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Eradication of Ovarian Cancer Stem Cells in Ovarian Cancer Using Stem Cell Therapy

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Abstract:
One of the most frequent gynaecological malignancies in the world and one of the main causes of cancer-based female death is ovarian cancer. About 3 out of 4 (72.4 percent) women with OC survive for at least one year following diagnosis for all forms of ovarian cancer. Five years after diagnosis, almost half (46.2 per cent) of women with OC are still living. Ovarian epithelial malignancies are mostly imported from the endometrial or fallopian tube epithelium. Ovarian cancer therapy is difficult because of a frequent recurrence of diseases and further difficult owing to chemical resistance. Cancer stem cells (CSCs) continue to get interest since they are known to withstand chemical treatment, to renovate themselves, and to re-populate the bulk cell tumour. CSCs also seem to respond quickly to environmental, immunological and pharmacological indications. The flexibility and capacity to inactivate or activate signaling pathways that support their lifespan has been and remains the difficulty in creating effective CSC-targeted treatments. The identification and comprehension of distinct ovarian CSC markers and the pathways may provide novel therapeutic possibilities that provide different therapy adjuvant choices. Here we will examine the characterization of ovarian CSC in OC and stem, isolation and enhancement of CSC and OCSCs signals and targeted therapies.

Key words:
Ovarian cancer, Cancer stem cell, chemotherapy, CSC marker, Stemness, pharmacologic.

Introduction

More than 19.3 million newly arrived cases of cancer and 10 million cancer deaths from cancer are projected worldwide in 2020 [1]. Patients living in less affluent areas have lower cancer survival than patients living in more affluent areas, according to studies from multiple countries and cancer sites [2]. After implementing social distance' policies in the Netherlands, the incidence of cancers other than skin cancer decreased by 25%, and skin cancers (excluding basal cell carcinoma) decreased by 60% [3]. The tumor microenvironment (TME) is a complex environment in which various neoplastic cell types and extracellular matrix proteins interact to control cancer cell biology [4]. The Cancer Genome Atlas (TCGA) is the world's largest and most complete multi-omics oncology cohort, allowing researchers to analyze mRNA expression, DNA methylation, and progenitor connections in 33 cancer types simultaneously [5]. Ovarian cancer (OC), also known as the "silent killer," is the most common gynecological cancer killer [6]. Ovarian epithelial malignancies are mostly imported from the endometrial or fallopian tube epithelium, unlike other human malignancies, where all initial tumors form de novo [7]. Because of its non-toxic properties and high attack rate, high mortality is difficult to detect early. Unfortunately, 60% of OC patients are discovered at a late stage, with a survival rate of just 29%. The early-stage illness, on the other hand, has a 92 percent 5-year survival rate [8]. Wnt / β-catenin, Hedgehog (Hh), protein kinase B (PI3K / Akt), /phosphatidylinositol-3-kinase epidermal growth factor (EGF), and alter growth factor-T (TGF-) are just a few of the pathways that CSCs use to spread is under control [9]. The surface and function markers of various specific cells such CD44, CD117, CD33, CD24, the molecular epithelial cell synthesis (EpCAM), and dehydrogenase aldehyde were all employed to identify and test ovarian stem cells for ovarian cancer (ALDH). After being removed from the initial source, ovarian cancer cells develop into colourful spheroids, including some mesenchymal and immune cell components, and ultimately spread into the peritoneal fluid, mostly by the physical migration of the material to metastasis to the omentum and peritoneum [10]. CSCs appear to be compatible with stem cell pathways and self-regeneration, both of which are involved in tumorigenesis. Cancer treatment can thus be accomplished by studying cancer cell self-regenerative pathways [11].

CSCs in Ovarian Cancer:

CSCs are cells that cause tumors to form (TICs). Ovarian carcinoma is one example of a CSC-driven illness. A group of scientists with a five-meter diameter identified VSEL (very tiny embryonic-like) stem cells, which stay latent in

adult human organs and tissue [24][25]. The homeobox (HOXD9) genes, SOX17 and forkhead box (FOXQ1, FOXL2) which govern proliferation, cell division, differentiation, the creation of body axis, and embryonic development, all have a role in ovarian cancer, according to the findings [26]. Bapat et al. were the first to disclose the presence of CSCs or progenitor cells in Ovarian Cancer patient ascites over a decade ago, demonstrating that cells from a single clone may appear identical to original tumor cells [27]. SFRP1, NANOG, LHX9, ALDH1A2, and ALDH1A1 are among the stem cell markers detected in both Ovarian surface epithelium (OSE) and the fallopian tube epithelium (FTE) [28]. Peritoneal ascites are present in the majority of patients, which may provide an optimal environment for OCSC survival and enrichment [29]. Aldehyde dehydrogenase isoform 1 (ALDH1A1) cells, CD44, CD133, CD24, CD117 (c-kit) and have been shown to include OCSCs. These markers might be used to distinguish stem cells from the remainder of the cancer cells [29][30][31][32]. CD44 is a transmembrane glycoprotein found on the cell surface that serves as a receptor for a variety of signals from the surrounding environment. This transcription factor controls gene expression in the regions of cellular differentiation and adherence to the extracellular matrix. This CSC surface marker is often used to detect CSCs in OC and other malignancies. It may be used alone or in conjunction with other possible markers to detect CSCs in OC and other malignancies [33][34][35]. According to Gil Mor and colleagues, the conventional CD44 variation, which was previously characterized as being critical in the attachment of free-floating cancer cells or cell clusters to the peritoneum, is one of the most significant prospective surface antigens for identifying Stemness in ovarian cancer [36][37][38]. CD117 is a receptor tyrosine kinase(RTK) that participates in a number of cell signaling pathways. CD117 overactivation has been identified in a variety of malignancies. In OC, high CD 117 expression has been linked to a low disease-free survival rate [39][40]. According to the research, CD24 is a small cell surface marker that has been discovered to be highly expressed in a variety of malignancies, including about 70% of initial tumors retrieved from 174 OC patients [41]. Malignant tumors often produce CD133, a glycosylated transmembrane protein that has been proven to be predictive of OC. Through a variety of signaling pathways, CD133 has the capacity to influence cancer stemness and metastasis [28]. A relatively small proportion of CD133+ cells were detected occasionally in the A2780V cell line. According to the current study, this cell surface molecule is an excellent predictor of ovarian cancer-initiating (stem) cells, either alone or through the conjunction with the ALDH1A1+ phenotype [42]. ALDH is a family of enzymes with 19 distinct isoforms that are responsible for converting aldehyde substrates to its carboxylic acids in the body [43][44]. ALDH+ cells displayed improved DNA repair and a higher number of drug efflux transporters in OC, showing that ALDH is involved in modifying drug resistance. Because ALDH+ cells display a wide range of CSC features, the amount of ALDH has been utilized to characterize OCSCs in a number of studies, including this one [45][46][47][48]. According to these studies, cells with the CD133+/ALDH1A1+ marker combination were considerably more likely to

Table 1: Gene involves in ovarian cancer

Transcription Factor/ Gene	Location	Mechanism	References
HOXD9	2q31.1	over-expression	[12]
TP53	17p13.1	*gain-of-function* (*GOF*) mutations	[13]
BRCA1/2	17q21/ 13q12.3	germline *BRCA* mutation	[14]
BRIP1	17q22	frameshift mutation	[15][16]
p53	17p13.1	over-expression	[17]
RAD51D	17q12	frameshifting insertions or deletions	[18][19]
PIK3CA	3q26.3	Gene amplification	[20][21]
KRAS	12p12	Gene amplification	[22][23]

commence sphere formation than cells with other surface characteristics. Silva et al. found that ALDH1A1+/CD133+ cells had more angiogenic capacity than the bulk of tumor cells. The presence of these cells in primary tumor specimens was associated with worse disease-free and overall survival in ovarian cancer [49].

Isolation and enrichment of CSCs:

Different approaches can be used to identify and isolate CSCs. CSCs can be isolated from solid tumours using MACS and FACS, which are depending on the cell surface or intracellular markers [50]. MACS is a low-cost monoparameter isolation approach, while FACS is a high-cost multiparameter isolation approach [51]. MACS is

similar to FACS in that it selects cell populations by using surface markers, but it takes less time and requires less expensive equipment [52]. CSCs are widely isolated from heterogeneous tumor cells using cell surface marker-based separation approaches [53]. Several markers were utilized to isolate CSCs from ovarian cell lines, including ALDH1/2, LGR5, CD133, LY6A, EpCAM, CD44, CD133, CD24, CD34, CD117, CDH1 and MyD88 [54][55][29][56][57][58][59][60][61][62]. CD44 is a well-known surface marker of SCs that promotes tumor growth and oncogenesis. In OC, high CD44 expression is linked to metastasis, recurrence, chemoresistance, and survival rate, while its reduction inhibits tumor cell proliferation and metastasis and reverses chemoresistance [63]. CD133 is a cell surface marker which can be used to distinguish CSCs from breast cancer, prostate cancer, glioblastoma, liver cancer cells, and colorectal cancer [53]. Glioma stem cells (GSCs) that were positive for the CD133 antigen were shown to be tumorigenic,

according to the research. Human lung cancer cell lines CD133+ and CD133-, as well as CD133- mouse glioma cell lines, were oncogenic, capable of colonization and self-renewal, and had the tumorigenic potential [64][65]. According to the results of another research, CD105 positive cells extracted through using MACS methodology demonstrated higher CSC features than CD105 +ve cells extracted using the MACS methodology. CXCR4 +ve cells were shown to have more capability for sphere formation and carcinogenesis when compared to CXCR4 -ve cells [66][67]. Another methodology for differentiating CSCs is the Aldefluor method, which is based on the enzyme aldehyde dehydrogenase and may be used to detect CSCs (ALDH). It is possible to image single cells in monolayer cultures with this technique, which may be useful in some situations. When compared to techniques that target the cell surface, this technique is more stable and has a lower specificity [68]. ALDHs are enzymes that help convert aldehydes into carboxylic acids like retinoic acid. Several lines of in vitro and clinical evidence point to a link among high ALDH expression and CSC-like characteristics in various cancers. A fraction of ALDH-high prostate cancer cells recovered by the Aldefluor test revealed increased migratory capacity and clonogenic capacity when comparing to ALDH-low prostate cancer cells [69]. The ALDEFLUOR, which is based on the degree of aldehyde dehydrogenase 1(ALDH1) enzyme activity, was utilized to identify cells from six ovarian cell lines and nine OC patients with increased sphere-formation potential, tumorigenicity, and invasiveness [70]. When ALDH+CD133+ cells were put into xenograft mice, it was shown that they were more capable of forming bigger and quicker tumors, as well as constructing three-dimensional spheres, than their negative counterparts in ovarian tumors [42]. Another technique to identify CSCs is to look for cell populations(SP) that have the capacity to pump out a drug (Hoechst33342 or Dye Cycle Violet) and have ABC transporter expression using Hoechst 33342 dye-staining [71][72][73][74]. The Hoechst 33342 dye is kept out by a transporter in this approach using SP cells. Chemotherapeutic drugs are expelled from the body as a consequence of this mechanism, which leads to chemotherapy resistance [71]. This procedure may also be used to identify CSCs without the use of a cell surface marker; however, it has lesser specificity, purity and has deleterious effects on isolated cells when compared to conventional techniques. In contrast, to control cells, isolated SP cells from the SK-OV-3 ovarian cell line displayed large quantities of CSC markers such as ABCG2, ATP-binding cassette, CD44, and nestin. These cells, despite their small size, have a strong capacity for self-renewal and multiplication [75].

Cancer stem cells and Stemness:

Ovarian cancer due to often peritoneal serous fluid, spheroids that remain cells can both live and multiply in a non-adherent status [76]. The study suggested that up to 70% of cases of ovarian cancer present with massive malignant ascites [77]. Passivity, differentiation, EMT, and plasticity are all aspects of stem molecular biology that are governed by a variety of topics, stem cells, cell divisions, extracellular matrix, host cells, and choice factors [78]. Exessive EMT activation is also responsible for cancer metastasis. Study revels that there is a possible link between EMT and the gain of stem cell properties in normal and cancer cell populations [79]. In vivo, These CSCs constitute a subpopulation of neoplastic cells that are able to divide by maintaining their Stemness with self-regenerating properties that aid tumor development and heterogeneity throughout tumor recurrence [80][81][82]. Due to their capacity to self-renew and specialize into diverse lineages of cancer cells, drug resistance in CSCs causes tumor recurrence after first chemotherapeutic therapy [83][84]. These systems were proven to have unique metabolic capabilities, so highly glycolytic functions in comparison to differentiated tumor cells [85][86][87]. This extraordinary metabolic behavior can result in resistance for the drug. Rodent ovarian CSCs have a better glycolysis rate in comparison to their parent cells, which can be related to chemotherapeutic resistance [88]. The ovarian CSCs, CD117 and CD44 reveal a excessive level of mitochondrial ROS, which suggests that the mitochondrial, a part of the respiration chain, is specially used to keep cells in a state of food stress and starvation condition [89]. These systems have many mechanisms of drug resistance, along with aldehyde dehydrogenase, ABC transporters, signaling pathways and DNA repair [90]. Hoechst 3342, a DNA binding dye, is a way for obtaining specific information related to the ABC function, which is located on the right side. Breast cancer resistance protein (ABCG2) and P-glycoprotein (MDR1) have a role in cancer prevention and chemotherapy resistance [91][92][93][94]. Although doxorubicin is out of the query like ABCB1 and ABCG2,

Paclitaxel only needs to be pumped out of MDR1 [95][91]. Therefore, the higher expression of those carriers is visible to be a multi-faceted data. ABCB1 and ABCG2 were detected in high concentrations in cancer stem cells from ovarian malignancies and breast respectively [96][97]. In ovarian tissue surgery, high amounts of ABCC3/MRP3, ABCB5 and ABCA1 were noted, and the greatest levels of ABCG2/BCRP, ABCB1/MDR1/P-GP, and ABCA1 were indicated in ovarian CSCs [97][98][99]. Because of the relationship between the ABC transporter, the kind of chemotherapy resistance, and the causes of resistance, it is necessary to pick a specific suppressor [100]. Another significant mechanism of CSC resistance is aldehyde dehydrogenase (ALDH), which is produced by the liver. Various human isoforms, ALDH, that's expressed particularly in the kidneys and liver [101]. ALDH work experience is taken into consideration as a prognostic marker of diverse kinds of cancer, which include lung cancer, breast cancer, pancreatic cancer, bowel cancer, and OC [102][103][104][105]. When lithium is utilized as an ALDH inhibitor, it has been discovered that ALDH has a cyclophosphamide resistance function that is compatible with the cyclophosphamide resistance function of the cyclophosphamide leukemic cell line L1210 [106]. Resistance to cyclophosphamide mediated by ALDH was also reported in medulloblastoma [107]. ALDH also deals with the Csc phenotype, formation of colonies, expression of self renewal markers and creation of tumors, and the EMT methodology of ovary cancer [108]. Therefore, inhibition of ALDH can play an crucial role in elevating the system's cognizance of the truth about narcotic drugs. It has been reported that ALDH1A1- siRNA sensitized ESA + CD44+ colon CSCs with high ALDH expression to cyclophosphamid [109]. The third mechanism that is responsible for the chemical resistance of CSCs is the participation of the family of proteins b-cell lymphoma-2 (BCL-2). This protein family plays an essential part instability between development and hematopoiesis, cell death, neurogenesis, and embryogenesis [110]. Many neoplastic and hematopoietic cells display the carcinogenic capability of the BCL-2 Protein [111][112]. According to the authors, high levels of BCL-XL and BCL-2 expression in leukemic CD34+ cells, as well as CD44+/CD24+/low levels of breast CSCs, may be present in leukemic CD34+ cells [113][114]. In order for Csc to survive and fight chemotherapy, an excessive level of BCL-2 protein production via signaling pathways is required. It was discovered that the expression of BCL-2 was accompanied with an increase in the level of sensitivity to oxaliplatin and FU-5 [90]. Already expressed Bcl-xl is seen in the majority of cases of recurrent chemoresistant ovarian tumors, and this is associated with a shorter disease-free time [115][116]. Inhibition of Bcl-xL boosts ovarian cancer cells' chemosensitivity in pre-clinical trials, and findings suggest that the most promising treatment approach to recurring ovarian epithelial malignancies is to block anti-apoptotic proteins [116][117]. Signal-like pathway of WNT /β-catenin and NOTCH also have chemoresistant procedures which are involved in the systems [118][119][120][121][122]. The link between the WNT pathway and cisplatin resistance in OV6+ – reduced systems are identified [123]. The NOTCH signaling system plays a critical role in the formation and self-renovation of tumors, angiogenesis, epithelial-mesenchymal transition (EMT) [124][125][126][127]. Knockdown of the Notch 1 receptor or the usage of a gamma-secretase inhibitor has been proven to bring about the sensitivity of oxaliplatin to colon most cancers cells as well [128]. In the biology of CSCs and platinum resistance, increased notch3 expression is significant. A gamma-secretase inhibitor (GSI) eliminates Csc by enhancing its sensitivity to the necessary platinum. Combination treatment, which involves tumor excision and SSC-centric treatment, is more successful than secular treatment in general [129].

OCSCs signaling pathways and targeted treatments:

Due to the importance of ovarian CSCs in drug resistance and recurrence, their elimination might be seen as an efficient therapeutic strategy for the resistance and recurrence of ovaries to cancer [130]. However, there are a variety of different options available, including using signaling channels, using surface markers as precise targets, and briefly discussing some other ways for eradicating the CSC.

Signaling pathway and targeted therapy:

In CSCs, one of the greatest treatment strategies is to target signaling pathways. However, Hedgehog (SHH), WNT, PI3K/PTEN, SONIC, NF-kB, and NOTCH are only a few of the important signaling pathways linked to stem cell traits. As a result, dysregulation of these signaling pathways may be linked to the survival of CSCs [131].

Wnt signaling:

The classical WNT signaling pathway is considered to be an important and protective mechanism throughout development and tissue homeostasis [132]. Dysregulation of the WNT pathway inhibits colonic crypt stem cell proliferation and differentiation while concurrently enhancing the expression of target genes such cyclin D and Cellular Myelocytomatosis (c-myc), leading in the formation of a cancer stem cell phenotype [133]. Furthermore, in CD44+/CD133+ colon CSCs, a substantial association between the WNT pathway and CSC characteristics was discovered [134]. This route is also linked to chemoresistance in ovarian cancer, according to the research [135]. The WNT pathway is used to maintain stem cells in the ovarian epithelium and to activate R-spondin through leucine-rich repeat-containing receptor. In ovarian cancer, the presence and chemoresistance of LGR6 and LGR5 in epithelial stem cells is essential [136]. WNT signaling inhibition may be utilized to destroy CSCs, which might be an excellent way to treat cancer [137]. PRI-724 blocks the

WNT pathway in colon cancer cells by binding to the CREB protein, resulting in the development of apoptosis in the cancer cells [138].

Pathway of sonic Hedgehog signaling:

The Sonic hedgehog pathway is part of several molecular and cellular mechanisms, including embryogenesis, development, and homeostasis of tissue in adults [139][134]. The SHH pathway has been implicated in the CSC maintenance in a range of cancers, including CML, breast cancer, lung cancer, pancreatic cancer, glioblastoma, and myeloma [140][141][142][143][144][145]. In myeloma CSCs, there has been an increase in the expression of SMO and Gli1 [146]. Because the SHH pathway is critical for CSC self-implantation and other properties, inhibiting it may cause CSC stemness to be disrupted via the differentiation of these cells [147][148]. Cyclopamine, when used as a Hedgehog antagonist in ovarian cell lines such as SKOV3, OV90, EX2, and TOV112D, has been demonstrated to diminish spheroid formation in a variety of ovarian cell lines [149]. Vismodegib is a Sonic hedgehog antagonist currently in phase 1 of a clinical trial for the treatment of metastatic basal tumor cells. It targets SMO and is being tested against these cells [147][148]. Sonidegib is another SMO antagonist that has been authorized by the FDA for individuals with advanced Basal cell carcinoma [150]. The 5E1 antibody blocks all three ligands of the hedgehog and Protein patched homolog proteins from joining together [151][152].

Notch signaling pathway:

The NOTCH canonical signaling system is one of the most important evolutionary routes throughout the growth and adult tissue homeostasis [153][154]. Dysregulation of NOTCH signalization in glioblastoma, pancreatic cancer, and breast cancer is critical to maintain and survive CSCs Through the NOTCH signaling pathway, Fascin, an actin-binding protein, controls breast CSCs. As a consequence, Fascin knockdown in breast cancer stem cell-like cells lowers pluripotent gene expression and sphere formation [155]. Signaling components like NOTCH is HES1, JAG1, NOTCH 1, JAG2 and NOTCH3 were shown to be overexpressed in Pancreatic Cancer Stem Cells, and γ-Secretase inhibitors (GSI) inhibited the formation of CSCs and tumorspheres. NOTCH suppression by HES1 knockdown lowered tumorsphere development in Pancreatic Cancer Stem Cells, but NOTCH activation by the Delta/Lag-2/Serrate peptide boosted tumorsphere development in pancreatic CSCs [156]. Targeting the NOTCH signaling pathway using a combination of GSI and Cisplatin improved chemosensitivity and reduced the amount of CSCs [129]. Using Jagged1, another group was able to increase Docetaxel susceptibility while simultaneously shrinking tumor size in Taxane-resistant cells [46]. The interaction of the γ-Secretase antagonist and cediranib maleate were studied in a Phase 1 clinical trial. A phase 1 clinical study for severe ovarian OC patients was also employed for the γ-secretase inhibitor [157]. Another method of suppressing NOTCH is to use monoclonal antibodies against Delta-like lignad4, which limit ligand binding. Enoticumab is an anti-DLL4 antibody used to treat ovarian tumors that have DLL4 overexpression. Demcizumab, an anti-DLL4 antibody, has also been utilized in the treatment of advanced OC [158].

Eradication of Cancer Stem Cell using surface markers:

Several techniques may be used to target Cancer Stem Cell surface markers like CD133, CD24, CD117, CD44 [159]. Hyaluronic acid-paclitaxel (HA-TXL) was used to target CD44+ SKOV3 cell lines, resulting in reduced tumor size [160]. A further research focused on CD133+ OVCAR5-Luc cells, which concluded in a marked reduction in tumor formation [161]. In nude mice, CD24 suppression lowered cell viability by triggering cell death and inhibited tumor formation in the SKOV3 cell line [162]. The CD117 surface marker has been linked to drug resistance in ovarian cancer [163]. CD117 enhances the Wnt/β catenin-ABCG2 pathway for Cisplatin/Paclitaxel resistance. Imatinib Mesylate has been used to treat a range of tumor types, including chemoresistant ovarian tumors [164][165]. The development of CD44+ and CD117+ chemoresistant ovarian CSCs was also suppressed by Paclitaxel and Salinomycin treatments [166]. In addition, Metformin reduced the number of ALDH+ CSCs and angiogenesis, according to another study [167]. Clostridium perfringens Enterotoxin (CPE) may also be employed in a Xenograft mice model to eradicate chemoresistant CD44+ ovarian CSCs [168].

Conclusion

Ovarian CSC elimination is critical for successful ovarian cancer therapy, since CSCs are the driving force behind disease progression, presentation, and recurrence despite conventional therapy. CSC indicators, CSC signalling pathways involved in renewal, and CSC niche are three possible targets for ovarian CSC eradication.

Because ovarian cancer is so varied, there are likely to be additional markers identifying distinct subpopulations of ovarian CSCs, as well as a variety of signalling pathways involved in CSC renewal. Cancer cell lines are useful for discovering CSC specific markers and signaling pathways, as well as studying the ovarian CSC microenvironment, however in vitro tumor formation studies could be improved by examining ovarian cancer patient tumor tissue in vivo. The expression, influence, and inhibition of selected ovarian CSC markers, signalling pathways, and factors from the CSC microenvironment should then be tested in clinical practice, where their expression, influence, and inhibition should be correlated not only with disease outcome, but also with their influence on chemoresistance. The study of CSC characteristics and their microenvironment characteristics in vitro and in vivo may lead to new treatment regimens for ovarian cancer eradication and recurrence prevention.

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