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Review Article: Ovarian Cancer

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ABSTRACT

The first record of cancer dates back to Ancient Egypt in 3000 BC, and it has been studied throughout history as an ancient illness. Oncology is the study of cancer, and during the past few decades, significant progress has been made in this area. Despite these initiatives, cancer still claims the lives of almost 10 million people annually. Since cancer is caused by a series of faults in one's own cells, finding a cure for it involves figuring out how to get rid of the malignant cells without harming one's own body. The diagnosis and treatment of ovarian cancer are the most challenging of all gynecological cancers. Due to its nearly symptomless early phases, this type of gynecological cancer is either discovered by chance for example, during a diagnostic laparoscopy or is detected at an advanced stage when symptoms start to manifest. Our capacity to detect and successfully treat this illness at a period when it is still curable is restricted by an insufficient understanding of early molecular events in ovarian carcinogenesis. Due to the aforementioned factors, ovarian cancer has acquired the moniker in the United States of America (The Silent Killer). This phenomenon results from the exceedingly limited early diagnostic resources (biomarkers) that we currently have. Given its high mortality rate, gynecological oncology research is heavily focused in this area. To promote growth, cells with mutant genotypes are chosen and then gradually altered, which might result in the growth of tumors. Spontaneous mutations are uncommon during each cell generation because to the rigorous mechanism for the detection of DNA errors and repair, and multiple mutations are required to orchestrate tumor formation. Once it has begun, the mutational accumulation is sped up by increased susceptibility to mutagenic agents, a breakdown of some aspect of the mutagenic repair system, or a combination of both. The Wnt/β-catenin canonical signaling pathway plays a role in cancer, wound healing, and developmental processes. However, research on the role of Wnt/canonical signaling in the development of ovarian cancer has just lately started to surface. Hence, the present focused on the most genes participated in ovarian cancer and the signaling pathway of the most important gene, Wnt/β-catenin.

1. Normal Ovarian Physiology

On each side of the pelvis, there are two paired organs called the ovaries, which each one weighs about 4-8 grams and has dimensions of 2.5–5 cm in length and 1.5–3 cm in diameter. The ovaries have two medial and lateral surfaces, two anterior or mesovarium borders, two posterior or free borders, and two tubal and uterine poles. The epithelial coat of the ovaries and the posterosuperior layer of the broad ligament are both continuous with the two layers of peritoneum that make up the mesovarium (1). The ovarian arteries provide the ovaries with blood, and hypothalamus controls the secretion of gonadotropin-releasing hormone (GnRH) that released by females in a cyclical fashion to preserve the menstrual cycle (2). To promote ovulation and preserve the corpus luteum, luteinizing hormone (LH) acts on ovarian follicle that develops as a result of follicle stimulating hormone (FSH) that encourages the release of progesterone and estradiol. Through a negative feedback loop, these steroidal hormones can prevent releasing of GnRH and prevents releasing of FSH and LH. However, estradiol induces an LH surge that is connected to ovulation when it is present in sustained high levels (3). Estradiol and testosterone's bioavailability is altered by the impacts of leptin, a hormone produced by fat cells, and insulin, a hormone produced by the pancreas, through changes in the liver's production of sex hormone-binding globulin (SHBG). The ovary can also be directly affected by insulin (4, 5).

2. Ovarian Cancer

2.1. Introduction

Ovarian cancer accounts for 6% of all female cancer deaths in the United States, making it the sixth most common cancer-related cause of death for females (6). Although, advancements in treatment of the disease continues to be the most fatal gynecological malignancy, approximately 69% of overall patients pass away from illness, in comparison with 19% of patients. It is mostly attributed for delaying detection brought on by a lack of an efficient screening plan; however, only 20% of individual patients have identified when tumor remain restricted to disease (7, 8). Hence, traditional surgery and chemotherapy can cure more than 80% of patients. Age, obesity, ovarian cancer in the family or other cancers act as risk factors for disease (9). Current accepted theory holds that ovulation repeatedly damages DNA and then repairs it, causing irreversible oxidative DNA damage that either triggers or facilitates the development of ovarian surface epithelial cells (OSE) tumors (10). Serous, mucinous, endometrioid, and clear cell histological subtypes of ovarian neoplasms are subdivided (11). The BRCA1, BRCA2, MLH1 and MSH2 genes are linked to hereditary frequent germline mutations. Development, wound healing, and cancer are all impacted by the Wnt/β-catenin canonical signaling pathway (12). It's interesting to note that all of these processes seem to be connected, either directly or indirectly, to the development of ovarian cancer. It has been shown that different ovaries have distinctive Wnt signaling molecule expression patterns, and that certain Wnts are expressed in human ovarian cancer cell lines. Further evidence that different ovarian cancer subtypes exhibit unique genetic abnormalities of Wnt/canonical signaling pathway components comes from reports of variations in the expression and function of Wnt/canonical signaling pathway components in normal vs malignant OSE cells (13, 14). Different studies predicted that ovarian cancer cells have abnormalities in Wnt/canonical signaling, which may cause and/or impact ovarian tumorigenesis. Also, it showed that Wnts can secret glycoproteins that interact with Frizzled (Fz) seven-transmembrane spanning receptors to either cause the cytosol to accumulate -catenin and the subsequent co-activation of target genes during transcription, to release intracellular Ca^{2++}, or to activate protein kinases (15-17). The canonical pathway involves the binding of Wnts to Fz receptors along with the co-receptors LDL-receptor related protein (15). This inhibits the β-catenin phosphorylation by the serine / threonine kinase, glycogen synthase kinase 3 (GSK3) within a large cytoplasmic complex (18). Inhibiting β-catenin phosphorylation prevents it from being degraded by the ubiquitin/proteasome system, which leads to a buildup of the cytosolic molecule in its uncomplexed state. Simple β-catenin then moves to the nucleus where it interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) to activate target genes like c-myc, l-myc, cyclin D, vascular endothelial growth factor (VEGF), bone morphogenetic protein 4 (BMP4), E-cadherin, and N-cadherin (19, 20). Aberrations in the Wnt/canonical pathway cause certain target genes to be inappropriately activated or silenced by β-catenin, which permits unchecked cell proliferation and/or changes in cell differentiation. β-catenin molecules can be involved in Wnt/canonical pathway as well as being sequestered to plasma membrane as a result of their interactions with cadherin cell adhesion molecules and β-catenin (21). Therefore, it has been suggested that the β-catenin molecules possess particular cadherin and β-catenin binding sites, even though the mechanism behind the selection of β-catenin molecules to the plasma membrane vs the cell nucleus has not yet been fully understood (22).

The expression of Wnt ligand and Fz receptor has been proven in earlier investigations. In addition, different reports demonstrated that ovarian cancers might precipitate β-catenin and LEF-l (23, 24). These data imply that although the canonical signaling pathway may be more activated in ovarian cancer cells, components of the Wnt/canonical signaling pathway are present in both healthy and malignant OSE. Approximately, 85% of mucinous carcinomas have ovarian serous carcinomas according to analyses of genetic mutations according to ovarian cancer histological subtypes (25). About 40% of ovarian endometrioid adenocarcinomas (OBAs) have mutations in the *CTNNBl* gene, which codes for β-catenin, which affect Wnt signaling (26). Although the most frequent cause of β-catenin deregulation in OEAs is mutation in the CTNNB 1 gene, β-catenin deregulation can also be caused by mutations in the APC, AXIN1, and AXIN2 genes. These findings imply that certain genetic alterations cause particular histological subtypes of ovarian cancer, and dysregulation of the Wnt/canonical signaling cascade might participate in development of disease (14, 27).

2.2 Epidemiology and Histopathology

Ovarian cancer is the most common gynecological cancer in North America, but accounting for only 4% of all female cancers (28). This happens as a result of ovarian cancers being missed when they are still in the early stages. The International

Federation of Gynecology and Obstetrics (F1GO) staging method is used to classify ovarian cancer, and stage 3 is where it is most frequently found. Stage 3 is linked to a 23-41% five-year survival rate (29). The OSE is estimated to be the source of 80–85% of ovarian neoplasms, which can be classified into the following histopathological subtypes: endometrioid, mucinous, and serous. Each of these histological subtypes accounts for roughly 75%, 20%, and 2% of epithelial ovarian tumors (30). The spectrum of tumors that make up each histological category of ovarian epithelial neoplasia ranges from benign to malignant. Serous and mucinous tumors often have a 70 to 85% benign propensity, whereas endometrioid and clear cell tumors typically have a high malignant propensity (31). The coelomic mesothelium, which also gives rise to the Müllerian duct and its descendants, is the source of the OSE. The uterus, the cervix, the fallopian tubes, and the top two thirds of the vagina are examples of derivatives of the MüllIerian duct (32). The OSE was derived embryologically from the coelomic mesothelium, which may have given the OSE the inherent aptitude for divergent differentiation along the MüllIerian pathways, which is thought to explain the considerable morphological variety of ovarian epithelial neoplasms. Interesting similarities between ovarian epithelial neoplasm subtypes and MüllIerian duct derivatives have been found by histological analysis of ovarian caricinomas (33). More particular, mucinous tumors are said to mimic endocervical epithelium while serous tumors resemble fallopian tube epithelium. As the name suggests, endometrioid tumors mimic the uterine endometrium, whereas clear cell tumors are thought to resemble mesonephric cells (34). At cellular/molecular levels, ovarian tumors are extraordinarily varied as 90% or more exhibit an epithelial histology. These epithelial ovarian cells that come from the coelomic epithelium were assumed to be the source of the disease (35). Clinically, complicated cystic masses are common clinical presentation of epithelial ovarian cancer cells that usually disseminate to peritoneal, diaphragmatic, and hepatic lymph nodes (36). Unlike other malignancies, ovarian cancer cells are able to spread throughout the peritoneal cavity without encountering any anatomical barriers (37).

2.3 Causes and pathogenesis

The recurrent injury to the ovarian surface epithelium during postovulatory healing can lead to a gradual buildup of genetic anomalies. According to gonadotropin theory, stimulation of surface epithelial cells by pituitary gonadotropin surges at ovulation and their continued high concentrations after menopause leads to accumulation of genetic alterations and carcinogenesis (38). According to other theory, ovulation, surface-epithelium repair, talc or asbestos exposure, endometriosis, pelvic inflammatory disease, and measles are all increase the risk of developing epithelial ovarian cancer. This increased risk may be explained by inflammation and changes in redox potential during these processes (39, 40). Women with impaired BRCA1 and BRCA2 function have a decreased ability to repair genetic damage, which increases their risk of disease (41). Since cyclooxygenase-2 (COX2) is necessary for the inflammatory environment in which ovulation takes place, this notion supports investigating the chemopreventive potential of COX2 inhibitors (42). Luteinizing hormone preovulatory surge causes an increase in cytokine expression, which causes a differentiation in follicle cells. Invaginations and inclusion cysts are also induced during ovulation. Under an influence of ongoing cytokine and hormonal stimulation, cyst cells can develop to take on Müllerian features, proliferate, and become ciliated or secretory. These cells eventually develop genetic anomalies (43). Rete ovarii tubules at the ovary's hilus, near the transition from mesothelium to OSE, also contain ciliated and secretory cells and have the capacity to enlarge to form cysts. It is uncertain if either cyst type contains malignant cells (44). It is yet unclear how any ovarian stem or progenitor cells might contribute to the development of epithelial ovarian cancer. In one study, the authors were able to demonstrate genes that encoded for epithelial ovarian cancer (EOC) biomarkers that previously thought to be over-expressed (45). However, it is crucial to note that none of these EOC markers, perhaps with the exception of CA-125, displayed appreciable over-expression. The results had normal ovarian tissue and the other of which contained EOC as well as normal and cancerous fallopian tissue. These findings support the idea that fallopian fimbriae are the source of EOC, and they also show that markers that previously over-expressed in EOC are fallopian origin but not ovarian (46).

2.4. Diagnosis and staging

The FIGO method, as amended in 1988, is the most widely used staging system. Its discoveries are primarily the result of surgical investigation. Only 20% of ovarian cancer patients receive a diagnosis when the tumor is still localized, despite the fact that 80% of people with this disease experience symptoms (47). The lack of specificity in these symptoms is fundamental cause, and the typical symptoms include mild stomach discomfort, stool irregularities, and unexplained weight loss to severe abdominal enlargement (48). Early diagnosis is challenging due to the symptoms generality and overlaps with other more prevalent gastrointestinal, genitourinary, and gynecological diseases (49). The most widely utilized biomarkers for early

identification of disease is the cancer antigen 125 (CA125). The using of CA-125 as a biomarker or tumor marker could increase in blood of some patients with specific types of cancers or other benign conditions. High specificity can be attained through tracking CA125 levels over time or using used in conjunction with transvaginal sonography (TVS), (50, 51). Currently, the most accurate method for determining whether ovarian cancer surgery is feasible is surgical staging, and survival of the patient depends critically on eradication of all macroscopically discernible tumor symptoms, preferably completely (52).

2.5 Biomarkers

There are currently few methods for evaluating suspected instances of ovarian cancer in their early stages, which rely on pelvic ultrasonography and the CA-125 test with a sensitivity and specificity level between 70-80% (50-52). The MUC16 gene in humans produces the protein known as CA-125, commonly referred to as mucin 16 or MUC16. The mucin family of glycoproteins includes MUC16 (53). MUC16 is a part of epithelia of female reproductive tract, respiratory tract, and ocular surface. Since MUC16 is heavily glycosylated, it produces a hydrophilic environment on the apical membrane of epithelial cells that functions as a lubricating barrier against foreign particles and pathogenic pathogens. The most used biomarker for ovarian cancer screening is CA-125 (54). Human epididymis protein 4 (HE4) was found as a biomarker for ovarian cancer by Moore and associates in 2008 (55). The WAP-four disulfide core domain 2 (WFDC2) gene is responsible for encoding and producing of HE4 protein, and discovered later to be expressed in some ovarian malignancies in addition to being expressed in pulmonary epithelial cells (56). Using a combination of CA-125 levels, HE4 expression, and menopausal state, a risk of ovarian malignancy algorithm (ROMA) was created based on these findings and is now used to predict the existence of malignant ovarian cancer. HE4 and CA-125 in the ROMA, in particular, have been linked to a higher sensitivity than any single biomarker (57).

2.6. Molecular genetics

Ovarian tumors from various patients have been discovered to contain a number of genetic and epigenetic alterations. Ovarian cancer, like other solid tumors, arises from a single cell that has acquired five or more genetic mutations or more (58). For ovarian oncogenesis, neoplastic cells can avoid going through the apoptotic process when TP53 is lost or mutated, which allows them to continue dividing even after experiencing DNA damage and accumulating more genomic rearrangements (59). George et al. (2016) reported that 10-15% of ovarian cancer cases are caused by genetic flaws in the DNA repair genes themselves (60). The lifetime risk of developing ovarian cancer for bearers of these genes ranges from 30-60% for BRCA1, 15-30% for BRCA2, and 7% for MLH1 and MLH2. The efficient repair of DNA double strand breaks through homologous recombination depends on BRCA1 and BRCA2 (61). Ovarian tumors have been shown to poss about 15 distinct oncogenes, with 11 of them exhibiting genomic amplification (62). Small G-protein Rab25 is one of the most frequently increased genes in ovarian tumors. Rab25 controls apoptosis, autophagy, aggression, motility, and apoptosis. Additionally, it has been demonstrated that it mediates survival in the face of stress, such as glucose deprivation, serum depletion, UV radiation and chemotherapy (63). Aurora kinase is necessary to growing of cells. Another class of amplified oncogenes are frequently found in ovarian cancer are necessary for cytokinesis to be completed, and when they are dysregulated, they produce aneuploidy, which is a characteristic of many malignancies (64). According to studies linking genetic mutations to clinical presentation and tumor morphological characteristics, neoplasm progress is sequential manner of adenoma (65, 66). These cancers characterize by genetic alterations in KRAS, BRAF, PIK3CA, and LOH on Xq indicating that the RAF/MAPK pathway is dysregulated in development of these tumors. Also, the mutant KRAS produces cause inappropriate activation of the PI3K, RAF/MAPK, and RAL-GEF pathways (67). High-grade tumors, on other hand, start off as surface epithelium, and expand quickly and don't have any precursor lesions that may be identified morphologically. High-grade serous cancers are more likely to exhibit TP53 mutations, possible BRCA1 and BRCA2 aberrations, LOH on 7q and 9p, and BRCA1 and BRCA2 mutations (68).

2.7. Signaling pathways

Essential pathway components including PIK3CA and AKT2, as well as PTEN-inactivating mutations, can all lead to the PI3K pathway becoming activated. This pathway is also activated in several malignancies by receptor tyrosine kinase autocrine or paracrine signaling (69). Multiple pathways underlie the promotion of cell growth and survival by PI3K-Akt signaling (70). The pro-apoptotic Bcl-2 family members Bad and Bax inhibited by Akt, can prevent the transcription of anti-apoptotic genes from being negatively regulated by the transcription factor NF-κB and pro-survival genes. Akt blocks p53 - mediated apoptosis by phosphorylating Mdm2. By inhibiting transcription factors, Akt also lessens the production of proteins that promote cell death (71). This comprises the 4E-binding protein (4E-BP) and the ribosomal protein S6 kinases (p70S6K). The latter causes the production of eIF4E, a translation initiation factor with anti-apoptotic and transforming properties *in vitro* (72). Ovarian cancer xenograft development has been demonstrated to be inhibited by PI3K and Akt, and these inhibitors may enhance cytotoxic effect of chemotherapy (73). This results in over-expression of genes that induce angiogenesis caused by JAK2 activation (74). The presence of nuclear localization of phosphorylated STAT3 in more than 70% of ovarian tumors is linked to a decline in overall survival (75). Transcriptional regulator More than half of ovarian tumors have constitutively active NF-κB, which has been linked to cancer survival, proliferation, and metastasis. The Rel family proteins p50 and p65 form heterodimeric complexes to form the bulk of NF-κB (76). A number of cytokines, including IL-1 and TNF, as well as growth factor eventually cause NF-κB releasing, and in more than 50% of ovarian tumors, the over-expressed protein kinase MEKK 3 might trigger it. Additionally, it causes the over-expression of genes that crucial for controlling cell survival. In line with these findings, NF-B has been linked to cancer cells resistance to chemotherapeutic agent and radiation-induced apoptosis (76, 77).

2.8. Wnt gene

2.8.1. Signaling Molecule

On human chromosomes, there 19 Wnt genes were discovered and identified. All Wnt proteins are roughly the same size, with molecular weights between 39 and 46 kDa (78). Wnts are secreted glycoproteins with lipid modifications that are palmitoylated on a conserved cysteine to help them target the cell membrane. Associating with glycosaminoglycans in the extracellular matrix after being secreted, Wnt proteins stay near to the cell surface (79). Additionally, findings have shown that Wnts can act as long-range morphogenic signals that are concentration-dependent and can influence distant neighbors (80). However, the precise mechanism underpinning this activity is still unknown.

2.8.2. Wnt Signaling Pathways

Wnts can activate different intracellular signaling pathways when they bind to Frizzled (Fz) receptors including Wnt/β-catenin canonical signaling system, the Wnt/Ca^{2+} pathway, and the planar cell polarity (PCP) pathway (14). Each of these pathways can be activated by various combinations of Wnt molecules, resulting in various cellular responses (81). This discovery was made in research were Wnt/, Wnt3/, Wnt8 or Wnt8 was over-expressed in Xenopus, which in turn caused Wnt/-catenin pathway to be specifically stimulated. Contrarily, it was discovered that over-expression of Wnt4, Wnt5, or Wnt1 stimulated the Wnt / Ca^{2+} pathway (14, 82). In over-expression tests, Fz receptors can be divided into similar functional groups depending on their capacity to activate one pathway as opposed to another. This association between certain Wnts and the intracellular pathway anticipate to be stimulated, despite the fact that these classifications may offer a useful tool for anticipating the activity of Wnts and Fzs (83).

2.8.3. Wnt/β-catenin pathway

The canonical Wnt/β-catenin pathway is the subject of extensive research and is covered in detail in the preceding chapter. Briefly, cytosolic buildup of β-catenin is necessary for signaling through this route. Multi-protein destruction complex targets β-catenin for deterioration in absence of Wnt activation. As a result, the destruction complex is repelled by wnt signaling causes a buildup of β-catenin in cytosol and subsequent activation of target genes (14, 84, 85).

2.8.4. Wnt/Ca^2 pathway

Studies on Xenopus have suggested that a certain subset of Wnt ligands and Fz receptors, including Wnt4, Wnt5, Wnt/1, and Fz2, can activate the Wnt/Ca^{2+} pathway (79). A heterotrimeric G protein is activated as part of this pathway, and calcium/calmodulin-regulated kinase II (CamKII) and protein kinase C are also activated (PKC), (86). Although the downstream targets of CamKII and PKC are not yet known, it has been demonstrated that in Xenopus, activating the Wnt/Ca^{2+} pathway can inhibit the Wnt/β-catenin pathway (87). Uncertainty exists over the degree at which this interaction takes place and whether or not it also occurs in mammals (14, 84).

2.8.5. Planar cell polarity pathway

Through the control of cytoskeletal architecture, the Wnt/PCP signaling pathway affects cell polarity, which can be deduced from cell shape and mobility. As it necessitates Fz receptors and Dvl molecules, the PCP pathway overlaps with the traditional signaling pathway. However, it differs from downstream processes since it does not include axin, GSK3, or β-catenin (84, 88).

2.8.6. Wnt/p-catenin signaling and tumorigenesis

The Wnt/canonical signaling cascade's primary and crucial element is β-catenin. It is also a crucial part of the cadherin cell adhesion complex because it uses β-catenin and α-actinin to connect cadherins at the plasma membrane with the actin cytoskeleton (84). Axin, a protein that facilitates the development of the catenin degradation complex is affected by CTNNB 1 gene (14). However, the loss of APC alone is insufficient for the development of carcinomas and metastasis. Additional mutations in various pathways, including as mutations that activate Ras and mutations that cause p53 to lose its function, are also necessary (89). Furthermore, β-catenin is only found in the nucleus of late dedifferentiated, mesenchyme-like tumor cells; it is not present in the plasma membrane in the center of primary tumors. As a result, additional signaling elements might be necessary for catenin to accumulate in nucleus. Additionally, phosphorylation of key tyrosine constituent parts might cause adherens junctions to dissociate (90). Interestingly, malignancies have been found to over-express tyrosine kinases and contain mutations in tyrosine phosphatase genes that may accelerate these phosphorylation processes. Increased β-catenin-dependent transcription is correlated with loss of cell adhesions, and associated with malignant prognosis (91).

2.9. Cadherins and ovarian tumorigenesis

The family of integral membrane glycoproteins known as cadherins mediates homotypic calcium-dependent cell-cell attachment. The E-, N-, and P-cadherins are three examples of the traditional cadherins that belong to this family of cell adhesion molecules (CAMs). These cadherins have been demonstrated to be crucial for the development of intercellular junctions, the maintenance of cell polarity, and the preservation of tissue integrity (92). Changes in cadherin expression or function have been suggested as crucial elements in carcinogenesis due to the fact that cell-cell interactions are frequently disordered in tumors and must be weakened in invasive and metastatic malignancies (73). Additionally, as cadherins play a role in tissue morphogenesis and cell sorting, improper or changed levels of cadherin expression within tissues may offer a mechanism for the development of metaplastic lesions or dysplastic derivatives which could be responsible for the establishment of the preneoplastic state (93).

E-cadherin gene has been classified as a tumor suppressor gene as a result of research linking E-cadherin deletion or decreased expression to the establishment of poorly-differentiated invasive carcinomas (94). Numerous studies have demonstrated that differentiating between various histological subtypes of ovarian cancer can be followed for expression of E- and N-cadherin. For example, serous and endometrioid ovarian tumors express both cadherin subtypes, in contrast to mucinous ovarian cancers, which only express E-cadherin and not N-cadherin. Interestingly, serous and mucinous subtypes of ovarian cancer trail endometrioid ovarian tumors in terms of risk for malignancy (95). It has demonstrated that EMTs take place as epithelial malignancies grow, giving these tumors an increase in motility and invasiveness. The Wnt/canonical signaling pathway among many other carcinogenic pathways induce EMT, a hall mark feature of which is the down-regulation of epithelial (E)-cadherin (96). It's interesting to note that research suggests the opposite might apply to ovarian cancer. It is believed that the OSE repeatedly rupturing and mending after ovulation causes carcinogenesis, which starts with the development of inclusion cysts in the ovarian stroma (97). These and ovarian cancers have both been demonstrated to express E-cadherin, whereas normal

OSE has only been demonstrated to express N-cadherin (98). Additionally, research looking at the transfection of regular OSE cells with E-cadherin has demonstrated that these cells start to produce inclusions cysts and take on a more invasive nature (99, 100). These findings in contrast with the well-known phenomena of EMT that takes place during cancer in other organs and suggest that the OSE may undergo a mesenchymal to epithelial phenotypic transition (79, 101, 102).

4. Conclusion

Ovarian cancer is one of the most deadly diseases impacting women worldwide. Inherently resistant cell populations have recently been connected to tumor recurrence, unsatisfactory treatment outcomes, and consequent disease relapse. However, the lack of models that faithfully reproduce the variety of ovarian cancer has hindered the study of these phenotypically and functionally complex cancer cells up to this point.

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