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REVIEW ARTICLE

Plasticity in Ovarian Cancer: The Molecular Underpinnings and Phenotypic Heterogeneity

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Abstract | Cellular plasticity, by large, is the ability through which cells morph into new phenotypic identity by trading-off with the previous one. This phenomenon has been observed in the normal and tumor cells in a very similar fashion. Occurrence of cellular plasticity, in malignancies like epithelial ovarian carcinoma (EOC) are well known but highly debated in terms of origin of the tumor for the inherent heterogeneity across subtypes. EOC has been termed as a clinically challenging malady for its subversive nature against chemotherapy. The management of ovarian cancer is mostly hindered by relapse with recalcitrance towards primary chemotherapy regimen e.g. platinum–taxol combination. Also, late detection preceded by peritoneal metastasis poses another challenge to the treatment. Underlying both these aspects of the disease, tumor heterogeneity turns out as the most critical factor. In the light of heterogeneity that can be across patients (inter-tumoral) and/or within a tumor (intra-tumoral), ovarian carcinoma is a multifactorial ailment. The governing factors behind this heterogeneity are—diverse genetic landscape among subtypes of EOC; the presence of cancer stem cell (CSC) niche and inherent plasticity of the cancer cells themselves. Apart from the well-studied mechanisms of plasticity, there are several emerging molecular players like lncRNAs, Hippo pathway and also phenomena like dedifferentiation of non-CSC neoplastic cells ,and transdifferentiation of CSCs. Here, we present an overview of the current knowledge on the evolution of EOC through cellular plasticity with emphasis on the three major aspects namely, subtype-specific genetic diversity; ovarian CSC and cancer cell duality between epithelial and mesenchymal lineages.

1 Introduction

The mainstay of human physiology rests upon the unique functioning of cellular clusters known as tissues in an organ-specific manner. Such diversified roles are attributed to the specific phenotypic identity of the cells which is an offspring of cellular differentiation. However, to quote the verbatim of Sir John Gurdon, the "highly differentiated cell types" too can display "remarkable plasticity"[1]. Understandably, such plasticity may not be welcome by our body from the point of view of homeostasis. It will be utter chaos causing an individual to perish if, for instance, the epithelial type II cells stop releasing surfactant into the alveolar space and glomerular cells start firing action potential in Bowman's capsule. Yet, in limited cases (wound healing; angiogenesis), under normal physiological conditions and in majority of tumours we observe extensive cellular plasticity giving rise to intra-tumoral heterogeneity[2-5]. Such abrogation in cellular identity is caused by, inter-alia, epigenetic modifications, which otherwise fine-tune the stability of differentiated state[6]. Such remodelling in chromatin structure

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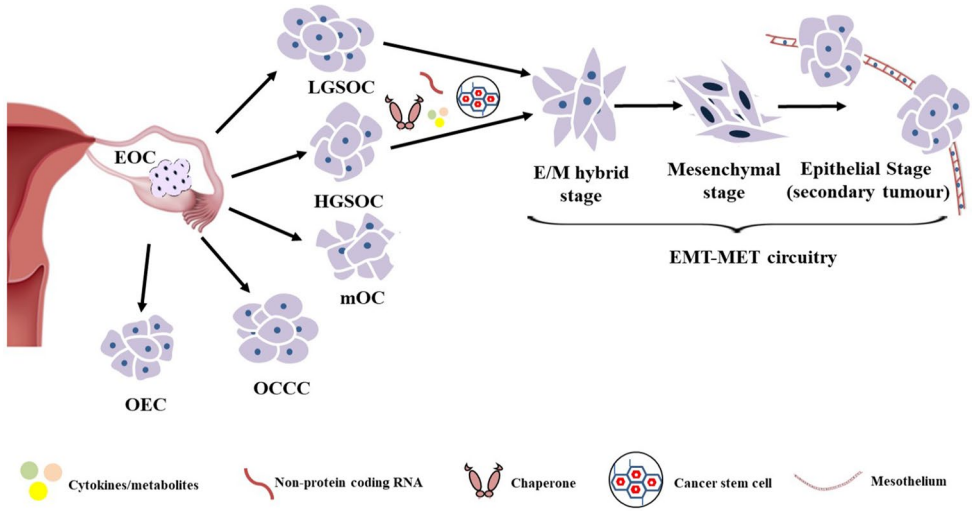

Figure 1: Cellular plasticity in precursors of epithelial ovarian cancer gives rise to different subtypes of the tumour which undergo (majorly in HGSOC: High grade serous ovarian carcinoma and in few cases of LGSOC: low grade serous ovarian carcinoma) EMT–MET cycle co-ordinated through several molecular regulators (ncRNA, CSCs, cytokines, etc.) throughout its process of dissemination and secondary tumour foci formation in omental mesothelium.

is directed by several cues from microenvironment such as mechanical stress, altered pH, pharmacological intervention, senescence, proliferative stress[7, 8]. The two other classical models of intra-tumoral heterogeneity, namely, stochastic and hierarchical model are currently refuted as mutually overlapping[7]. The third tenet is the plasticity model which can also lead to heterogeneous behaviour of the tumours. There are several ways through which the model depicts the plastic nature: transdifferentiation of stem cells into lineages other than the expected during homeostasis, interconversion of various stem cell (SC) pools, dedifferentiation and transdifferentiation of non-SC cells[2, 9–13].

Here, we have focussed our review, on the several aspects of cellular plasticity and how that gives rise to tumoral heterogeneity with respect to epithelial ovarian cancer (EOC) which is notoriously known for the poorest mortality rate among all gynaecological malignancies despite having low incidence rate (6.6/100,000 worldwide age-standardized incidence in 2018)[14]. The overall 5-year survival rate is only 38–40% that ranks this malignancy as the eighth leading cause of cancer-related deaths among women worldwide[14, 15]. Such alarming numbers for EOC can be traced back to the fact that ovarian cancer itself is a heterogeneous disease characterised with inherent plasticity mediated by both cancer cells and cancer stem cells. The challenge to treat the patients lies in the fact that we still follow 'same-size-fits-all' criterion when it comes to primary treatment which majorly is either platinum–Taxol dual chemotherapy followed by surgery and an optional follow-up chemotherapeutic regimen (neo-adjuvant chemotherapy or NACT) or by upfront surgery followed by platinum–Taxol treatment. The partial success of this decade-old practice in treating EOC patients can be attributed to intra-tumoral and inter-tumoral heterogeneities. The underlying causality of such a feature of this multifactorial disease rests upon three aspects: diverse genetic landscape among subtypes of EOC; presence of cancer stem cell (CSC) niche and inherent plasticity of the cancer cells (Fig. 1). In the following sections, we have discussed about these three aspects which impart plasticity at the cellular level and heterogeneity at the level of tumour in EOC.

1.1 Diverse Genetic Landscape in Subtypes of EOC

1.1.1 Phenotypic Plasticity in the Ovarian Surface Epithelium

Despite being the most widely studied, the origin of epithelial ovarian cancer is still debatable, and this leads to difficulties in the treatment and management of the cancer. It was widely accepted, until recently, that the tumours arise in the ovarian surface epithelium, which is the outermost lining of the ovary. Cells of the ovarian surface

epithelium have a cuboidal morphology and are derived from the coelomic epithelium that share common characteristics of the peritoneal mesothelial cells[16]. The ovarian surface epithelium is composed of highly undifferentiated cells that exhibit both mesenchymal and epithelial characteristics and can interchange between the two phenotypes in response to environmental stimuli. These uncommitted cells express common epithelial markers like, cytokeratin types 7, 8, 18 and 19 as well as N-cadherin and vimentin which are specific to mesenchymal cells[16]. Another mesenchymal characteristic of these cells is the secretion of MMPs and collagen, which might help in the breakdown of the OSE and ovarian cortex during ovulation[17]. This cellular plasticity of the ovarian surface epithelium plays a role in its post-ovulatory repair which helps in extracellular matrix remodelling[17]. Failure of these cells to undergo EMT might result in the aggregation of epithelial cells, resulting in the formation of inclusion cysts which are a proposed initiation site of some of the subtypes of epithelial ovarian carcinoma[18].

Another, more recently accepted origin of high-grade serous ovarian cancer (HGSOC), the most prevalent subtype of epithelial ovarian carcinomas is the fallopian tube epithelium which comprises of a layer of pseudostratified epithelial cells derived from the Mullerian duct[19, 20]. Contrary to the ovarian surface epithelium, the fallopian tube epithelium is well-differentiated into ciliated and secretory cells. These cells are committed and do not undergo EMT[19]. Recent evidence indicating that epithelial neoplasms first arise in the fimbriae of the fallopian tubes and then metastasize to the ovarian surface has challenged the previous notion of ovarian surface epithelium being the primary site of tumour initiation[21]. In patients with BRCA mutations, tubal intra-epithelial carcinomas were discovered in the fimbriated end of the fallopian tube in 87% of the cases[22, 23]. These cells share many characteristics with the high-grade serous carcinomas, including a high prevalence of *TP53* mutations, evidence of DNA damage as well as the type of cell involved[22].

1.1.2 Heterogeneity and Cancer Cell Plasticity Across the Ovarian Cancer Subtypes

Ovarian carcinomas are characterised by significant heterogeneity in their morphology, histology, genetic markers as well as in their clinical outcome. This is one of the major problems arising in elucidating its pathogenesis, as ovarian cancer is not one single disease but composed of tumours arising from almost every cell type in the ovary as well as extra-ovarian gynaecological tissue. Ovarian cancer is classified into three subtypes, germ-cell, sex cord-stromal cell and epithelial cell tumours based solely on the histopathology[24]. Amongst these three subtypes, epithelial ovarian cancer is the most prevalent and accounts for more than 90% of the cases[21]. Furthermore, based on their varied morphology as well as genetic heterogeneity, Shih and Kurman had broadly classified epithelial ovarian cancers, into type I and type II[25].

Type I tumours are more indolent in nature and include low-grade, endometroid, clear cell, and mucinous subtypes. Nearly two-third of these tumours carry mutations in *KRAS*, *BRAF* and *ERBB2* genes while type-II tumours consisting of high-grade serous, high-grade endometrioid, undifferentiated carcinomas are more aggressive and presented in the advanced stage. These tumours, particularly the HGSOC ones, are genetically unstable and harbour *TP53* mutation and *CCNE1* gene amplification[25]. Each of these subtypes is associated with its own distinct molecular alterations and clinico-pathogenesis that arise from distinct progenitors through cellular plasticity and accumulation of driver and passenger mutations cumulatively giving rise to a highly heterogeneous disease.

1.1.2.1 High-Grade Serous Ovarian Carcinoma High-grade serous are highly unstable tumours, characterized by an overwhelming presence of mutations in the *TP53* gene in more than 90% of the cases. A small number of cases are also accompanied by germline or somatic mutations in *BRCA1* and *BRCA2* which lead to increased genomic instability in the tumours[26]. Treatment includes standard platinum–taxol-based cytotoxic therapy except in cases with *BRCA* mutations, which respond well to PARP inhibitors. Mutations in *KRAS*, *BRAF*, *ERBB2* occur infrequently in HGSOC. Mutations in other genes such as *RB1*, *CDK12*, *CDK113* with an overwhelming presence of gene amplification in several key signalling pathways (PIK3CA/AKT, Notch) are characteristics of this subtype[27, 28].

In addition to this, the HGSOC tumours also possess a heterogeneous culmination of different cellular phenotypes probably due to the mixed origins of the tumour leading to various subtypes. Two large studies from US (TCGA: The Cancer Genome Atlas) ($n=489$) and Australia (AOCS: Australian Ovarian cancer Group) ($n=285$) classified HGSOC into further subtypes based on their molecular profiles which

can distinctly exert functional heterogeneity in HGSOC tumour cells[29, 30]. In the TCGA study, four subgroups were identified: mesenchymal, differentiated, immunoreactive, and proliferative. In the AOCS study, six prognostic subgroups were identified (c1–c6). Out of those, two subgroups had displayed traits of predominantly low-grade endometrioid subtypes and serous low malignant potential and the remaining four were similar to the higher grade and advanced-stage cancers of serous and endometrioid morphology. There was another novel subgroup with tumours co-expressing both N-cad and P-cad along with the loss of differentiation markers (CA125 and Muc1). Except the subtypes being comprised of tumour histotypes not studied in TCGA database, in the high-grade serous ovarian cancer subgroups, the poorest prognosis is associated with mesenchymal (TCGA) or C1 subgroup (AOCS) which refer to the fact that such heterogeneity demands a specialized treatment regimen other than the standard chemotherapy[31].

1.1.2.2 Low-Grade Serous Ovarian Carcinoma Though the tumour cells exhibit similar histopathological features, low-grade serous OC (LGSOC) is genetically and clinically quite distinct from its high-grade counterpart and thus belongs to the type I class. They have functional *TP53* and significant mutations in *BRAF*, *KRAS*, and *ERBB2*. Activation of MAPK signalling pathway has also been reported along with its correlation with chemoresistance in LGSOC. Unlike their high-grade counterpart, LGSOC tumours do not respond well to standard chemotherapy, and treatment regimen majorly involves upfront cytoreductive surgery[32].

Contrary to HGSOC which does not have any morphologically distinct intermediate stages, LGSOC are reported to originate from benign tumours and progress into invasive carcinomas through distinct intermediate stages. They transition from a benign serous cystadenoma into an atypical proliferative tumour to a non-invasive micropapillary serous stage (non-invasive MPSC) which eventually becomes invasive (invasive MPSC) as observed in almost 75% of the cases [33]. The transformation of each stage into a more invasive one indicates the existence of cancer cell plasticity which, however, due to low mitotic rate and absence of aneuploidy/polyploid nature remain well-differentiated and does not lead to complex genomic instability and extreme heterogeneity. LGSOC is characterised with prevalent *KRAS*/*BRAF* mutations but the overall frequency of mutation is low with highly resistant nature (response rate is only of 4–5%) to treatment in the neoadjuvant, adjuvant and recurrent setting, possibly due to lower mitotic rate [34]. Due to rare incidence, detailed studies on the molecular evolution of this apparent mutationally stable well-differentiated disease are still lacking.

Interestingly, LGSOC, even after recurrence, retain their low-grade phenotype which supports the view that high-grade serous carcinoma does not progress from low-grade serous. However, it has been reported for a small percentage of cases that LGSOC, after recurrence, progresses and evolves into high grade serous indicating the existence of cellular and molecular plasticity[32]. A few cases of mixed morphology such as aneuploid HGSOC phenotype with micropapillary feature of LGSOC without any *KRAS* mutations were also observed [35]. Malpica et al. (2004), reported high-grade serous tumours arising from borderline serous in 2% of the cases. Similarly, in another report by Parker et al. (2004), women with borderline serous carcinomas, recurred as high grade serous [36, 37]. Collectively, these reports suggest a possibility that few low grades can transform into high-grade serous carcinomas through mechanisms that are yet to be elucidated.

1.1.2.3 Ovarian Endometrioid Carcinoma Ovarian endometrioid carcinomas (OEC) are generally of low grade and low stage and have a strong association with endometriosis, particularly with cystic ovarian endometriosis[38, 39]. Ovarian endometrioid carcinomas include two distinct pathological types—endometrial carcinogenesis which involves the malignant transformation of the endometrium (24%)[40]; and transdifferentiation of the ovarian surface epithelium into malignant cells that closely resemble the endometrium of the uterus. This generation of endometrium like malignant cells from the surface of the ovary, first reported by Samson and Santesson, contributes to the highly plastic nature of the ovarian cancer[40]. Genetic alterations in this subtype include mutations in *PTEN* (21%) along with activating *PIK3CA* mutations. 30% of the cases also had mutations in *ARID1A* along with activated Wnt signalling. Mutation in β-catenin gene, *CTNNB1*, has also been reported in endometrioid carcinomas[41, 42]. The primary treatment regimen for ovarian endometrioid carcinoma involves debulking surgery followed by platinum–taxol-based chemotherapy[38].

1.1.2.4 Ovarian Clear Cell Carcinoma Most cases of ovarian clear cell carcinomas (OCCC) are also closely associated with endometriosis and frequently co-occur with ovarian endometrioid carcinoma[32]. OCCC also arises de novo, from the ovarian surface epithelium[38]. These tumours have a dense cellular stroma with clear or hobnail shaped cells arranged in cysts and tubules, closely resembling renal clear cell carcinomas in morphology[32, 43]. This strong resemblance of ovarian clear cell carcinomas to clear cell carcinomas of the kidney, can be attributed to the plasticity of the ovarian surface epithelium. At the genomic level, clear cell carcinomas have been reported to harbour mutations in *ARID1A* (50%) and *PIK3CA* (33%) along with less prevalent *KRAS* and *PTEN* mutations as well[32]. Clear cell carcinomas are easily diagnosed at earlier stages but are less responsive to platinum-based chemotherapy especially at the later stages.

1.1.2.5 Mucinous Ovarian Carcinoma Mucinous ovarian carcinoma (mOC) is the rarest subtype but was initially thought to have a much more significant occurrence since metastasis from other malignancies, commonly those from the gastrointestinal tract were mistakenly categorised as mucinous ovarian carcinoma[43]. The cell of origin for mucinous tumours is still unknown, however, mucinous borderline ovarian tumours have been suggested to be putative precursors[44]. There is not enough evidence to suggest if the plasticity of the ovarian surface epithelium might also give rise to the mucinous type tumours as is the case with endometrioid and clear cell subtypes. These tumours have the worst clinical outcome even though they are diagnosed at early stages and due to the relatively low number of occurrences, this subtype is still poorly understood and much not known about the genetic mutations it harbours. Few reports, however, have shown mutations in *KRAS* (50%) and amplification in the *HER2* gene (20%)[32].

1.2 Cancer Stem Cell Plasticity

Although still not well understood for other subtypes, high grade serous ovarian cancer (HGSOC), due to its biological features and clinical characteristics represents a typical example of CSC-driven disease[45]. The standard treatment of de-bulking surgery and chemotherapeutics initially reduces the tumour size and temporarily improves patient symptoms but in over 70% of all cases the disease relapses. Recently, CSCs have been implicated to be a prime cause of relapse and chemoresistance[46]. The CSC hypothesis states that the CSCs due to their inherent quiescent and chemoresistant nature "survive" the majority of the chemotherapeutics that are designed to target actively proliferating cells (in the S or M phase of the cell cycle) and by having ability to self-renew themselves and differentiate, they recapitulate a continuously growing tumour leading to relapse and even more aggressive, drug-resistant disease[47]. These cells then initiate various differentiation programs that give rise to heterogeneous phenotypes found within a tumour[45].

Bapat et al. (2005) first identified and characterized the presence of ovarian cancer stem-like cells from tumour cells isolated from ascites of advanced-stage HGSOC patients. Using a combination of single-cell cloning, anchorage-independent growth, and spheroid formation techniques they identified cells that possessed classical stem cell and tumorigenic properties [48]. Subsequently, various studies using ovarian cancer cell lines, in vitro tumour-spheres, tumour xenografts and primary tumours have shown that presence of cell surface markers like CD133, CD24, CD144 with or without CD117, epithelial cell adhesion molecule (EpCAM), as well as functional assays like Hoechst and DCV exclusion (the "side population") and Aldehyde Dehydrogenase-1A1 (ALDH1A1) activity allow to enrich the CSC like population [49–52]. It was shown that xenografting only 100 cells dissociated from patient-derived in vitro grown spheroids recapitulated the original tumour, whereas 100,000 unselected cells were unable to produce similar outcome[53]. Similarly, the $CD133^{+}$ cell population isolated from patient-derived xenografts exhibited an approximately 20-fold increased tumorigenicity, with tumour formation starting from only 100–500 cells[54]. Malignant ascites is often comprised of tumour spheroids that are enriched with CSCs. These tumour cell spheroids resist anoikis (cell death due to loss of anchorage), survive and proliferate even in the absence of adhesion to any substratum. Interestingly, cells from the ascites of chemoresistant patients are predominantly epithelial and have been shown to bear an increased expression of genes associated with stemness compared to cells isolated from the ascites of chemo naive patients[55]. Several other studies have also investigated various putative ovarian CSC marker (*ROR1*, *OCT4*, *SOX2*, *NANOG*, *ABCB1*, *ABCG2*) expression and correlated with aggressiveness and chemoresistance of the disease[56-60].

Intriguingly, the expression of CSC markers varies between tumours within the same subtype and different populations of CSCs having different tumorigenic capacity can be isolated from the same tumour type using these markers alone or in combination which indicate a significant heterogeneity among the OCSCs[61, 62]. This heterogeneity might also be governed by different signalling pathways and this is well elucidated in a study conducted by Singh et al. (2016) where they have shown that CSCs at early stage of chemoresistance possessed higher tumorigenic potential compared to CSCs of late stage of chemoresistance and this functional heterogeneity was dictated by IGF-1R-AKT signalling[63]. The presence of diverse CSC markers may also imply the existence of different subpopulations of CSCs which having differential stemness and tumorigenic properties or plasticity and belong to different states of cellular differentiation or different phases of the disease [45]. These two phenomena can exist at the same time in a tumour and contribute to the intra-tumoral heterogeneity. However, most of the standard characterization methods of CSCs experience critical limitations due to technical bias. The use of putative CSCs post-sorting with limited markers, utility of patient-derived/cell-line xenografts of varying generations or application of differentiation-inhibiting factors in cell growth medium to favour tumour spheres formation might contribute to the improper observational estimation of CSC.

The cellular plasticity model has been recently described for CSCs of various tumours that bring a new level of complexity and heterogeneity within a tumour [7, 64, 65]. According to this concept, many non-transformed differentiated cells are able to alter their state and acquire a plastic behaviour in response to inflammation, injury, senescence and oncogenic stresses. In an elegant study, Katz et al. (2009) have shown that teratomas derived from the inoculation of murine embryonic stem cells into nude mice can confer an appropriate microenvironment to support the growth of tumorigenic human ovarian cancer cells. This hESC-derived microenvironment favoured the growth of $CD44^{+}ALDH^{+}$ self-renewing cells that sustained tumour growth through a process of tumorigenic differentiation into $CD44^{-}ALDH^{-}$ cells that in turn, were able again to de-differentiate giving rise to the self-renewing $CD44^{+}ALDH^{+}$ cell population [66]. Another report by Cui et al. (2018) has shown the ovarian CSC population can be maintained via cellular dedifferentiation. DDB2 (damage-specific DNA-binding protein 2) suppresses the non-CSC to CSC conversion by binding to *ALDH1A1* promoter through competing with C/EBPβ, an activator of *ALDH1A1* and thereby inhibiting the promoter activity of the *ALDH1A1* gene. De-repression of *ALDH1A1* expression in *DDB2* deficient cells contributes to expansion of the CSC subpopulation by converting non-CSCs to CSCs[67]. These observations highlight the manifestation of plasticity by ovarian cancer stem cells which emphasize the complexity to define this cellular population.

Emerging data also provide sufficient evidence that CSCs have the potential to transdifferentiate into various cell lineages other than the original lineage from which the tumour arose, although the efficiency of such transdifferentiation is believed to be relatively low. $CD44^{+}$ ovarian CSCs were shown to serve as vascular progenitor cells and could form $CD34^{+}$ endothelial cell-derived blood vessels in a VEGF-independent but IKK beta-dependent manner when cultured in Matrigel. Similarly, Liu et al. (2013) showed that ovarian CSC-derived clone CP70SR01 exhibited neuron-like morphology in a modified induction medium and expressed α-internexin and pan-neuronal markers in vitro. This clone also had the potential to transdifferentiate into adipocyte and osteoclast-like cells under induced conditions[68]. Furthermore, Ramakrishnan et al. (2013) have shown that ovarian cancer cells could fuse with $CD45^{+}$ hematopoietic cells and co-expressed both epithelial and hematopoietic cell markers and exhibited elevated stemness and migratory abilities[69]. These observations of the transdifferentiation of CSCs into different stromal cells in tumours provides a new dimension for explaining the plasticity and functional heterogeneity in cancer cells and their stromal compartments which makes it even more complex than expected.

The heterogeneity in CSCs, their inherent plasticity and the ability to transdifferentiate combined with unstable genetic status or dominant mutation/amplification of certain critical genes ultimately creates an overwhelming intra-tumoral heterogeneity which throws a distinct challenge to therapeutic efficacy (Fig. 2). The other well recognised and well-explored biological phenomenon underlying intra-tumoral heterogeneity as well as site-specific tumoral heterogeneity is epithelial-to-mesenchymal transition and the reverse phenomenon of mesenchymal-to-epithelial transition.

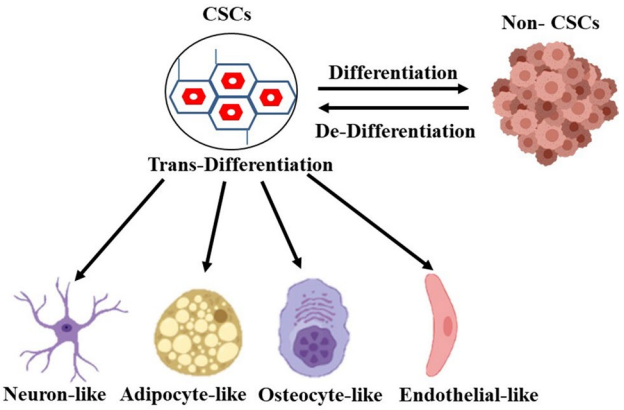

Figure 2: Cancer stem cell plasticity works as a driver of tumour heterogeneity resulting in CSC differentiation into different types of non-CSCs and these non-CSCs can reverse back to CSCs as well (dedifferentiation). Moreover, CSCs can trans-differentiate into different types of stromal like progenitor cells.

1.3 EMT–MET Circuit and Plasticity

Epithelial–mesenchymal transition (EMT) is classically related as a prologue to metastasis in tumour progression[70, 71]. Successful colonization and formation of micro- and macro-metastatic tumour requires shedding of the mesenchymal properties (completely/partially) in a diametrically opposite process to EMT called as Mesenchymal-epithelial transition (MET)[72]. The process of cuboidal sheet-like layer of epithelial cells undergoing apical polarity loss and taking up the phenotype of a motile, invasive slender cell has been a conserved mechanism across classes of animal kingdom serving from embryo development to organ maturation (Type I and II). EMT, in carcinogenesis follows a similar pattern except in an untimely fashion due to molecularly distinct triggers (Type III)[70]. The distantly metastasized cells, upon reaching organ parenchyma, re-assume the histological phenotype of the primary tumour through MET. The process of MET is also regulated by the partial pressure of oxygen (pO_2), activation of FGF2/FGFR axis, membrane expression of progesterone receptor α (mPRα) and downregulation of Notch signalling[73-75]. This corroborates that EMT–MET circuitry imparts plasticity to the cells that is required for both chemoresistance and anoikis-resistance[72, 76, 77].

1.3.1 Epithelial Ovarian Carcinoma and EMT Plasticity

The role played by the EMT program in EOC can be attributed in two aspects—origin of the disease and progression of the tumour[78]. The inherent plastic nature of epithelial ovarian tumour cells could be caused by the secretion TGF-β and Activin-A, pro-tumorigenic cytokine from TGF-β superfamily which are naturally produced post-ovulation[79, 80]. The current paradigm regarding the origin of HGSOC has been confounded by multiple theories. A minor fraction of "tumour initiating cells" with both mesenchymal- and stem cell-features are assumed to promote tumour initiation. Repression of a critical epithelial marker Pax2 (paired box 2) in oviductal cells followed by the formation of pre-cancer lesion typical secretory cell outgrowths (SCOUTS) is shown to develop serous tubal intraepithelial carcinomas (STIC). This whole process is orchestrated by EMT[81].

Unlike many epithelial cancers, the advanced stage EOC undergoes peritoneal metastasis majorly through transcoelomic route except a few cases of hematogenous pathway (via ERBB-3 expression)[82, 83]. In this way, cancer cells are directly shed into the peritoneal cavity and survive as single-cell entity or multicellular aggregate (MCA) also known as spheroids in ascetic fluid[72, 84]. MMPs are also known to be involved in the EMT process by inducing cleavage of E-cadherin, leading to abrogation of cell-cell junctions, translocation of b-catenin to the nucleus and upregulation of Wnt signalling[85]. In ovarian cancer, *WFDC2* (WAP four-disulphide core domain protein 2) encoding human epididymis secretory protein 4 (HE4), a recently studied member of serine protease inhibitor family (WAP) induces MMP2 expression along with Akt2 and thus imparts EMT plasticity and survival benefit to metastatic tumour[86]. One of the most studied factors involved in metastasis in OC is Lysophosphatidic acid (LPA) which is abundantly present in the ascitic fluid[80, 87]. It is constitutively produced

by the mesothelial cells of the peritoneum. LPA is reported to promote cell adhesion, invasion and migration and enhance cellular motility by inducing the cleavage of the extracellular domain of E-cadherin[30, 88].

The low-grade serous carcinoma which is believed to be originating from serous cystadenomas can also possess the capability to undergo EMT[36]. The conversion of borderline serous carcinoma to low-grade invasive epithelial ovarian tumour is a gradual process mediated by EMT through elevated expression of transcription factors such as Snail, Slug, Twist, Zeb, ZNF143, and ZNF281[89, 90]. PI3K/Akt is shown to downregulate E-cadherin upon p53 depletion which leads to stimulation of invasiveness in low-grade carcinoma[91].

Such a dualistic state of tumour cells leads to the assumption that one should target the intermediate stage of EMT rather than terminal stages. The advent of the concept of collective invasion which includes "leader cells" and "follower cells" highlights the distinct population of cells that 'lead' the invasion and they have been identified to express p-cad, e-cad, cytokeratin-14 and cytokeratin-8[92]. Such discovery augments the need of an approach for the collection of such dualistic cells.

The nature of cancer cells in a tumour mass, as we know, is polyclonal which happens due to gradual genetic perturbations in malignant cells. Also, the tumour microenvironment communicates critical cues for not only maintaining the heterogeneity but also to impart plasticity to individual cells, a much-required weapon to deal with cytotoxic therapies as well as to survive the physical hurdles faced within the body during dissemination through circulatory fluid and secondary colonization. While undergoing metastasis, the primary site for colonization of the ovarian cancer cells is the omentum. Although, omentum, the ventral layer of peritoneal membrane consists of large numbers of macrophages, adipocytes, and lymphocytes, the single layer of fatty tissue made up of mesothelial cells is the first site of contact for disseminated tumour mass (DTM). Pre-requisite to such cellular dynamics is the "reprogramming" of tumour cells that switche them from a proliferative to invasive physiology to augment degradation of the underlying matrix. Downregulation of E-cadherin is indispensable to these events which ultimately leads to interaction between α5β1-integrin expressed by spheroid and fibronectin expressed by mesothelium. Even at times, the patients respond to chemotherapy with no apparent existence of secondary tumour but dormant cells often stay back in certain niches and appear later as metastatic foci. Such niches are largely composed of a myriad of different cells such as metastasis-associated macrophage (MAM), cancer-associated fibroblast (CAF), endothelial cells, NK T-cell[93]. The dormant tumour cells are safeguarded from immune-surveillance by induction if TGF-β through IL-6 secretion by NK cells[94]. Also, the non-proliferative state in OC cells is maintained by MAPKK4 through the upregulation of JNK signalling[95]. Thus, the cells are provided favourable microenvironment during dormancy of the tumour.

Cancer stem cells may also transit between states, exhibiting distinct features and abilities to disseminate and give rise to metastatic lesions, which may influence cancer progression and therapy response. This dynamic behaviour has been associated with the induction of the EMT program. Kurrey *et al.* (2009) showed that transfection of EMT inducers, Snail and Snail2, in ovarian cancer cells led to de-repression of the stemness genes, including Nanog and KLF4, and 4- to 5-fold increases in the size of a $CD44^{high}$/$CD117^{high}$ CSC population giving us another example that the induction of EMT in more-differentiated cancer cells can generate CSC-like cells[96].

Activation of EMT program results in a reversible switch of phenotypic features, which encompasses a spectrum of cells, from epithelial to mesenchymal-like cancer (stem-like) cells, as well as hybrid intermediate states (E/M hybrid stage), in which cells conserve epithelial features, but also express mesenchymal markers[97]. Strauss et al. (2011) reported a subset of ovarian cancer cells with a hybrid phenotype that drove tumour growth, giving rise to tumour cells with partial EMT phenotype, and differentiated epithelial cells[98]. Therefore, tumour cell stemness could be associated with an intermediate state of EMT. Another ideation of functionality of EMT is the presence of feedback circuit instead of a more straight-forward "all or none" principle. The idea stems from the observation of hybrid cells expressing both the motile (mesenchymal) and placid (epithelial) phenotypes. Several studies have backed up this notion. Jolly et al. (2018) has shown that knocking down epithelial splicing regulatory protein 1 (ESRP1) at the hybrid state of H1975 lung cancer cells disrupts the ESRP1-hyaluronic acid synthase 2 (HAS2)-CD44 feedback loop which abrogates Zeb-1 expression[99]. An earlier report published in 2008 by Bracken et al. had identified a double negative feed-back process mediated by two pro-EMT transcription

factors ZEB-1 and SIP-1 which bind to the E-box elements near the TSS of miR-200a, miR-200b and miR-429 in 300-bp segment promoter located 4 kb upstream of miR-200b[100]. A similar negative loop was also reported for miR-34a/b/c promoters mediated by SNAIL and ZEB-1[101].

1.3.2 Emerging Molecular Factors

Till date, several reviews dealing with the prevalence of plasticity in EOC have majorly talked about epigenetic modifications that in turn alters the expression profile of certain sets of phenotypic genes that confer the epithelial–mesenchymal distinction. A study by Hu et al. (2019) has identified the intrinsically divergent nature of HGSOC through single-cell transcriptomics of fallopian tube epithelial cells (FTE), the presumable origin of serous ovarian cancer (SOC) and demarcated six FTE subtypes[102]. This study is first of its kind to associate FTE, one of the contenders of site-of-origin in EOC with SOC subtypes. Also, this study has shown through deconvolution analysis that the FTE subtypes match with the ovarian cancer cell state in the tumour. Here they report that KRT17 positive population, among the FTE subtypes, is associated with the mesenchymal phenotype. Also, the role of TGF-β signalling, activin-A in inflammation-induced EMT reprogramming were extensively reported[79, 80]. Expression of a mesenchyme-tissue-specific transcription factor of helix-loop-helix domain-containing family Tcf21/Pod-1 has been reported in HGSOC cells to be associated with epithelial phenotype by inhibiting S2 to bind on the E-box element of *slug* gene. However, co-expression of both the transcription factors is linked to the greater potential of E-to-M transition[103]. Such intricacies command a better understanding of the EMT phenomenon in ovarian carcinoma. Hence, in the following section, we have focussed our discussion on such factors and some age-old evolutionary tricks of nature that possibly play a critical role in the EMT–MET phenomenon and have recently made a mark in terms of knowledge in this regard.

1.3.2.1 Non-Genetic Modification The natural course of development for living cells is challenged with external adversities. The survival, hence, is imperative on adaptation. Tumour cells, like others, are no exception to this fact. We always observe a bi-phasic response from a population of tumour cells upon challenging with therapeutic perturbations. The reason for it is not only the genetically hard-wired intrinsically resistant cells but the persisters which arise through the general course of evolution, known as bet-hedging[104] which is neither heritable nor mutationally altered in somatic cells[105]. Rather it is a diversified survival reversible response through a myriad of cellular signals and epigenetic modulation[106, 107]. This theory has been assessed well by looking into the phenomenon of non-mutational mechanism of androgen independence in prostate cancer[104]. But such studies can have a global implication in other cancers like ovarian carcinoma which is known to be highly chemoresistant. Also, the cells can forge this evolutionary trick in giving rise to a motile phenotype.

Bet-hedging: It refers to the stochastic alterations in the phenotypic trait(s) of organisms in the face of fluctuating environmental stress(es). This is a quintessential phenomenon of adaptive evolution.

1.3.2.2 Long Noncoding RNAs (lncRNAs) LncRNAs are a type of non-protein coding RNAs with their transcripts having a length in excess of 200 nucleotides. LncRNAs have shown a great deal of potential in studies for its implications in cancer biology, playing role in critical cellular functions including cell cycle progression, proliferation, differentiation, invasion, metastasis and apoptosis[108-110]. Albeit emerging as a new type of small-molecule regulators in cancer progression, the exploration of the relationship of lncRNAs with EOC and its contribution to EMT/MET in EOC has just taken off[111].

Upregulation of the ZFAS1 (ZNFX1 antisense RNA 1), a regulator of mammary gland development, was reported in EOC and correlated negatively with overall survival of ovarian carcinoma patients[112]. It has been established that ZFAS1 overexpression enhances proliferative and migratory potential along with chemoresistance in EOC cells. miR-150-5p was found to be a potential target of ZFAS1 that suppresses the transcription factor Sp1. Notably, inhibition of miR-150-5p can partially restore migration and proliferation as a result of the depletion of ZFAS1. In this way, the ZFAS1/miR-150-5p/Sp1 pathway proves to be critical in aggravating migration, differentiation and chemoresistance in EOC.

In a separate study by Qiu et al. (2014) , lncRNA HOTAIR (HOX transcript antisense RNA) expression in EOC tissues was assessed and upon suppressing HOTAIR in three highly metastatic EOC cell lines (HEY-A8, SKOV3.ip1, and HO8910-PM), and show a significant reduction in migration and invasion[113]. Moreover, the pro-metastatic effects were partially regulated by MMPs alongside EMT-specific genes. Especially, siRNA-mediated silencing of HOTAIR increased expression of *CDH1* (gene encoding E-cadherin)

with a simultaneous decrease in the expression of *vimentin* and *snail*.

TGF-β signalling has also been shown to serve as a major EMT-promoting factor, facilitating metastasis in EOC and breast cancer. Albeit the link between lncRNA and TGF-β in EOC is unknown, the lncRNA status in mouse mammary epithelial NMuMG cells after TGF-β induction of EMT has been reported, recognizing a subset of lncRNAs dysregulated after TGF-β induced EMT with lncRNA-HIT running this process by targeting *CDH1*. These findings reveal a prominent role of lncRNAs in EMT in breast cancer progression and warrant more studies dissecting the relation between lncRNA status and TGF-β-induced EMT in EOC tumours[114]. Collectively, such reports suggest a direct/indirect relationship between lncRNA and regulation of EOC invasion and metastasis, as well as novel mechanisms involved in EMT in EOC, which can potentially result in identifying both new biomarkers of disease assessment and also therapeutic targets for epithelial ovarian cancer.

1.3.2.3 Hippo Signalling Pathway One of the important emerging promoters of EOC is the Hippo pathway signalling, which has been shown to affect several key signalling molecules via various types of PTMs[115]. Hippo signalling, classically known for maintenance of organ size and tumorigenesis in flies, has recently been observed to play an oncogenic role in ovarian cancer[115, 116]. The pathway is a network of tumour suppressors encoding signalling molecules, receptor, scaffolding regulated by warts (insecta homolog) kinase. Different modules of this pathway such as Yki homolog YAP (Yes-associated protein)/its paralog TAZ (also called as WW Domain containing transcription regulator 1-WWTR1), MAT1/2 (mammalian Ste20-like kinases 1/2) and LATS1/2 (large tumour suppressor 1/2), due to deregulated PTMs, have been associated to different types of cancer including EOC[116]. A tissue microarray study on 70 individuals with ovarian cancer has linked nYAP expression with poor overall survival. This happens due to the failure of phosphorylation of YAP at S127 by LATS 1/2 and subsequent failure of 14-3-3 to retain YAP in the cytoplasm. Anchorage-independent growth and enhanced migratory potential has also been found in vitro due to Yap2 overexpression. Since there is no reported activating mutation in Hippo signalling in EOC, a wealth of information about the PTMs can be therapeutically targeted to inhibit EMT.

1.3.2.4 Metabolic Reprogramming TGFβ1, a well-known potent EMT inducer, is reported to induce the expression of the sialyltransferase 1 (ST3GAL-1)[117]. Sialylation of the EGFR by ST3GAL enhances EGFR expression and activates EMT, which promotes resistance to paclitaxel in vitro and in vivo. Additionally, pyruvate dehydrogenase kinase 1 (PDK1) leads to EMT and platinum recalcitrance via phosphorylation of EGFR. An inhibitor of EGFR tyrosine kinase, Erlotinib, reverses this PDK1-induced platinum resistance in vitro, and genetic perturbation of PDK1 in vivo also decreases platinum resistance[118]. This work done by Zhang et al. (2019) has suggested that PDK1, the quintessential molecule of the Warburg effect, mediates chemoresistance through the phosphorylation of EGFR. Amphiregulin (AREG), otherwise inhibited by miR-34c-5p, induces EMT as well as resistance to docetaxel and carboplatin, and CSC-like features in vitro through AREG-EGFR-ERK pathway activation[119]. The study has also showed an inverse correlation between overall survival and AREG expression in 65 ovarian cancer patients. Fatty acid synthase (FASN) is considered as one of the oncogenes in tumour formation for a myriad of cancers[120-122]. FASN is reported to be augmented in the disseminating tumour of peritoneal metastatic EOC. FASN transcriptionally regulates *CDH1* and *CadN* (encoding N-cadherin) genes which favours enhanced colony formation and migratory abilities of cells[123]. Cyclooxygenase-2 (COX-2) or Prostaglandin-endoperoxide synthase 2, a well-known pro-inflammatory cytokine, has been associated in an inverse correlation with E-cadherin. Also, depletion of Cox-2 by its inhibitors such as celecoxib, palbociclib causes reduced translocation of Snail, a vital cog in EMT alteration[124, 125].

1.3.2.5 Changes in Stress Chaperones As the cellular milieu faces constant stress conditions like pH alteration, the appearance of reactive radical species (RRS), infection by microorganisms and so on, the chaperone system orchestrates the critical defense towards the misfolded proteins[126]. The stress-induced chaperones are also known as chaperone holdases as they tether to the misfolded proteins until the stress condition persists and do not allow aggregation formation. Myriad of studies have linked stress chaperones to EMT and chemoresistance. Tumour necrosis factor-associated protein 1 (TRAP1), a chaperone, induces oxidative phosphorylation resulting in the secretion of cytokines and remodelling of gene expression. Reduced TRAP1 expression causes cisplatin resist-

ance due to the reduction of inhibition of p70S6K, a kinase that induces Snail (with resulting *CDH1* repression) and it is often activated in ovarian cancer[127]. Another stress chaperone is mortalin which induces EMT in breast cancer cells. Silencing of mortalin causes a concomitant increase in platinum sensitivity ovarian cancer cell lines[128]. This is an instance which shows EMT-mediated cellular plasticity can confer survival advantage against chemotherapy to ovarian cancer cells.

1.3.2.6 Micro-RNAs Micro-RNAs, another class of non-coding RNAs ranging from 17 to 24 nucleotides in length, can regulate EMT and chemoresistance through interaction with different transcripts, leading to degradation and subsequent prevention in their translation[129]. Indeed, recent reports have described nine microRNAs associated with platinum resistance in ovarian cancer, out of which three are direct EMT regulators: miR-152, miR-27b, and miR-496[111, 130]. However, the most well-accounted EMT-repressing micro-RNA family is the miR-200 family[131, 132]. Decreased expression of miR-200b promotes EMT and subsequent cisplatin resistance by direct physical inhibition of Zeb1 and Zeb2. Another miRNA, miR-1294 enhances cisplatin sensitivity and induces MET in vitro by directly inhibiting the anti-apoptotic gene insulin-like growth factor 1 receptor (*IGF1R*), consequent to decreased expression of *AKT*, *ErbB* and *mTOR*[78, 133]. In fact, miR-1294 expression was found to be lesser in EOC patients with platinum-resistance in comparison to platinum-sensitive counterparts. It has been implied that miR-363 itself inhibits Snail-induced EMT and thereby mitigates in vivo platinum resistance[134, 135]. Moreover, miR-363 expression is found to be lower in patients with platinum-resistant EOC in comparison to platinum-sensitive cases. MiR-186-5p expression suppresses Twist1-induced EMT, and higher sensitivity to platinum-based therapy both in vitro and in vivo[136, 137]. Lower level of miR-186 expression was correlated with resistance and poor survival in serous ovarian adenocarcinoma tumours belonging to FIGO stage IIIC or IV[137]. There are also miRNAs with opposing roles in EMT and chemoresistance wherein they promote such mechanisms e.g. miR-20a which induces cisplatin resistance and EMT in OVCAR3[138, 139]. Overexpression of miR-181a induces EMT and resistance to paclitaxel in SKOV3 cells through overexpression of P-glycoprotein[140]. Moreover, cancer-associated adipocytes (CAA) and cancer-associated fibroblasts (CAF) can secrete exosomes carrying miR-21, an EMT-promoting micro-RNA, which had been found to cause paclitaxel resistance in OVCA432 and SKOV3 cells[141].

2 Conclusion

Cellular plasticity plays a significant role in various biological processes as well as in promoting cancer cell metastasis. It is not only the ovarian cancer cells that display plasticity during metastasis but the ovarian surface epithelium, which is, apart from the fallopian tube (serous tubal intraepithelial carcinoma) one of the progenitors of high grade serous ovarian carcinoma, in itself is highly plastic. It bears both epithelial and mesenchymal characteristics which innately helps in the process of post-ovulatory repair. This dynamic nature of the epithelial cells of the ovarian surface also contributes towards the overall heterogeneity and plasticity of ovarian cancer. Different subtypes of EOC present examples of such cancer cell plasticity governed by genetic signatures but the molecular mechanisms are yet to be elucidated. The scope for future therapy lies in understanding these underlying molecular factors. Alongside such inherent property of the tumour cells, the dynamics and heterogeneity can also be attributed to the Ovarian CSCs which play an important role in tumour formation and dissemination, thus advancing disease progression particularly for HGSOC. Resistant dormant CSCs can "wake up" later and cause tumour recurrence which is more chemoresistant than the primary tumour. While talking about ovarian cancer plasticity, one must take into account EMT–MET circuitry even more. Because, apart from the contribution of CSCs in EMT program, it is the inherent duality (of both mesenchymal and epithelial phenotypes) of epithelial ovarian cancer cells and especially high-grade serous tumour heterogeneity that make the cells more prone to such morphological transition leading to spread of the disease. Though growing evidences show that EMT can impart chemotherapy resistance and stemness, the distinct underlying molecular and genetic mechanisms and environmental cues associated with subtypes of EOCs are yet to be identified. Moreover, the evolutionary dynamics as well as the surrounding ecosystem of tumour have the tendency of influencing the phenotypic state of the cells. Such cross-talks command for better understanding the intricate association between inter and intra-tumoral heterogeneity with cellular plasticity critically and clinically

to usher in therapeutic progression in epithelial ovarian carcinoma.

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All authors have participated in concept design and preparation of the manuscript. PR, PP, MM and SM have contributed in literature mining and data interpretation. PR has also critically analysed the manuscript and all authors have agreed upon the submitted version of the manuscript.

Compliance with Ethical Standards

Conflict of interest

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Pritha Ray is interested to investigate and detect the key molecular switches associated with metastasis and chemoresistance and develop new therapeutic and diagnostic strategies for epithelial ovarian cancer.