *PTEN* [32]. Moreover, knockout of either *NF1* or *PTEN* conferred platinum resistance in an *in vivo* genetically engineered model of HGSC [42].

However, while the selection of genetically acquired mutations is clearly important in the evolution of platinum-resistant disease, other adaptations leading to altered tumour-microenvironmental interactions are now thought to play a major role. For example, a pronounced platinum-induced desmoplastic stromal response, which is also associated with primary chemotherapy resistance in EOC [43], was observed in recurrent HGSCs that retained *BRCA1* mutated status [32]. Importantly, HGSCs are unusual by virtue of the fact that platinum sensitive relapses are common, implying that transient chemoresistance due to adaptations induced by stresses and microenvironmental changes may play a role in these recurrences [44]. Understanding the dynamic interplay between EOC tumour cells and their microenvironment, how this influences the response to platinum treatment and how this is itself modulated by chemotherapy is critical for the development of therapeutic strategies to improve patient

outcome (Figure 1). Furthermore, as EOC is frequently diagnosed at a late stage and has a unique mode of spread within the peritoneal cavity, it is necessary to understand EOC platinum resistance within this context. The following sections will describe the mechanisms of EOC progression, the unique EOC TME and the role of various cell types within the TME in disease progression and platinum resistance.

Note on the following sections: With regard to EOC cell line histotypes, it is worth noting that many of the most commonly used cell lines in ovarian cancer research are unlikely to be derived from HGSCs. For example, the SKOV3 cell line is the most widely used in *in vivo* xenograft studies but is likely endometrioid or CCOC in origin. Furthermore, although the murine ID8 syngeneic model used for immunocompetent *in vivo* studies referred to herein recapitulates the rapid peritoneal spread associated with HGSC, it originates from transformed ovarian surface epithelia and has wild-type p53. Where individual studies are described, we have assigned likely origin of the cell lines used based on the available literature [45-47]. Where the histotype(s) of primary cells/tissues is unselected or not stated, we use the term EOC.

3. Ovarian cancer tumour microenvironments

EOCs generally remain confined within the peritoneal cavity and distant metastases are rare [48, 49]. Mechanisms of spread include direct but generally superficial invasion into adjacent organs such as the bladder and bowel, and the development of metastatic deposits on the omentum, peritoneum and abdominal organ serosal surfaces. These deposits are thought to be seeded, at least in part, by free floating multicellular aggregates (tumour spheroids) which are either shed directly into ascitic fluid from the tumour surface or are formed by the coalescence of individual shed tumour cells. Tumour spheroids are carried passively to sites of colonisation via ascitic fluid flow (transcoelomic metastasis) [50-52], although evidence for haematogenous spread to the omentum has also been reported [53]. EOCs display a strong tropism for the omentum, and omental metastases play an active role in promoting further tumour dissemination and ascites formation (Figure 2). In addition to tumour cells and spheroids, malignant ascites contains variable proportions of benign mesothelial cells, fibroblasts macrophages and other immune effector cells, as well as a plethora of chemokines, cytokines and other soluble factors [54]. As such, malignant ascites also acts as a reservoir of pro-inflammatory, tumour promoting soluble and cellular agents [55, 56]. Over one third of EOC patients have malignant ascites at diagnosis, and the development of ascites is invariably associated with recurrent disease and chemoresistance, and is a significant cause of morbidity and mortality [54].

3.1. Role of the omentum in ovarian cancer progression and chemoresistance

The omentum is a large, adipose-rich apron-like fold of the visceral peritoneum, which performs an important role in limiting infection and promoting wound healing within the peritoneal cavity [57]. These immunological and angiogenic properties, together with its adiposity, make the omentum fertile ground for metastatic colonisation, and EOCs have a predilection for metastasis to this organ through both transcoelomic and haematogenous routes [53, 58, 59]. The mechanisms behind this tropism involve a complex signalling and metabolic dialogue between tumour cells and other cells in the omental microenvironment. EOC tumour cells are able to create pre-metastatic niches within the omentum by secreting various factors into the peritoneal fluid. For example, HGSC, CCOC and endometrioid EOC- cell lines secrete TGF-β1, which has been shown to activate omental fibroblasts towards a cancer associated fibroblast (CAF) phenotype, thereby favouring tumour cell adhesion and invasion [60]. Together with bone marrow, omental adipose tissue is a rich source of mesenchymal stem cells (MSCs). These multipotent stromal progenitor cells are recruited to sites of inflammation,

including tumours, where they generally increase metastatic potential [61]. However, resident omental MSCs may also have a role in the formation of pre-metastatic niches in ovarian cancer: a CAF-like phenotype was acquired by human omental MSCs in response to TGF-β1 secreted by EOC cell lines, and omental MSCs from EOC patients (both with and without omental metastases) showed enhanced expression of the CAF/myofibroblast marker α-SMA compared with those from women with benign conditions. Furthermore, these CAF-like MSCs were able to increase metastasis of a co-transplanted endometrioid/CCOC cell line *in vivo* compared with control omental MSCs [62]. Other investigators have isolated cancer associated MSCs (CA-MSCs) from both primary ovarian tumours [63, 64], omental metastases [64] and normal regions of omenta from EOC patients [65]. Co-culture of non-HGSC tumour cell lines with omental MSCs from HGSC patients has been shown to increase tumour cell migration, proliferation and platinum resistance compared with control subcutaneous adipose MSCs [65]. CA-MSCs increased cancer initiating stem cell (CSC) marker expression in both HGSC and non-HGSC cell lines via STAT3 activation that could be blocked by dual IL-6/LIF inhibition, indicating some redundancy of function of these cytokines [66]. Primary ovarian tumour CA-MSCs also increase tumour cell proliferation *in vitro* and *in vivo* compared with control MSCs (adipose or bone marrow MSCs from healthy donors). These CA-MSCs had elevated expression of bone morphogenetic proteins (BMPs, part of the TGF-β superfamily) and increased the formation of spheroids and stem-like characteristics of co-cultured primary HGSC cells [63]. Subsequent work revealed that ovarian tumour cell-secreted Hedgehog (HH) ligands stimulated CA-MSCs to secrete BMP4, which in turn increased tumour cell HH ligand secretion in a positive feedback loop. BMP4 increased ovarian cancer cell stemness and platinum resistance in HGSC and non-HGSC cell lines both *in vitro* and *in vivo,* which could be blocked using the HH pathway inhibitor, Sonidegib [67]. Using a 6-gene expression classifier, it was possible to delineate EOC reprogramming of MSCs to CA-MSCs. Reprogramming was dependent on the ovarian TME since it required both tumour cell secreted factors and hypoxia *in vitro*, and was most effective in xenograft models. Interestingly, EOC cell lines (HGSC and non HGSC) were able to reprogram normal omental and ovarian MSCs but not bone marrow MSCs, which may be another mechanism underlying the omental tropism of EOC [64].

The omentum is also rich in so-called 'milky spots', which are primitive secondary lymphoid tissues lying just beneath the mesothelium, consisting of lymphocytes, macrophages and some plasma cells and supplied by blood and lymphatic vessels. Milky spots play an essential role in dealing with pathogens and are also major implantation sites for peritoneal metastases in EOC [68, 69]. Using xenograft (CCOC cell line) and immunocompetent *in vivo* models of EOC, primary ovarian tumours were found to cause an influx of neutrophils to milky spots, which formed neutrophil extracellular traps (NETs), thus creating a pre-metastatic niche which entrapped EOC tumour cells circulating in peritoneal fluid. Neutrophil recruitment and NET formation were dependent on IL-8 (CXCL8), GRO-α/β (CXCL1/2), G-CSF (CSF3) and MCP-1 (CCL2) secreted by EOCs and omental metastatic colonisation could be blocked by a small molecule inhibitor (SMI) of peptidyl arginine deiminase type IV (PADI4), an enzyme essential for NET formation. Moreover, the number of NETs was significantly increased in omental specimens from women with early stage HGSC and LGSC compared with cancer-free controls, particularly in HGSCs, which have higher metastatic potential [59].

Adipocytes also play an essential role in omental metastasis. Co-culture experiments with human omental adipocytes and non-HGSC tumour cell lines and *in vivo* xenograft models revealed that adipocytes participate in metastatic colonisation of the omentum, firstly by secreting cytokines (e.g. CXCL8, IL-6 and CCL2) and tissue inhibitors of matrix

metalloproteinases (e.g. TIMP-1) which provide a homing signal to EOCs, and secondly through EOC-stimulated lipolysis and release of free fatty acids. This fuels tumour cell proliferation and is accompanied by increased lipid accumulation and enhanced fatty acid oxidation in EOC cells [70]. This metabolic reprogramming of tumour cells engenders a pro-survival chemoresistant phenotype (section 7). Exosomes (see section 3.2) released by stromal cells in omental metastases may also promote EOC chemoresistance. For example, cancer associated adipocytes isolated from HGSC omental metastases promoted paclitaxel resistance in a non-HGSC cell line *in vitro* and *in vivo* via exosomal-mediated delivery of miR21 resulting in downregulated APAF1 [71].

As well as being a favoured site for metastasis, the omentum may actively participate in the formation of malignant ascites and the widespread peritoneal tumour dissemination found in late-stage EOC. A recent study in an immunocompetent mouse model of EOC showed that macrophages were in close association with tumour cells colonising omental milky spots. The researchers identified a particular subset of tissue resident omental macrophages that were maintained independently of bone marrow monocytes. Specific depletion of these macrophages reduced the formation of ascites and metastasis to the diaphragm, although not omental colonisation [72]. These tissue resident macrophages were also shown to promote CSC-like and epithelial-mesenchymal transition (EMT) characteristics in ascitic tumour cells [72], features associated with increased invasiveness and chemoresistance, as discussed in section 5.

3.2 Ascitic fluid and chemotherapy resistance

Ascitic fluid has been shown to protect EOC cells from apoptosis and increase drug efflux, thereby promoting chemoresistance [73, 74]. Various proteins, bioactive lipids and extracellular vesicles have been implicated in this phenomenon. Multiplex immunoassays have revealed elevated levels of several cytokines in malignant ascitic fluid [75]. While some, such as IL-10, contribute to immunosuppression and tumour cell evasion from immunosurveillance [76, 77], others such as IL-6 and CXCL8 [78, 79] are also linked to platinum resistance. IL-6 is reportedly secreted by tumour cells and CAFs in response to platinum treatment, and enhances chemoresistance via STAT3-mediated enrichment of CSCs and upregulation of cIAP-2 [79-81]. Malignant ascites also contains adipokines, secreted by omental and peritoneal adipocytes. Levels of leptin in ascitic fluid have been found to associate with poor prognosis [75, 82] and recently leptin was shown to increase EOC cell line resistance to taxanes [83]. Tumour produced VEGF-A plays a pivotal role in ascitic fluid formation by increasing vascular permeability [84].

Lysophosphatidic acid (LPA) is a growth factor found at high levels in EOC ascites. While tumour cells are known to synthesise and release LPA, recent work suggests that tumour associated macrophages (TAMs) may be the main producers of ascitic fluid LPA in EOC [85]. LPA species are lipid mediators which act through G-protein coupled receptors (GPCRs) to promote survival, proliferation, migration and platinum resistance [86-88]. LPA promoted metastasis in an endometrioid/CCOC cell line xenograft model, particularly in combination with hypoxia [89]. LPA was shown to activate HIF-1α in non-HGSC cell lines under normoxic conditions via Gαi2-Src signalling leading to EMT [90], thereby highlighting a potential mechanism of chemoresistance. EOC ascitic fluid also contains a plethora of eicosanoids and related lipid mediators [91]. Eicosanoids are synthesised from arachidonic acid (AA) via cyclooxygenase (COX), lipoxygenase and CYP450 epoxygenase enzymes and their dysregulation contributes to the pro-tumourigenic immunosuppressive TME [92, 93]. PGE_2, a major COX-2 metabolite, has been shown to directly contribute to platinum resistance in

HGSC and non-HGSC cell lines, acting via its GPCR, PTGER3, through RAS/MAPK/ERK and leading to ETS1/ELK-mediated transcriptional upregulation of the ABC transporter CFTR [94]. A direct role for CFTR in drug efflux has not been demonstrated, although speculatively, its known function in GSH flux [95] may play a role in platinum resistance. By contrast, another study investigating the adipocyte-secreted lipidome did not find any evidence for PGE_2-mediated chemoresistance in EOC. Rather, the eicosanoid precursor, AA, was found to induce chemoresistance in both HGSC and non-HGSC cell lines, albeit at very high concentrations [96]. TAMs appear to be major producers of ascitic fluid AA, via secretory phospholipase (PLA2G7), and of the 5-lipoxygenase AA metabolite leukotriene $(LT)B_4$. Levels of both these lipids have been found to associate with adverse outcome [97].

Profiling of immune effector cells in ascites has revealed phenotypes consistent with immune suppression. Moreover, *in vitro* incubation of immune cells isolated from normal tissues in malignant ascitic fluid is able to induce an immunosuppressed phenotype. Various cytokines, chemokines and lipid signalling molecules are implicated in this phenomenon, as well as ascitic fluid metabolites [98]. This particular metabolic milieu may also contribute to chemoresistance through metabolic reprogramming of EOCs and other cells within the TME. Unlike solid tumours, malignant ascitic fluid has a neutral rather than acidic pH [89]. Although mild hypoxia has been reported [89], pO2 levels are higher than those in solid tumours and not dissimilar to those of normal peripheral tissues [99]. Moreover, glucose levels in ascitic fluid are frequently, but not always, below the normal range for fasting blood [100]. However, malignant ascites contains higher levels of free fatty acids than its benign counterpart [101]. These free fatty acids are secreted by omental adipocytes and support tumour cell survival, metastasis and chemotherapy resistance by inducing tumour cell metabolic reprogramming (see section 7).

Another emerging area in the EOC ascitic microenvironment is the potential role of exosomes in EOC progression and chemoresistance. Exosomes are a type of extracellular vesicle (EV) surrounded by a phospholipid bilayer, which are released by cancer cells and other cell types within the TME. Exosomes and other EVs are thought to mediate cell:cell communication through their cargos of proteins and nucleic acids (e.g. miRNAs), and recent studies have implicated them in contributing to EOC immunosuppression, peritoneal dissemination and chemoresistance [102, 103]. Ascitic fluid exosomes have been implicated in the formation of premetastatic niches in the peritoneal cavity, a feature which is potentially exploitable therapeutically. Proof of concept was provided by the work of de la Fuente *et al*. [104], who created an implantable device (the metastasis (M)-trap) consisting of exosomes purified from clinical EOC ascitic fluid samples embedded in a 3D scaffold. When implanted within the peritoneal wall, the device provided a focus for metastasis in a non-HGSC cell line xenograft model. This reduced the extent of disease dissemination and prolonged survival, particularly if the device was removed after metastatic focus formation. As exosomes are stable in the circulation, appear to have low immunogenicity in animal models, and have minimal clearance by the liver and spleen, they are attractive as potential vehicles for the delivery of therapeutic agents. However, the source of exosomes would require careful evaluation for immunogenicity and potential pro-tumourigenic effects prior to clinical use. As EOC patients generally undergo omentectomy, the omentum is a potential source of autologous therapeutic exosomes. In a recent study, exosomes released by fibroblasts isolated from normal regions of clinical omentectomy specimens were transfected with the tumour suppressor miR-199a-3p. These engineered exosomes reduced intraperitoneal tumour burden in a non-HGSC cell line xenograft model when administered either intraperitoneally or intravenously [105].

Finally, the influence of mechanical stresses in the TME is a burgeoning area of research. Using microfluidics systems to model fluid sheer stress exerted on non-HGSC cell line tumour spheroids by ascitic fluid, researchers have demonstrated increased expression of EMT markers [106, 107], and CSC markers associated with activated EGFR and PI3K/AKT signalling with concomitant increases in platinum resistance [107, 108].

4. Cancer associated fibroblasts

One of the most dominant components of the TME are CAFs, which are active players in tumour progression and metastasis through their interactions with cancer cells and other cells in the TME via cytokine/growth factor-mediated signalling and extracellular matrix (ECM) remodelling.

4.1 Origin of CAFs in ovarian cancer

In EOC, tumour cells reprogram resident fibroblasts or MSCs to become CAFs by secreting cytokines such as TGF-β, IL-1β, IL-6, CXCL8 and TNF-β [109-111], signalling molecules such as HH ligands [67] and Wnt7a [112] or bioactive lipids such as LPA [113]. Both HGSC and non-HGSC EOC cell lines have been shown to induce peritoneal mesothelial cells to adopt a CAF-like phenotype through TGF-β activation of SMAD3 [114, 115]. This process, known as mesothelial-to-mesenchymal transition (MMT), is accompanied by increased fibronectin expression and creates a premetastatic niche, facilitating tumour cell adhesion to, and invasion of, the peritoneal mesothelium in mouse models of metastasis [114-116]. Reprogramming of CAFs involves wide-ranging epigenetic alterations, including changes in expression of miRNAs 31, 214 and 155 [117]. Recently, nicotinamide-N-methyl transferase (NNMT) was identified as a master switch in the epigenetic reprogramming of CAFs in HGSC. Stromal NNMT expression was found to be necessary and sufficient for the CAF phenotype and functions, and NNMT knockdown or inhibition reduced tumour burden in non-HCSC cell line xenograft and immunocompetent *in vivo* models. NNMT catalyses the transfer of a methyl group from S-adenosyl methionine (SAM; the universal methyl donor) to nicotinamide, leading to SAM depletion and genome-wide DNA and histone hypomethylation, which associate with the widespread changes in CAF gene expression [118].

4.2. Role of CAFs in ovarian cancer progression and chemoresistance

EOC CAFs are characterised by expression of α-SMA, although there is considerable heterogeneity in CAF marker expression both within and between EOC histotypes [119, 120], as there is with other solid tumours [121]. Functionally, CAFs secrete ECM components and modifying enzymes as well as myriad cytokines and growth factors, including IL-6, RANTES (CCL5), MCP-3 (CCL7), CXCL8, IP-10 (CXCL10), I-TAC (CXCL11) and SDF-1 (CXCL12), culminating in increased angiogenesis, tumour cell proliferation, escape from immunosurveillance, invasion and metastasis [109-111, 117, 122]. Gene expression signatures reflecting reactive stroma, signified by the abundance/activation of CAFs, have been shown to be associated with a poor clinical response to platinum therapy in both HGSC and endometrioid EOCs [43, 123-125]. CAFs contribute to EOC chemoresistance through multiple mechanisms. These can be via the action of secreted cytokines such as CCL5, which was shown to increase platinum resistance of a non-HGSC EOC cell line *in vitro* via STAT3 and PI3K/AKT activation [126], and IL-6, which induced EMT and *in vitro* paclitaxel resistance in an HGSC cell line and in primary EOC cells via JAK2/STAT3 [127]. Patient-derived CAFs have also been shown to induce EMT in HGSC and non-HGSC cell lines *in vitro* via exosomal delivery of TGF-β1 [128]. Other mechanisms involve cell:cell contact, such as the interaction between mesothelial-derived CAFs, whereby TGF-β-stimulated fibronectin-1 expression in patient omental mesothelial cells induces chemoresistance in HGSC and CCOC cell lines through integrin

binding and PI3K/AKT activation [129]. CAFs have also been shown to promote HGSC chemoresistance in patient-derived xenograft (PDX) models by increasing cysteine and GSH availability in the TME for uptake by tumour cells, leading to decreased platinum accumulation. This effect was abrogated by IFN-γ secreted by $CD8^+$ effector T cells, which upregulated CAF expression of γ-glutamyltransferase (GGT)5 and downregulated that of the system xc^- cystine/glutamate antiporter through JAK/STAT activation. This resulted in decreased cysteine and GSH synthesis and increased GGT-mediated breakdown of extracellular GSH [130]. Finally, CAFs also play a role in EOC chemoresistance through biophysical means. The formation of fibrotic stroma is characterised by enhanced collagen and glycosaminoglycan deposition by CAFs in response to TGF-β, resulting in increased tissue stiffness and solid stress. This, together with the increased interstitial pressure caused by leaky tumour vessels, induces blood vessel collapse and reduces perfusion of oxygen and chemotherapeutic drugs, both of which contribute to chemoresistance [131]. The angiotensin receptor blocker Losartan was shown to normalise tumour stroma by decreasing ECM deposition thereby decreasing solid stress and increasing paclitaxel perfusion/efficacy in non-HGSC cell line xenograft models. ECM depletion was associated with changes in expression of fibrosis-associated miRNAs in both tumour cells and stromal fibroblasts [132]. Ovarian CAFs also participate in tumour angiogenesis both directly and indirectly through cytokine-mediated interactions with other cells in the TME [109]. Activated CAFs were also found to promote vessel leakiness via secretion of the microfibrillar associated protein (MFAP)5, which bound endothelial cell αVβ3 integrin and stimulated a calcium-dependent increase in lipoma preferred partner (LPP) expression via FAK/ERK/MLC2/CREB. Endothelial LPP expression increased focal adhesion, stress fibre formation, motility and monolayer permeability, whereas silencing of LPP improved tumour perfusion of paclitaxel *in vivo* [133].

4.3. Targeting CAFs in ovarian cancer

The considerable heterogeneity in CAF markers is a challenge for the development of CAF-targeted therapies. Moreover, markers such as fibroblast activation protein (FAP) or α-SMA are shared with other normal cell types, so targeted therapies designed to eliminate CAF subtypes are likely to be associated with significant systemic toxicity. Blocking the activity of FAP, a serine peptidase expressed on the cell surface of CAFs, has been developed as a less toxic strategy. In EOC, high stromal expression of FAP was associated with adverse outcome and platinum resistance [134]. However, phase II trials of a FAP-directed humanised monoclonal antibody, Sibrotuzumab, in metastatic colorectal cancer failed to demonstrate any benefit [135]. The anti-FAP/IL-2v fusion protein RO6874281 has been developed as a strategy to preferentially retain cytotoxic/natural killer (NK) cells in the TME. This drug is currently undergoing phase I clinical trials in advanced solid tumours in combination with a PD-1/PD-L1 checkpoint inhibitor, or as monotherapy/combination with anti-EGFR or anti-HER2 directed therapies (trial numbers NCT0338672, and NCT02627274, respectively). Crosstalk between tumour cells and fibroblasts via Wnt, HH and TGF-β signalling promotes both CAF and CSC phenotypes (for therapeutic strategies targeting CSCs see section 6).

It has become apparent that CAF subpopulations can have tumour suppressive as well as tumour promoting phenotypes in some cancer types (e.g. breast cancer), and elimination of CAFs (e.g. by targeting α-SMA) increased tumour aggressiveness in mouse models of pancreatic cancer, reviewed in [136, 137]. As yet, tumour suppressive CAFs have not been identified in EOC. Nevertheless, these observations suggest that targeting discrete CAF subpopulations, or stroma normalisation therapies may be preferable to CAF elimination. Therefore, functional characterisation of CAF subpopulations and identification of molecular markers which define tumour-promoting CAF phenotypes will allow the development of

selective targeting or stroma normalisation strategies for EOC. A recent study identified CD49e (ITGA5) as a universal CAF marker in primary HGSCs. Isolated CAFs were further separated into a FAP-high subpopulation which promoted invasion and carboplatin resistance in EOC cell lines (HGSC and non-HGSC), and a FAP-low subpopulation which did not. The transcription factor TCF21 was found to act as a master regulator which inhibited the pro-tumourigenic/pro-chemoresistant phenotype when transfected into FAP-high CAFs [138]. Using a systems biology approach on gene expression data from laser capture microdissected tumour and stroma from HGSCs, Yeung and co-workers identified a stromal-specific signature associated with adverse outcome that involved TGF-β-dependent and independent SMAD signalling. Computational predictions identified calcitriol (vitamin D3) as a potential drug targeting this pathway. Calcitriol suppressed SMAD signalling in CAFs grown *in vitro* and inhibited tumour growth in an HGSC cell line xenograft model [139]. Targeting the epigenetic regulation of fibroblast activation such as that mediated by NNMT, or by inhibiting stromal fibrosis by Losartan-mediated blocking of angiotensin (both described above) are also potential stromal normalisation strategies. A phase II clinical trial on Losartan in combination with FOLFORINOX in pancreatic cancer is currently under way (NCT01821729).

4.3. Summary and conclusions

The presence of reactive stroma is associated with poor clinical outcome in EOC and CAFs have been demonstrated to promote EOC progression, metastasis and chemoresistance. CAF-directed therapies such as monoclonal antibody-mediated blocking of FAP activity have failed to demonstrate clinical benefit in other malignancies; however, using an anti-FAP/IL-2v fusion molecule to trap NK cells within the TME is one approach currently undergoing phase I trials in advanced solid tumours as an adjunct to immunotherapy. Other strategies involve targeting fibroblast-CSC crosstalk, which are discussed in more detail in section 6. As well as directly promoting chemoresistance of tumour cells, CAF activation results in collagen deposition and stromal fibrosis, which is associated with mechanical stress and poor drug perfusion. This effect could be ameliorated in preclinical models of EOC using the drug Losartan. As with other tumours, EOC CAFs are heterogeneous in terms of origin and marker expression. Understanding how different CAF subpopulations are shaped by the TME, together with their functional characterisation, will enable the development of therapies aimed at targeting specific CAF subpopulations or achieving stromal normalisation.

5. Tumour associated macrophages

Cells of both innate and adaptive immunity are co-opted by EOCs towards the creation of a tumour-promoting, immunopermissive TME. These include tumour-associated macrophages (TAMs), tumour-associated neutrophils, myeloid-derived suppressor cells (MDSCs), T-cells and NK cells [140, 141]. This section will focus on TAMs, which represent the most abundant infiltrating immune population in EOC tumours and ascites, and which have a critical role in disease progression (Figure 3).

5.1 Origin of tumour associated macrophages and role in ovarian cancer progression

Macrophages are developmentally plastic and, depending upon cues in the TME, TAMs can reversibly exhibit two main phenotypes across a spectrum: those resembling classically activated (M1-like) and those resembling alternatively activated (M2-like) macrophages. M1 macrophages exhibit a pro-inflammatory phenotype and form part of the host defence against bacterial pathogens, whereas the physiological role of M2 macrophages is to respond to helminth infections, clear cell debris and facilitate wound repair. While M1-like macrophages exhibit tumouricidal properties, M2-like TAMs are immunosuppressive and promote angiogenesis, ECM remodelling, invasion and metastasis [142-145]. In EOC, high levels of

$CD163^+$ (M2-like) TAMs and low M1/M2 ratios infiltrating tumours, or in ascites, predict adverse outcome and poor clinical response to chemotherapy both in studies on mixed histotypes and on HGSCs [146, 147], and a high M1-specific gene signature was most closely associated with good prognosis in HGSC [148]. Thus, strategies to reverse the polarisation from M2 to M1 have the potential to enhance response to both cytotoxic and immunotherapies.

EOC TAMs originate from bone marrow-derived monocytes which are recruited by tumour-secreted cytokines/growth factors such as M-CSF (CSF1), VEGF, CCL2, CCL5 and MIP-4 (CCL18), and from self-maintained tissue resident macrophages which originate from yolk sac erythro-myeloid progenitor cells during embryonic development [72, 149]. Polarisation towards the M1 phenotype is stimulated by factors such as LPS, TLR agonism, IFN-γ, IL-12, TNF-α and GM-CSF (CSF2), and requires NF-κB activation. By contrast, polarisation towards a M2 phenotype is stimulated by TGF-β, IL-4, IL-10, IL-13, CCL2, CSF1 and PGE_2 [142-144] and involves STAT6 activity. M2 polarisation by EOCs has been shown to be driven by tumour cell HOXA9-dependent TGF-β and CCL2 secretion [150]. The metabolic TME plays a central role in macrophage recruitment and polarisation. Macrophages accumulate in regions of hypoxia/necrosis in response to the release of chemoattractants and through hypoxia-mediated inhibition of macrophage mobility. Furthermore, TAMs residing within tumour hypoxic niches are known to mediate therapy resistance (reviewed in [151]). Using both HGSC and non-HGSC cell line models, Wen and colleagues showed that hypoxia-induced tumour cell production of the 5-lipoxygenase AA metabolites 5-HETE and LTB_4 promoted infiltration of TAMs via upregulation of MMP-7, an effect that could be reduced *in vivo* by the 5-lipoxygenase inhibitor, Zileuton [152]. However, it remains to be determined whether this drug has anti-cancer properties in EOC. *In vitro* studies have identified a role for exosomes secreted by hypoxic non-HGSC cell lines in miRNA-mediated macrophage M2 polarisation [153, 154]. In mouse models of lung cancer and melanoma, polarisation towards an M2 phenotype was found to be driven by HIF-1α expression in response to the high levels of lactic acid released by tumour cells through anaerobic or aerobic glycolysis [155]. Analogously, lactic acid released by primary EOC cells promoted differentiation of co-cultured human monocytes towards a phenotype combining pro-tumourigenic (M2-like) and pro-inflammatory features, that was dependent on HIF-1α stabilisation and autocrine CSF1 production. The acquired phenotype was similar to that of TAMs isolated from primary EOC tumours [156]. A novel mechanism for the metabolic reprogramming of TAMs was recently identified in a syngeneic mouse model of EOC, where tumour cell-secreted hyaluronan triggered cholesterol efflux from macrophage cell membranes via ABCA1/G1. The resulting lipid raft depletion increased response to IL-4 and reduced response to IFN-γ in a STAT6 and PI3K/AKT-dependent manner [157].

M1 macrophages are characterised by their production of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-12, IL-18 and IL-23, expression of MHC-II, as well as co-stimulatory molecules CD80 and CD86 and upregulated iNOS. M1 macrophages are capable of tumour cell killing through production of ROS and reactive nitrogen species, the stimulation of an antigen-specific Th1 inflammatory response, as well as activating NK cells. M2 macrophages, on the other hand, are phenotypically diverse, with various subtypes associated with tissue remodelling, angiogenesis, mediation of Th2 humoral immunity, and inflammatory suppression. As mentioned above, TAMs most closely resemble M2 macrophages. M2-like TAMs express scavenger receptors such as CD163 and CD206, promote angiogenesis via VEGF, CXCL8 and CXCL12 secretion and mobilisation from the ECM via MMP-9. M2 macrophages also promote tumour proliferation via secretion of growth factors, and invasion through MMP, uPA and cathepsin-mediated ECM remodelling. TAMs lack MHC-II

expression and antigen-presentation ability, and recruit immunosuppressive Tregs through the secretion of cytokines such as IL-10 and TGF-β, as well as chemokines such as CCL2, MIP-1α (CCL3), MIP-1β (CCL4), CCL5 and MIP-3α (CCL20) [158-160]. Through expression of immune checkpoint ligands on their cell surface, TAMs limit cytotoxic T-cell response contributing to immune evasion. For example, EOC TAMs express PD-L1 on their cell surface and macrophage/dendritic cell expression of PD-L1 predicted better response to PD-L1/PD-1 directed immunotherapy [161]. EOC cells can also evade TAM-mediated phagocytosis through expression of CD47 or CD24 which bind macrophage SIRPα and Siglec-10, respectively, and as such are novel immunotherapeutic targets for EOC [162, 163].

A critical role for TAMs in EOC progression and metastasis was first demonstrated by Robinson-Smith *et al*. [164], who found that specific depletion of macrophages in CCOC and HGSC cell line xenograft and immunocompetent mouse models reduced primary tumour growth and profoundly reduced metastasis and ascites formation. The mechanisms behind this phenomenon have been explored in other studies. TAMs have been shown to promote spheroid formation in non-HGSC cell line xenograft and immunocompetent mouse models of transcoelomic metastasis which was dependent on TAM-secreted EGF [165], although there is also evidence that spheroids are shed directly from tumour surfaces [50]. Tissue resident omental TAMs support a pre-metastatic niche by promoting CSC formation in omental-colonising EOC cells, as described earlier [72]. M2 macrophages may enable peritoneal metastasis by facilitating adhesion of tumour cells to the mesothelium. Carrol and co-workers demonstrated that M2 macrophage-secreted CCL4-activated CCR5/PI3K signalling in mesothelial cells triggering upregulation of P-selectin [166]. This enabled CD24-mediated tumour cell adhesion to mesothelial cells both *in vitro* and *in vivo*. M2 polarisation was found to play a direct role in ascites formation in immunocompetent mouse models of EOC, by promoting vascular permeability, which could be reversed using the CSF1R inhibitor GW2580 [167].

5.2. Interaction of TAMs with chemotherapy, immune and anti-angiogenic therapies

The interaction between TAMs and chemotherapy is context-specific, whereby TAMs can either enhance or antagonise drug efficacy depending on the type of cancer and drug. Similarly, different chemotherapy drugs can reprogram TAMs towards tumour-promoting or tumour inhibitory phenotypes [168, 169]. In an *in vitro* cell line model of HGSC, the reciprocal Wnt-mediated dialogue between tumour cells and TAMs in tumour spheroids promoted both CSC formation and M2 polarisation [170], an effect which likely contributes to chemoresistance. Furthermore, exosomal miR-223 released by hypoxic TAMs polarised *in vitro* by IL-4 was shown to increase cisplatin resistance in a non-HGSC cell line both *in vitro* and *in vivo* [171]. Clinical data associating high M1/M2 macrophage ratios in pre-treatment tumours/ascitic fluid with a longer platinum free interval supports this notion [147]. In turn, platinum treatment of both non-HGSC and HGSC cell lines has been shown to promote M2-polarisation in co-cultured monocytes in a PGE_2 and IL-6-dependent manner [172]. By contrast, paclitaxel treatment was shown to reprogram TAMs towards an M1 profile via direct TLR4 stimulation in mouse models of breast cancer and melanoma and an increase in M1-associated gene expression was observed in clinical EOC tumours following paclitaxel monotherapy [173]. Interestingly, targeting macrophages by CSFR1 blockade synergised with platinum drugs but not with paclitaxel in a mouse model of lobular breast cancer by initiating an intratumoural Type I IFN response [174].

The apoptotic cell debris generated by chemotherapy triggers an inflammatory response involving cytokine production and the release of lipid mediators such as PGE_2, which can

promote tumour growth and metastasis leading to therapy failure [175]. Other eicosanoids such as the CYP450 epoxygenase-generated epoxyeicosatrienoates (EETs; which are inactivated by soluble epoxide hydrolase, sEH) stimulate the resolution of inflammation and clearance of apoptotic debris by macrophages. By using the dual COX-2/sEH inhibitor, PTUPB, Gartung *et al.* were able to suppress the debris-mediated cytokine/lipid mediator surge, thus suppressing EOC tumour growth in immunocompetent and non-HGSC cell line xenograft models [176]. On the other hand, some chemotherapy drugs such as taxanes are capable of promoting immunogenic cell death (ICD), characterised by damage-associated molecular patterns (DAMPs) which trigger an intrinsic Type I IFN response by binding to TLRs on antigen-presenting cells. However, oxaliplatin appears to be the only platinum-based drug to elicit significant ICD [177, 178]. It appears that by themselves, these chemotherapy-induced immunogenic effects do not improve outcome in HGSC [179], although they could be harnessed by combining chemotherapy with immune checkpoint inhibitors or other immunotherapies. However, this needs to be balanced against the detrimental effects of chemotherapy on local and systemic immunity [180]. Although durable responses do occur, trials of PD-1/PD-L1 checkpoint inhibitors either alone or in combination with platinum-based regimens have been disappointing in EOC. A probable factor is the low mutational burden and immunogenicity associated with HGSCs, and FDA approval has been granted for Pembrolizumab only in the restricted setting of MMR deficient/MSI-high EOCs [16, 181]. Nevertheless, combinations involving PARP inhibitors appear to be more promising perhaps due to the fact that PARP inhibitors induce a strong IFN response as identified in preclinical models [182, 183]. Speculatively, the M2 polarising effect of platinum drugs on macrophages could contribute to the failure of platinum/checkpoint inhibitor combination therapies. Combinations of immune and anti-angiogenic therapies, however, hold promise as their normalising effect on tumour vasculature may enable infiltration of lymphocytes into the tumour epithelial bed, while also reducing hypoxia and M2-polarised TAM accumulation [184], converting tumours from an 'immune excluded' to an 'inflamed' phenotype [185]. However, the so-called 'immune desert' phenotype is associated with lack of lymphocyte infiltration in the tumour and stroma due to tumour cell epigenetic silencing of CCL5 and may need alternative approaches [186]. Ongoing clinical trials of PD-1/PD-L1 checkpoint inhibitor combination therapies in EOC are reviewed in [187]. There are many more immune-targeted therapies for EOC in preclinical/clinical development but these lie beyond the scope of this review [188].

5.3. Macrophage-targeted therapies

Given the critical role of TAMs in cancer progression, there has been much interest in the development of macrophage-targeted therapies [189]. Preclinical data and clinical trials relevant to EOC are summarised in Table 2. The CSF1/CSF1R and CCL2/CCR2 axes are critical for monocyte recruitment and TAM survival. CSF1R-directed therapies have shown promise in preclinical models and a number of trials combining CSF1R-targeted therapies with immune checkpoint inhibitors are ongoing. A potential mechanism of resistance to CSF1R-directed therapy is the chemokine-mediated recruitment of polymorphonuclear MDSCs by CAFs observed in mouse models of cancer. However, this could be reversed using a CXCR2 antagonist [190]. Antibody-mediated targeting of CCL2 did not achieve significant benefit or durable CCL2 reduction in trials on advanced solid tumours including EOCs [191, 192]. Other approaches include the development of SMIs of CCR2 (e.g. PF-04136309), although no preclinical data on EOCs have been published as yet. Bisphosphonates (e.g. clodronate) have been used to deplete monocytes/macrophages in mouse models of EOC, demonstrating the central role of TAMs in EOC metastasis [164]. Liposomal delivery encourages selective uptake by phagocytes and targeted macrophage delivery of bisphosphonates using nanotechnology is

an area of active research [189]. The chemotherapeutic drug, trabectedin, has been approved for the treatment of partially platinum sensitive relapsed EOC, and combination/sequencing trials are ongoing [193]. As well as killing cancer cells, trabectedin selectively kills monocytes and macrophages [194], which is thought to contribute to its anti-cancer properties. However, rather than eliminating TAMs, harnessing their tumouricidal properties either by reprogramming towards an M1 phenotype or by blocking the anti-phagocytic signals on the tumour cell surface (e.g. CD47/SIRPα and CD24/Siglec-10) may be an advantageous approach [162, 163, 195]. Epigenetic modulation can be used to reprogram macrophages towards an M1 phenotype. For example, inhibiting ornithine decarboxylase (ODC), the rate limiting enzyme for polyamine synthesis, leads to M1 polarisation by altering histone modifications leading to activated transcription. Treatment with the ODC inhibitor, DFMO has been shown to reduce EOC tumour growth in an immunocompetent *in vivo* model, particularly in combination with 5-azacytidine [196]. Finally, M2 macrophage-targeted nanocarrier-mediated delivery of M1-polarising transcription factor mRNAs offers a potential means of specifically repolarising TAMs without the complications of systemic toxicity [197].

5.4. Summary and conclusions

Studies on mouse models of EOC demonstrate a crucial role for TAMs in peritoneal dissemination and ascites formation. TAMs display a range of phenotypes along a spectrum between M1 (pro-inflammatory, tumouricidal) and M2 (pro-tumourigenic, pro-angiogenic, immunosuppressive) activation states and an M2-skewed TAM population associates with clinical platinum resistance in EOC. Various TAM-targeted therapies are currently in preclinical and clinical development (including monocyte/macrophage-targeted therapies such as CSF1R inhibitors), which are currently being trialled in combination with immune checkpoint inhibitors. However, approaches which promote the anti-tumourigenic properties of TAMs may be advantageous and also limit systemic toxicity. These include blocking tumour cell anti-phagocytotic signals e.g. the development of CD47/SIRPα-blocking monoclonal antibodies, currently undergoing phase I clinical trials. Alternatively, strategies to reprogram TAMs towards the M1 phenotype are currently in preclinical development. A better understanding of the mechanisms governing macrophage polarisation, as well as characterisation of the functional diversity of TAMs within the EOC TME, will greatly assist in this regard. Finally, the fact that different cytotoxic chemotherapeutic drugs have different effects on TAM polarisation may be an important consideration when devising treatment combination strategies.

Target	**Drug**	**Details**	**Reference/trial number**
CSF1R	GW2580 (SMI)	Reduced ascites in an immunocompetent mouse model of EOC.	[167]
	AC708 (SMI)	Partially overcame-resistance to anti-VEGF therapy in immunocompetent and HGSC PDX mouse models of EOC.	[198]
	BLZ945 (SMI)	Combination with docetaxel reduced tumour growth and lung metastasis in an immunocompetent mouse model of EOC.	[199]
	ARRY-382 (SMI)	Phase Ib/2. Combination with PD-1/PD-L1 CPI (Pembrolizumab) in advanced solid tumours. Completed.	NCT02880371 [200]

	Cabiralizumab	Phase I. Combination with anti-PD-1/PD-L1 CPI (Nivolumab) in advanced solid tumours. Completed.	NCT02526017
	LY3022855 (mAb)	Phase I. Combination with anti-PD-1/PD-L1 (Durvalumab) or anti-CTLA-4 (Tremelimumab) in advanced solid tumours. Completed.	NCT02718911
CSF1R/c-Kit	PLX3397 (SMI)	Phase I/2a. Combination with anti-PD-1/PD-L1 therapy (Pembrolizumab) in advanced solid tumours. Terminated (insufficient evidence of clinical efficacy).	NCT02452424
CCL2	Carlumab (CNTO 888)	Phase I monotherapy for treatment-refractory advanced solid tumours. Completed. Modest effects achieved (disease stabilisation) in 4/33 patients (including one EOC patient).	[191]
		Phase Ib. Combination with standard chemotherapy in advanced solid tumours. Completed. No significant anti-tumour response or sustained effect against CCL2 achieved.	NCT01204996 [192]
Monocytes/ macrophages	Clodronate liposomes (bisphosphonate)	Reduced metastasis and ascites formation in CCOC and HGSC cell line xenografts and an immunocompetent mouse model of EOC.	[164]
Monocytes/ macrophages (caspase-8)	Trabectidin	Selectively cytotoxic to monocytes and macrophages. Reduced angiogenesis in an immunocompetent mouse model of EOC.	[194]
CD47 (SIRPα) (phagocytosis)	Hu5F9-G4 (mAb)	Phase I dose escalation study in advanced solid tumours. Completed. Partial remission achieved in 2 EOC patients.	NCT02216409 [195]
	IBI188 (mAb)	Phase I dose escalation study in advanced solid tumours. Recruiting.	NCT03763149
CD24 (Siglec-10) (phagocytosis)	Anti-CD24 mAb	Blocking CD24 prevented binding to macrophage Siglec-10 promoting phagocytosis of primary human EOC cells *in vitro*, and reduced tumour growth in an immunocompetent mouse model of EOC.	[163]
M1 reprogramming	DFMO 5-azacytidine	Combined ornithine decarboxylase and DNA methyltransferase inhibition increased M1 macrophages and inhibited tumour growth in an immunocompetent mouse model of EOC.	[196]
	CD206-targeted nanocarrier of IRF5 and IKKβ mRNAs	Reversed tumour-promoting phenotype of macrophages and caused tumour regression in an immunocompetent mouse model of EOC.	[197]

Table 2. Examples of macrophage-targeting strategies relevant to ovarian cancer – preclinical studies and clinical trials

Abbreviations: SMI: small molecule inhibitor, mAb: monoclonal antibody, RCT: randomised controlled trial, EOC: epithelial ovarian cancer, HGSC: high grade serous ovarian carcinoma, CCOC: clear cell ovarian carcinoma, CPI: checkpoint inhibitor, CTLA-4: Cytotoxic T-lymphocyte-associated protein-4, CSF1R: colony stimulating factor 1 (M-CSF) receptor, CCL2: C-C Motif chemokine ligand 2 (MCP-1/ monocyte chemoattractant protein-1); SIRPα: Signal regulatory protein α, Siglec-10: Sialic acid binding Ig-like lectin 10, DFMO: α-difluoromethylornithine; IRF5: Interferon regulatory factor 5, IKKβ: Inhibitor of nuclear factor κB kinase β.

6. Cancer stem cells, EMT and therapy resistance

The original cancer stem cell theory purports that only a small subset of tumour cells is capable of self-renewal and repopulating tumours following therapy. Current understanding supports a less rigid hierarchy, where cancer cells can reversibly adopt a CSC phenotype according to fluctuating microenvironmental conditions. Similar to solid tumours, ascitic tumour spheroids provide an environment conducive to chemoresistance by providing a hypoxic niche for CSC development [201-203]. CSCs possess the ability to survive once detached from the ECM, a pre-requisite for metastasis. Such anoikis resistance may engender chemotherapy resistance through shared pro-survival, anti-apoptotic mechanisms. For example, Bcl-2 upregulation was observed in HGSC and non-HGSC cell line spheroid models compared with adherent cultures, conferring both anoikis and platinum resistance [204]. Candidate genes involved in anoikis/platinum resistance in HGSCs have been identified through tumour expression/epigenetics profiling and *in vitro* functional genomics screens. These include upregulation of CBX2, a polycomb transcriptional repressor [205], downregulation of DOK2, a tyrosine kinase docking protein [206], and ABHD2, an α/β hydrolase family member [207], although the precise mechanisms involved for these genes remain to be elucidated. While ovarian CSCs remain to be defined unequivocally, markers of stemness and associated pathways play a role in chemoresistance, given that they are enriched in spheroid cultures of EOC cell lines and primary tumour cells, which are platinum resistant relative to adherent cultures. Moreover, stem cell markers are also enriched in post-chemotherapy clinical EOC samples and cell line models [80, 208-213]. Besides anoikis resistance, other features of CSCs contribute to their inherent chemoresistance, such as their quiescent state [214] and enhanced autophagy [215]. CSCs from primary HGSCs and non-HGSC cell lines had upregulated DNA polymerase η, which enhanced platinum resistance via increased translesional synthesis [216]. Similarly, CSCs isolated from a panel of HGSC cell lines were shown to be resistant to PARP inhibitors via increased DMC1 recombinase and enhanced HRR efficiency [217]. CSCs are also characterised by efficient drug efflux mechanisms involving ABC transporters. In EOC, c-kit/Wnt/β-catenin-mediated upregulation of ABCG2 was observed in non-HGSC cell lines during spheroid formation or hypoxic treatment and the associated paclitaxel/cisplatin resistance was reversed by ABCG2 knockdown [218]. In another study, hypoxia treatment upregulated ABCB1 and ABCG2 expression in non-HGSC cell lines and primary EOC cells via NOTCH1/SOX2 signalling, which enhanced paclitaxel resistance and spheroid formation [219].

EMT, a process critical for cancer metastasis, and the CSC phenotype are mechanistically linked. Indeed, the acquisition of stemness appears to be largely attributable to activation of the EMT programme through epigenetic mechanisms [220]. Like stem cell markers, EMT characteristics are associated with chemotherapy resistance in cell line models and clinical

EOCs [221-223] and a direct role for the EMT transcription factors *snail* (SNAI1) and *slug* (SNAI2) in platinum resistance was also identified by knockdown experiments using an endometrioid EOC cell line [224]. Mechanistically, the induction of EMT during the acquisition of platinum resistance in HGSC, endometrioid and CCOC cell lines has been linked to DNA damage response via ATM/ATR phosphorylation of ubiquitin-specific peptidase 1 (USP1) triggering deubiquitination and stabilisation of *snail* [225]. Other pathways implicated in EMT and chemotherapy resistance in EOC include aberrant Wnt signalling, reviewed in [226], hyperactive EGFR/STAT3 mediated signalling in an endometrioid EOC cell line [227], and Notch3-mediated suppression of platinum-induced ERK phosphorylation and apoptosis in a CCOC cell line [228]. A number of studies have identified a role for enhanced TGF-β signalling in EMT and acquired chemotherapy resistance in clinical EOC samples and HGSC cell line xenograft models [229, 230]. A recent study on tumour spheroids isolated from HGSC, CCOC and endometrioid EOC ascites samples found them to be composed of tumour cells, CAFs and leukocytes. Single cell transcriptomics revealed activation of EMT pathway genes in tumour cells isolated from spheroids relative to disseminated single tumour cells. This study also identified a pivotal role for TGF-β secreted by spheroid CAFs in the EMT phenotype and chemoresistance of spheroid tumour cells, which was mediated via upregulated ZEB1 [231].

There are many targeted therapies against CSC surface markers, EMT/CSC pathways and CSC niches in preclinical/clinical development [232], as well as potential to repurpose existing drugs. Studies/trials relevant to EOC are listed in Table 3.

In summary, CSCs are a rare subpopulation of tumour cells, which are capable of self-renewal and tumour repopulation following therapy. Current thinking holds that tumour cells can reversibly adopt a CSC phenotype in response to fluctuating microenvironmental conditions, and that activation of the EMT programme through epigenetic modulation is a prerequisite for the acquisition of stemness. CSCs are enriched within EOC tumour spheroids and their anoikis-resistant phenotype facilitates transcoelomic metastasis. CSCs are also inherently chemoresistant, which involves various mechanisms including increased DNA repair capacity, replication bypass, drug efflux and autophagy. Moreover, markers of stemness increase in clinical/experimental EOCs following chemotherapy. Development of strategies to eliminate CSCs in EOC has been hampered by the fact that CSCs have not yet been unequivocally defined in this disease. Nevertheless, antibodies targeting known CSC surface markers such as EpCAM have shown clinical benefit in the management of ascites in chemotherapy refractory EOC. Other approaches involve targeting CSC signalling pathways, such as Wnt, HH and Notch, with some Notch inhibitors showing evidence of clinical activity in phase I trials on solid tumours. However, the bone toxicity associated with Wnt-targeted therapies may preclude their use in EOC patients. Finally, CSC-targeting SMIs showing promise in preclinical EOC models include ALDH1A inhibitors and the anti-inflammatory drug, licofelone.

Target	**Drug**	**Details**	**Reference/trial number**
EpCAM + CD3 (T cell co-receptor)	Catumaxomab (Removab)	Phase II clinical trial for ascites in chemotherapy-refractory EOC. Completed. Prolonged puncture-free interval and improved quality of life.	NCT00326885 [233]
CD44 (hyaluronic acid receptor)	RO5429083 (mAb)	Phase I dose escalation study in advanced solid cancers. Completed. Response depended on CD44 splice isoform expression.	NCT01358903 [234]

	SPL-108 (uPA peptide)	Phase I safety and efficacy study combined with paclitaxel in EOC. Active.	NCT03078400
CD44v6 (hyaluronic acid receptor splice isoform)	AMC303 (mAb)	Phase I/Ib safety and pharmacokinetic study in advanced solid tumours of epithelial origin. Active.	NCT03009214
Smoothened (HH signalling)	Vismodegib (GDC-0449) (SMI)	Phase II. Placebo controlled trial as maintenance therapy in EOC patients in 2nd or 3rd complete remission. Completed. Sought magnitude in PFS was not achieved. Frequency of HH expression less than expected.	NCT00739661 [235]
	BMS-833923 (XL139) (SMI)	Phase I dose escalation in advanced solid tumours. Completed.	NCT01413906
	Sonidegib (LDE225) (SMI)	Phase Ib dose escalation in combination with paclitaxel in platinum resistant EOC. Completed. Modest clinical activity noted.	NCT02195973 [236]
γ-Secretase (Notch pathway)	RO4929097 (SMI)	Phase II. Monotherapy for recurrent and/or metastatic platinum resistant epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Completed. Had insufficient activity as a single agent.	NCT01175343 [237]
	LY900009 (SMI)	Phase I dose escalation study in advanced cancers. Completed. Limited activity as monotherapy.	NCT01158404 [238]
Pan-Notch	Crenigacestat (LY3039478) (SMI)	Phase I dose escalation study in advanced solid tumours. Active.	NCT02836600
	BMS-906024 (SMI)	Phase I dose escalation in advanced or metastatic solid tumours. Completed. Sustained Notch inhibition and clinical activity observed.	NCT01292655 [239]
DLL4 (Notch pathway)	MEDI0639 (mAb)	Phase I dose escalation in advanced solid tumours. Completed. Preliminary evidence of anti-tumour activity observed.	NCT01577745 [240]
Wnt receptor	Ipafricept (OMP-54F28) (Fzd8 cysteine rich domain fused to human Ig Fc)	Phase Ib dose escalation study in combination with carboplatin and paclitaxel in patients with recurrent platinum sensitive EOC. Completed. Bone toxicity limits further development in EOC.	NCT02092363 [241]
	Vantictumab (OMP-18R5)	Phase I dose escalation in advanced solid tumours. Completed. Interim results suggested manageable bone toxicity and clinical activity in neuroendocrine tumours.	NCT01345201 [242]
Beta-catenin/CBP (Wnt pathway)	PRI-724 (SMI)	Phase I dose escalation in advanced solid tumours. Terminated due to low enrolment.	NCT01302405 [243]

Porcupine (Wnt signalling)	ETC-1922159 (SMI)	Phase I dose escalation in advanced solid tumours, as monotherapy and in combination with CPI (Pembrolizumab). Active.	NCT02521844
TGF-β	AVID200 (TGF-β ectodomain fused to human IgG Fc)	Phase I dose escalation in advanced solid tumours. Active.	NCT03834662
	Vactosertib (TEW-7197) SMI of TGFBR1	Phase I dose escalation in advanced solid tumours. Completed. Clinical activity associated with tumour fibroblast TGF-β response expression signature.	NCT02160106 [244]
Pan PI3K/mTOR (integrin-targeted prodrug)	SF1126 (SMI)	Phase I dose escalation in advanced solid tumours and B cell malignancies. Completed. Stable disease was best response.	NCT00907205 [245]
Pan PI3K/mTOR	SAR245409 (SMI)	Phase Ib dose escalation study of SAR245409 in combination with MEK inhibitor (MSC1936369B; Pimasertib) in advanced solid tumours. Completed. Partial responses seen in 3 LGSCs.	NCT01390818 [246]
		Phase II RCT in combination with Pimasertib vs. Pimasertib and placebo in recurrent unresectable LGSC. Completed. Pimasertib alone was just as effective.	NCT01936363 [247]
CXCR4 (SDF-1α/CXCL12)	Plerixafor (Mozobil) (SMI)	Phase I dose escalation in advanced pancreatic, ovarian (HGSC), and colorectal cancers. Completed.	NCT02179970
	LY2510924 (SMI)	Phase I dose escalation in advanced solid tumours in combination with PD-1/PD-L1 blocker (Durvalumab). Terminated.	NCT02737072
	MSX-122 (SMI)	Phase I dose escalation for refractory metastatic or locally advanced solid tumours. Suspended.	NCT00591682
STAT3	BBI608 (Napabucasin) (SMI)	Synergised with paclitaxel and reduced tumour burden in an endometrioid/CCOC cell line xenograft model and a syngeneic murine model of EOC.	[248]
COX/5-LOX	Licofelone (SMI)	Reversed stem-like properties in HGSC and non-HGSC cell lines and synergised with paclitaxel in an HGSC PDX model.	[249]
ALDH1A	637A (SMI)	Pan-ALDH1A SMI selectively killed CSCs in HGSC and non-HGSC cell lines and synergised with cisplatin *in vitro* and *in vivo*.	[250]
ALDH1A1	CM37 (SMI)	Isoform-specific SMI inhibited HGSC spheroid formation *in vitro* and	[251]

		ALDH1A1 knockdown reduced *in vivo* tumour formation	
Survivin (EMT)	MX106 (SMI)	Overcame chemoresistance of HGSC and non-HGSC cell lines *in vitro* and inhibited tumour growth and metastasis in a xenograft model.	[28]
Secreted clusterin (EMT)	AB-16B5 (mAb)	Phase I dose escalation in advanced solid malignancies. Completed. Some evidence for EMT modulation and disease stabilisation.	NCT02412462 [252]

Table 3. Examples of cancer stem cell/EMT-targeted drugs relevant to ovarian cancer – preclinical studies and clinical trials. Adapted from [232]. Abbreviations: EOC: epithelial ovarian cancer, HGSC: high grade serous ovarian carcinoma, LGSC: low grade serous ovarian carcinoma, EMT: epithelial-mesenchymal transition, CSC: cancer stem cell, EpCAM: epithelial cell adhesion molecule, PI3K: phosphoinositide 3-kinase, mTOR: mammalian target of rapamycin, HH: Hedgehog, DLL4: Delta like canonical notch ligand 4, uPA: Urokinase-type plasminogen activator, Fzd8: Frizzled-8, CXCR4: C-X-C chemokine receptor 4, SDF-1α: Stromal cell derived factor 1α, STAT3: Signal transducer and activator of transcription 3, COX: Cyclooxygenase, 5-LOX: 5-Lipoxygenase, CPI: checkpoint inhibitor CBP: CREB binding protein, ALDH1A: Aldehyde dehydrogenase 1A, SMI: small molecule inhibitor, mAb: monoclonal antibody, PFS: progression-free survival, PDX: patient-derived xenograft.

7. Metabolism and therapy resistance

7.1. Glycolysis, oxidative phosphorylation and the pentose phosphate pathway

The reliance on aerobic glycolysis for ATP production over that of mitochondrial respiration (the Warburg effect), is considered to be a hallmark of cancer. Although less efficient at generating ATP than oxidative phosphorylation (OXPHOS), aerobic glycolysis favours anabolic reactions required by proliferating cells and also protects cells from oxidative stress through NADPH generated via the oxidative branch of the pentose phosphate pathway (PPP). Nevertheless, aerobic glycolysis is also a feature of normal cells that are rapidly proliferating, such as activated T cells. Moreover, cancer cells are capable of OXPHOS, reflecting their metabolic plasticity and ability to adapt to fluctuating nutrient and oxygen availability within the TME [253-256]. Perhaps due to this plasticity, contradictory findings on the association of glycolytic activity with chemoresistance in EOC emanate from studies on both cell lines and primary cultures. However, regardless of glycolytic capability, enhanced OXPHOS and resistance to glucose deprivation appear to be common metabolic features of platinum resistance in these studies [257-260]. Enhanced OXPHOS has been observed in platinum resistance acquired in PDX models of HGSC [258, 261], and oxidative metabolism has been shown to drive IL-6 and CXCL8 mediated inflammation and chemoresistance in HGSC cell lines [262]. On the other hand, targeting glycolysis with 2-deoxyglucose (2DG) has been shown to sensitise a non-HGSC EOC cell line to cisplatin [263]. However, 2-DG also inhibits other pathways of glucose utilisation (see later), so this effect may not be due to targeting glycolysis *per se*. Pastò *et al.* [258] identified an association between clinical platinum resistance (relapse at <6 months) and resistance to glucose deprivation in primary EOC cells isolated from ascitic fluid following carboplatin therapy. Resistant cells also showed enhanced OXPHOS, increased autophagy and increased platinum resistance *in vitro* and in xenografts. This association was independent of EOC subtype, and also predicted clinical resistance in a cohort of chemonaïve patients. Thus, contrary to predictions of the Warburg hypothesis, glucose addiction appears to correlate with good prognosis in EOC and elevated OXPHOS appears to be associated with activation of pro-survival mechanisms such as enhanced autophagy, engendering resistance to

nutrient depletion as well as chemoresistance. Studies on EOC CSC metabolism have also led to discrepant findings. For example, spheroid cultures of an established endometrioid EOC cell line and of cell lines derived from primary HGSCs showed stem-like characteristics, chemoresistance and enhanced glycolytic activity [264]. However, other studies have shown that increased OXPHOS and resistance to glucose deprivation is a feature of CSCs from primary EOCs [265], and that targeting the stem cell marker ALDH1A sensitised non-HGSC and HGSC cell lines/primary tumours to platinum *in vivo* and selectively killed CSCs partly by inducing mitochondrial uncoupling proteins and reducing OXPHOS [250]. Thus, observations regarding glycolysis *vs.* OXPHOS in platinum resistance may be context dependent. Lastly, whether elevated OXPHOS is causally related to platinum resistance remains to be determined. Although biguanide drugs such as metformin inhibit OXPHOS at high concentrations by inhibiting mitochondrial complex I [266], at therapeutic doses their effects may be mediated through compensatory activation of the energy sensor AMPK-activated protein kinase (AMPK; see later).

As mentioned above, the oxidative branch of the PPP generates NADPH, which participates in biosynthetic reduction reactions and also protects against oxidative stress by regenerating reduced glutathione (GSH). As platinum drugs exert cytoplasmic toxicity by sequestering GSH and generating ROS, upregulation of PPP activity is associated with platinum resistance [267]. Increased G6PD expression and PPP activity was identified in chemoresistant EOC cell line models, while inhibition of G6PD, the gateway enzyme to PPP, increased platinum sensitivity [260, 268]. While reduced glycolysis and increased reliance on OXPHOS would lead to reduced PPP-mediated NADPH production, OXPHOS requires enhanced oxidative stress response and detoxification mechanisms associated with chemoresistance [269].

7.2. Amino acid metabolism

Chemoresistant EOC cells were shown to have increased dependence on glutamine as an energy substrate, which was metabolised via the TCA cycle and OXPHOS; this dependence was downstream of c-myc induced glutamine transporter ASCT2 and mitochondrial glutaminase (GLS) expression. Both GLS knockdown and inhibition sensitised resistant HGSC and endometrioid EOC cell lines to platinum *in vitro* [270]. It is known that glutamine fed into the TCA cycle can generate NADPH by malic enzyme-mediated conversion of malate to pyruvate, which protects cells against oxidative stress and may be a mechanism of glutamine-mediated platinum resistance. A subsequent study confirmed that a platinum resistant endometrioid EOC cell line was dependent on glutamine metabolism; however, in this model, glutamine was principally used for nucleotide biosynthesis rather than in OXPHOS or to replenish TCA cycle intermediates (anaplerosis) [271]. Glutamine and cysteine metabolism may also be a factor in the intrinsic chemoresistance of CCOCs. HNF-1β, a transcription factor whose expression is characteristic of this EOC histotype, was shown to protect against oxidative stress, perhaps reflecting its evolution in the endometriotic cyst, an environment rich in free iron and ROS [272]. In a CCOC cell line, glutamine was metabolised exclusively to GSH and other amino acids, and HNF-1β-mediated upregulation of the GSH biosynthetic enzyme, glutamate-cysteine ligase catalytic subunit (GCLC), enhanced GSH production and carboplatin resistance *in vitro* and *in vivo* [273]. Another group showed HNF-1β to increase glucose uptake and glycolysis in CCOC cell lines whilst reducing proliferation rates [274]. The same group found increased expression of GCLC and the cystine importer rBAT together with increased intracellular GSH levels. HNF-1β was also found to increase platinum resistance under hypoxic conditions, reduce levels of ROS and protect cells against extracellular oxidising agents. However, there was no evidence for enhanced PPP activity or NADPH production

[275]. Since mitochondrial respiration rates were not measured, the exact mechanisms through which HNF-1β maintains redox balance remain to be elucidated.

7.3. Glycogen metabolism

The ability to store glycogen as a source of glucose is thought to enable cancer cells to adapt to hypoxic and glucose deficient microenvironments thus enabling survival in conditions of metabolic and oxidative stress [276]. A metabolic trait particular to CCOCs is their high levels of cytoplasmic glycogen stores. A study on a CCOC cell line revealed that hypoxia induced glycogen synthesis via HIF-1α-mediated induction of glycogen synthase (GYS)1 in cooperation with PI3K/AKT-mediated phosphorylation and inactivation of glycogen synthase kinase (GSK)3β. Hypoxia also increased resistance to platinum treatment, although a direct role for glycogen metabolism in chemoresistance was not identified [277]. However, a recent study showed that 2-deoxyglucose (2DG) enhanced carboplatin sensitivity of CCOC cell lines *in vitro* and that dual treatment was accompanied by reduced glycogen synthesis. 2DG treatment also synergised with carboplatin in CCOC PDX models. Moreover, these effects were achieved using less than 10-fold the dose of 2DG than those reported for other cancer types, which would avoid the known toxicities associated with this drug [278]. 2DG inhibits glycolysis but also has other metabolic effects such as inhibition of the PPP and N-linked glycosylation [279]. However, its hexokinase metabolite, 2-deoxyglucose-6-phosphate, may also be a competitive inhibitor of phosphoglucomutase, which carries out the first step of glycogen synthesis [280]. Taken together, the evidence suggests reliance on glycogen utilisation is a targetable metabolic vulnerability in CCOC.

7.4. Metabolic coupling in the tumour microenvironment

The metabolism of cancer cells is intimately linked to that of other cells within the TME, which evolves out of a state of competition for limited nutrients towards a state of 'symbiosis/ parasitism', where cancer cells subvert the metabolism of normal cells within the TME to support tumour growth and progression [281]. The best known example of this paradigm of metabolic coupling is the 'reverse Warburg effect' [282], whereby cancer cells generate ROS which induces aerobic glycolysis in neighbouring CAFs through activation of NF-κB. In turn CAFs generate lactate, which is shuttled into cancer cells via monocarboxylate transporters (MCTs) to be metabolised via the TCA cycle and OXPHOS after conversion to pyruvate. In a hereditary HGSC cell line, tumour cell ROS production was found to driven by mutant *BRCA1* [283], whereas EOC tumour cell-secreted LPA has also been shown to rapidly induce a glycolytic shift in normal fibroblasts as well as CAFs [113]. Another example of fibroblast-cancer cell metabolic coupling is the recent finding that CAFs isolated from HGSCs supported glycogen utilisation by HGSC and non-HGSC cell lines under normoxia via p38MAPK-dependent cytokine release (e.g. CCL5, CXCL10, IL-6), resulting in phosphorylation and activation of phosphoglucomutase-1. The mobilised glucose was used to fuel glycolysis and the PPP, facilitating tumour cell proliferation and early metastasis [284].

The metabolic coupling between EOCs adipocytes in the omentum plays a central role in EOC progression and therapy resistance. As described earlier, the ability of EOCs to utilise fatty acids in the adipose-rich TME initiates and sustains peritoneal metastasis [285], whereby EOCs stimulate lipolysis in omental adipocytes, causing them to release free fatty acids into the TME. Omental adipocytes induce expression of the fatty acid receptor CD36 in HGSC and non-HGSC cell lines, facilitating fatty acid uptake [286]. EOCs shift their metabolism away from glycolysis and towards fatty acid oxidation (FAO) and - paradoxically - lipid biosynthesis (see later), promoting tumour progression and metastasis [286, 287]. Expression of salt-inducible kinase (SIK)2 in EOCs appears necessary for metastatic colonisation of the adipose-rich

omental microenvironment. Omental adipocytes were shown to induce calcium-dependent autophosphorylation of SIK2 in HGSC, CCOC and endometrioid EOC cell lines. In turn, SIK2 augmented AMPK-induced phosphorylation and inactivation of acetyl CoA carboxylase (ACC) and also stimulated cell proliferation in a PI3K/AKT-dependent manner. ACC performs the first step in fatty acid biosynthesis and its product, malonyl CoA, is an allosteric inhibitor of carnitine palmitoyltransferase (CPT)1, the rate limiting enzyme of FAO. Thus adipocyte-induced SIK2 activation enhanced FAO in EOC cells [288]. Intriguingly, SIK2 appears to be a multifunctional protein which also localises to the centromere and is required for the initiation of mitosis, and its depletion was found to sensitise non-HGSC cell lines to paclitaxel in culture and in xenograft models [289]. A recent study also implicated the fatty acid transporter FABP4 in EOC fatty acid metabolism and chemoresistance: co-culture of HGSC and non-HGSC cell lines with omental adipocytes induced increased expression of CD36 and FABP4 fatty acid transporters. Knockdown of FABP4 resulted in manifold epigenetic and metabolic changes including reduced FAO, ROS and lipid peroxidation, while an SMI of FABP4 increased sensitivity to carboplatin *in vitro* and *in vivo* [290]. Enhanced FAO may also enable survival in the ascitic microenvironment, since targeting CPT1A was shown to reduce anoikis resistance and spheroid formation in HGSC cell lines and reduce tumour burden in a PDX model of HGSC [291]. Furthermore, somatic deletion of the transcriptional repressor NKX2–8 in HGSC may provide an added survival advantage in the lipid rich peritoneal microenvironment. NKX2-8 knockout in HGSC cell lines led to metabolic reprogramming towards enhanced fatty acid oxidation and increased platinum resistance *in vivo* and in adipocyte conditioned medium, and its deletion was associated with clinical platinum resistance [292]. An intriguing link between lipid metabolism and the TME, was the discovery that the ECM protein collagen (COL)11A1, expressed by CAFs and some EOCs, enhanced platinum resistance, fatty acid oxidation and biosynthesis in HGSC, CCOC and endometrioid EOC cell lines via discoidin domain receptor (DDR)2-Src-Akt-AMPK activation [293]. The mechanism through which FAO contributes to platinum resistance has not been fully elucidated. While it is known to protect cells against ROS through NADPH production via malic enzyme and isocitrate dehydrogenase 1 (IDH1) [294], this is in the context of energy stress where the PPP is impaired, which is signalled by the energy sensor AMPK [295]. Moreover, targeting fatty acid synthase (FASN) has also been shown to sensitise non-HGSC cell lines and primary HGSCs to platinum therapy *in vitro* and *in vivo* [296, 297]. While simultaneous activation of fatty acid oxidation and lipid biosynthesis appears bioenergetically unfavourable, evidence from breast cancer cells suggests it affords the flexibility to channel redox potential to cytosolic NADPH in conditions of high oxidative stress, or to the mitochondrion for respiration when oxidative stress is low [298].

Other perturbations in lipid metabolism are manifest in EOC CSCs, which have been shown to have elevated levels of unsaturated lipids. This is hypothesised to maintain stemness by increasing membrane fluidity, which facilitates asymmetric cell division and self-renewal [299]. Inhibition of fatty acid desaturases, particularly SCD1, inhibited sphere formation in non-HGSC cell lines and primary HGSC cells *in vitro*, and also inhibited cell line tumour initiation *in vivo*. Upregulation of SCD1 expression was mediated by NF-κB in a positive feedback loop [300].

One *caveat* to bear in mind in the field of cancer metabolism is the fact that many *in vitro* experimental systems use culture media with supraphysiological glucose concentrations, which are above normal blood levels and well above those expected in highly proliferative, poorly vascularised tumours [301]. Although discrepant findings regarding EOC metabolism and chemoresistance may reflect metabolic plasticity and heterogeneity of primary tumour cells and cell lines, differences in medium nutrient composition may also play a role, especially in

studies relying solely on *in vitro* experiments. *In vivo* metabolic flux analysis using metabolites labelled with stable isotopes has the potential to shed light on the metabolic heterogeneity of EOCs as it has for other solid tumours such as lung cancer [302]. Nevertheless, mechanistic insights into cancer metabolism rely to some degree on *in vitro* models, so attempts to better characterise and replicate the nutrient composition of EOC TMEs would greatly assist in identifying exploitable metabolic vulnerabilities.

7.5. Metabolism-targeted therapies

Given that metabolic reprogramming is a cancer hallmark, there has been considerable interest in the development/repurposing of drugs to exploit metabolic vulnerabilities in cancer. Table 4 summarises some of the preclinical and clinical studies of these drugs in EOC. The drug 2DG inhibits hexokinase and phosphoglucoisomerase and has been used for many years as an experimental inhibitor of glycolysis. Other effects of 2DG include inhibition of glucose transporters, increased oxidative stress via inhibition of the PPP, induction of autophagy and, at high doses, inhibition of N-linked glycosylation leading to ER stress [279]. 2DG has been shown to sensitise EOC cell lines to platinum drugs *in vitro*. However, results of phase I clinical trials of 2DG alone or as a combination with conventional chemotherapy on advanced solid tumours have not achieved significant therapeutic benefit at tolerable doses [303, 304]. Nevertheless, preclinical *in vivo* data suggest that CCOCs may be particularly vulnerable to the effects of 2DG on glycogen metabolism, and physiologically achievable doses of 2DG synergise with carboplatin, as discussed earlier [278]. Other areas explored *in vitro* are 2DG combination treatments targeting different metabolic pathways [305, 306]. SMIs targeting specific enzymes/transporters involved in glycolytic metabolism are currently in development and include the MCT1 inhibitor AZD3965 which targets lactate influx/efflux. AZD3965 has shown anti-tumour effects in preclinical models of solid tumours such as lung and breast cancer [307, 308] and a phase I clinical trial on solid tumours and lymphomas is ongoing. MCT1 expression is associated with disease progression in EOC [309] and knockdown of MCT sensitised an endometrioid EOC cell~~s~~ line to cisplatin *in vitro* and *in vivo* [310], suggesting a potential benefit of this approach.

The anti-diabetic drug metformin inhibits mitochondrial respiration, leading to activation of the energy sensor AMPK which switches cells from anabolic to catabolic metabolism, enhancing fatty acid oxidation and inhibiting fatty acid synthesis. Metformin has been shown to inhibit CSC formation in non-HGSC cell line tumour spheres [311], and to sensitise HGSC PDX tumours to cisplatin [261]. A phase II clinical trial combining metformin with conventional chemotherapy confirmed these observations in HGSC samples *ex vivo*. Moreover, interim results suggested survival was longer than expected, supporting the use of metformin in phase III trials [312]. Preclinical *in vitro* and xenograft data also support the combination of metformin with PARP inhibitors, where there appears to be a benefit even in *BRCA* wild-type EOC cell lines [313].

The requirement for glutamine has been shown to dramatically increase in transformed cells [314]. The first step in glutamine utilisation is carried out by GLS, and the GLS-targeted SMI Telaglenastat (CB-839) has been shown to induce apoptosis in cultured non-HGSC cell lines [315]. This drug has been shown to synergise with PARP inhibitors in VHL-mutated renal cell carcinomas in a HIF-2α dependent manner [316]. As EOCs frequently have upregulated HIF-1/2α, a phase I clinical trial investigating CB-839 in combination with Niraparib in platinum resistant HGSCs and CCOCs is currently under way. The pyruvate dehydrogenase complex/oxoglutarate dehydrogenase complex inhibitor Devimistat (CPI-613) prevents entry of both glucose and glutamine into the TCA cycle, and is currently undergoing a phase III trial

in pancreatic cancer as a combination therapy [317]. Specific activity of CPI-613 against ovarian CSCs has been observed in preclinical studies using HGSC cell lines [318].

Unlike most adult tissues, cancer cells carry out *de novo* fatty acid biosynthesis. Fatty acid synthase inhibitors have shown efficacy against multiple cancer types, including EOC, where sensitisation to cisplatin has been observed *in vitro* and *in vivo* [296, 297] (Table 4). A series of next generation fatty acid synthase blockers with enhanced bioavailability have been developed, such as TVB-2640, which has achieved partial responses in advanced platinum resistant EOC when combined with paclitaxel [319]. SMIs of other fatty acid biosynthetic enzymes such as ATP-citrate lyase (ACLY) have also been developed recently [320], which may be active against HGSCs with *USP13* amplification [321]. On the other hand, targeting fatty acid oxidation using the CPT1A inhibitor Etomoxir also inhibits tumour growth in HGSC cell line xenografts [291]. However, clinical development of this drug has been halted due to severe hepatotoxicity. Stearoyl CoA desaturase 1 (SCD1) produces monounsaturated fatty acids from stearate and palmitate and is essential for EOC CSC maintenance as described above [300]. SCD1 upregulation was shown to protect HGSC and non-HGSC cell lines from lipid peroxidation-mediated ferroptosis [322]. As ferroptosis is a newly recognised mechanism of cisplatin-mediated cell death [323], there is potential for a synergistic cytotoxic interaction. Development of tumour-specific CYP4F11-activated SDC1 inhibitors potentially avoids the toxic effects observed in *in vivo* models, in some tumour types [324].

Metabolic programming is central to the activation and differentiation of immune effector cells. Thus, potential effects of cancer-targeted metabolic therapies on immune function should be taken into consideration and ideally requires preclinical data from immunocompetent *in vivo* models. However, modulating immune function through metabolic targeting is a potential therapeutic strategy in cancer and immunometabolism is a rapidly growing field [325].

7.6. Summary and conclusions

Platinum resistance is associated with metabolic reprogramming in EOC, and understanding these adaptations may highlight targetable metabolic vulnerabilities. An emerging picture from cell line and PDX models indicates that platinum resistant EOC cells are inherently resistant to glucose deprivation and have elevated OXPHOS, features shared with EOC CSC phenotypes described by some studies. *In vitro* studies have demonstrated that metformin inhibits OXPHOS in cancer cells, although whether this is its mechanism of action at physiologically achievable doses remains uncertain. Nevertheless, metformin sensitises HGSC PDX tumours to cisplatin and interim results from a phase II clinical trial showed a reduction in CSC markers in tumours treated with neoadjuvant metformin. Several studies have identified increased dependence on glutamine in platinum resistant EOC cell lines, although there were differences in its metabolic fate. The glutaminase-targeted drug, Telaglenastat, has shown preclinical activity against EOC and is currently undergoing a phase I trial in platinum resistant EOC in combination with a PARP inhibitor. The ability to utilise glycogen stores may partly underly the inherent chemoresistance of CCOC, but also represents a particular metabolic vulnerability of this histotype. This is illustrated by its unique sensitivity to 2DG (which inhibits various aspects of glucose metabolism, including glycogen synthesis) in *in vivo* models at doses that would be achievable clinically.

Metabolic coupling between tumour cells and omental adipocytes is fundamental to EOC disease progression. The associated metabolic shift in tumour cells towards increased fatty acid oxidation and lipid biosynthesis engenders chemoresistance, although the mechanisms involved have not been fully defined. However, agents which target fatty acid oxidation such

as Etomoxir are associated with significant hepatotoxicity, which precludes their clinical use. By contrast, targeting fatty acid synthesis appears to be less toxic and several small molecule inhibitors of fatty acid biosynthetic enzymes are in preclinical/clinical development in EOC.

Finally, while EOC metabolic vulnerabilities have been highlighted by *in vitro* studies, such studies do not capture the metabolic heterogeneity of the TME and the ability of tumour cells to adapt to fluctuating microenvironmental conditions. Techniques measuring metabolic flux *in vivo*, complemented by *in vitro* studies that better represent the *in vivo* environment of EOC, together with the study of stromal and immune effector cell metabolism, will accelerate the development of targeted therapies.

Target	**Drug**	**Details**	**Reference/trial number**
Hexokinases Glucose metabolism Glycogen metabolism	2-deoxyglucose (2DG)	Sensitised HGSC and non-HGSC ovarian cancer cell lines to cisplatin and carboplatin *in vitro*.	[326]
		Low doses sensitised CCOC tumours to carboplatin by disrupting glycogen utilisation in cell line and PDX models.	[278]
		2DG combined with metformin caused growth arrest and apoptosis of non-HGSC cell lines *in vitro*.	[305]
		Synergised with glutaminolysis inhibitor (aminoxyacetate) to inhibit non-HGSC cell line growth *in vitro*.	[306]
MCT1 (lactate transport)	AZD3965	Phase I dose escalation study in advanced solid tumours or lymphomas. Active.	NCT01791595 [327]
Mitochondrial complex I (activation of AMPK metabolic switch)	Metformin	Sensitised HGSC tumours to cisplatin in PDX models of platinum resistance.	[261]
		Phase II clinical trial of metformin as neoadjuvant/adjuvant therapy combined with platinum-based chemotherapy in stage II-IV EOC. Completed. Decreased CSCs and increased tumour cell platinum sensitivity *ex vivo*.	NCT01579812 [312]
		Preclinical study combining Metformin with PARP inhibitor (Olaparib) on HGSC and non-HGSC cell lines *in vitro* and in non-HGSC cell line xenografts showed significant anti-tumour effect regardless of *BRCA1* status.	[313]
	IM156 (Metformin derivative with increased potency)	Phase I clinical trial in advanced solid tumours and lymphoma. Active.	NCT03272256
GLS (glutaminolysis)	CB-839 (Telaglenastat)	Enhanced sensitivity of non-HGSC cell lines to PI3K/mTOR inhibitors and induced apoptosis as a single agent *in vitro*.	[315]
	CB-839 (Telaglenastat)	Phase I Dose escalation of CD-839 in combination with PARP inhibitor	NCT03944902

		(Niraparib) in platinum resistant *BRCA* wild-type ovarian cancer patients. Active.	
PDC OGDC (TCA cycle)	CPI-613 (Devimistat)	Specifically targeted HGSC cell line CSCs, reduced sphere formation *in vitro* and tumourigenicity *in vivo.*	[318]
FASN (fatty acid synthesis)	Cerulenin	Induced apoptosis and sensitised non-HGSC cell lines and primary EOC cells to cisplatin.	[296]
	Orlistat	Increased platinum sensitivity in a platinum resistant endometrioid EOC cell line xenograft model.	[297]
	TVB-3166	Induced apoptosis and anoikis in HGSC and non-HGSC cell lines *in vitro*. Inhibited tumour growth in a cell line xenograft model.	[328]
	TVB-2640	Phase I clinical trial in advanced solid tumours. Completed. Prolonged stable disease observed with monotherapy and partial responses observed when combined with paclitaxel in EOC.	NCT02223247 [319]
ACLY (fatty acid synthesis)	Knockdown of USP13	*USP13* amplification frequent event in HGSC and activates ACLY and α-ketoglutarate dehydrogenase. Knockdown of USP13 inhibited cell line xenograft growth and synergised with PI3K/AKT inhibition.	[321]
	NDI-091143	Low nanomolar allosteric inhibitor of ACLY (drug development study).	[320]
CPT1A (fatty acid oxidation)	Etomoxir	Sensitised HGSC cells to anoikis and inhibited growth in PDX model.	[291]
	Perhexiline	Sensitised *NKX2-8*+/- HGSC cell lines to cisplatin in an adipose microenvironment and *in vivo* (cell line and PDX models).	[292]
SCD1 (monounsaturated fatty acid synthesis)	CAY10566	Induced lipid peroxidation, ferroptotic and apoptotic cell death in HGSC and non-HGSC cell lines. Sensitised HGSC cell lines to ferroptosis inducers *in vivo*.	[322]
		Inhibited HGSC and non-HGSC cell line and primary EOC sphere formation *in vitro* and cancer initiating capacity *in vivo*.	[300]

Table 4. Examples of metabolism-targeted drugs relevant to ovarian cancer – preclinical studies and clinical trials.

Abbreviations: EOC: epithelial ovarian cancer, HGSC: high grade serous ovarian carcinoma, CCOC: clear cell ovarian carcinoma, CSC: cancer initiating stem cell, PDX: patient-derived xenograft, MCT1 monocarboxylate transporter 1, GLS: mitochondrial glutaminase, PDC: pyruvate dehydrogenase complex, OGDC: oxoglutarate dehydrogenase complex, ACLY: ATP-citrate lyase, USP13: Ubiquitin specific peptidase 13, CPT1A: carnitine palmitoyltransferase 1, FASN: fatty acid synthase, SCD1: stearoyl CoA desaturase 1. AMPK: 5' adenosine monophosphate-activated protein kinase, *NKX2-8*: NK homeobox 8.

8. Summary and closing remarks

Platinum resistance remains a significant obstacle in the treatment of EOC. While the genetic landscape of EOCs contributes to intrinsic or acquired platinum resistance, therapeutic outcome is profoundly influenced by the TME, where the interplay of stromal, immune and metabolic factors can directly or indirectly modulate response to therapy. The TME is thus an attractive target both to sensitise EOCs to platinum therapy, or as alternative therapeutic strategy for platinum resistant disease. Given that cancer-associated stroma can have a tumour limiting role in some contexts, current thinking holds that it is preferable to normalise - rather than eliminate - CAFs in order to inhibit the formation of resistance promoting CSC niches, as well as to improve drug perfusion by inhibiting stromal fibrosis.

Our concept of tumour cell metabolism has also changed since the original Warburg hypothesis, in that the TME has taken centre stage: cancer cells are now recognised as being metabolically plastic and able to adapt to fluctuating microenvironmental stresses as well as co-opting neighbouring cells for their metabolic needs. Understanding how these specific interrelationships in the unique EOC TME contribute to platinum resistance and evolve during chemotherapy exposure is key to developing effective metabolism-targeted therapeutic strategies.

Despite original expectations, initial checkpoint inhibitor trials have proved disappointing in the management of EOC. However, combination therapies employing anti-angiogenic drugs aimed at normalising the tumour vasculature to improve lymphocyte infiltration/drug delivery appear promising. Given the central role of TAMs in modulating immune responses, targeting TAMs may be a useful adjunct to checkpoint inhibitor/immune therapies. Again, analogously to CAFs, strategies to normalise or, in this instance, repolarise rather than eliminate TAMs may prove advantageous. The effects of different chemotherapy drugs on local and systemic immune function have become particularly relevant in the era of immunotherapy. Identifying the best combinations/sequences is the next challenge in the therapeutic management of EOC.

Finally, since current preclinical models of the ovarian TME cannot capture the variation exhibited by clinical EOCs, either between or within different histotypes, clinical trials need to be accompanied by detailed molecular profiling. This strategy is necessary for the identification of robust biomarkers predictive of therapeutic response which will drive the development of personalised therapy.

List of abbreviations

AA: arachidonic acid
ABCA1: ATP binding cassette subfamily A member 1
ABCB1: ATP Binding Cassette Subfamily B Member 1/ Multidrug resistant 1 (MDR1)
ABCG2: ATP binding cassette subfamily G member 2 (Junior Blood Group)
ABHD2: Abhydrolase domain containing 2
ACC: Acetyl Coenzyme A carboxylase
ACLY: ATP-citrate lyase
AKT2: AKT Serine/Threonine Kinase 2 (protein kinase B)
ALDH1A: Aldehyde dehydrogenase 1A
AMPK: 5' adenosine monophosphate-activated protein kinase
APAF1: Apoptotic peptidase activating factor 1
ARID1A: AT-rich interaction domain 1A
ASCT2: Sodium-dependent neutral amino acid transporter type 2/ Solute carrier family 1 member 5 (SLC1A5)
ATM: Ataxia telangiectasia mutated serine/threonine kinase
ATR: ATR serine/threonine kinase
BAX: BCL2 associated X, apoptosis regulator
Bcl-2: B cell lymphoma 2 (BCL2 apoptosis regulator)
BER: Base excision repair
BIRC5: Baculoviral IAP repeat containing 5 (Apoptosis inhibitor survivin)
BMP: Bone morphogenetic protein
BRAF: B-Raf proto-oncogene, serine/threonine kinase
BRCA1/2: Breast cancer gene 1/2
c-kit: KIT proto-oncogene, receptor tyrosine kinase
CA-MSC: Cancer associated mesenchymal stem cell
CAF: Cancer-associated fibroblast
CBP: CREB binding protein (CREBBP)
CBX2: Chromobox 2
CCL2: C-C Motif chemokine ligand 2 (MCP-1/ monocyte chemoattractant protein-1)
CCL3: MIP-1α (macrophage inflammatory protein-1 alpha)
CCL4: MIP-1β (macrophage inflammatory protein 1 beta)
CCL5: RANTES (regulated upon activation, normal T cell expressed and secreted)
CCL7: MCP-3 (monocyte chemoattracting protein-3)
CCL18: MIP-4
CCL20: MIP-3α
CCNE1: Cyclin E1
CCOC: Clear cell ovarian carcinoma
CCR5: C-C Motif chemokine receptor 5
CD: Cluster of differentiation
CDKN2A/B: Cyclin dependent kinase inhibitor 2A/B
CFTR: CF transmembrane conductance regulator
cIAP: Cellular inhibitor of apoptosis
COL11A1: Collagen type XI alpha 1 chain
COX: Cyclooxygenase
CPT1: Carnitine palmitoyltransferase 1
CREB: cAMP responsive element binding protein
CSC: Cancer initiating stem cell
CSF1: Colony stimulating factor 1 (M-CSF/macrophage colony stimulating factor)
CSF2: GM-CSF (granulocyte-monocyte colony stimulating factor)

CSF3: G-CSF (granulocyte colony stimulating factor)
CSF1R: Colony stimulating factor 1 receptor
CTLA-4: Cytotoxic T-lymphocyte-associated protein 4
CTNNB1: Catenin beta 1
CTR1: Copper transporter 1 (SLC31A1; Solute carrier family 31 member 1)
CXCL1/2: C-X-C motif chemokine ligand 1/2 (Gro-α/β)
CXCL8: IL-8
CXCL10: Interferon-γ induced protein (IP-10)
CXCL11: I-TAC (Interferon-inducible T-cell alpha chemoattractant)
CXCL12: SDF-1 (Stromal cell-derived factor-1)
CXCR2: C-X-C motif chemokine receptor 2
CYP450: Cytochrome P450
CYP4F11: Cytochrome P450 family 4 subfamily F member 11
DAMPs: Damage associated molecular patterns
DDR2: Discoidin domain receptor tyrosine kinase 2
2DG: 2-Deoxyglucose
DFMO: α-Difluoromethylornithine
DMC1: DNA meiotic recombinase 1
DOK2: Docking protein 2
DSB: Double-strand break
ECM: Extracellular matrix
EET: Epoxyeicosatrienoic acid
EGF: Epidermal growth factor
EGFR: Epidermal growth factor receptor
ELK: ETS Transcription factor ELK1
EMA: European medicines agency
EMSY: EMSY transcriptional repressor, BRCA2-interacting
EMT: Epithelial-mesenchymal transition
EOC: Epithelial ovarian cancer
ER: Endoplasmic reticulum
ERBB2: Erb-B2 receptor tyrosine kinase 2 (HER2)
ERCC1: ERCC excision repair 1, endonuclease non-catalytic subunit
ETS-1: ETS proto-oncogene 1, transcription factor
EV: Extracellular vesicle
FABP4: Fatty acid binding protein 4
FAK: Focal adhesion kinase
FAO: Fatty acid oxidation (β-oxidation)
FAP: Fibroblast activation protein alpha
FASN: Fatty acid synthase
FDA: US food and drug administration
FIGO: International Federation of Gynaecology and Obstetrics
Gαi2: GNAI2 (G protein subunit alpha I2)
GCLC: Glutamate-cysteine ligase catalytic subunit
GGT5: γ-Glutamyltransferase 5
GLS: Glutaminase (mitochondrial)
GPCR: G protein coupled receptor
GSH: Glutathione (reduced)
GSK3β: GSK3B (glycogen synthase kinase 3 beta)
GSSG: Glutathione disulphide (oxidised)
GYS1: Glycogen synthase 1

5-HETE: 5-Hydroxyeicosatetraenoic acid
HGSC: High grade serous ovarian carcinoma
HH: Hedgehog
HIF-1α: Hypoxia Inducible factor 1 subunit alpha
HIF-2α: Hypoxia inducible factor 2α /EPAS1 (Endothelial PAS domain protein 1)
HKII: HK2 (hexokinase 2)
HNF-1β: hepatocyte nuclear factor-1β /HNF1B (HNF homeobox 1B)
HOXA9: Homeobox A9
HRR: Homologous recombination repair
ICD: Immunogenic cell death
ICL: Interstrand crosslink
IDH1: Isocitrate dehydrogenase (NADP+-dependent) 1
IFN: interferon
IKKβ: IKBKB (Inhibitor of nuclear factor kappa B kinase subunit beta)
IL: interleukin
iNOS: NOS2 (Inducible nitric oxide synthase)
IRF5: Interferon regulatory factor 5
JAK/STAT: Janus kinase/signal transducer and activator of transcription
KRAS: KRAS proto-oncogene, GTPase
LGSC: low grade serous ovarian carcinoma
LIF: LIF interleukin 6 family cytokine
LOX: Lipoxygenase
LPA: Lysophosphatidic acid
LPP: Lipoma preferred partner
LPS: Lipopolysaccharide
LTB_4: Leukotriene B_4
mAb: Monoclonal antibody
MAPK/ERK: Mitogen activated protein kinase/extracellular signal regulated kinase
MCT: Monocarboxylate transporter
MDSC: Myeloid-derived supressor cell
MET: MET proto-oncogene, receptor tyrosine kinase
ME1: Malic enzyme 1
MFAP5: Microfibril associated protein 5
MHC-II: Major histocompatibility complex, class II
MHEJ: Microhomology end-joining
MLC2: MYL2 (myosin light chain 2)
MMP: Matrix metalloproteinase
MMR: Mismatch repair
MMT: Mesothelial-to-mesenchymal transition
MSC: Mesenchymal stem cell
MSI: Microsatellite instability
mTOR: Mammalian target of rapamycin
MYC: MYC proto-oncogene, BHLH transcription factor
NER: Nucleotide excision repair
NET: Neutrophil extracellular trap
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
NF1: Neurofibromatosis type 1
NHEJ: Non-homologous end-joining
NK: natural killer
NKX2–8: NK2 homeobox 8

NNMT: Nicotinamide-N-methyl transferase
NOTCH1: Notch receptor 1
NRAS: NRAS proto-oncogene, GTPase
ODC: Ornithine decarboxylase
OXPHOS: Oxidative phosphorylation
PADI4: Peptidyl arginine deiminase 4
PARP: Poly (ADP-ribose) polymerase
PD-1/PD-L1: Programmed cell death protein-1/ (PD)-ligand 1
PDX: Patient-derived xenograft
PGE_2: Prostaglandin E_2
PI3K/AKT: Phosphoinositide 3-kinase/ protein kinase B
PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1
PLA2G7: Phospholipase A2 Group VII (secretory)
PPMID: Protein phosphatase, Mg2+/Mn2+ dependent 1D
PPP: Pentose phosphate pathway
PPP2R1A: Protein phosphatase 2 scaffold subunit alpha
PTEN: Phosphatase and tensin homologue
PTGER3: Prostaglandin E Receptor 3
PTUBP: 4-(5-phenyl-3-{3-[3-(4-trifluoromethylphenyl)-ureido]-propyl}-pyrazol-benzenesulfonamide
RAD51B: RAD51 paralogue B
RB1: Retinoblastoma
rBAT: Neutral and basic amino acid transport protein/ SLC3A1 (Solute carrier family 3 member 1)
ROS: Reactive oxygen species
SAM: S-adenosyl methionine
SCD1: Stearoyl-CoA desaturase 1
sEH: Soluble epoxide hydrolase
Siglec-10: Sialic acid binding Ig-like lectin 10
SIK2: Salt inducible kinase 2
SIRPα: Signal regulatory protein alpha
α-SMA: α-Smooth muscle actin (ACTA2; Actin alpha 2, smooth muscle)
SMAD3: Mothers against decapentaplegic homologue family member 3
SMI: Small molecule inhibitor
SNAI1; Snail family transcriptional repressor 1 (snail)
SNAI2: Snail family transcriptional repressor 2 (slug)
SOX2: SRY-box transcription factor 2
Src: SRC proto-oncogene, non-receptor tyrosine kinase
STAT: Signal transducer and activator of transcription
STIC: Serous tubal intraepithelial carcinoma
TAM: Tumour associated macrophage
TCA: Tricarboxylic acid cycle
TGF-β1: TGFB1 (Transforming growth factor-β1)
TIMP: Tissue inhibitor of metalloproteinase
TLR: Toll-like receptor
TME: Tumour microenvironment
TNF-α: Tumour necrosis factor alpha
TNF-β: Tumour necrosis factor-beta/ LTA: lymphotoxin alpha
TP53: Tumour protein 53

Treg: Regulatory T cell
uPA: Urokinase-plasminogen activator
USP: Ubiquitin specific peptidase
VDAC1: Voltage dependent anion channel 1
VEGF: Vascular endothelial growth factor
VHL: Von Hippel-Lindau tumour suppressor
Wnt7a: Wnt (Wingless) family member 7A
ZEB1: Zinc finger E-Box binding homeobox 1
ZNF217: Zinc finger protein 217

Figure Legends

Figure 1. Influence of the tumour microenvironment on ovarian cancer platinum resistance

Through their secretion of cytokines, growth factors, and lipid mediators, TAMs and CAFs induce EMT and stem-like properties in tumour cells. This leads to therapy resistance through upregulation of ABC transporters leading to increased drug efflux, increased replication bypass of platinum DNA lesions through upregulated DNA polymerase η, as well as activating the anti-apoptotic machinery. Prior to export, platinum drugs are conjugated via glutathione-S-transferase to reduced glutathione (GSH). This process is supported by CAFs through their supply of GSH and cysteine (used for GSH synthesis), and is inhibited by IFN-γ secreted by infiltrating $CD8^+$ T cells. Reduced GSH is regenerated from glutathione disulphide (GSSG) via NADPH. NADPH can be generated from glucose via anaerobic or aerobic glycolysis through the PPP. Cancer cells can also use alternative fuels (depicted in red) such as lactate, glutamate and FA, which are fed to the TCA cycle for mitochondrial respiration. In conditions of nutrient stress, NADPH can be generated from TCA intermediates derived from glutamine and FA via ME1 (glutamine and FA) and IDH1 (FA). CAF-secreted cytokines promote tumour cell glycogenolysis, which is also linked to platinum resistance. In omental metastases, tumour cells become metabolically coupled to adipocytes and switch to using FA as fuel by increasing FA oxidation. Active mitochondrial respiration engages pro-survival protective mechanisms against ROS that also increase platinum resistance. Tumour cells either produce lactate themselves or stimulate lactate production by CAFs. TAMs are recruited to regions of hypoxia and are polarised to a tumour promoting M2 phenotype via tumour secreted factors and lactate. Thus, mechanisms of platinum resistance may be context-specific, reflecting tumour cell adaptability to fluctuating microenvironmental conditions. Finally, CAFs and TAMs can contribute indirectly to chemotherapy resistance by creating a fibrotic stroma with leaky blood vessels, both of which lead to poor drug perfusion Abbreviations: CAF: cancer associated fibroblast, EMT: epithelial-mesenchymal transition, FA: fatty acids, FAO: fatty acid oxidation, GSH: glutathione (reduced), GSSG: glutathione disulphide (oxidised), IDH1: isocitrate dehydrogenase 1, LPA: lysophosphatidic acid, ME1: malic enzyme 1, PPP: pentose phosphate pathway, ROS: reactive oxygen species, TAM: tumour associated macrophage, TCA: tricarboxylic acid cycle.

Figure 2. Transcoelomic metastasis in ovarian cancer

Tumour cells are shed as single cells or as spheroid clusters into the peritoneal fluid, where they are carried passively to sites of metastasis. In parallel, factors secreted by primary tumours favour the creation of premetastatic niches in the omentum through the generation of CAFs from fibroblast, mesenchymal stem cell or mesothelial precursors, which facilitate tumour spheroid adhesion and invasion. Tumour-secreted cytokines also promote the recruitment of neutrophils to omental milky spots, which extrude chromatin to create NETs (neutrophil extracellular traps), a premetastatic niche which traps tumour cells circulating in the peritoneal fluid. Crosstalk between the colonising tumour cells and macrophages within the omental milky spots favours the acquisition of tumour cell CSC-like properties, increasing the number of CSCs in tumour spheroids, promoting ascites formation and widespread peritoneal metastases. Abbreviations CAF: cancer associated fibroblast, CSC: cancer stem cell, Mϕ: macrophage.

Figure 3. Macrophage polarisation within the ovarian cancer microenvironment
Tumour cells secrete cytokines such as TGF-β, as well as signalling molecules such LPA, HH, and Wnt ligands, which induce fibroblasts, mesothelial cells and mesenchymal stem cells to adopt a CAF-like phenotype. In turn, CAFs secrete various chemokines/cytokines into the TME which foster the acquisition of CSC-like properties in tumour cells. Through deposition of ECM components such as collagen, CAFs create a fibrotic stroma which is thought to contribute to immune suppression through reduced oxygen perfusion. Omental adipocytes secrete various cytokines/chemokines which trigger homing of tumour cells to the omentum. Mutual metabolic reprogramming between adipocytes and tumour cells results in lipolysis in the former and a metabolic switch towards fatty acid oxidation in the latter, which is associated with a metastatic chemoresistant phenotype. Polarisation of M1 macrophages towards M2-like TAMs occurs in response to signalling molecules including TGF-β, IL-4, IL-10, IL-13, CSF1 and PGE_2, as well as lactate and hyaluronan. Reverse polarisation to an M1 phenotype is promoted by IFN-γ, CSF2, TNF-α and stimulation of TLRs. M1 macrophages can directly kill tumour cells through ROS and NO production as well as by phagocytosis. Phagocytosis can be blocked via expression of CD24 and CD47 by tumour cells, which bind Siglec-10 and SIRPα, respectively. Through antigen presentation on MHC-II molecules, M1 macrophages promote an anti-tumour Type I adaptive immune response by stimulating TH1 cells via interactions between MHC-II and TCR along with costimulatory CD80/CD86:CD28 interactions, as well as cytokine-mediated stimulation of CD8+ cytotoxic T cells. Conversely, M2-like TAMs inhibit cytotoxic T cells/NK cells and recruit/stimulate Tregs through secretion of immunosuppressive cytokines/chemokines and promote the immunosuppressive functions of MDSCs through TGF-β secretion. TAMs also display the immune checkpoint ligand PD-L1 on their cell surface, which blocks cytotoxic T cell activity. TAMs secrete pro-angiogenic cytokines and release VEGF from the ECM via MMP-9 secretion, and promote tumour cell invasion through ECM remodelling. Through secretion of various factors such as EGF, TAMs promote a CSC-like phenotype in tumour cells. Together, these interactions create a pro-metastatic, chemoresistant and immunosupressive microenvironment. Abbreviations: CAF: cancer associated fibroblast, ECM: extracellular matrix, FA: fatty acid, HH: hedgehog, LPA: lysophosphatidic acid, MDSC: myeloid derived tumour suppressor cell, MHC: major histocompatibility complex, NK: natural killer cell, NO: nitric oxide, ROS: reactive oxygen species, TAM: tumour associated macrophage, TCR: T cell receptor, TH: T helper cell, Treg: regulatory T cell.

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