The role of reproductive hormones in epithelial ovarian carcinogenesis

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Abstract

Epithelial ovarian cancer comprises ~85% of all ovarian cancer cases. Despite acceptance regarding the influence of reproductive hormones on ovarian cancer risk and considerable advances in the understanding of epithelial ovarian carcinogenesis on a molecular level, complete understanding of the biologic processes underlying malignant transformation of ovarian surface epithelium is lacking. Various hypotheses have been proposed over the past several decades to explain the etiology of the disease. The role of reproductive hormones in epithelial ovarian carcinogenesis remains a key topic of research. Primary questions in the field of ovarian cancer biology center on its developmental cell of origin, the positive and negative effects of each class of hormones on ovarian cancer initiation and progression, and the role of the immune system in the ovarian cancer microenvironment. The development of the female reproductive tract is dictated by the hormonal milieu during embryogenesis. Intensive research efforts have revealed that ovarian cancer is a heterogenous disease that may develop from multiple extra-ovarian tissues, including both Müllerian (fallopian tubes, endometrium) and non-Müllerian structures (gastrointestinal tissue), contributing to its heterogeneity and distinct histologic subtypes. The mechanism underlying ovarian localization, however, remains unclear. Here, we discuss the role of reproductive hormones in influencing the immune system and tipping the balance against or in favor of developing ovarian cancer. We comment on animal models that are critical for experimentally validating existing hypotheses in key areas of endocrine research and useful for preclinical drug development. Finally, we address emerging therapeutic trends directed against ovarian cancer.

Key Words
- ovarian cancer
- hormone action
- reproductive
- immune
- endocrine

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Introduction

Ovarian cancer is the fifth leading cause of cancer-related deaths among women and the gynecologic malignancy with the highest mortality rate in the USA (http://seer.cancer.gov/statfacts/html/ovary.html; accessed May 2015). Diagnosis is often delayed due to nonspecific symptomatology and a lack of early screening and detection methods (Goff *et al.* 2007, Andersen *et al.* 2010). Despite considerable research, the etiology of ovarian cancer remains elusive. A positive family history is a major risk factor for developing the disease (Walker *et al.* 2002), particularly in women with breast cancer-associated genes (BRCA) 1 and 2 mutations or genetic mutations associated with hereditary nonpolyposis colorectal cancer syndrome (Lu & Broaddus 2005). Additional

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risk factors include increasing age with a predominance of disease occurrence/diagnosis in the fifth and sixth decades of life, early menarche (Gong *et al*. 2013), menopause after the age of 52 years (Tung *et al*. 2003), nulliparity (Tung *et al*. 2003), polycystic ovarian syndrome (PCOS, Schildkraut *et al*. 1996, Chittenden *et al*. 2009), primary infertility, endometriosis (Brinton *et al*. 2004), and lifestyle factors, such as tobacco use (Faber *et al*. 2013) and obesity (Calle *et al*. 2003, Olsen *et al*. 2007, Leitzmann *et al*. 2009). Each of these factors is coincident with fluctuations in reproductive hormones.

In recent years, the field of ovarian cancer research has more closely questioned and examined the true site of origin of the cancerous cells. It has been proposed that certain subtypes of tumors may arise from the distal fallopian tubes (FTs) rather than from the ovarian surface epithelium (OSE) and that stemlike cells within the cancerous tissue are responsible for tumor recurrence after successful initial remission (Cannistra 2004, Cooke & Brenton 2011). These advances have changed our understanding of the disease. Here, we provide an overview of the endocrine influences on tumor development and microenvironment of ovarian cancer, a tissue with more cellular heterogeneity than previously recognized. We discuss several relevant ovarian cancer animal models and summarize the current treatment options and future therapeutic trends.

Developmental origins

Until week 8 of human embryonic development, the internal reproductive tract is indifferent and undifferentiated in both genders. It consists of a set of two unipotential ducts – the Wolffian ducts (WDs) and the Müllerian ducts (MDs), also known as mesonephric and paramesophric ducts respectively. The MDs derive from cells of the coelomic epithelium (mesodermal in origin) that invaginate caudally toward the WDs and progress toward the urogenital sinuses. As the WDs regress, part of the coelomic epithelial cells proliferate and form the gonadal ridges (Byskov 1986). Early in embryonic development, the gonadal ridges and the mesonephros (urinary excretory organ of the early-stage embryo) are closely connected, but as the embryo grows, the structures separate. In females, the mesonephros degenerates and only a few mesonephric cells remain connected with the gonadal ridge. This cell mass is covered on its surface by the germinal epithelium and eventually develops into follicle-containing ovaries (Byskov 1986).

The etiology of epithelial ovarian cancer (EOC) is complex and not yet fully elucidated. Several hypotheses, all based on valid observations, have been discussed over the years, such as incessant ovulation (Fathalla 1971, Casagrande *et al*. 1979), cyclic or chronic inflammation (Ness & Cottreau 1999, Ness & Modugno 2006, Somigliana *et al*. 2006), stromal changes (Cramer & Welch 1983), influence of androgen/progesterone (Risch 1998) or gonadotropins (Biskind & Biskind 1944, Cramer & Welch 1983), and follicle depletion (Smith & Xu 2008). No single hypothesis, however, provides an all-inclusive explanation for the underlying pathogenesis of EOC.

Ovarian cancer tissues of origin: lessons from embryologic development

EOCs are traditionally classified into histologic subtypes based on morphological and functional features, and the tissues they mimic: serous (FT epithelium), endometrioid (proliferative endometrium), clear cell (endometriosis), mucinous (gastrointestinal tract or endocervical epithelium), and transitional cell/Brenner (urinary tract epithelium) (Chen *et al*. 2003). Ovarian/reproductive tract embryonic development and the close relationship of the structures in the early-stage embryo may be a reason for the propensity of OSE to differentiate into various types of epithelia during malignant transformation (Naora 2005). Likewise, de-differentiation of ovarian epithelia into one of the earlier developmental or embryonic tissues may explain the various ovarian cancer histologies. In accordance with our current understanding that ovarian cancer subtypes likely arise from other cell types within the female reproductive tract (FRT) than within the OSE, what has been historically termed 'ovarian cancer' could potentially be redefined in an embryologic descriptive manner as 'adenocarcinomas of Müllerian origin', although this designation may still not be entirely accurate and thus not acceptable to all (Dubeau 2008).

Serous cancers The epithelial cells covering the ovaries have historically been considered the site of origin of all ovarian cancers but recent evidence suggests that high-grade serous carcinoma (HGSC) originates from FT epithelium or the tuboperitoneal junction rather than the OSE (Piek *et al*. 2003, Crum *et al*. 2007, Kindelberger *et al*. 2007, Seidman *et al*. 2011, Tone *et al*. 2012). HGSCs are thought to originate in serous tubal intraepithelial carcinoma (STIC) lesions in the FTs, where ovulation-related oxidative injury can result in genetic alterations and malignant transformation of the secretory epithelium

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of the FT fimbriae. This theory is supported by the presence of occult neoplastic/STIC lesions found in up to 10% of FTs from *BRCA* mutation carriers who had undergone prophylactic bilateral salpingo-oophorectomies (Leeper *et al*. 2002, Crum *et al*. 2007). In a case series of prospectively identified EOC, evaluation of FT mucosa and ovarian tumors demonstrated similar genetic abnormalities and a monoclonal origin, implying a single primary site with secondary spread to other organs (Salvador *et al*. 2008). Based on this evidence implicating the FT as the origin of high-grade serous EOC, some groups have proposed performing salpingectomies as risk reduction surgery rather than oophorectomies in certain patients (Dietl *et al*. 2011).

The presence of a STIC lesion may potentiate the establishment of a 'p53 signature' (Lee *et al*. 2007), a putative p53 immunostain positive precursor lesion in the transition from nonmalignant distal FTs epithelium to carcinomatous epithelium, irrespective of whether a woman is a *BRCA* mutation carrier or not. However, whether or not the p53 signature truly represents a malignant precursor lesion has not been entirely elucidated yet, as equivalent lesions were also found in a high percentage of FTs of women without detectable STIC lesions or carcinomas (Lee *et al*. 2007). The observation that, when concurrently present in a woman, STIC lesions and ovarian carcinoma are associated in the majority, albeit not all, of the examined cases with identical *TP53* mutations led to the hypothesis that the presence of a p53 signature in STIC lesions may reflect a precursor lesion for high-grade serous ovarian carcinoma was. This finding represented the basis for the postulation that clonal expansion and proliferation of cells with mutated *TP53*, loss of their polarity, and eventual shedding from the FTs may ultimately result in adhesion of these cells to the ovarian and/or peritoneal surface, thus giving the impression that the cancer originated from the epithelium of those surfaces (Lee *et al*. 2007, Jarboe *et al*. 2008). A recently published Swedish population-based cohort study of over 5 million women supports this hypothesis, as removal of the FTs by itself, or concomitantly with other benign surgery, was found to be an effective measure to reduce ovarian cancer risk in the general population (Falconer *et al*. 2015). This has been primarily attributed to the removal of STIC lesions with surgery.

In other, rarer cases, HGSCs lack *TP53* mutations but are found to have *KRAS* mutations, suggesting that they may arise from low-grade serous carcinomas (Dehari *et al*. 2007), which typically develop in a stepwise fashion, starting as benign serous lesions and progressing to atypical or serous borderline tumors on acquisition of a *KRAS* or *BRAF* mutation and eventually developing into invasive cancers.

Endometrioid and clear cell cancers The FTs present an open conduit between the lower genital tract and the peritoneal cavity that enables the transport of potential carcinogens (Cramer *et al*. 1982, Huncharek *et al*. 2003), pathogens, inflammatory mediators, and malignant cells from other locations of the reproductive tract to the ovaries. For example, retrograde menstruation may transfer endometrial or cervical cells to the ovaries (Sampson 1927, D'Hooghe & Debrock 2008) as a possible developmental etiology for the endometrioid and clear cell histologies of EOC (Martin 1997, Drapkin & Hecht 2006, Wiegand *et al*. 2010). Eutopic endometrium possesses the ability to activate pathways that are essential for malignant transformation. In the event of retrograde menstrual flow, those molecular alterations may facilitate endometrial tissue implantation on the surfaces of ovaries and/or peritoneum, thereby enabling tissue invasion and ultimately the manifestation of cancer (Jarboe *et al*. 2008, Bulun 2009). This correlates well with clinical observations and molecular studies that endometrioid and clear cell cancers develop from endometriotic implants in the ovaries and/or pelvis (Veras *et al*. 2009), as well as epidemiologic data that ligation, as opposed to surgical resection, of the FTs is protective primarily against these two subtypes of ovarian cancer (Rosenblatt & Thomas 1996, Madsen *et al*. 2015).

Mucinous cancers and transitional cell (Brenner) cancers The origins of ovarian mucinous and transitional cell cancers are not yet fully unraveled. The majority of mucinous cancers bear no resemblance with MD-derived phenotypes but are characterized by the presence of goblet cells similar to mucosa derived from the gastrointestinal tract (Seidman & Khedmati 2008), whereas transitional cancers have been suggested to possibly arise from metaplastic transitional epithelial nests near the tuboperitoneal junction (Kuhn *et al*. 2013). These nests can invaginate into the paratubal and ovarian tissue and form so-called Walthard nests, which, when embedded into the ovaries, can activate the ovarian stroma to produce androgens that facilitate the development to transitional cell tumors (Kuhn *et al*. 2013).

Mucinous and transitional cell cancers are strongly associated; about 25% of tumors with a mucinous component contain a Brenner component, and ~16% of tumors with a Brenner component contain a mucinous

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component (Seidman & Khedmati 2008). The additional finding of amplification of chromosome 12q14–21 by comparative genome hybridization in a mucinous ovarian carcinoma and a coexisting transitional tumor gave rise to the hypothesis of a potential clonal relationship between these tumors (Pejovic *et al*. 1999).

Moreover recently, while not related to ovarian cancer, the epitheliotropic human papilloma virus types 16 and 18 were detected in the upper genital tract of women at high risk of developing EOC. Although it is premature to make a definitive statement based on this study, it is possible that the ascent of altered endocervical cells through the female genital tract may alter the tissue environment and facilitate development of mucinous type EOC (Bilyk *et al*. 2014).

Ovarian cancer and stem cells

Today, ovarian cancer is recognized as a disease with significant intra-tumor heterogeneity harboring multiple cell populations. Based on the isolation of cells with pluripotent stem cell character from murine ovaries and observations that cells with various degrees of chemosensitivity exist in ovarian cancers, it has been proposed that stem cells might be present in the premalignant epithelia that could give rise to cancers (Szotek *et al*. 2008, Rizzo *et al*. 2011, Auersperg 2013). Using protocols and markers to describe stem cells in the bone marrow (Goodell *et al*. 1996) or in malignancies of other organs, such as endometrial cancer or gastrointestinal tumors (Chiba *et al*. 2006, Friel *et al*. 2008, Fukuda *et al*. 2009), 'side population' cells, a distinct subpopulation of cells, has been identified in ovarian cancer, as well as in other types of cancers, in functional assays, which are viewed to possess stem cell characteristics (Boesch *et al*. 2014). These cells express the ATP-binding cassette transporter proteins G2 and B1 (Szotek *et al*. 2006, Hu *et al*. 2010, Boesch *et al*. 2014), drug transporter proteins that confer differential responsiveness and potential resistance to various chemotherapeutic agents. Additional proteins have been discussed as candidate ovarian cancer stem cell (CSC) markers, such as CD44 (Bapat *et al*. 2005), MyD88 (Alvero *et al*. 2009), and CD133 (Ferrandina *et al*. 2008); their potential role, however, remains to be elucidated.

In the breast, mammary stem cells are proposed to be recruited in a hormone-responsive process, enabling cell growth, regeneration, and functional differentiation during different phases of a woman's reproductive life (Joshi *et al*. 2012). In an analogous situation, epithelial stem cells in the female genital tract may also be responsive to hormonal stimuli. The niche in which they reside may serve to transmit systemic hormonal signals to the cells, as suggested for the mammary stem cell niche (Joshi *et al*. 2012). To date, the existence of CSCs in the human adult ovary is still a topic of debate. The existence of these cells would provide a plausible explanation for both the heterogeneity of ovarian cancer and its recurrence after effective initial treatment (Mor *et al*. 2011). During ovarian cancer treatment, the putative CSCs may persist quiescently in tissue niches and, due to their slow rate of cell cycling, remain unaffected by cytotoxic drugs. At later time points, they may become activated by various microenvironmental stimuli to self-renew and proliferate, causing disease recurrence (Foster *et al*. 2013, Shah & Landen 2014). Gene expression profiling studies comparing normal OSE with that of ovarian serous papillary adenocarcinoma demonstrated that human OSE is certainly multipotent, albeit not omnipotent, and capable of initiating ovarian cancer (Bowen *et al*. 2009). The relevance of this finding, however, remains to be established, as prevailing theories do not support the idea that OSE is the precursor lesion for all EOCs but, rather, indicate that the different ovarian cancer subtypes derive from distinct cell types within the FRT. Additionally or alternatively, within the ovaries, cells lacking stem cell properties may (re-) acquire CSC properties in the presence of stress stimuli, as a consequence of cell plasticity (Tata *et al*. 2013). Whether these cells qualify as 'true' CSCs, however, is also controversial.

Reproductive hormones and epithelial ovarian carcinogenesis

Following menarche, the cyclic rise and fall of circulating hypothalamic–pituitary–gonadal hormonal levels govern ovarian function (Kronenberg *et al*. 2008). Each month, immediately prior to ovulation, gonadotropin levels surge briefly (Kronenberg *et al*. 2008), signaling OSE cells in the vicinity of preovulatory follicles to secrete lysosomal and proteolytic enzymes that digest the wall of the follicles, thereby facilitating oocyte release (Land 1993, Murdoch 1996). At the site of follicular rupture, the OSE becomes exposed to the stromal microenvironment (Wu *et al*. 1992, 1993). Fragments of the OSE become invaginated in the ovarian cortical stroma where inflammatory cells accumulate to facilitate wound repair (Radisavljevic 1977). Auto- and paracrine signals stimulate the OSE to proliferate and migrate to cover the wound area (Okamura & Katabuchi 2001). While the OSE invaginations and formed inclusion cysts become surrounded by epithelium,

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gene mutations can occur, as OSE is particularly susceptible to genetic alterations during mitosis (Godwin *et al.* 1992, Roby *et al.* 2000).

The formation of ovarian clefts and inclusion cysts increases with aging (Kronenberg *et al.* 2008). This coincides with the observed higher frequency of inclusion cysts in postmenopausal than in premenopausal women (66% vs 51%; Kronenberg *et al.* 2008). Genetic alterations, cellular metaplasia, and neoplastic transformation occur at the sites of repetitive tissue wounding and repair, suggesting that the microenvironment at these sites may facilitate carcinogenesis (Kronenberg *et al.* 2008). Repeated tissue injury in the ovary and subsequent inflammation and stromal reactions in the context of wound healing, as well as epithelial cell proliferation, may result in genetic alterations that can certainly explain, at least in part, malignant transformation. Furthermore, epithelial–mesenchymal transformation (EMT) has been demonstrated in the post-ovulatory OSE (Auersperg *et al.* 1999, Ahmed *et al.* 2006). However, if the postovulatory OSE fails to undergo EMT and maintains its epithelial characteristics while being trapped within the stroma, carcinogenesis may occur (Auersperg *et al.* 2001). Repeated stimulation of the ectopic epithelium by stromal estrogens results in proliferation, aggregate formation and the development of inclusion cysts that are prone to metaplasia and malignant transformation. Irrespective of designation, the influence of reproductive hormones on the development and progression of ovarian cancer likely exists.

Estrogens and ovarian carcinogenesis

Numerous data implicate a role for estrogens in ovarian carcinogenesis, although the extent of its influence and the mechanistic details are unclear, given that the disease is predominantly seen in older women at or beyond the age of menopause, when estrogen levels are significantly lower than in premenopausal women. Ovarian tumor cell proliferation increases with estrogen exposure, and the estrogen receptors alpha and beta (ERA and ERB respectively) are present in ~60–100% of ovarian tumors resected from patients (Lindgren *et al.* 2004, De Stefano *et al.* 2011). Stimulation of ERA increases cell proliferation, while ERB exerts the opposite effect. As ovarian cancer progresses, ERB expression is gradually lost (Lau *et al.* 1999, Bardin *et al.* 2004, Lazennec 2006), in part at a genetic level, in part due to promoter hypermethylation (Suzuki *et al.* 2008, Yap *et al.* 2009). Conversely, ERA expression remains unchanged or increases (Chan *et al.* 2008), resulting in a rise in the ERA/ERB ratio that evokes upregulation of tumor promoting and downregulation of tumor suppressing genes and their products (Cancer Genome Atlas Research Network 2011), thus facilitating tumor invasion and metastasis formation. In the ovary, estrogen regulates nuclear factor kappa B (NFKB) signaling, while NFKB transrepresses ERB signaling in ovarian granulosa cells (Chu *et al.* 2004).

Moreover, genetic susceptibility studies suggest that the polymorphism rs1271572 within the promoter of ERB might impact the risk of ovarian cancer, particularly in women younger than 50 years (Lurie *et al.* 2011). Particularly, the presence of the rs1271572 TT genotype was found to confer an increased risk of malignancy (Lurie *et al.* 2011).

In a recent study, changes in the rate of ovarian cancer incidence were analyzed comparing the years before (1995–2002) and after (2003–2008) the 2002 Women's Health Initiative (WHI) announcement of the association of menopausal hormone therapy (MHT, also known as hormone replacement therapy) and breast cancer risk (Yang *et al.* 2013). A marked reduction in MHT use around 2002 led to an accelerated decline of ovarian cancer incidence rates, specifically in endometrioid histology ovarian cancers. Although this strong temporal association is not proof for a causal role of hormones in ovarian carcinogenesis, it presents an intriguing hypothesis and suggests that more research is required to answer this question (Yang *et al.* 2013). Similarly, the Million Women Study reported an increased risk of both incidental and fatal ovarian cancer with the use of MHT, which was more pronounced for estrogen-only agents than for combinations containing estrogen and a synthetic progesterone (Beral *et al.* 2007). Unfortunately, the efficacy of ER blockers (e.g., tamoxifen) or aromatase inhibitors (e.g., letrozole) has not been universally successful in treating ovarian cancer (Hatch *et al.* 1991, Zheng *et al.* 2007, Ito *et al.* 2011), although the response rates to tamoxifen in platinum-refractory ovarian cancer have been higher than some cytotoxic agents (Markman *et al.* 1996). Therefore, although it is possible that estrogens are involved in the early steps of malignant transformation, some of the tumors do not appear to depend on estrogens for sustained growth.

Gonadotropins and ovarian carcinogenesis

The prolonged use of oral contraceptives agents, irrespective of whether or not they inhibit ovulation, was shown in several epidemiologic studies to reduce the risk of

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ovarian cancer (Rosenberg *et al*. 1994, Lurie *et al*. 2007, Cibula *et al*. 2010, Grimbizis & Tarlatzis 2010, Ness *et al*. 2011). The decreased release of endogenous estrogen during oral contraceptive use may be a consequence of reduced circulating gonadotropins levels, achieved via negative feedback regulation (Syed *et al*. 2001, Zheng *et al*. 2007).

The role of gonadotropins in ovarian carcinogenesis is particularly important given the hypergonadotropic hormonal conditions found in postmenopausal women, the most commonly affected category of patients. With the natural decline of a woman's ovarian reserve during aging, circulating gonadal steroid levels decrease while circulating pituitary gonadotropin levels rise. The constellation of low gonadal steroids, mainly estrogen, and high gonadotropin levels is characteristic for the early years after menopause (Chakravarti *et al*. 1976), consistent with the time period during which the incidence of ovarian cancer peaks. As menopause advances, gonadotropin levels decline slightly, although they remain elevated compared to the premenopausal state.

OSE expresses receptors for the pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in both the normal and cancerous states (Zheng *et al*. 1996, Mandai *et al*. 1997, Minegishi *et al*. 2000, Parrott *et al*. 2001). Expression of these receptors is higher in the early stages of epithelial ovarian carcinogenesis than in more advanced stages (Lu *et al*. 2000, Zheng *et al*. 2000), suggesting that LH and FSH are involved in activating oncogenic pathways in metaplastic OSE. This hypothesis would explain the increased rate of EOC in the peri- and postmenopausal period. The LH has also been implicated in epithelial ovarian carcinogenesis by inducing vascular endothelial growth factor (VEGF) via the phosphatidylinositide-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (Liao *et al*. 2012) and upregulating survivin, resulting in apoptosis inhibition (Zhang *et al*. 2011). Similarly, VEGF is a target of FSH through the PI3K/AKT pathway (Wang *et al*. 2002, Sasson *et al*. 2003). Given the promoter effects of LH and FSH on VEGF, gonadotropin-induced VEGF expression may significantly contribute to ovarian tumor neovascularization and progression.

Human chorionic gonadotropin (hCG) comprises a group of three different molecules: regular hCG, hyperglycosylated hCG, and free β-hCG. Free β-hCG is found in many gynecologic malignancies and promotes cellular proliferation and invasion in non-gestational malignancies (Muller & Cole 2009). While free β-hCG has been evaluated in uterine, cervical, vaginal, and ovarian malignancies, the highest sensitivity for serum β-hCG was observed in ovarian tumors, likely due to more advanced stage malignancies commonly seen with ovarian compared to other gynecologic malignancies (Muller & Cole 2009). Elevated serum β-hCG and aberrant p53 tissue expression were correlated with advanced stage, grade, age, large residual tumor size, and poor prognosis (Vartiainen *et al*. 2008). Although the combination of serum β-hCG and p53 may provide helpful prognostic information, few assays are currently able to detect normal and moderately elevated concentrations of serum β-hCG, or the available assays detect regular hCG and β-hCG together, which can obscure the results (Vartiainen *et al*. 2008). Thus, the clinical utility of using β-hCG as a biomarker is limited by the specificity and sensitivity of commercially available assays.

Although the link between elevated gonadotropins and ovarian cancer risk seems plausible, studies conducted in infertility patients contrast this theory. Although gonadotropin levels rise during hormonal infertility treatment, there has been no definitive link to an increased risk of ovarian cancer with their medical administration (Rizzuto *et al*. 2013). There may be a higher risk of borderline ovarian tumors in subfertile women treated with *in vitro* fertilization (Rizzuto *et al*. 2013), but the preponderance of data offers no convincing evidence for an elevated risk of invasive ovarian tumors associated with ovulation induction agents, including human menopausal gonadotropin, hCG, gonadotropin agonists or antagonists, and others. Nonetheless, more research in this field is required for a definitive answer.

Antiapoptotic function of gonadotropins In addition to their roles in activating oncogenic pathways, gonadotropins possess the ability to inhibit cellular apoptosis (Fig. 1). LH prevents Fas-induced apoptosis in OSE cell lines (Slot *et al*. 2006), while FSH does so through effects on antiapoptotic proteins, such as Bcl2, during folliculogenesis (Tilly *et al*. 1995). hCG binds the same receptor as LH (McFarland *et al*. 1989) and is frequently elevated in gynecologic malignancies (Tanyi & Scholler 2012). hCG inhibits apoptosis of OSE cells via upregulation of insulin-like growth factor 1 and has been shown to suppress cisplatin-induced apoptosis (Kuroda *et al*. 2001). Similarly, FSH may also protect ovarian cancer cells against cisplatin-induced apoptosis by modulating caspase activity (Huang *et al*. 2003*a*,*b*).

NFKB was found to mediate antiapoptotic responses in both ovarian cancer cell lines and cultured primary ovarian cancer cells treated with the LH releasing

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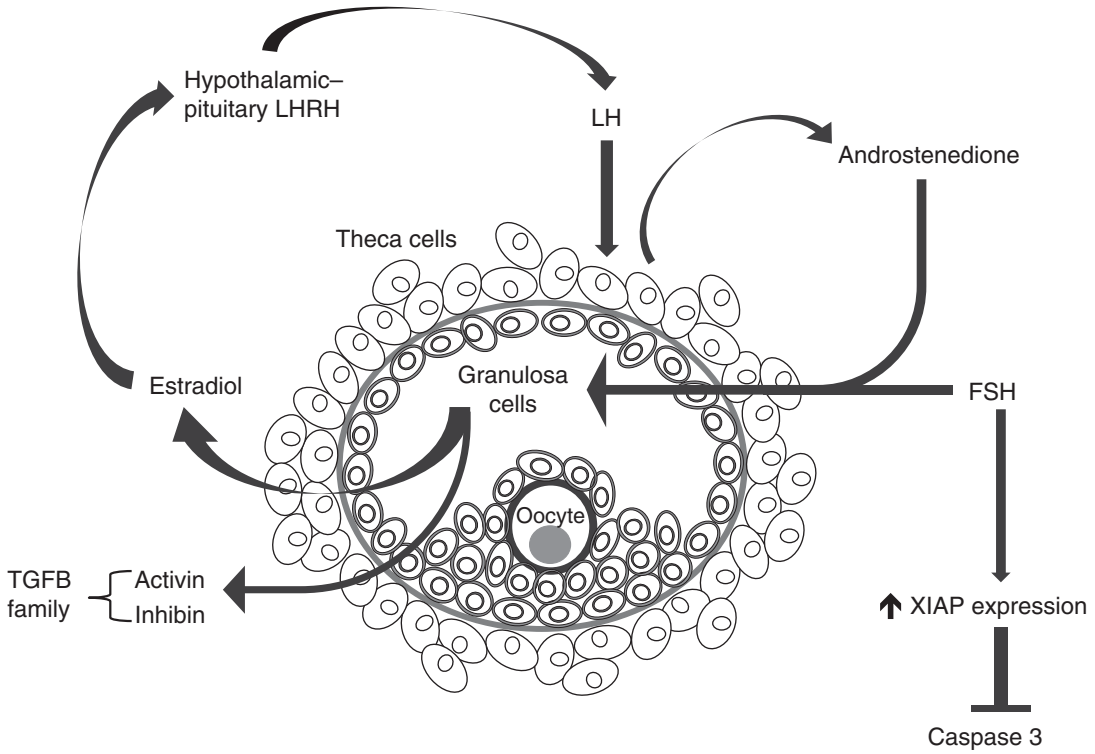

Figure 1

Hormonal interactions at the level of the oocyte. During the early phase of the menstrual cycle, FSH levels are elevated and bind FSH receptors located on granulosa cells. Theca cells express LH receptors. LH binding to theca cells promotes androstenedione production. Androstendione is subsequently, upon entering granulosa cells and under the influence of FSH, converted to estradiol. Activins and inhibins are members of the TGFB superfamily and function antagonistically to positively and negatively regulate FSH activity, respectively. FSH promotes XIAP expression thereby promoting follicular development. XIAP inhibits pro-apoptotic caspase 3 activity. LH, luteinizing hormone; LHRH, LH releasing hormone; FSH, follicle-stimulating hormone; TGFB, transforming growth factor beta; XIAP, X-linked inhibitor of apoptosis.

hormone (LHRH) analogue triptorelin that were less sensitive to doxorubicin-induced apoptosis compared to untreated cells (Gründker *et al.* 2000). LHRH and its receptor are expressed both within and on the surface of EOC cells. However, in contrast to the pituitary gland, where LHRH receptor signal transduction is mediated by protein kinase C (Stojilkovic & Catt 1995), the LHRH antiproliferative effect in ovarian tumor cells results from impeding mitogenic signal transduction of growth factor receptors and oncoproteins with tyrosine kinase activity, such as epidermal growth factor (Emons *et al.* 1996).

In EOC, apoptosis is influenced by the inhibitors of apoptosis (IAP) proteins. For example, X-linked IAP (XIAP), a crucial inhibitor of apoptotic signaling, directly inhibits caspase 3, a proapoptotic protease that is activated by both the intrinsic mitochondrial and the extrinsic death ligand-mediated apoptosis pathways, thereby suppressing Fas ligand and tumor necrosis factor alpha (TNFA)-induced apoptosis (Takahashi *et al.* 1998). Additionally, XIAP modulates the cytochrome *c*/caspase 9 dependent mitochondrial death pathway (McNeish *et al.* 2003). In cultured ovarian rat granulosa cells, FSH modulated the expression of XIAP, via NFKB activity, thus promoting follicle growth and inducing antral formation (Wang *et al.* 2003). On the contrary, FSH withdrawal or decreased levels of XIAP in granulosa cells led to follicular atresia.

Regulation of gonadotropin levels through inhibins and activins Inhibins and activins are members of the transforming growth factor beta (TGFB) family of cytokines, which influences cellular/tissue growth and differentiation and plays a role in regulating the immune system. In the ovary, inhibins and activins are produced by granulosa cells, and their primary role is to act as direct negative and positive regulators, respectively, of pituitary FSH expression and secretion (McLachlan *et al.* 1987, Burger 1993, Coss *et al.* 2010).

Activins are also expressed outside of the ovaries, such as in adrenal glands, spleen, and bone marrow (Luisi *et al.*

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2001), and contribute to raising FSH levels. In rodent-derived ovarian granulosa cells, FSH in the presence of activin was mitogenic (Miró & Hillier 1996), offering an additional mechanistic explanation for how gonadotropins may be involved in the development of ovarian cancer during early menopause. Conversely, serum inhibin levels become undetectable after menopause when a woman's ovarian reserve has diminished. It is not yet understood how inhibins contribute to human ovarian carcinogenesis. In inhibin A-deficient mice, the observation of gonadal tumors seems to support a tumor suppressive role for inhibin (Matzuk *et al*. 1992), but in humans, the serum inhibin levels are elevated rather than decreased in certain types of ovarian cancer (Healy *et al*. 1993). Several hypotheses are proposed to explain this paradox, including the possible unresponsiveness of human ovarian cancer cells to inhibin (Matzuk *et al*. 1996), loss of heterozygosity involving the chromosomal region that encodes inhibin A (Watson *et al*. 1997), or constitutive activation of a pathway normally opposed by inhibin (Robertson *et al*. 2004). A clear understanding is further complicated by the fact that neither a receptor nor a binding protein for inhibin has yet been identified. Betaglycan, the TGFB type 3 receptor (TGFBR3), and InhBP/p120, a membrane-tethered proteoglycan, were identified as putative inhibin receptors, but TGFBR3 does not appear to be expressed in pituitary gonadotropes, and InhBP/p120 does not bind inhibins in conventional receptor binding assays (Bernard *et al*. 2002). In addition, neither appears to generate inhibin-specific intracellular signals, although both proteins appear capable of promoting inhibin-mediated antagonism of activin signaling (Bernard *et al*. 2002).

Despite the questionable role of inhibins in promoting ovarian carcinogenesis, it is interesting that combined inhibin and CA-125 assays detect 95% of all ovarian cancer types (Robertson *et al*. 1999, 2002). To date, this combination represents the most reliable clinical biomarker available for ovarian cancer diagnostics.

Gonadotropin influence on ovarian stroma Apart from the OSE, gonadotropins impact the mesenchymal-derived cells of the ovarian stroma. The significance of the ovarian stroma in the pathogenesis of ovarian cancer has become increasingly clear in recent years through its numerous interactions with the OSE. Moreover, a high proportion of stroma in the cancerous ovary is associated with a decreased overall survival (OS) of patients (Labiche *et al*. 2010). This may be the result of insufficient drug penetration or drug resistance mechanisms dependent on cell adhesion (Anttila *et al*. 2000, Labiche *et al*. 2010).

Among the tumor-associated stromal cells that contribute to the pathogenesis of ovarian cancer are cancer-associated fibroblasts (CAFs), omentum-derived adipocytes, mesenchymal stem cells (MSCs), angiogenic precursor cells, and various types of immune cells that are actively recruited to the site of disease (Musrap & Diamandis 2012). In addition, the ovarian stroma harbors two types of steroidogenic cells, granulosa and theca cells, which support oocytes within growing follicles. Evidence suggests that granulosa cells derive in part from OSE (Sawyer *et al*. 2002). They express the receptor for FSH, while the receptor for LH is expressed on the surface of theca cells in early stage follicles and on granulosa cells in later follicular maturation (Webb & Campbell 2007). Theca cells are thought to be mesenchymal derived (Young & McNeilly 2010). Premenopausally, the pulsatile release of LH induces them to produce androstendione, a precursor androgenic steroid hormone, which subsequently enters granulosa cells where it is converted to estradiol under the influence of FSH (aromatization; Liu & Hsueh 1986, Simpson 2002, Kronenberg *et al*. 2008). Monthly gonadotropin surges cause periods of elevated estrogen levels in the ovarian stroma that could promote epithelial cell proliferation and mutagenesis, thereby creating changes favorable for carcinogenesis in the peri- and postmenopausal period. Indeed, gene expression profiling of ovarian cancer cells exposed to estrogen demonstrated upregulation and expression of cancer-related and proangiogenic genes (Simpson 2002). Subpopulations of multipotent cells with the capacity to self-renew were identified among both granulosa (Kossowska-Tomaszczuk *et al*. 2009) and theca cells in mice (Honda *et al*. 2007), but not in humans. This observation has led to the hypothesis that follicular fluid may contain MSCs, which could be isolated, expanded, and potentially used for therapeutic purposes (Heng *et al*. 2005). One of the shortcomings of the gonadotropin hypothesis is that it does not account for the failure of MHT to protect against ovarian cancer, even though MHT lowers circulating gonadotropin levels.

Androgens and ovarian carcinogenesis

Human OSE is responsive to androgens (Edmondson *et al*. 2002), which are present at high levels in developing follicles (McNatty *et al*. 1979) as well as in the peripheral circulation. Androgens increase cellular proliferation and decrease cell death, thus, potentially influencing ovarian

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neoplastic transformation. Moreover, human ovarian cancer cells not only express 17β-hydroxysteroid dehydrogenase, the enzyme that converts the weaker androgen androstendione to the more potent testosterone (Blomquist *et al*. 2002), but also overexpress the androgen receptor (Ilekis *et al*. 1997, Lau *et al*. 1999). Within the androgen receptor gene, a trinucleotide (CAG) repeat polymorphism was inconsistently associated with an increased risk of developing EOC (Menin *et al*. 2001, Santarosa *et al*. 2002, Schildkraut *et al*. 2007, Ludwig *et al*. 2009).

Higher serum androstenedione and DHEA levels, as well as the use of exogenous androgens, has been associated in some studies with an increased risk of ovarian cancer (Helzlsouer *et al*. 1995, Cottreau *et al*. 2003, Olsen *et al*. 2008). In contrast, oral contraceptives that do not inhibit ovulation may protect against ovarian cancer by decreasing both systemic and epithelial microenvironment androgen levels (Gaspard *et al*. 1983, Murphy *et al*. 1990, Coenen *et al*. 1996).

Systemic hyperandrogenism occurs in women with PCOS and obesity. Both conditions can impair reproductive capacity and are reported to amplify ovarian cancer risk (Schildkraut *et al*. 1996, Collaborative Group on Epidemiological Studies of Ovarian Cancer 2012). Interestingly, PCOS has been linked in some cases with risk alleles of the FSH receptor (Themmen & Huhtaniemi 2000, Gromoll & Simoni 2005). In particular, the FSH receptor single nucleotide polymorphisms Thr307Ala and Asn680Ser have been associated with significantly increased susceptibility to serous and mucinous subtypes of ovarian cancer (Yang *et al*. 2006). There are studies, however, that do not support the hypothesis that androgens impact the ovarian cancer risk significantly (Cottreau *et al*. 2003, Greer *et al*. 2005, Rinaldi *et al*. 2007, Olsen *et al*. 2008), indicating that a definitive answer to this question is still pending.

Progesterone and ovarian carcinogenesis

Progesterone, an endogenous steroid hormone produced by the ovarian corpus luteum during the luteal phase of the menstrual cycle in reproductive age women, may be the common link between the hormonal and immunologic pathways. It mediates its effects via two intracellular receptor isoforms, PRA and PRB, which have distinct and differing functions in tissues of the FRT. Progesterone can attenuate and downregulate inflammatory mediators and confer potent antiproliferative and anti-inflammatory properties in the FRT, particularly by suppressing constitutive NFKB activation. As an immune modulator, progesterone promotes a humoral response, upregulating interleukin 4 (IL4), IL5, IL6, and IL10 production and inhibiting T cell proliferation (Canellada *et al*. 2002, De León-Nava *et al*. 2009). Additionally, progesterone exerts anticarcinogenic effects by inhibiting NFKB-regulated proinflammatory chemokine expression (CXCL1 and CXCL2), resulting in the suppression of proteins involved with metastasis and tumor invasion (Hernandez *et al*. 2010, Kavandi *et al*. 2012).

Although the *in vivo* relationship between inflammatory mediators and progesterone (or other hormonal factors) remains to be clarified, both seem to be important constituents of the ovarian tumor microenvironment and to contribute to the complex process of carcinogenesis. This is supported by observations that a portion of patients with endometriosis, a proinflammatory state of ectopic endometrial tissue in the pelvic peritoneum or ovaries, were resistant to therapy with progesterone or progestins (contraceptive steroids), although others experienced reduced tissue inflammation and pain relief (Bulun *et al*. 2006, Bulun 2009). PRB is expressed in eutopic endometrium but not in ectopic endometrium (Attia *et al*. 2000). Conversely, PRA is present in ectopic endometrium (Attia *et al*. 2000), albeit at very low levels. Alterations of PRA and PRB levels, paired with deficient expression of 17β-hydroxysteroid dehydrogenase type 2, an estradiol metabolizing enzyme, are thought to contribute to the unresponsiveness of endometriotic tissue to progesterone (Bulun *et al*. 2006).

The role of progesterone as an essential hormone regulating female reproductive organs is also established through its effects within the uterus. Several uterine pathologies are attributed to aberrant PR signaling, and accordingly, therapies targeting progesterone signaling are used to treat uterine pathologies, such as endometrial hyperplasia or low-grade endometrial cancer. One of the critical functions of progesterone in the uterus is to antagonize the tropic actions of estrogen on the endometrium. PR expression status in endometrial carcinoma is considered an independent prognostic factor (Ballester *et al*. 2013, Zhang *et al*. 2013) and increased PRA expression has been demonstrated in ER positive endometrial cancer (Singh *et al*. 2007).

In ovarian cancer cells, induction of PRB activity suppressed tumorigenicity and induced senescence (Takahashi *et al*. 2009). The invasive endometrioid subtype of ovarian cancer may be associated with variations of progesterone receptors, specifically when the PROGINS allele (rs1042838) is present (McKenna *et al*. 1995, Rowe *et al*. 1995, Manolitsas *et al*. 1997, Lancaster

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et al. 1998, Spurdle et al. 2001, Tong et al. 2001, Lancaster et al. 2003, Pearce et al. 2008). On the contrary, the *+331G/A* polymorphism in the progesterone receptor promoter, which alters the expression of PRB, is associated with a reduced risk of endometrioid and clear cell ovarian cancers (Berchuck et al. 2004). This may be due to the preferred production of PRB over PRA isoforms, which affects the growth and spread of endometriosis (Berchuck et al. 2004), the presumed precursor condition for those cancers (Ness 2003).

Further support for the protective effect of progesterone against ovarian carcinogenesis is gained from clinical observations. Epidemiologic data demonstrate that women with a history of twin pregnancies, and thus exposure to higher progesterone levels, are less likely to develop ovarian cancer than women with singleton pregnancies. Moreover, the protective effect of pregnancy is more pronounced in women older than 35 years, more proximal to the high risk period for ovarian cancer development, than in younger women (Whiteman et al. 2003). Indeed, the incidence rate of ovarian cancer increases during the menopausal years, when a woman's progesterone level declines – another strong indicator for the shielding effect of progesterone against the development of ovarian cancer.

Endocrine influences on the immune milieu in ovarian cancer

The immune system in premenopausal women undergoes cyclic changes coinciding with the menstrual cycle. Estrogen and progesterone are the key regulators of the immune system in the FRT (Ghosh et al. 2014) and their receptors are expressed on most immune cells (Couse et al. 1997, Dosiou et al. 2008). In the first half of a 4-week menstrual cycle (follicular phase; estrogen-driven) up to the early postovulatory phase, the FRT appears to be dominated by proinflammatory helper T lymphocyte 1 (Th1) cells, which exert their effects through macrophages and cytotoxic T cells ($CD8^+$) (Oertelt-Prigione 2012). During this phase, regulatory T cells ($CD4^+CD25^+FOXP3^+$) also peak in number. These cells are responsible for immune modulation and the establishment of tolerance (to self-antigens). Conversely, the second half of the cycle (luteal phase; progesterone-driven) is characterized by decreased Th1 and regulatory T cells and increased monocytes and Th2 cells that promote proliferation of B lymphocytes.

During menopause, systemic immune function declines, which may be directly related to declining estrogen levels (Ghosh et al. 2014). A generalized inflammatory state devoid of protective immune factors, but with elevated levels of monocytes and consequently proinflammatory cytokines such as TNFA and IL6, is established in the FRT (Gameiro et al. 2010, Ghosh et al. 2014; Fig. 2A). Additionally, the total number of lymphocytes decreases during the postmenopausal years (Giglio et al. 1994, Yang et al. 2000). It is not yet clear if this is purely related to the lack of estrogen and progesterone or if other factors of aging contribute to this decline (Miller 1996, Chakravarti & Abraham 1999).

The immune system recognizes ovarian cancer cells through their expression of tumor-associated antigens (TAAs), such as p53, Her2/neu, NY-ESO1, MUC1, MAGE-A1,3,4,10, survivin, folate receptor alpha, and others. Tumor-reactive infiltrating T lymphocytes (TILs) identify TAAs spontaneously and respond with tumor-specific cytolytic activity (Santin et al. 2000). In fact, direct killing of tumor cells by cytotoxic T lymphocytes ($CD8^+$) is an effective antitumor immune response that positively impacts progression-free survival (PFS) and overall patient survival (Zhang et al. 2003, Hwang et al. 2012, Bachmayr-Heyda et al. 2013). Conversely, the presence of a high $CD4^+/CD8^+$ TIL ratio correlated with poorer prognosis (Sato et al. 2005).

Tumors, however, have the ability to modify the balance of TILs and their function in favor of a suppressive immune microenvironment (Di et al. 2013). IL6 may be the primary immunoregulatory cytokine in epithelial ovarian carcinogenesis (Maccio & Madeddu 2012). Produced by monocytes/macrophages as well as malignant cells, IL6 participates in multiple tumorigenic activities and demonstrates both proinflammatory and anti-inflammatory effects during EOC progression. IL6 diverts the immune response from a Th1 (cell-mediated immunity) to a Th2 (humoral) response (Fig. 2B). The shift from a Th1 to a Th2 immune response is considered one of the mechanisms by which tumors evade immune destruction. Additionally, malignant cells are able to evade immune surveillance and immunologic destruction through other mechanisms, including the expression of immunosuppressive factors, impaired antigen presentation, and downregulation of intracellular adhesion molecules. The Th2 cytokines IL6 and IL10 have been shown to inhibit an inflammatory response in the tumor microenvironment (Cândido et al. 2013). High IL6 levels in the tumor microenvironment are associated with chemotherapy resistance and impaired immune cell efficiency. These functions prevent immune cell infiltration and effective apoptotic signaling (Yigit et al. 2010).

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A

	Menstrual cycle phase		Menopause
	Follicular phase	Luteal phase	
	Estrogen-driven	Progesterone-driven	Estrogen-deprivation
FRT immune response	Th1 (menstrual and early follicular)	Th2 (mid-late luteal)	
Dominant cytokines	IL1	IL4 TNFA	IL6 TNFA
Systemic immune response	Cellular	Humoral	Chronic state of inflammatory activity

B

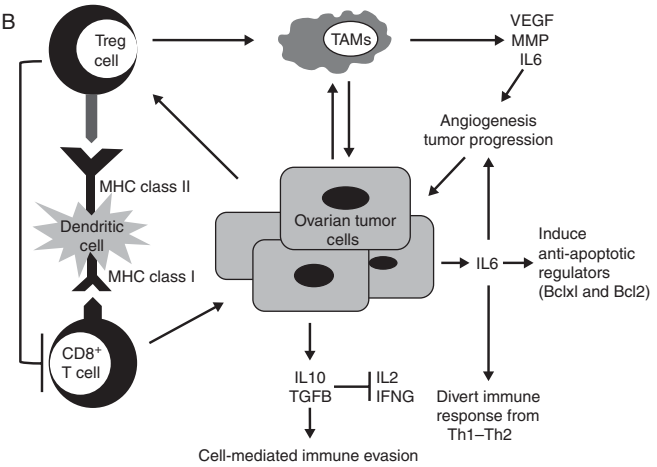

Figure 2

(A) Immune changes in relationship to hormonal status. (B) Interactions in the tumor microenvironment between tumor cells and various immune modulators. Cancer cells alter immune responses by promoting an immunosuppressive humoral T2 immune response. Ovarian tumors also elaborate immunosuppressive cytokines, particularly IL6, IL10, and TGFB. Antitumor cytokines, including IL2, are inhibited by IL10. Tumor-associated macrophages express angiogenic factors, including VEGF, further promoting tumor vascularization. Treg, regulatory T cells; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; IFNG, interferon gamma; TGFB, tumor growth factor beta; IL6, interleukin 6; IL10, interleukin 10; MHC, major histocompatibility complex.

Ovarian cancer cells polarize monocytes and macrophages toward an immunosuppressive M2 (aka tumor associated) phenotype within the tumor microenvironment. This also enables the malignant cells to evade immune surveillance (Hagemann *et al.* 2006). The tumor-associated macrophages (TAMs) express angiogenic factors, such as VEGF and matrix metalloproteinases (Torres *et al.* 2009), and thus play a central role in mediating tumor vascularization, a process imperative for tumor growth and propagation. Accordingly, the presence of high numbers of TAMs in the ovarian microenvironment is associated with poorer clinical prognosis (Colvin 2014). TAMs also promote tumor invasion in a TNFA- and NFKB-dependent manner (Hagemann *et al.* 2006). This process may be facilitated in the perimenopausal and early menopausal period as circulating and local levels of steroidogenic hormones decrease, while the cellular immune response normalizes following initiation of hormone replacement (Stopińska-Głuszak *et al.* 2006).

The combination of a generally impaired systemic immune system with a pro-inflammatory immune microenvironment in the FRT could facilitate ovarian cancer propagation. Gene expression profiling on serous and endometrioid ovarian, peritoneum, and FT tumors identified molecular subtypes with high and low immune signatures (Tothill *et al.* 2008). Tumors with high immune signatures were associated with better OS (Tothill *et al.* 2008), suggesting that active immune signaling within the tumor confers better long-term control of ovarian cancer. Further delineation of these gene signatures is needed to identify whether they might indicate particular immune cell subsets and/or cytokines important for this survival benefit. Better characterization of hormonally induced immune changes related to these gene signatures in the postmenopausal FRT may subsequently identify potential areas for preventative intervention.

Hormones and NFKB in ovarian cancer

NFKB is a significant link between inflammation and tumor development. NFKB is a proinflammatory heterodimeric transcription factor that is found ubiquitously in many different cells of the body (Perkins 2007). It is activated by various cytokines and mitogens in response to inflammatory/immunologic changes, or other stressors, and the activation of its signaling by inflammatory mediators enhances tumorigenesis (Cohen *et al.* 2000). NFKB also mediates the effects of steroid hormones, including estrogen, progesterone, and androgen (Stein & Yang 1995, Supakar *et al.* 1995, Kalkhoven *et al.* 1996, McKay & Cidlowski 1998). The steroid/receptor complexes interact directly with NFKB inhibiting its transactivational activity (McKay & Cidlowski 1998, 1999, Chadwick *et al.* 2005, Kalaitzidis & Gilmore 2005, Kerdivel *et al.* 2013).

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NFKB signaling is constitutively activated in some epithelial-derived tumors (Deregowski *et al*. 2002, Karin *et al*. 2002). In these tumors, NFKB mediates tissue invasion and adhesion, thereby facilitating metastasis formation, as well as promoting angiogenesis. In addition, NFKB binds to specific sites in the promoter of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), an oncogenic protein present in EOC (Yang *et al*. 2008). PIK3CA is an important mediator of tumor cell response to stress *in vivo*. NFKB binds to the PIK3CA promoter after stimulation with TNFA and upregulates its gene expression (Yang *et al*. 2008). The *PIK3CA* gene itself is activated by growth factor receptor tyrosine kinases. Recently, it was hypothesized that PIK3CA is expressed at low levels in the cytoplasm of tumor cells during the initial phases of tumor growth, supporting the proliferation of tumor cells (Yang *et al*. 2008). However, as tumor growth progresses, nutritional support for tumor cells decreases potentiating metabolic and ischemic stress to the cells. These stresses activate NFKB to bind to the PIK3CA promoter resulting in gene expression and amplification of other downstream pathways that promote tumor cell survival and proliferation. Further exploring the NFKB pathway interactions may elucidate important biologic underpinnings to ovarian carcinogenesis.

Animal models of endocrine influences on the pathogenesis of ovarian cancer

Biskind & Biskind (1944) developed one of the first animal models for hormone mediated ovarian cancer in 1944. In that model, ovaries were transplanted into the spleen of castrated rats, which led to the disruption of the hypothalamic–pituitary–gonadal feedback loop and loss of Graafian (antral) follicles. The loss of Graafian follicles resulted in the proliferation of the OSE, its invagination into the ovarian cortex, ovarian stromal proliferation, and in some cases, tumor formation (Biskind & Biskind 1944, Guthrie 1957). However, if one ovary was left *in situ* to participate in the endocrine feedback, no proliferative changes were observed in the OSE suggesting the changes in OSE proliferation had been a consequence of hormonal alterations, specifically, the lack of negative feedback by estrogens and testosterone.

Mice thymectomized at a neonatal age experienced immune-mediated ovarian dysgenesis and developed ovarian tumors, potentially as a consequence of the continuous ovarian hyperstimulation by gonadotropins (Nishizuki *et al*. 1979). In a subset of transgenic mice expressing a chimeric LH β subunit in their pituitary gonadotrophs, granulosa and stromal ovarian tumors were also observed. Again, tumor development was attributed to elevated gonadotropin (LH) levels (Risma *et al*. 1995). Moreover, ovarian tumors developed in mice lacking inhibin A, a hormone that suppresses FSH secretion. The resulting elevation of gonadotropin (FSH) levels in the animals was thought to underlie ovarian cancer development (Matzuk *et al*. 1992).

In more recent years, rodents treated with raloxifene, a selective ER modulator, demonstrated persistent elevations of serum LH levels in the absence of the preovulatory LH surge (Cohen *et al*. 2000, Long *et al*. 2001). In a study assessing the effects of raloxifene on ovarian morphology, rats were noted to develop granulosa cell hyperplasia following treatment, in a dose dependent manner, while one rat developed a granulosa cell tumor (Long *et al*. 2001), supporting the idea that hormonal imbalances can result in malignant transformation. Similar results were observed in ERA knockout mice in which the hypothalamic–pituitary–gonadal feedback mechanism was disturbed (Korach 1994). Once more, the increased incidence of ovarian tumors in those animals was attributed to elevated serum gonadotropin levels.

Although the number of ovarian cancer mouse models currently available remains limited, novel approaches to animal models in the last several years have brought major advances to the field. For example, patient-derived xenograft mouse models were developed that more closely mimic the true biologic progression of ovarian cancer in women and can be utilized for preclinical drug development (Kolfschoten *et al*. 2000). Another mouse model targeted cancer development in the FTs rather than the ovary by deleting the genes for *DICER*, an essential gene for microRNA synthesis, and phosphatase and tensin homolog (*PTEN*), a key negative regulator of the PI3K pathway. In these DICER–PTEN double-knockout mice, tumors appeared to arise from the FTs and subsequently spread to the ovary and peritoneal cavity, providing a model for FT-derived, aggressive serous carcinoma resembling human serous EOC (Kim *et al*. 2012). Interestingly, salpingectomy prevented the development of ovarian cancer in the double-knockout mice while oophorectomy did not, confirming FT origin. This model did not demonstrate similarities to the typical transformation that human FT secretory epithelial cells undergo during early steps of the disease pathogenesis nor did it demonstrate the formation of STICs, the pre-invasive dysplastic lesions found in association with HGSCs

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(Kindelberger *et al*. 2007, Lee *et al*. 2007). To address these points, Perets and colleagues recently developed *de novo* a mouse model of HGSC through *Pax8*-driven Cre-mediated recombinations resulting in deletions of genes that are commonly altered in the FT secretory epithelium in HGSCs (*BRCA*, *TP53*, and *PTEN*; Perets *et al*. 2013). This approach achieved both the development of precursor STIC lesions and that of advanced disease, including established HGSC and metastases, in the animals. Genomic alterations in the animals' tumors were similar to those found in corresponding patients with HGSC (TCGA 2011), thus supporting the hypothesis that HGSCs may indeed originate in the FTs and making this model a valuable tool for future research on the pathogenesis of ovarian serous carcinogenesis (Perets *et al*. 2013).

Apart from rodents, other animal models used to study ovarian cancer include primates, specifically macaques, and hens. In both, progestins were found to have a chemopreventive effect against ovarian (and oviductal) cancer (Rodriguez *et al*. 1998, 2002, Barnes *et al*. 2002, Trevino *et al*. 2012). The effect was independent of ovulation (Rodriguez *et al*. 2013) and likely due to the differential expression of TGFB in the ovarian epithelium, with a decreased expression of TGFB1 but an increased expression of TGFB2/3 isoforms. Because this expression pattern is associated with the induction of apoptosis in the OSE (Rodriguez *et al*. 2002), it could enhance the clearance of genetically damaged ovarian epithelial cells (Rodriguez *et al*. 2012). The discovery that the protective effect of OCPs against ovarian cancer is not due to ovulation inhibition alone has consequently sparked interest to design oral contraceptive formulations with ovarian cancer-protective potential for women.

The significance of animal models for this and other areas of ovarian cancer research has increased considerably in recent years after the discovery that the majority of established ovarian cancer cell lines do not correlate well with their reported cells of origin (Korch *et al*. 2012, Domcke *et al*. 2013). Genomic profiling, however, has been shown to be of great value in identifying cell lines that are suitable as models of ovarian cancer (Domcke *et al*. 2013).

Therapeutic strategies for (epithelial) ovarian cancer

The standard of care is to treat newly diagnosed ovarian cancer with cytoreductive surgery followed by platinum–taxane-based adjuvant chemotherapy. The surgery serves not only to remove the cancerous organ and its surrounding tissues but also to disrupt the hypothalamic–pituitary–gonadal endocrine axis. While up to 80% of patients initially respond to this treatment, the relapse rate is high. Relapse within 6 months of platinum-based treatment has a particularly poor outcome and resistance to platinum agents represents an obstacle for effective treatment.

Endocrine treatment approaches

Endocrine therapy may be a treatment option for women with recurrent or metastatic ovarian cancer for whom traditional chemotherapies have failed, as ovarian cancer cells tend to express receptors for reproductive hormones. It is unknown, however, which subgroup of patients is most likely to benefit from hormonal therapy.

Among the best evaluated and most frequently used hormonal agents for the treatment of ovarian cancer are the selective ER modulator tamoxifen (Schwartz *et al*. 1982, Hatch *et al*. 1991, Ahlgren *et al*. 1993, Johnson *et al*. 1993, Scambia *et al*. 1995, Bartlett *et al*. 1996, Hofstra *et al*. 1999, Benedetti Panici *et al*. 2001, Hiscox *et al*. 2004, Markman *et al*. 2004, Hasan *et al*. 2005, Wagner *et al*. 2007, Hurteau *et al*. 2010, Williams *et al*. 2010), the selective ER antagonist fulvestrant (Argenta *et al*. 2009), and the aromatase inhibitors letrozole (Papadimitriou *et al*. 2004, Smyth *et al*. 2007, Ramirez *et al*. 2008) and anastrozole (del Carmen *et al*. 2003, Krasner 2007). Other hormonal agents that have been evaluated in this context are progesterone receptor agonists (Ho 2003, Niwa *et al*. 2008, Diep *et al*. 2013) and antiandrogens, including flutamide and bicalutamide (Levine *et al*. 2007).

Hormonal inhibitors, when used in the palliative setting, serve to alleviate patients' symptoms while exposing them to less toxicity than conventional cytotoxic therapy. Hormonal agents can also play a beneficial role in modulating the tumor immune environment. Nevertheless, the response rates to these agents have been disappointing thus far, ranging between 0 and 30% depending on the agent used, the histologic subtype of the tumor, and the patient population. The small numbers of patients included in the studies, their varying disease stages, different histologic subtypes, and treatment regimens before commencing hormonal therapy, as well as inconsistencies in determining the malignant cells' receptor status, make it difficult to form solid conclusions regarding the reasons. Clearly, randomized phase III clinical trials are indicated. Epidemiologic data suggest that the endometrioid histology ovarian cancers may be the most responsive to hormonal influences, at least in the

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initial transformation of the epithelium. The decline in incidence of this tumor subtype was the most dramatic in the period following the WHI, when MHT sharply decreased (Yang *et al*. 2013).

Progestins may possess a protective effect against ovarian cancer development that is attributed to the induction of OSE apoptosis (Rodriguez *et al*. 2002), while nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the growth and proliferation of ovarian cancer cell lines. Although the mechanisms are not yet known, it was hypothesized that these agents, given in combination, may have a beneficial synergistic effect on ovarian cancer chemoprotection and prevention (Rodriguez *et al*. 2012). Indeed, ovarian cancer cell lines demonstrated loss of viability and marked induction of caspase 3 by 48 h after treatment with progesterone and celecoxib. It remains to be determined whether the combination of these drug classes can be given over prolonged time periods to premenopausal women to protect them against the early steps of ovarian carcinogenesis. In the premenopausal period, cellular heterogeneity is thought to be negligible, and the molecular pathways mediating the effects of chemopreventives are still somewhat intact. Therefore, the combination of progestins and low-dose NSAIDS could potentially provide effective ovarian cancer chemoprotection (Rodriguez *et al*. 2012).

Finally, Müllerian-inhibiting substance (MIS), also known as anti-Müllerian hormone, may be cytotoxic against MD-derived tumors (Donahoe *et al*. 1979, 1981), as demonstrated with various ovarian cancer cell lines and in animal experiments. Presently, however, MIS is not yet applicable to be tested as an anticancer agent in a clinical setting (reviewed in Wong *et al*. (2014)).

Treatments targeting downstream results of endocrine influences

Given the emerging data on the efficacy of immune therapies in a subset of cancer types and an appreciation of the immunogenicity of EOC (Zhang *et al*. 2003), immunotherapeutic agents have been investigated in patients with ovarian cancer (Preston *et al*. 2011). The approaches encompass active and passive immune strategies ranging from attempts to deplete immunosuppressive regulatory T lymphocytes, the use of vaccines against TAAs, adoptive cell therapies, and various combinations of immune modulatory agents and modalities (Preston *et al*. 2011, Zsiros *et al*. 2014). Several groups are also exploring the effects of standard chemotherapeutic agents and radiotherapy on the ovarian cancer immune milieu. While some immune-based approaches appear promising, others have not yet led to desirable effects. The heterogeneity of ovarian cancer cells and the changes in response to hormonal influences as a tumor evolves likely allow the tumor cells to escape immune recognition and elimination, contributing to variable responses to immunotherapy. Trials are ongoing using immune modulatory agents in combination with chemotherapy, radiotherapy, and molecularly targeted agents (Zsiros *et al*. 2014).

Anti-angiogenic treatment with bevacizumab, a monoclonal antibody (mAB) directed against VEGFA, has been studied in recent years for advanced, first-line therapy of ovarian cancer in combination with carboplatin and paclitaxel and for recurrent ovarian cancer following treatment with platinum-based regimens. Bevacizumab attempts to overcome the increased VEGF secretion by the CAFs and TAMs that are recruited under the influence of elevated systemic gonadotropin levels during menopause. Bevacizumab was also reported to possess immunomodulatory activity enhancing immune responses against cancer cells (Zsiros *et al*. 2014). In a recently reported open-label phase III trial (AURELIA), the addition of bevacizumab to chemotherapy resulted in significantly improved PFS and objective response rate (ORR) in patients with platinum-resistant ovarian cancer, although the OS was not significantly different compared to those patients who did not receive bevacizumab (Pujade-Lauraine *et al*. 2014). The reported median PFS in this trial was 6.7 months vs 3.4 months by RECIST criteria (hazard ratio (HR) 0.48, $P<0.001$, on unstratified log-rank test; HR 0.42, $P<0.001$, on stratified log-rank test). The ORR was 30.9% in the bevacizumab/ chemotherapy group and 12.6% in the chemotherapy-alone group ($P<0.001$), while the median OS was 16.6 months vs 13.3 months in those groups (HR=0.85, $P=0.174$), respectively. Estrogen modulates angiogenesis under physiologic and pathologic conditions and has been shown to directly affect tumor growth by regulating VEGF expression (Dabrosin *et al*. 2003). Although there is a relationship between endocrine regulation and angiogenesis, the significance of specific hormonal interactions, particularly estrogen, with bevacizumab in the setting of ovarian cancer is unclear. Bevacizumab may oppose increased VEGF production from ovarian intratumoral estrogen derived from *in situ* aromatization (Sasano & Harada 1998), effectively slowing, but not abrogating, tumor proliferation as demonstrated by ORRs without altering survival outcomes. Various clinical trials have evaluated the rational combination of aromatase inhibitors and bevacizumab in breast cancer, but none to date in ovarian cancer.

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Various signaling pathways have been implicated in gonadotropin-induced proliferation, invasion, and metastasis formation in ovarian cancer, such as the RAS/RAF/MAPK/ERK (Pilarski *et al*. 2012, Stewart *et al*. 2012, Hilliard *et al*. 2013, Smolle *et al*. 2013), PI3K/PTEN/AKT/mTOR (Cancer Genome Atlas Research Network 2011, Huang *et al*. 2011, Yamamoto *et al*. 2011, 2012, Carden *et al*. 2012, Abe *et al*. 2013, Dobbin & Landen 2013), and Wnt/β-catenin signaling pathways (Bodnar *et al*. 2014, Ford *et al*. 2014, Qi *et al*. 2014). Gonadotropin (FSH and LH) receptors share various downstream signaling pathways, including PI3K and MAPK, and consequently, the potential crosstalk between gonadotropins and molecular pathway signaling is of great interest in exploring targeted cancer therapies. Binding either FSH or LH to their respective receptors activates ERK1/2, a subgroup of MAPKs that is involved with inhibiting apoptotis and promoting cellular proliferation and invasive potential (Mertens-Walker *et al*. 2012). Likewise, both FSH and LH stimulate phosphorylation of the serine/threonine kinase AKT in turn causing the activation of mTOR, a major driver of carcinogenesis (Mertens-Walker *et al*. 2012). Despite evidence that gonadotropin activity influences carcinogenesis, the specific mechanisms underlying the interactions between gonadotropins and carcinogenic molecular signaling remain to be better characterized.

Activation of the MAPK signaling cascade by FSH leading to phosphorylation of ERK1/2 in normal and immortalized OSE as well as EOC cell lines was first demonstrated by Choi *et al*. (2002). *KRAS* and *BRAF* gene mutations lead to constitutive activation of RAS/RAF/MAPK/ERK pathway signaling (Stewart *et al*. 2012). Endometrioid carcinomas exhibit common molecular abnormalities with uterine endometrioid adenocarcinomas, including *CTNNB1* (β-catenin), inactivation of the PTEN on chromosome 10, microsatellite instability, and *KRAS* mutations (Stewart *et al*. 2012). The functional loss of *PTEN*, a mutation found in ~20% of ovarian endometrioid carcinomas, impairs tumor suppressive activity (Swiersz 2002, Dobbin & Landen 2013). *KRAS*, but not *BRAF*, mutations have been found to have an association (29% vs 3% respectively) with endometriosis-associated ovarian endometrioid adenocarcinomas compared to those tumors in which endometriosis was not identified (Stewart *et al*. 2012). This suggests that *KRAS* mutations and MAPK pathway activation play a role in the development of endometriosis-associated ovarian carcinomas (Stewart *et al*. 2012).

Deregulation of PI3K/AKT/mTOR occurs when downstream targets of PI3K are modified, or mutated. Gonadotropins have been shown to induce gonadotropin-stimulated invasion activity of ovarian tumor cells by activating PI3K *in vitro* (Choi *et al*. 2006); FSH has been shown to increase the expression of VEGF and subsequently angiogenesis by upregulating the expression of survivin, which is activated by the PI3K pathway via AKT signaling (Huang *et al*. 2008, Mertens-Walker *et al*. 2012). Furthermore, a relationship between PI3K/AKT signaling and FSH-induced EMT in EOC cell lines has been shown (Yang *et al*. 2014).

Gonadotropins play a profound role in ovarian carcinogenesis including activation of multiple molecular signaling pathways directly involved with potentiating proliferation and invasion. The discovery of pathway-specific activation in different ovarian tumor histologies may guide chemotherapy selections targeted to specific pathway activity. Although specific genetic mutations are found in different ovarian tumor histologies, which has implications for therapeutic potential, targeting a single pathway may quickly lead to therapeutic resistance as other involved pathways compensate. Ultimately, the complexity of molecular signaling, redundancy, and crosstalk between signaling pathways poses significant challenges to designing effective therapies, particularly, but not exclusively, for recurrent/refractory disease.

Steps to facilitate and advance future immunotherapy of ovarian cancer

In accordance with greater interest to advance more personalized medicine, gene expression profiling studies with linkage to clinical and pathologic features have been performed to identify novel molecular subtypes of ovarian cancer (Tothill *et al*. 2008). Six novel, distinct, and clinically relevant molecular subtypes were found for serous and endometrioid cancers that were driven by both the tumor and the host tissue and displayed distinct patterns of immune cell involvement (Tothill *et al*. 2008). Of particular interest were the findings in high-grade cancers that two of the subtypes, C2 and C4, were found to have an elevated immune signature while the C5 subtype was noted to have a low immune signature. Additionally, evaluation for clinical correlation among the six molecular subtypes revealed that patients with the C5 subtype trended toward early chemotherapy relapse and shorter OS (Tothill *et al*. 2008). Analogous subgroups were identified in the Cancer Genome Atlas, with strikingly similar relationships to survival, further supporting the influence of the immune system in ovarian cancer

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(Cancer Genome Atlas Research Network 2011). Given the interplay between hormonal factors and immune modulators in the ovarian tumor microenvironment, future research will ideally inform a greater understanding of tumor biology and pathogenesis in high-grade serous and endometrioid ovarian carcinomas and, potentially, the utility of combining hormonal or immunotherapy options for ovarian cancer treatment or prevention.

Summary and conclusions

While the specific key elements of epithelial ovarian carcinogenesis are multifactorial and the site of origin of the disease has not yet been fully elucidated, it is probable that reproductive hormones play a central role in the development of the disease. Their involvement, both systemically and locally within the ovarian microenvironment, appears to extend beyond the early stages of malignant transformation. The hormonal milieu likely modulates tumor cell evasion from immunologic surveillance/elimination, cellular proliferation, and tumor progression by the upregulation of stimulatory proteins crucial for angiogenesis (Schiffenbauer *et al*. 1997), neovascularization (Wang *et al*. 2002), tissue invasion (Choi *et al*. 2006), and cell adhesion (Schiffenbauer *et al*. 2002). These effects may be influenced by the heterogeneity underlying (epithelial) ovarian cancer and differ by tumor type and histology. Further investigation into the complex relationships and interactions between hormonal factors and the tumor immune microenvironment will help shed light on the etiology and development of (epithelial) ovarian cancer and ideally, lead to novel, effective therapeutic options.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review. The findings of this work do not necessarily represent the opinion of the U.S. government.

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