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Ovarian Cancer Recurrence: Role of Ovarian Stem Cells and Epithelial-to-Mesenchymal Transition

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Abstract

Despite the remarkable progress made in delineating the pathogenesis of ovarian tumor during the last two decades, the 5 years survival of these patients is very low, with 80% of them succumbing to their resistant disease. Understanding the key determinants of this resistance is of paramount importance if the prognosis of this tumor has to be improved. Here are summarized the role of cancer stem cells and epithelial to mesenchymal transition (EMT) in determining tumor recurrence in ovarian cancer. Indeed, the existence, and more importantly the acquisition of stem-cell traits by tumor cells both during tumor progression and during treatment might explain the ability of these cells to give rise to tumor recurrence and to be resistant to treatment.

Keywords: Ovarian cancer; Cancer stem cell; Epithelial to mesenchymal transition; Resistance to therapy

Introduction

Epithelial ovarian carcinoma (EOC) represents the sixth most common cancer in both European and North America women and the leading cause of death from gynecological malignancies [1,2]. This is due to the lack of effective screening tests accounting for advanced disease diagnosis and the fact that after an initial response to chemotherapy (combinations of platinum salts and taxanes), TUMORS relapse with chemo-resistant traits.

In the last years insights into the biology of ovarian carcinoma have questioned the historical view of its origin developing from the ovarian surface epithelium into cancers resemble the fallopian tube (serous), endometrium (endometrioid), mucin-secreting endo-cervical glands (mucinous) and glycogen-filled vagina rests (clear cell). Indeed, recently, ovarian cancer has been categorized in two types based on clinical, cellular, and molecular characteristics [3]. Type I EOCs are low grade and include low-grade-serous, -endometrioid, mucinous and a subset of clear cell carcinomas. They are relatively indolent, with large and confined masses to the ovary at diagnosis and, more importantly, are genetically stable. Type I tumors arise from morphologically recognizable precursor lesions such as endometriosis, cortical inclusion cysts or low precursor lesions (borderline tumors) in ovarian cortex [4,5]. Type II tumors include the high-grade serous carcinoma -HGSC-, high grade-endometroid carcinoma, undifferentiated carcinoma, some clear cell and carcinosarcomas. They are highly aggressive and disseminate early in their clinical course; are rarely associated with morphologically recognizable precursors lesions, and both the epithelium lining the ovary and the fallopian tube epithelium have been advocated as the cells of origin [6-9]. This classification better reflects the heterogeneity of the ovarian cancers. The recent efforts made by our laboratory to classify patient-derived ovarian xenografts based on Type I and II classification (Ricci et al, paper submitted) represent the first step in trying to personalize therapy in this disease.

The remarkable progress made on delineating the biology of ovarian tumor did not however translate into clinical therapeutic benefits, as the 5yr survival for this tumor in the last two decades increased only from 37 to 45% [10]. Most patients with advanced disease will respond to front line therapy, but 80% of them will eventually relapse within 12-18 months with a resistant tumor [11]. Understanding the key determinants of this resistance is of paramount importance if the prognosis of this tumor has to be changed. We will here summarise the importance of cancer stem cells and epithelial to mesenchymal transition (EMT) in determining tumor recurrence and the poor response after first line therapy.

Ovarian Carcinoma : Biological Characteristics

Different from other epithelial tumors, ovarian cancer is often diagnosed when it has already spread into the peritoneal cavity. Due to the lack of an anatomical barrier, ovarian carcinoma cells spread directly, disseminate throughout the peritoneal cavity, forming nodules on the surface of the parietal and visceral peritoneum including omentum, peritoneum, diaphragm and small bowel mesentery [12]. In particular, tumors can disrupt the ovarian capsule and malignant cells shed into the peritoneal cavity and be transported by normal peritoneal fluid throughout the abdomen. Malignant cells in the peritoneum generally aggregate and form spheroid-like structures, which subsequently implant on the walls of the peritoneal cavity, with varying extent of peritoneal invasion and leading to severe clinical complications, with ascites and bowel obstruction. In many cases lymph node metastases and peritoneal spread co-exist. Even rare, distant spread of ovarian carcinoma can involve any organ, including the brain. The presence of ascites is thought to be the combined result of lymphatic obstruction and increased production of peritoneal fluid by cells lining the peritoneal cavity [13]. The presence of ascites has been correlated with the peritoneal spread and is associated with poor disease prognosis. In addition, it seems that malignant ascites acts as a reservoir of soluble factors and cellular components with pro-inflammatory and tumor-promoting effects [14].

Even if diagnosed at late stage, ovarian tumor is chemosensitive with the great majority of the patients responding to first line therapy

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(carboplatin and taxol); however most of them will relapse with resistant disease and succumb to their disease. The intense research of the past 30 years has led to the identification of several mechanisms for platinum-resistance in tumor cells, including cell based specific mechanisms, enhanced DNA repair mechanism, enhanced glutathione cell content, etc (for a detailed review see [15]). Recently, two interconnected pathways have been advocated as important determinants for tumor recurrence and resistance to therapy in different human tumors, including ovarian cancer: the existence of the cancer stem cells (CSCs) and the activation of the epithelial to mesenchymal transition (EMT) process [16].

Ovarian Cancer Stem Cells

The cancer stem cell hypothesis states that tumors are hierarchically organized and their long term maintenance is due to the existence of self-renewing cancer stem cells (CSCs). This model has generated considerable interest as these cells seem to possess two clinical relevant properties: the ability to self-renew that sustains and maintains tumor and to be resistant to chemotherapy [17,18]. Indeed transcriptional signatures specific to CSCs are predictive of poor overall patients survival [19], and experimental and clinical evidence suggests that CSCs survive many commonly used anticancer agents, both cytotoxic and targeted agents, implying that these cells are responsible only for recurrent disease but also for the concomitant resistance to treatment [17,20].

During the past years, many efforts were made to define the ovarian cancer stem cell [21]. The first report on ovarian CSCs was from studying the ascites of an ovarian cancer patient, which yielded spheres in culture, and could be propagated as xenograft tumors over several generations [22]. Ovarian CSCs were detected by the phenotypic expression of surphace markers (i.e. CD133 [23-26], CD117 [27,28], CD44 [28-30] and CD24 [31]), by the presence of biochemical characteristics such side population (SP) [32-35], and aldehyde dehydrogenase (ALDH) activity [26,36-38] (Table 1), although not specific for ovarian tissues, but widely used for the definition of CSC in several other tumors. Baba and colleagues demonstrated that CD133+ cells isolated from established cell lines had greater tumor initiation capacity than CD133- cells and were much more resistant to chemotherapy [23]. When the combined expression of CD133 and ALDH positivity was used as a predictor [26], it was shown that ALDH+, CD133+ and ALDH+/CD133+ cells from fresh tumors generated larger tumors more rapidly than their negative counterparts. In addition, both ALDH+ and CD133+ALDH+ ovarian cells were also highly angiogenic, consistent with the fact that ovarian CSCs could be responsible for metastasis formation by promoting tumor angiogenesis [39]. Ovospheres, cancer tumor spheres, generated from ascites of 5 patients with serous ovarian cancer were highly enriched for CD44 and CD117 expression, more resistant to chemotherapy, and more tumorigenic than their negative counterpart [28]. Alvero et al. isolated CD44+ cells both from primary cell lines and fresh tumor or ovarian ascites, and these cells gave rise to tumors in mice [40]. Expression analysis of CD44+ and CD44- cells revealed that Myeloid Differentiation Factor 88 (MyD88), an activator of NFκB signaling pathway, was upregulated in CD44+ cells, linking CD44 expressing cells with high capacity for repair and chemoresistance. Gao et al. recently reported CD24 as a putative CSC marker in ovarian cancer [31]. They established cell lines from serous and mucinous ovarian tumors, and found that CD24+ cells were more quiescent and chemoresistant than CD24- cells. We were able to established two tumor initiating enriched cell cultures from fresh tumor samples bearing the characteristics of CSCs [41]. Indeed, these cells were able to form tumors when transplanted in nude mice at very low number and tumors could be serially transplanted; they were able to self-renewal *in vitro*, to differentiate and to be more resistant to several cytotoxic agents than the differentiated cells derived from them. Unfortunately, none of the markers associated with stemness in ovarian cancer were found in our CSC enriched cultures. On the contrary, they displayed a mesenchymal phenotype, expressing N-cadherin (mesenchymal marker) and being negative for E-cadherin (epithelial marker).

Up to now a clearly definitive phenotype for ovarian CSC is lacking. A better understanding of the above mentioned markers could help to define the hierarchical organization of ovarian cancer cells and help in understanding the pathogenesis of this cancer [42]. A further

Marker	Type of marker	Source	Stem-like characteristics	Reference
Side Population	Biochemical	Mouse ovarian cancer cell lines Primary ovarian xenografts cell lines Human ovarian cancer cell line Patients ascites	Tumorigenicity, chemoresistance, asymmetric division Tumorigenicity, high proliferation rate, low apoptotic events Tumorigenicity, chemoresistance, low apoptotic events, clonogenicity, high expression of stemness genes Tumorigenicity, chemoresistance, low apoptotic events	[20] [79] [80,81] [81]
ALDH	Biochemical	Human ovarian cancer cell lines, ovarian tumor xenografts	Tumorigenicity, chemoresistance, self-renewal	[68]
CD133	Surface marker	Human ovarian cancer cell lines Primary ovarian tumors Primary ovarian xenografts	Tumorigenicity, chemoresistance, asymmetric division, self-renewal Clonogenicity, high proliferation rate Tumorigenicity	[18] [72] [73]
CD117	Surface marker	Primary ovarian tumor xenografts	Tumorigenicity, chemoresistance, self-renewal	[78]
CD24	Surface marker	Primary ovarian cell line	Chemoresistance, high expression of stemness genes, self-renewal	[26]
ALDH+/CD133+	Biochemical+ urface marker	Human ovarian cancer cell lines, patient tumors Primary ovarian tumors and ascites	Tumorigenicity, chemoresistance, spheres formation, angiogenic capacity Tumorigenicity, spheres formation	[74] [22]
ALDH+/CD44+	Biochemical+ surface marker	Human ovarian cancer cell lines	Chemoresistance	[75]
CD44+/CD24-	Surface marker	Human ovarian cancer cell lines Human ovarian cancer cell lines	Tumorigenicity, chemoresistance, self-renewal, spheres formation Chemoresistance, clonogenicity	[76] [77]
CD44+/MyD88+	Surface marker+ cytoplasmatic adaptor protein	Primary ovarian tumors and ascites	Tumorigenicity, chemoresistance, low apoptotic events, self-renewal, spheres formation	[19]
CD44+/CD117+	Surface marker	Primary ovarian tumor spheroids	Tumorigenicity, chemoresistance, high expression of stemness markers, self-renewal, spheres formation	[24]

Table 1: Identification of ovarian cancer stem cell markers.

complication is given by the recent cumulating data on the intratumoral heterogeneous expression of these stemness markers [43].

Epithelial-to-Mesenchymal Transition (EMT)

EMT is a biological process that allows a polarized epithelial cell, which normally interacts with the basement membrane via its basal surface, to undergo multiple biochemical changes and to acquire a mesenchymal cell phenotype, showing evidence of enhanced migratory capacity, resistance to apoptosis and greatly increased production of extra-cellular matrix (ECM) components [44,45]. The completion of an EMT program is characterized by the degradation of underlying basement membrane and the formation of a mesenchymal cell that can migrate away from the epithelial layer in which it originated. This process is highly dynamic; the phenotypic plasticity provided by EMT is transient and reversible with the possibility to re-convert to an epithelial status (mesenchymal to epithelial transition-MET) [16,46].

Many factors (both intracellular and extracellular) can induce EMT. Among intracellular factors, mutations in oncogenes and tumor suppressor genes, altered expression of microRNAs and gene promoter methylation have all shown to be able to induce EMT [44,45]. Cytokines, matrix components and growth factors derived from stromal cells can induce tumor cells to undergo EMT, highlighting the key role of tumor micro-environment [47,48]. Transforming growth factor (TGF) β signaling is one of the major inducer of EMT in cancer [49] (Table 2). All the different signals converge in the activation of EMT-transcription factors (such as Snail, ZEB and basic helix-loop-helix families) which induce and/or maintain the mesenchymal phenotype. The downregulation of E-cadherin (E-cad) is one of the leading events in EMT and is considered a hallmark of this process. EMT is characterized by a switch in cell membrane cadherins (from E- to N- cadherin), a change from apical-basal to front-back polarity and acquisition of motility enabled in part by the restructuring of the actin cytoskeleton [46].

The demonstration of EMT is based on the loss of some epithelial markers (downregulation of E-cad, occludins and claudins, desmoplakin and epithelial cytokeratins, including 8, 18 and 19) and the acquisition of mesenchymal markers (up-regulation of vimentin, N-cadherin, fibronectin, alpha-smooth muscle actin) detected both by western blot analysis and immo-histochemistry [50-52]. In addition, EMT molecular mechanisms can be analyzed by studying the expression levels and functionality of the EMT-inducing transcriptional factors, notably Snail, Slug, zinc finger E-box binding homeobox 1 and 2 (ZEB1 and 2), Twist, and FOX2 [46,50]. All these markers however do indicate that a cell underwent an EMT transition, but not really the degree to which epithelial cells were engaged in the EMT process. It has been shown that cancer cells may undergo a partial EMT, with some cells retaining many epithelial traits and acquiring some mesenchymal ones, and other cells losing all traces of their epithelial origin and becoming fully mesenchymal [53]. This causes technical problems in that it is not always possible to define the morphological and immunohistological criteria for EMT in clinical specimens [54]. It is increasingly accepted that *in vivo* tumor cells more frequently undergo a more plastic and dynamic process defined as 'EMT like' and 'partial or incomplete EMT'.

The clinical role of E-cad in ovarian carcinoma is not entirely settled (for a recent review see [55]). E-cad expression has been reported to be reduced in primary ovarian carcinomas, but is re-expressed in ovarian carcinoma effusions, with significantly higher levels compared to patient-matched primary carcinomas [56], suggesting that ovarian carcinoma cells undergo incomplete EMT. E-cad protein expression in primary ovarian carcinomas and solid metastasis did not differ between

Marker	Source	Features	Reference
E-cadherin	Human ovarian tumor samples Human ovarian tumor samples Human ovarian tumor samples	Reduced expression in primary tumors, but higher expressed in carcinoma effusions Low E-cad. mRNA expression in carcinoma effusions correlates with poor survival High levels correlates with a better survival	[36] [37] [38]
Claudins	Ovarian cell lines human tissues Human ovarian tumor samples Human ovarian tumor samples	Higher expression in ovarian cancer than in normal tissue Higher expression in ovarian cancer than in normal tissue Higher expression in primary tumors, ascites fluid and metastasis than in normal tissue	[40] [41] [42]
Alpha2beta1 integrin	Ovarian cancer cell lines	Higher expression in spheroid cultures respect to monolayer cultures	[43]
N-cadherin Vimentin	Ovarian cancer stem-like spheres	Higher expression in tumor-initiating sphere cultures than in more differentiated cell cultures	[27]
N-cadherin, P-cadherin	Human ovarian tumor samples	Expression of mesenchymal markers defined a subtype of ovarian cancer associated with poor OS	[45]
Twist	Ovarian cancer cell lines	Upregulation associated with chemoresistance	[58]
TLR, TGFβ, ECM, FN1, PDGFRB, COL3A1	Human ovarian tumor samples	High protein levels associated with chemoresistance	[59]
Snail, slug, Twist, MMP2	Human ovarian tumor samples, ovarian cancer cell lines	Higher expression in chemoresistant than in sensitive samples, associated with stemness phenotype	[57]
TGFβ	Human ovarian tumor samples Ovarian cancer cell lines	Upregulation of this pathway correlatesd with chemoresistance	[60] [63]
E-cadherin, beta catenin, NF-kappaB, TGFβ, Wnt signaling	Human ovarian tumor samples	Overexpression associated with poor prognosis	[61]
Snail, slug, Twist2, Zeb2	Human ovarian tumor samples, ovarian cancer cell lines	Upregulation associated with chemoresistance	[14]
EndothelinA	Ovarian cancer cell lines	Upregulation associated with chemoresistance	[62]

OS: Overall Survival
TLR: Toll-like receptor
TGFβ: Transforming Growth Factor β
ECM: Extra-Cellular Matrix
FN1: Fibronectin1
PDGFRB: platelet-derived growth factor receptor
COL3A1: collagen3α1

Table 2: EMT markers in ovarian cancer.

patients with short-term versus long-term survival [56], whereas lower E-cad mRNA expression in ovarian carcinoma effusions correlated with poor survival [57]. Recently, high expression of E-cad was associated with better survival in high grade serous ovarian carcinoma, with opposite findings for N-cad [58]. The expression and clinical significance of tight junction claudin proteins is another example of the discordance between classic EMT and expression patterns in this cancer. Claudins are a family of proteins involved in the control of paracellular diffusion in epithelia [59] and have been reported to be more highly expressed in ovarian carcinoma compared to normal OSE [60-62].

The cytokines in the ascitic fluids (i.e. VEGF, IL6, IL8, bFGF) might trigger and/or stabilize EMT through paracrine-autocrine loops. It has been shown that mesenchymal markers (N-cad and vimentin) are upregulated when ovarian tumor cells, from clinical specimens and/or stabilized cell lines, are cultured to form spheroids under low adherence conditions [41,63]. Recently it was elegantly demonstrated that EMT enhanced ovarian cell invasion into the mesothelial layer of the peritoneal cavity and this was consistent with the evidence that lower E-cad mRNA in ovarian carcinoma effusions correlated with poor survival [57]. These data align with other recent data in which the expression of epithelial and mesenchymal markers was correlated with the ability of ovarian cancer spheroids to remodel the extracellular matrix [64]. While these data would suggest that ovarian cells expressing a mesenchymal program display a more effective mesothelial clearance *in vitro*, a predefined step in peritoneal invasion, the contribution of EMT in tumor progression is less clear. Tothill et al. [65] defined by gene expression profiling 6 subgroups (C1-C6) of ovarian tumors with distinct molecular and histophatologic characteristics. C1 was defined as the "stromal signature" subgroup and had a gene signature that overlapped with some of the EMT genes found to be present in ovarian cells competent for mesothelial clearance and most importantly was uniquely enriched for vimentin and correlated with the poorest patient survival. Increased expressions of Snail and Twist transcriptional factors were immohistochemically demonstrated in ovarian tumor specimens and were correlated with high grade, poor prognosis and lack of E-cadherin expression [55].

Cross-Talk between CSC and EMT: Evidence in Resistant Ovarian Relapse

Increasing evidence suggests a tight cross-talk between EMT and CSC (Figure 1). Mani et al. were the first to report that the induction of EMT by transcription factors Twist and Snail conferred stem-like properties to breast-immortalized epithelial cells [66]. Specifically, differentiated mammary epithelial cells undergoing EMT through TGFβ treatment and/or forced expression of E-cad transcriptional repressors, were able to give rise to $CD44^{high}/CD24^{low}$ cells, with stem cell properties. Again, miRNA-200 family members have been shown also to suppress expression of polycomb protein Bmi1, which has been shown to support the stem-cell state in both cancer cells and embryonic stem cells [67]. Hence, by suppressing miRNA-200 expression, Zeb1 is able to enhance expression of Bmi1. miRNA-200 has been reported

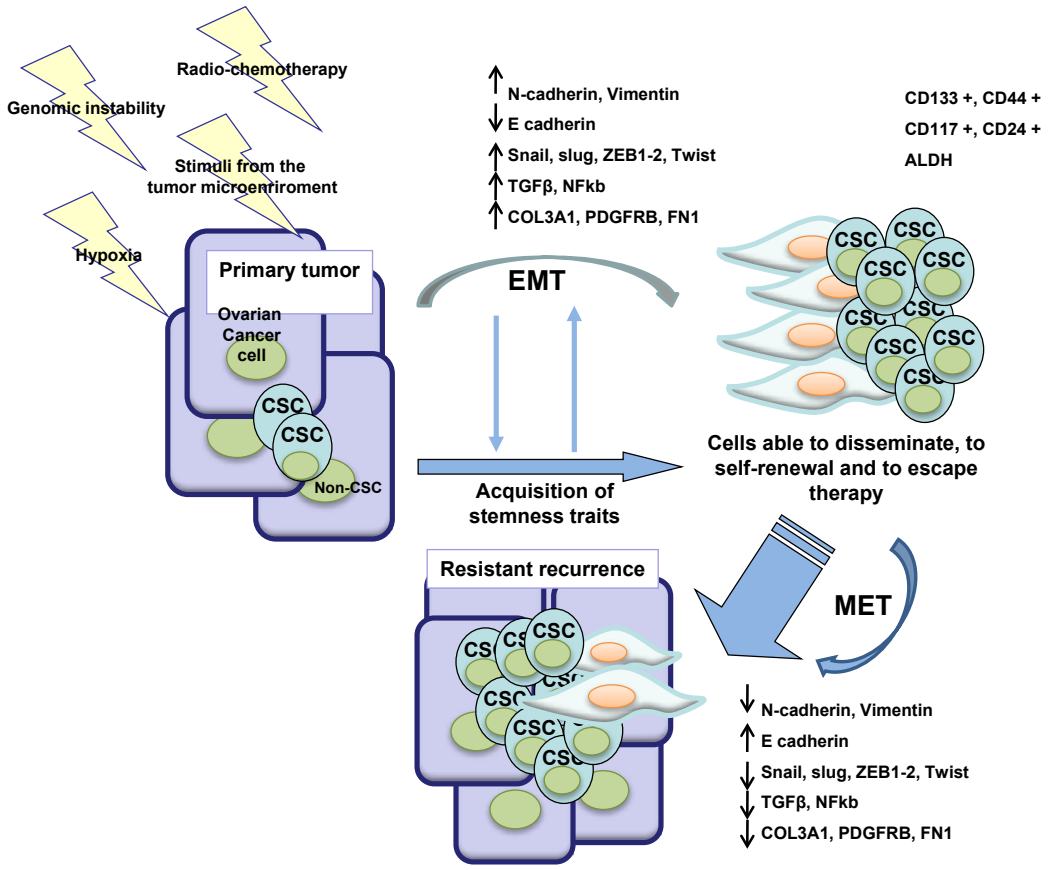

Figure 1: Induction of EMT, acquisition of stemness traits and enrichment of cancer stem cells account for a resistant recurrence in ovarian carcinoma. CSC: cancer stem cell; EMT: epidermal to mesenchymal transition; MET: mesenchymal to epithelial transition.

also to suppress expression of Suz12 [68], a histone-modifying enzyme, required for the transcriptional repression of the *E-cad* gene (*CDH1*) by the Zeb1 and Snail EMT-TFs [69]. Similar bidirectional negative feed back loops exist between Snail and miRNA-34 [70], and miRNA-34 has been demonstrated to suppress stemness in prostate and colon cancer stem cells [71,72]. Nuclear β-catenin, a marker of active Wnt-β-catenin cascade signalling, an important stemness pathway, has been specifically observed at the invasion front of colorectal carcinoma, where EMT occurs [73]. *CDH1* gene encoding E-cad is a direct negative regulator of Wnt signalling; in fact its cytoplasmic tail binds β-catenin, sequestering it within the adherens junction complex and preventing its translocation to the nucleus where it can act as a transcriptional co-factor of TCF-LEF complexes. Therefore, Snail, through its ability to repress E-cad expression, might not only contribute to the suppression of epithelial characteristics, but also reinforce Wnt-βcatenin signalling [74].

All this newly generated evidence couples with the cumulating experimental data where carcinoma cells, including ovarian cancer cells, with stem cell properties and/or undergoing EMT are generally more resistant to apoptosis and to cytotoxic and targeted agents. Enrichment in CSCs in chemoresistance and recurrent ovarian carcinomas has been reported [29,75,76]. Treatment of two different ovarian cancer cell lines with cisplatin and paclitaxel resulted *in vitro* in an enrichment in cells expressing CSC markers at the protein and mRNA levels and *in vivo* in the development of tumor, whose burden and metastatic potential were higher than the ones obtained after transplantation of control untreated cells [77]. Recent published data from the same authors demonstrated that paclitaxel given systemically caused enhanced expression of stemness marker (Oct4 and CD117) and that this effect was partially reversed by the concomitant treatment with a JAK2/STAT3 inhibitor [78]. Again *in vivo* and *in vitro* data demonstrated a survival advantage of side population (SS) cells in ovarian cancer cells treated with carboplatin and in ascites from patients relapsing following chemotherapy compared with untreated chemotherapy naïve ovarian patients [79]. Twist expression has been correlated to paclitaxel resistance *in vitro* in OVCA433 and OVCA432 cell lines [80]. Strong association between EMT and resistance to platinum-based therapy was found comparing gene expression profiles in 23 pair primary tumors and corresponding recurrence (defined as relapse after two or more lines of chemotherapy) in ovarian carcinoma samples [81]. In this experimental setting, it was found that resistance was associated with the activation of specific pathways, i.e. the toll-like receptor (TLR) signaling pathway (such as MyD88), the TGFβ signaling pathway (such as BMP7, TGFB3, TGFBR2), and networks involved in cell communication, extracellular matrix (ECM) interaction, and focal adhesion (such as FN1, PDGFRB and COL3A1). Latifi et al. demonstrated that cisplatin treatment of patients tumor slices, metastatic ovarian tumor cells (from ascites), and ovarian cancer cell lines, generated cells with combined EMT and CSCs features [82]. They also demonstrated these changes were ERK-pathway dependent and indeed the inhibition of ERK2 by UO126 (a MEK inhibitor) interfered with EMT and CSC cell phenotypes. These data further support the molecular link between cisplatin resistance, EMT and CSC in epithelial ovarian cancer. It was hypothesized that during chemotherapy residual ovarian tumor cells could acquire EMT and CSC-like phenotypes. Low cisplatin concentrations induced EMT by facilitating matrix remodeling and motility of residual cells and subsequent increases in cisplatin concentration generate CSCs expressing CD133 and CD117, providing growth advantage to the very few surviving residual cells and being responsible for tumor recurrence. TGFβ pathway, affecting both EMT and stemness, has been correlated in gene expression studies of ovarian carcinomas with resistance to platinum-based therapy [83]. EMT-related genes were also found to be associated with poor survival in ovarian cancer patients [84].

The possibility of interfering with both EMT and stemness pathways has been advocated as a new therapeutic strategy to reverse platinum sensitivity. Through the manipulation of key EMT signaling molecules, Haslehurst et al were able re-sensitize cisplatin resistant cells to the effects of drug. Using the A2780 ovarian cell line and its cisplatin resistant sub-line they showed that when Snail and Slug were knocked down in the resistant cell line, the EMT phenotype was largely reversed and drug sensitivity restored [85]. They translated these results to a panel of primary ovarian carcinoma samples, and demonstrated that a group of EMT-related genes provided a reasonable model of classifying primary ovarian tumors according to their chemoresistance status. The blocking of Endothelin A in A2780 cells *in vitro* resulted in sensitization to chemotherapy and reduced cell growth, with concomitant decrease in Snail levels [86]. Recently, treatment with a dual PI3K/mTOR inhibitor NVP-BEZ235 was able to prevent the EMT induced by TGFβ and hypoxia treatment in ovarian and pancreatic cell lines [87], interfering with the expression of HIF1α and with TFGβ induced hyposphorylation of SMAD2/3 and Akt/GSk-3β with reduced expression of Snail. Interestingly, in nude mice transplanted with SKOV3 cells, drug treatment significantly increase E-cad mRNA levels demonstrating for the first time that NVP-BEZ235 can prevent, *in vivo*, microenviroment and growth factor induced EMT.

The efforts made to target specifically ovarian CSCs were based on the direct targeting of markers found associated with stemness in ovarian carcinoma. For example, CD44 was exploited as it functions as an adhesion molecule binding to hyaluronic acid (HA). CD44 binding to HA could regulate cellular migration and metastases, and indeed targeting CD44 was associated with a decrease in metastases in an ovarian tumor model [88]. Inhibitors of CD117 kinase activity, such as imatinib, have been developed and demonstrated to be highly effective in gastrointestinal tumor and leukemia [89]. Imatinib has demonstrated some efficacy against ovarian cancer cell lines *in vitro*. Unfortunately, phase 2 clinical trials using imatinib, both in recurrent disease and as a maintenance agent in ovarian cancer patients following a complete clinical remission, demonstrated no efficacy [90,91]. The knockdown of *ALDH1A1* gene was found to restore the chemosensitivity in ovarian cancer cell lines [36]. Disulfiram, an ALDH1 inhibitor, was shown to be preferentially toxic against ALDH+ ovarian cancer cells, and highly synergistic with cisplatin in *in vitro* ovarian CSCs [92]. The effect of metformin on ovarian cancer stem cells from cancer cell lines and patients tumors was recently reported [93]. This effect was additive with cisplatin and FACS analysis confirmed that metformin reduced ALDH+ ovarian CSCs. Consistent with this, metformin also inhibited the formation of CSC generated tumor, was synergic with cisplatin and significantly reduced the growth of ALDH+ CSC xenografts *in vivo*.

The Hedgehog signaling pathway was found to be important in the growth and development of ovarian cancer spheroid-forming cells derived from ovarian cancer cell lines and its inhibition by cyclopamine significantly inhibited ovarian cancer spheroid growth [94]. Also Notch pathway was shown to be critical for the regulation of ovarian CSCs and resistance to platinum. γ-secretase inhibitor (GSI) depleted CSCs and increased tumor sensitivity to platinum in CD44+ cells sorted from ovarian cancer cell lines. Again, silencing of Notch3, by siRNA strategy, was shown to increase the response to platinum therapy [95].

Conclusions

Despite the increase in knowledge on the biology of ovarian cancer, most of the patients diagnosed with this tumor will succumb with a resistant disease. In ovarian tumors, as in others, two key elements at the basis of drug resistance have been recently identified: the existence of cancer stem cells and the induction of an EMT program. These two characteristics have been recently advocated as being responsible for both tumor heterogeneity and the extreme tumor plasticity, that make complete response to therapy difficult to achieve in patients (Figure 1). EMT and stemness can be considered traits of the extreme plasticity of tumor cells that can shift from a stem cell-on to a stem cell-off state along with the activation of an EMT and/or MET process. The interference with pathways involved in self-renewal while has been proven in some experimental settings to have antitumor effect and to reverse resistance to therapy, calls caution as all these potential approaches interfere with physiological processes and could have unexpected toxicities in a long-term frame.

As we tried to underlie, activation of EMT and/or stemness pathways not only depend on the oncogenic tumor cell drivers and/or inactivation of cell tumor suppressors, but are likely to rely on more flexible mechanisms, such as epigenetic changes of gene expression as recently suggested [16,96]. The tumor micro-environment and the inflammation generally associated with tumors, including ovarian carcinomas, have a master role in changing temporally and spatially the tumor cell phenotype and in somehow helping tumor cells to evade therapy. All this knowledge will possibly allow the implementation of new therapeutic approaches that specifically target tumor micro-environment (i.e. antiangiogenic therapy or interference with the inflammatory micro-environment). It is envisioned however that these treatment modalities should be used in an adjuvant setting and/or in conjunction with current therapeutic modalities to potentially be able to have long-lasting curing effects, prevent recurrence and possibly prolong patient's survival.

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