Ovarian cancer is the most lethal cancer of the female reproductive tract, accounting for ~15,000 deaths per year according to the National Cancer Institute and American Cancer Society. This review article covers risk factors for the development of ovarian cancer, current detection strategies, prognostic markers, treatment strategies, etiology of tumorigenesis, and ovarian somatic stem cells. While the etiology of ovarian cancer is still unknown, several theories have been proposed as the mechanism of carcinogenesis. One theory states that the surface epithelium undergoing invagination and forming inclusion cysts that are exposed to growth factors and cytokines. The “gonadotropin theory” has also been proposed. Other reigning models for tumorigenesis include the stochastical model where a distinct population of cells acquires somatic mutations leading to metastasis, and the hierarchical model where the tumor is initiated by cancer stem cells (CSCs). CSCs isolated from primary tumors have the ability to regenerate the tumor and reconstitute the original tumor phenotype with as few as 100 cells. CSCs from ovarian carcinomas display the cell surface markers CD44+CD117+CD133+. CSCs are also thought to account for chemotherapy resistance through the expression of highly selective transporters ABCG2 and MDR1 and activation of TLR4/MyD88. The side population has been characterized by their ability to efflux lipophilic substrates, including the dye Hoechst 33342 and many chemotherapy agents. This ability has been attributed to the expression of the transporters ABCG2 and MDR1.

Key words: Cancer stem cells, Side population, Ovarian cancer etiology, CD133, CD44, CD117

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Introduction

Ovarian cancer (OCA) is the eighth most common and the fifth cause of cancer death in women, responsible for ~15,000 deaths per year with over 21,000 new cases in 2008 according to the American Cancer Society and National Cancer Institute. This makes it the most lethal malignancy of the female genital tract. If ovarian cancer is found at an early stage, the 5-year survival rate is 92%. However, less than 20% of ovarian cancer is diagnosed at an early stage which decreases the 5-year survival rate to 15-45% (Nossov et al., 2008). The most common form of OCA is epithelial, which can be further divided into 4 main pathologies: serous (70%), endometriod (20%), mucinous (5-10%), and clear cell (5-10%) (Neesham, 2007). Other forms of OCA arise from the germ cell or stromal cell layer.

Risk factors for ovarian cancer

Several risk factors increase the possibility for ovarian cancer. The most well known is hereditary mutations in BRCA1 or BRCA2, which accounts for 10% of cases (Carvalho and Carvalho, 2008; Landen et al., 2008). Mutations in BRCA1 in a first degree relative increase OCA risk by 40-50%, while mutation in BRCA2 increase risk by 20-30% (Soegaard et al., 2008). Other risk factors include mismatch repair mechanism mutations, polycystic ovarian syndrome (PCOS) (Landen et al., 2008), infertility (Cetin et al., 2008), smoking (Modugno et al., 2002; Rossing et al., 2008), talcum powder use, ovarian cysts, endometriosis, and hyperthyroidism (Ness et al., 2000). Both BRCA and nibrin (NBN) proteins function in double-strand break repair, cell cycle control, meiosis, and telomere formation. In one case study, the OCA patient was found to have heterogous mutations in both BRCA and NBN (Porhanova et al., 2008). Heterozygous BRCA results in hereditary breast cancer, while NBN heterozygosity results in Nihmengen Breakage Syndrome (NBS). NBS has been implicated in increased cancer risk as well as
other severe yet non-cancer related syndromes such as growth and mental retardation (Huang et al., 2008). A considerable portion of the literature suggests that NBS increases the risk for B-cell non-Hodgkin’s lymphoma (Huang et al., 2008) and melanoma (Debniak et al., 2003), but has not been associated with either hereditary or sporadic prostate cancer (Hebbring et al., 2006) despite claims that NBS can be characterized by gonadal failure (Gladkowska-Dura et al., 2008). One group suggested that NBS may contribute to the formation of rare ovarian carcinomas (Plisiecka-Halasa et al., 2002), but further evidence is needed to confirm that finding. PCOS was reported to increase OCA risk 2-fold (Schildkraut et al., 1996; Cetin et al., 2008). It was suggested that infertility drugs and treatments alter the hormonal environment, thereby acting as co-factors in cancer formation. It was also proposed that infertility in itself could a risk factor most likely due to endometriosis and ovulatory abnormalities. However, infertility could be a symptom of OCA rather than a cause (Venn et al., 1999). Women with a history of endometriosis greater than 10 years are at particularly increased risk, although it has not been linked to the cause of cancer (Cetin et al., 2008).

More recently inflammation has been proposed to be a causative agent. Viral and bacterial agents produce chronic inflammation, which can lead to cancer in the GI tract, liver, and other cells mediated by oxidative stress producing reactive oxygen species (ROS), which reduce cellular adhesion by altering the MMP:TIMP ratio to promote metastasis, and reactive nitrogen species (RNS) forming adducts, which induce DNA and protein damage (Hold and El-Omar, 2008). Pelvic inflammatory disease has also been associated with OCA. Inflammation is known to promote increased cellular division, DNA excision and repair, oxidative stress, and a high concentration of cytokines and prostaglandins (Ness et al., 2000).

Factors that decrease the risk for OCA include multiple pregnancies, lactation lasting longer than 24 months, and oral contraceptive use (Ness et al., 2000; Landen et al., 2008), suggesting that decreased ovulation and cyst formation are protective against cancer formation. The first pregnancy is known to decrease the risk by 50% with a moderate decrease with subsequent pregnancies. Tubal ligation and hysterectomy also reduces the risk, especially in combination. Age at menarche, age at menopause, and menstrual pattern are not associated with risk (Ness et al., 2000).

Detection strategies

Current detection strategies include ultrasound and blood analysis for the tumor marker CA-125 (Neesham, 2007). However, both techniques have their drawbacks. The ovarian surface is dynamic in premenopausal women, so cancer could be mistaken for functional cysts. The CA-125 blood test is a measure of epithelial antigen protein expressed on the coelomic epithelium, which includes the ovarian epithelium (Neesham, 2007). However, the test lacks sensitivity, detecting only 50% of stage 1 disease, and has a high false positive rate (Lowe et al., 2008; Nossov et al., 2008) that can result from a variety of situations including gynecological origin such as endometriosis, fibroids, hemorrhagic ovarian cysts, menstruation, acute pelvic inflammatory disease, and first trimester pregnancy. Endometrial, pancreas, bladder, breast, liver, and lung cancer can also cause a false positive as well as inflammatory conditions, renal disease, and cirrhosis (Neesham, 2007). Blood analysis for CA-125 is only appropriate for detection of epithelial OCA (90% of OCA). More
recently mesothelin, an epithelial biomarker, and HE4 were proposed as possible candidates for early detection to complement the CA-125 serum test to help improve the sensitivity (Hellstrom and Hellstrom, 2008; Lowe et al., 2008; Nossov et al., 2008).

**Prognostic markers**

OCA can be classified into two broad categories: high-grade and low-grade. High-grade tumors are characterized by rapid growth and relative sensitivity to chemotherapy without the presence of a definite precursor lesion. Low-grade tumors are classified by less rapid cell growth, relatively insensitivity to chemotherapy, and shared molecular characteristics similar to low-malignancy potential neoplasms. Molecular and pathway analysis indicates that the two grades utilized different signaling pathways that share p53 as a common branch point. Low-grade tumors have intact p53 while high-grade tumors have dysfunctional p53 (Landen et al., 2008).

Prognostic factors are characterized by tumor grade, disease stage, and vascular invasion. Tomić et al. (2003) correlated p53 overexpression with vascular invasion. Nm23 and Her2 correlated with vascular invasion, high grade, and advanced disease stage. Univariate analysis for advanced clinical stage, high grade, vascular invasion, and positive staining for p53, nm23, and Her2 proteins indicated overall shorter survival. However, using Cox multivariate analysis, only the stage correlated to survival. Cox proportional hazard regression multivariate analysis of early stage showed that only vascular invasion correlated to survival, while nothing correlated to an advanced disease stage.

**Treatment**

Treatment usually involves cytoreductive surgery followed by a chemotherapy regimen of platinum-based chemotherapy such as carboplatin-taxane (Rocconi et al., 2008). Agents used with cytoreductive surgery tend to induce expression of Cyclooxygenase-2 (COX-2). COX-2 mRNA and protein overexpression has been found in ovarian serous adenocarcinomas and were associated with altered expression of p53 and SMAD4 and increased expression of Her-2 (Erkinheimo et al., 2004). When COX-1 and COX-2 mRNA and protein expression were analyzed from patients who had not undergone cytoreductive treatment, COX-1 expression was elevated and compartmentalized to the epithelium, whereas normal ovarian epithelium did not express COX-1 or -2 mRNA at a detectable level (Gupta et al., 2003).

Microtubule-interfering agents (MIA) have been used to treat Her-2 positive breast cancer; however, it was found that MIA increase prostaglandin E2 (PGE2) synthesis via increasing COX-2 mRNA levels (Subbaramaiah et al., 2000). This makes COX-2 an attractive target for prevention and treatment. While epidemiological evidence from case-controlled studies suggests that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of breast cancer, cohort studies disagree. A population-based study from Long Island found an inverse relationship between regular aspirin use (defined as 1 or more tablets per week for 1 year) and breast cancer risk in hormone-receptor positive tumors. However, the Women’s Health Study found no correlation between low-dose of aspirin (100 mg every other day) and reduction of risk for breast or OCA. The non-COX-specific NSAID indomethacin inhibits ovulation in a dose-dependent manner, implying that it could decrease the risk of OCA (Crew and Neugut, 2006). Treatment with indomethacin, SC-560 (COX-1 specific inhibitor), or celecoxib (COX-2 specific

**Table 1.** Factors that increase or decrease the risk for formation of ovarian cancer.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Factors that decrease risk</th>
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<tr>
<td>Genetic mutations</td>
<td>Multiple pregnancies</td>
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<td>BRCA 1/2</td>
<td>Lactation&gt;24 months</td>
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<td>Nibrin protein</td>
<td>Oral contraceptive use</td>
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<td>Polycystic ovarian syndrome (PCOS)</td>
<td>Tubal ligation</td>
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<td>Infertility</td>
<td>Hysterectomy</td>
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<td>Ovarian cysts</td>
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<td>Endomeetriosis</td>
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<td>Hyperthyroidism</td>
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<td>Inflammation</td>
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<td>Personal habits</td>
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<td>Smoking</td>
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<td>Talcum powder use</td>
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**Fig. 2.** Hierarchial model of tumorigenesis and formation of cancer stem cells.
inhibitor) only reduced cell numbers at a concentration of 50-100 times greater than what can be achieved in vivo (Gupta et al., 2003).

While the initial response rate to first-line platinum-based chemotherapy is 65-80%, most ovarian carcinomas relapse, contributing to a low 5-year survival rate (Fehrmann et al., 2007).

Etiology

The etiology of epithelial OCA remains mostly unknown. Several theories have been proposed as the mechanism for carcinogenesis. One such theory indicates that the ovarian surface epithelium (OSE) can undergo invagination and form inclusion cysts. These inclusion cysts can then undergo neoplastic transformation either through access to stromal-derived growth factors, cytokines, and bioactive compounds, which are normally restricted by the tunica albuginea, or from neoplastic progression in crypts promoted by an autocrine mechanism from OSE-derived cytokines and hormones that accumulate to bio-active levels (Auersperg et al., 2001). Another theory is the “gonadotropin theory” (Bose, 2008). The gonadotropin theory suggests that pituitary gonadotropins, i.e., luteinizing hormone (LH) and follicle stimulating hormone (FSH), overstimulate the ovarian tissue causing excessive ovulation. Androgens, estrogens, progesterones, and insulin-like growth factor-I (IGF-I) may also contribute to cancer pathogenesis (Lukanova and Kaaks, 2005) as well as a genetic component. Currently, about 10% of OCA cases are hereditary (Carvalho and Carvalho, 2008; Landen et al., 2008). Of these, 90% are due to BRCA1 or BRCA2 mutations (Landen et al., 2008). Other contributing genes could be alterations of p53 expression and overexpression of Her2/neu, PIK3A, AKT, and c-myc (Tammela and Odunsi, 2004). P27kip1 has been proposed as an oncogene because of its ability to expand stem cells even though it mainly functions as a cyclin-dependent kinase inhibitor (CKI) to regulate the cell cycle. Using a knock-in version of P27 that was unable to bind to the Cdk:cyclin complex (P27ck-) produced spontaneous tumor formation in multiple tissues, including ovarian hyperplasia (Besson et al., 2007). The other reigning models for tumorigenesis include the stochastical model, where a distinct population of cells acquires somatic mutations leading to metastasis, and the hierarchical model, where the tumor is initiated by cancer stem cells (CSCs) (Odoux et al., 2008).

Cancer stem cells (CSCs)

Cancer stem cells (CSCs) are described as “multipotent cells capable of forming heterogeneous tumors in immunodeficient mice at high efficiency” (Polyak and Hahn 2006). Five defining criteria has been established to verify the existence of CSCs: 1) self-renewal, 2) restriction to a small percentage of the tumor population, 3) ability to reproduce the heterogenous tumor phenotype, 4) multipotent differentiation into non-tumorigenic cells, and 5) expression of distinctive cells markers (Clarke et al., 2006; Daleeba et al., 2007; Olempska et al., 2007; Zhang et al., 2008). Based on this criteria, CSCs have also been referred to as cancer-initiating cells (Zhang et al., 2008) or tumor-initiating cells (Clarke et al., 2006). CSCs are thought to be somatic stem cells that have undergone mutations transforming them into a cancer phenotype (Dontu et al., 2004). Evidence has suggested the presence of ovarian somatic stem cells, although their source differs (Bukovsky et al., 2004; Johnson et al., 2005). Others have suggested that CSCs are formed from lineage-restricted or differentiated cells with a cancer phenotype that dedifferentiate into CSCs (Srivastava and Nalbantoglu, 2008), a phenomenon that has been seen in cell culture with the epithelio-mesenchymal transition (EMT) (Bukovsky et al., 2004). CSCs were first identified in acute myeloid leukemia (Lapidot et al., 1994) and have since been identified in many types of solid tumors including ovarian (Bapat et al., 2005; Zhang et al., 2008), breast (Al-Hajj et al., 2003), prostate (Collins et al., 2005), liver (Chiba et al., 2006; Suetsugu et al., 2006), brain (Singh et al., 2003), lung (Dome et al., 2006), melanoma (Griechnik et al., 2006), colon (O’Brien et al., 2007; Odoux et al., 2008), and pancreas (Olempska et al., 2007). Moreover, expression of CD133 (a neural stem cell marker) has been found in the aforementioned systems and is thought to correlate with CSC (Baba et al., 2009). While CD133 has been used to sort for hematopoietic stem cells, Ferrandina et al. (2008) used flow cytometry to isolate CD133+ cells from primary ovarian carcinomas. The CD133+ cells represented less than 1% of the total population, which is one of the defining characteristics of CSCs. The CD133+ cells were able to form colonies and had a higher proliferation potential than CD133- cells. Upon comparing the percentage of CD133+ in 8 normal ovaries, 5 benign ovarian tumors, 16 primary ovarian carcinomas, and 25 omental metastases, Ferrandina et al. (2008) found that the ovarian carcinomas has a significantly higher percentage than all other groups.

Baba et al. (2009) showed that CD133+/+ has also been found in the OCA cell lines OVCAR-8, while CD133+/- has been found in the OCA cell lines A2780, PEO1, OVCA432, OVCA2, and OV90. A single CD133- cell from A2780 or PEO1 produced more CD133+ cells. In contrast, a single CD133+ cell from the same cell lines was able to undergo asymmetric division and produce CD133+ and CD133- cells. Further investigation by immunohistochemical analysis revealed that 10 of 32 advanced stage primary serous epithelial ovarian carcinomas contained CD133+ cells at the luminal edges of glandular structures. Since a characteristic of CSCs is to form xenograft tumors, CD133+ and CD133- cells isolated from A2780 were injected into nude mice. CD133+ cells showed heightened aggressiveness with a larger tumor size and shorter latency. Immunohistochemical analysis of the xenograft tumors showed that the tumors derived from...
CD133\(^{+}\) cells contained both positive and negative staining suggesting that the original cells underwent asymmetric division. Tumors derived from CD133\(^{+}\) cells showed no to extremely low staining for CD133. CD133\(^{+}\) cells from cell lines showed increased resistance to cisplatin than CD133\(^{-}\) progeny.

Several other groups found CD44\(^{+}\) in human epithelial OCA and breast tumor cells (Al-Hajj et al., 2003; Dontu et al., 2004; Bapat et al., 2005; Bourguignon et al., 2008; Zhang et al., 2008). Bapat et al. (2005) isolated clones from the ascite samples of a malignant grade IV serous adenocarcinoma. Nineteen of sixty-five clones were immortalized, which showed variations in morphology and growth rates. Ten representative clones were selected and showed an up-regulation CD44, as well as c-met, epidermal growth factor receptor, E-cadherin (9 of 10), Snail (2 of 10), and Slug. Snail and Slug are known mediators of the EMT (Kurrey et al., 2005). Two of the immortalized clones, designated A2 and A4, were selected for the remaining experiments. Bapat et al. (2005) showed that the two clones had continued mutagenesis, evidenced by an increased proliferation rate and ability to form organized spheroids. These clones also showed the stem cell markers Nestin, Oct4, and Nanog, which was reduced upon tumor formation in nude mice.

Bourguignon et al. (2008) used the breast cancer cell line MCF-7 and OCA cell line SK-OV-3.ipl (established from ascites that developed in a nude mice given an intraperitoneal injection of SK-OV-3 cells) to show that hyaluronan-CD44 interaction recruits Nanog into the complex. Nanog is functionally coupled to Stat-3, which is a transcription factor involved with control of cell death and apoptosis. A differential global gene expression profile of CD44\(^{+}\) and CD44\(^{-}\) showed that there was a correlation with genes belonging to families associated with control of cell death and apoptosis, signal transduction, transcription regulation, and control of cell differentiation. One of these genes was myeloid differentiation factor 88 (MyD88), which was up-regulated 10-fold in CD44\(^{+}\) cells. MyD88 is a component of the toll like receptor 4 (TLR4) pathway and led to NF-\(\kappa\)B activation causing an increase in IL-6, IL-8, MCP-1, and GRO\(\alpha\) levels. When CD44\(^{+}\) cells were treated with paclitaxel, a known ligand of TLR4, there was an increase in NF-\(\kappa\)B production. CD44\(^{+}\) cells underwent apoptosis in response to paclitaxel treatment. The MyD88 pathway was shown to play an important role in chemotherapy resistance in CD44\(^{+}\) cells and recapitulation of the original tumor.

**Side Population (SP)**

The side population (SP) was first found in hematopoietic stem cells by their ability to efflux the lipophilic dye Hoechst 33342; subsequently, they were shown to protect recipients from lethal irradiation at low cell doses (Goodell et al., 1996). SP cells have since been found in cell lines established from solid tumors, including neuroblastoma (JF, SK-N-SH, IMR32, LAN-1, and LAN-3) and epithelial OCA (SK-OV-3 and PA-1) (Hirschmann-Jax et al., 2004), and in a variety of tissues and tumor types (Patrawala et al., 2005; Moserle et al., 2008). SP cells are characterized by their expression of highly selective transporters ABCG2 (Zhou et al., 2001) and multidrug resistance-associated transporter p-glycoprotein (MDR1) (Hirschmann-Jax et al., 2004) and the other ABC transporters ABCB1, ABCC1, and ABCC2 (Patrawala et al., 2005). These transporters give them the ability to efflux lipophilic substrates such as the dye Hoechst 33342 and many types of chemotherapy agents such as doxorubicin and imatinib (Jones et al., 2004), leading to chemotherapy resistance and tumor redevelopment (Hombach-Klonisch et al., 2008; Rocconi et al., 2008). SP cells were shown to be
sensitive to reserpine (Patrawala et al., 2005) and to the ABCB1 inhibitor verapamil (Goodell et al., 1996; Srivastava and Nalbantoglu, 2008), which reverses their phenotype (Moserle et al., 2008).

Patrawala et al. (2005) analyzed the SP various cancer cell lines including prostate, breast, colon, bladder, glioma, melanoma, cervix, and ovary. Even though the SP is rare (~0.01-5%), the authors were able to develop a system that would reliably detect a SP of ~0.01%. SP cells displayed an increased tumorigenicity compared to non-SP cells, forming tumors with as few as 100 SP cells with ~60% efficiency, whereas 200,000 non-SP did not. Purified SP cells were passaged in vivo, resulting in an increase in the population of SP cells similar to the first-generation tumor, suggesting that SP cells give rise to non-SP cells. SP cells also expressed Notch and β-catenin in higher levels, suggesting that SP cells have stem-like features. Dysregulation of Wnt/β-catenin, Jagged/Notch, and Hedgehog signal pathways have been implicated in carcinogenesis (Perryman and Sylvester, 2006).

Sztok et al. (2006) sorted SP and non-SP cells from human OCA cell line MOVCAR 7 and 4306 by ability to efflux Hoechst 33342 and flow cytometry. Upon culturing equal numbers of the cell, SP cells from both cell lines formed colonies, survived numerous passages, and produced both SP and non-SP cells. Non viable cells were gated out using propidium iodine to minimize the confounding cytotoxic effect of Hoechst 33342. Cell cycle analysis revealed that a majority of SP cells to be in G1, whereas non-SP cells had a higher percentage of cells in S phase. By injecting purified SP (82.6% purity) and non-SP (92.3%) cells from MOVCAR 7 in to the dorsal fat pad of nude mice, SP cells showed a potential to initiate earlier tumor growth at lower numbers.

Moserle et al. (2008) analyzed SP and non-SP cells from cell lines established from patients diagnosed with stage IIib to IV epithelial OCA and xenografted into nude mice (designated PDOVCA#1-6) for their proliferation capacity, cell cycle status, apoptosis level, and tumorigenicity. The resulting tumors were then sorted based on their ability to efflux Hoechst 33342 to separate the SP cells and non-SP cells to 98±1% and 90±3% purity respectively. Compared to non-SP cells, SP cells had a higher proliferation, reduced apoptosis rate (not due to Hoechst 33342), and increased tumorigenicity based on growth time and number of injected cells. Cell cycle analysis revealed that there were more non-SP cells in S and G2/M phase. The higher proliferation and reduced apoptosis of SP cells translated into a higher tumorigenicity, displaying both a greater efficiency and increased rate. The purified SP cells also generated tumors that contained both SP and non-SP cells similar to those measured in tumor resulting from unsorted cells. Furthermore, IFN-α treatment correlated to the SP cells and reduced their proliferation through up-regulation of the transcriptome. However, it did not modify the expression of ABCG2 and MDR1 transporters.

Conclusions

While the etiology of cancer has remained elusive, several theories about tumorigenesis have been proposed. Perhaps the most intriguing is the theory that cancer can be initiated from CSCs. Not only do CSCs have the ability to reconstitute the original tumor phenotype, they seem to do so more rapidly and with a lower cell count number than their related progenitors. The CSCs also account for chemotherapy resistance, particularly paclitaxel and doxorubicin, two of the current chemotherapy agents used clinically, through expression of the highly selective transporters ABCG2 and MDR1. Clearly, the need to be able to identify and target CSCs remains necessary for successful treatment of OCA. Evidence suggests that OCA CSCs can be identified as CD44+CD117+CD133+. While CSCs and the SP have been defined differently, there are some similarities between the two populations. Both populations seem to contribute to chemotherapy resistance via the transporters ABCG2 and MDR1 have tumorigenic properties, and stem cell-like characteristics. However, further experiments are required to examine if the SP can more stringently match the definition of CSCs (Moserle et al., 2008).

A molecular analysis of CSC and the SP could provide valuable insight into gene dysregulation and signaling pathways that may stimulate tumorigenesis, as shown with MyD88 being involved with chemotherapy resistance. CSCs and/or the SP could show differences between high- and low-grade tumors as indicated by their sensitivity to chemotherapy as one of their differentiating characteristics.

To verify the gonadotropin hypothesis, experiments are needed to show that exposure to gonadotropins can induce ovarian epithelium transformation into a cancer phenotype.

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