Roles of the ovarian surface epithelium in ovulation and carcinogenesis

William J. Murdoch and Anna C. McDonnel

Reproductive Biology Program, University of Wyoming, Laramie, WY 82071, USA

Although ovarian mechanisms of ovulation have been a subject of investigation for more than a century, essential regulatory pathways remain uncertain. A role for the ovarian surface epithelium in ovulation has recently been demonstrated. Ovarian surface epithelial cells in close contact with the apical wall of preovulatory ovine follicles secrete a urokinase-type plasminogen activator in response to surge concentrations of (locally delivered) gonadotrophins. Urokinase activates latent collagenases and stimulates release of tumour necrosis factor α from thecal endothelium. Tumour necrosis factor α progressively induces matrix metalloproteinase gene expression, apoptosis and inflammatory necrosis. Collagenolysis and cellular death are a prelude to stigma formation and ovarian rupture. Epithelium exfoliated from the dome of ovulatory follicles is replenished by generative stem cell replication and migration from the wound edges. Common epithelial ovarian cancer has been related to successive bouts of ovulation and mitosis. The integrity of the DNA of surface cells circumjacent to the ovarian rupture site is compromised during the ovulatory process. Clonal expansion of an epithelial cell with damaged (unrepaired) DNA is a putative factor in carcinogenesis. Ovarian cancer is a deadly insidious disease because typically it is asymptomatic until the malignancy has reached beyond the ovaries.

Anatomy and embryonic origin of the ovarian surface epithelium

Ovarian surface epithelial cells vary in type from simple squamous to cuboidal to low pseudostratified columnar. The surface epithelium is supported over the ovarian cortical interstitium (tunica albuginea) by a basement membrane (Fig. 1) and is held together laterally by desmosomes and gap or tight junctional complexes. Surface cells are continuous at the hilum with the mesothelium of the ovarian ligament (mesovarium) and peritoneum. Preferential outgrowth of a preovulatory follicle brings it into close apposition with the ovarian surface. In most mammals, the entire surface of the ovary, other than those regions disrupted by ovulation, is covered by epithelial cells. However, in equids, the ovarian epithelium (and ovulation) is restricted to a discrete area of depression known as the fossa, and the remainder of the ovary is encased by serosa-containing elastic bands of connective tissue (Walt et al., 1979). Ovarian surface epithelial cells have a mesodermal derivation shared with the epithelia of the urogenital system and adrenal cortex. Mesoderm segregates during embryonic development into pluripotent mesenchyme and coelomic epithelium (peritoneal mesothelium). Mullerian mesothelium is the precursor of oviductal, endometrial, and cervical epithelia. Ovarian surface epithelium differentiates after invagination of the coelomic mesothelium over the gonadal ridges (Byskov, 1986). In species with an ovulation fossa, the cortex (with modified epithelium) migrates into the medullary portion of the ovary during the postnatal period (Walt et al., 1979). Early investigators assumed that ova were derived from the ovarian surface; hence, the misnomer ‘germinal’ epithelium.

Role of the ovarian surface epithelium in the mechanism of ovulatory follicular rupture

The contention that ovarian surface epithelial cells participate actively in the biomechanics of gonadotrophin-induced...
ovulatory follicular rupture was initially supported by circumstantial anatomical evidence. Several studies indicated that connective tissue degeneration begins at the ovarian surface and advances toward the follicular wall. Proteolytic enzymes released from cytoplasmic granules of epithelial cells appeared to degrade the tunica albuginea and underlying theca, thereby weakening the apical follicular wall (Bjersing and Cajander, 1975).

The notion that the ovarian epithelium has a function in the ovulatory mechanism was discounted when Rawson and Espey (1977) reported that ovulation still occurred from some rabbit follicles in which the surfaces had been scraped. However, the efficacy of surface epithelial removal was not confirmed (and numbers of ovulatory ovarian rupture points were reduced by scraping). Ovulation in frogs in vitro (Schuetz and Lessman, 1982) and sheep in vivo (Colgin and Murdoch, 1997) is blocked merely by handling the surface of ovaries (which disrupts the surface epithelium) inhibits ovulation in pigs (Hall et al., 1993).

Collagen breakdown and cellular death (apoptosis and inflammatory necrosis) within the apex of the preovulatory ovine follicle are hallmarks of impending ovulation. An integrative model is presented in which gonadotrophic upregulation of plasmin at the ovarian surface–preovulatory follicular interface

Plasmin (fibrinolysin) is a pleiotropic serine protease that is derived from the zymogen plasminogen by enzymatic activation. Two forms of PA have been characterized in vertebrates: urokinase (u) and tissue (t) types. Most functional studies indicate that uPA mediates tissue degradation, whereas tPA (which has a strong affinity for fibrin) modulates thrombolysis (Danø et al., 1985).

An increase in plasmin biosynthesis within the apical hemisphere and conjoined tunica albuginea of preovulatory follicles in ewes has been attributed to secretion of uPA by ovarian surface epithelial cells (tPA was undetectable). When ovarian surface epithelium was removed, the follicular increase in uPA was negated (Colgin and Murdoch, 1997). Furthermore, ovulation was suppressed by intrafollicular injection of uPA (but not tPA) antibodies (Colgin and Murdoch, 1997) or α2-antiplasmin (Murdoch, 1998a). In addition, plasminogen activators were increased preferentially within the apices of preovulatory pig (Smokovitis et al., 1988) and rat (Peng et al., 1993) follicles. Intrabursal administration of inhibitors of the PA–plasmin system decreased ovulation rates in rats (Tsairri and Reich, 1991).

Sheep ovarian surface epithelial cells secrete uPA in a basal direction (that is, towards the tunica albuginea and apical follicular wall) in response to LH. Receptors for LH on ovarian surface cells are upregulated at pro-oestrus by oestradiol of preovulatory follicular origin (Murdoch et al., 1999a). Ovarian epithelium in close proximity to the preovulatory follicle is readily exposed to surge concentrations of LH owing to an acute increase in permeability of the thecal vascular wreath (Cavender and Murdoch, 1988). Secretion of PAs by gonadotrophin-stimulated thecal and granulosal cells of rodent follicles has been established; both uPA and tPA contribute to the efficiency of ovulation, although ovulatory rates are not altered in mice with a single gene deficiency (Hägglund et al., 1996).

Plasmin-induced endothelial secretion of TNF-α

The cytokine TNF-α is expressed as an integral transmembrane precursor protein that yields an extracellular domain subunit upon cleavage. Mature (soluble) TNF-α is a noncovalent homotrimer. Plasma membrane glycoprotein receptors for TNF-α (RI, RII) are present on virtually all nucleated cells, including those of the mammalian ovary (Terranova, 1997).

TNF-α is localized to the thecal endothelial cells of preovulatory ovine follicles. Immunostaining of endothelium within the follicular apex declined abruptly with the approach of ovulation, although cells within the counterpart basal wall were unaffected. The cytokine was secreted, within a limited diffusion radius, into the progenitor site of rupture (Murdoch et al., 1997). Bioactive TNF-α was truncated from endothelial cells by plasmin (Murdoch et al., 1999b). Preovulatory follicles of other species (for example,
ratos, cows, humans) secrete TNF-α (Terranova, 1997), although cellular and molecular release processes have not been elucidated.

Target tissue effects of TNF-α are receptor subtype- and concentration-dependent. Receptors bind trimeric ligand through a homologous extracellular amino terminal motif. The cytoplasmic segment of TNFRI contains a death domain that, upon receptor aggregation, can evoke a proteolytic cascade leading to apoptotic (internucleosomal) DNA fragmentation and cellular dissolution. Non-lethal transcriptional events (such as MMP gene expression) also can be activated by TNFRI and TNFRII ligation. It remains unclear which mechanisms dictate the pathway of signal transduction outcome towards genomic stimulation or without programmed death (Warzocha and Salles, 1998). At high tissue concentrations, TNF-α initiates microvascular coagulation associated with acute inflammation and necrotic cellular death (Larrick and Wright, 1990). The addition of TNF-α to perfusates of rat ovaries enhances ovulation rates elicited by LH (Brännström et al., 1995).

**Collagenolysis**

Type I (interstitial) collagen is the primary supportive fabric of the ovarian–follicular wall. Basement membranes that circumscribe thecal capillary beds and on which granulosal cells and ovarian surface epithelium abut are composed of type IV collagen (Luck, 1994). Mammalian collagenases belong to a family of metalloproteinases that truncate each of the polypeptide chains of collagen at sites near the N-terminus; the enzymes share many structural and functional attributes, but differ in substrate specificities (Birkedal-Hansen, 1995). Collagen catabolism is a prerequisite of follicular distension and ovulatory rupture (Woessner et al., 1989).

In preovulatory ovine follicles, there is a direct association of apical plasinogen accumulation (Colgin and Murdoch, 1997) with the onset of collagenolysis (Murdoch and McCormick, 1992). Explants of follicular wall release fragments of collagen upon exposure to plasin, and injection of α2-antiplasmin into preovulatory follicles suppresses collagenase bioactivity of tissue extracts (Murdoch, 1998a). Intrafollicular injection of TNF-α antibodies, which prevent ovulation (Murdoch et al., 1997), also inhibit the increase in collagenolysis (Johnson et al., 1999).

Matrix-degrading effects of metalloproteinases are dependent upon de novo production, proteolytic activation, and endogenous tissue inhibitor (TIMP) concentrations. Excision of latent collagenases by plasin, permitting a second (autolytic) cleavage of the Cys–Zn2+ bond that stabilizes the propeptide, exposes the catalytic domain of the enzyme (Birkedal-Hansen, 1995). An accessory effect of
TNF-α on follicular MMP-1 and -2 biosyntheses is exerted at transcription (Johnson et al., 1999; Gottsch et al., 2000). Steroidogenic (granulosal–thecal) cells and fibroblasts are sources of MMPs. A co-ordinate increase in production of TIMPs by the granulosal cells of periovulatory follicles serves to limit the extent of tissue destruction, assuring that a viable corpus luteum can be formed (Smith et al., 1999).

**Cellular death**

As the time of ovulation approaches in ewes, there is an increase in apoptosis (plasma membrane phosphatidylserine translocation and internucleosomal DNA fragmentation) among cells within the follicle-associated ovarian surface epithelium (that is, after the gonadotrophin-induced release of uPA) and adjacent tunica albuginea and apical follicular wall. The initial apoptotic wave is succeeded by necrosis (indiscriminate DNA degradation and cellular lysis), extravasation of blood cells, and vascular collapse. At the ischaemic site of impending rupture, follicles are essentially devoid of ovarian surface and granulosal epithelia (Murdoch et al., 1999c). The cytotoxic response within the formative ovulation papilla is mediated by TNF-α (Murdoch et al., 1997, 1999b). Apical ovarian cells are safeguarded from destruction by the lipophilic ovulation inhibitor, indomethacin, which abrogates (via a prostaglandin-independent biophysical effect on the plasma membrane) TNF-α signal transmission (Murdoch and Lund, 1999).

The surface of ovulatory sheep ovaries is not completely restored until after luteal involution; in some instances, small nests of epithelial cells become incorporated into the cortical interstitium (Murdoch, 1994). It has been proposed that ovarian inclusion bodies of surface epithelium are normally eliminated via the Fas apoptotic system (Ghahremani et al., 1999).

**Common (surface) epithelial ovarian cancer**

Although the surface epithelium represents only a diminutive fraction of the diverse cell types that comprise the ovary, it accounts for over 90% of all cancers attributed to this complex organ. Recognition of the principal role of the ovarian surface epithelium in malignancy has been credited to Sir Spencer Wells in 1872 (Hamilton, 1992).

**Epidemiology**

Ovarian cancer is the fifth most frequent cancer in women (after cancers of the breast, colorectum, lung and endometrium). Ovarian cancer carries a 1-in-70 lifetime risk. Diagnoses of epithelial ovarian cancer increase with age (average age at initial presentation is 61). Most cases are sporadic; 5–10% are familial. Risk among first degree relatives (mother, sister, daughter) can be as great as 50%. Incidences are highest in the industrialized cultures of Europe and North America. Circumstances that avert ovulation (use of oral contraceptives, multiparity, lactation) protect (by approximately 40%) against the development of ovarian neoplasia. Ovarian cancer ranks fourth in cancer-related deaths. It is the most common cause of fatality from a gynaecologic malignancy. Less than 25% of patients with advanced disease survive beyond 5 years (Runnebaum and Stickeler, 2001).

**Disease progression**

There are four basic stages of advancement in ovarian cancer (International Federation of Gynecology and Obstetrics). Stage I is defined by the formation of epithelial inclusion cysts that invade the ovarian cortex. Inclusion bodies are apparently formed when surface cells become entrapped within the ovarian wound created at ovulatory follicular rupture or during luteal resorption. Prognosis is good if the cyst has not ruptured and growth is limited internally to one (Ia) or both (Ib) ovaries. Malignant cells are extruded into the peritoneal cavity when an inclusion cyst ruptures (Ic). Peritoneal spread of cancer cells is the hallmark of stage II disease; this stage is subclassified depending upon the degree of pelvic extension (a: oviducts–uterus; b: other pelvic tissues) and generation of ascites fluid (c). Stage III is epitomized by the development of tumours involving one or both ovaries with peritoneal implants outside the pelvis (a: microscopic seeding; b and c: nodules ≤ or ≥ 2 cm in diameter, respectively) or positive retroperitoneal or inguinal nodes (c). Superficial liver metastasis and malignant extension to the small bowel or omentum are typical of invasive stage III. Stage IV disease is defined by ovarian growth with distant disseminated metastases to encompass pleural effusion and parenchymal liver (Hamilton, 1992).

Ovarian surface epithelial cells generally undergo metaplasia into a Mullerian duct derivative with morphological attributes akin to tubal, endometrial or endocervical epithelia: papillary serous, endometrioid or mucinous tumours, respectively. Clear-cell tumours, the most lethal subtype, are distinguished by epithelial nests in a fibromatous mesh. Unclassified epithelial growths exhibit a range of histological features. Borderline epithelial ovarian tumours, usually of the serous or mucinous types, have a low potential for growth or metastasis and present at an earlier stage than carcinomas (Feeley and Wells, 2001).

Early-stage ovarian cancer does not manifest conspicuous symptoms. Increased abdominal girth and pelvic pressure are indicative of the accumulation of ascites fluid and widespread metastases. Facial hair, thinning of the scalp, decreased breast size, and increased sex drive are sometimes evident, and these symptoms have been ascribed to androgen production by tumours (Tavassoli, 1994).

**Aetiology**

The sequence of events that leads to ovarian cancer is multifactorial and not adequately understood (Hamilton, 1992). It appears that the first step in tumorigenesis involves genomic disturbances to the ovarian surface epithelium that arise from ovulation (Fig. 3). Common epithelial ovarian
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**Fig. 3.** Prospective role of ovulation in the chronology of ovarian carcinogenesis.

Ovarian cancer is, in most cases, a unifocal disease ultimately arising by clonal expansion from a single transformed cell. Several aberrant steps are required to yield a malignant phenotype with a distinct growth advantage. Heredity is a determinant, especially in aggressive early-onset disease. Metastatic spread is protease-dependent. Ovarian cancer is generally considered to have some level of hormonal involvement. Local biochemical modulators can also affect behaviour of ovarian cancer cells. Some studies indicate that exposure to exogenous chemicals (for example, talc) and viruses (for example, mumps, which can cause premature ovarian failure) may increase susceptibility to ovarian cancer.

**Ovulatory factor.** The ‘incessant ovulation hypothesis’ of ovarian cancer was proposed by Fathalla (1971). The fact that anovulation prevents ovarian carcinoma lends incidental support to this hypothesis. Repeated ovulations, without long dormant periods, were suggested to cause malignant transformation of epithelium. In addition, ovulation, and therefore ovarian cancer, was more common in women than it was in most other species because females of other species are either pregnant or lactating for most of their reproductive lives. Accordingly, peritoneal carcinomatas occur in intensive egg-laying domestic hens (Fredrickson, 1987). There is some anecdotal evidence that borderline tumours can be provoked in women treated with fertility drugs (that is, menopausal or chorionic gonadotrophins and clomiphene citrate) used for superovulation in assisted reproduction programmes (Shoham, 1994).

Inflammatory mediators and reactive oxidants are generated during the ovulatory process (Ness and Cottreau, 1999). Persistence around the ovulatory wound of ovarian surface epithelial cells with DNA strand breaks and oxidative base (8-oxoguanine) damage (Murdoch et al., 2001) could be a determinant of carcinogenic onset. A genetically altered progenitor cell, with unrepaired DNA, but not committed to death, could give rise to a transformed phenotype that is propagated upon healing of the ovulatory wound. Oxoguanine is arguably the most important mutagenic lesion in DNA, in which a mispairing with adenine during replication causes a GC → TA transversion often detected in tumour cells (Grollman and Moriya, 1993). Fortunately, sublethal damage to DNA that is inflicted upon bystander ovarian surface epithelial cells at ovulation is normally reconciled by repair enzymes, including poly(ADP-ribose) polymerase and the base excision polymerase β, induced on a localized basis by progesterone of luteal derivation (Murdoch, 1999b, 2001). Progesterone also activates p53 expression and inhibits basal and oestrogen-stimulated proliferative responses in sheep ovarian surface epithelial cells (cell cycle arrest), thus affording the time required for DNA repair (Murdoch and Van Kirk, 2002).

Most human ovarian cancer cells exhibit aneuploidy (Berek et al., 1993). Induced chromosomal anomalies have been detected in rat and mouse ovarian surface epithelial cells subjected to repetitive subculturing, adding indirect support to the contention that mitotic reactions precipitated by superfluous ovulation contribute to the pathogenesis of common ovarian cancer (Godwin et al., 1992; Roby et al., 2000). Anomalous ovarian cells sloughed during the ovulatory process may account for cases of disseminate disease in which the ovaries remain relatively uninvolved.

A simplified ‘cumulative’ ovulation model for ovarian cancer is not absolute. Protection is conferred by tubal ligation or hysterectomy in spite of uninterrupted ovulation; protection provided by a single gestation with breast feeding is far superior to the predicted benefit of those missed ovulations that would have occurred without pregnancy, and the advantage of short-term oral contraceptive use persists well after discontinuance (Scott, 1984). Moreover, overall disease occurrence has remained relatively constant over recent decades, despite the widespread application of ovulation-stimulating drugs (Glud et al., 1998).

**Genetic predisposition.** Three distinct hereditary conditions are associated with familial ovarian cancer: (1) dominant site-specific disease; (2) breast–ovarian cancer
syndrome, with the clustering of breast and ovarian cancer cases in extended pedigrees; and (3) the Lynch type II cancer family syndrome, in which ovarian cancer is inherited together with non-polyposis colorectal and endometrial cancers (Auersperg et al., 2001). Congenital ovarian cancer occurs at an earlier age (35–40 years) than sporadic malignancy. Inheritance of deleted or malfunctioning tumour suppressor genes (for example, those that overexpress competitive mutant forms of the growth-inhibitory BRCA1/2, p53, DOC-2 or ARHI genes) is a possible basis for developing ovarian neoplasia as a result of ovulation (Aunoble et al., 2000). Because site-specific familial ovarian cancer is acquired on an autosomal chromosome, (unaffected) males can transmit predisposing genes to their daughters (Amos and Struwing, 1993).

Proteolytic enzymes. Members of the PA–plasmin cascade are of particular importance in the pathobiology of common epithelial ovarian cancer. Urokinase is the primary PA secreted by epithelial ovarian cancer cells. Phenotypes of ovarian tumours with high malignant and recurrent potentials accumulate uPA; it is liberated (with MMPs) from cells in membrane vesicles. The catabolic end-product of uPA action, plasmin, activates latent collagenases, which digest basement membranes and interstitial connective tissue matrices, providing an avenue for tumour cell invasiveness (Stack et al., 1998). Urokinase also facilitates tumour angiogenesis and growth (Rabbani, 1998). Immunoneutralization of uPA inhibits ovarian cancer cell invasion in vitro (Kobayashi et al., 1992) and the spread of human ovarian cancer in nude mice is reduced by antisense inhibition of uPA (Wilhelm et al., 1995).

Endocrine factors. Development of ovarian cancers has been related to excessive gonadotrophin production attributable to the onset of the menopause or premature ovarian failure. Receptors for gonadotrophic hormones have been detected in some cell lines and linked (via expression of growth factors) to increased proliferative and decreased apoptotic rates (Konishi et al., 1999). Some ovarian tumours produce or can interconvert sex steroid hormones. Increased circulatory concentrations of progestogens, androgens or oestrogens have been correlated with tumour volume. It has been argued that steroid hormones emanate from sources outside the tumour, namely stromal ovarian and adrenal tissues. More than half of malignant ovarian tumours contain receptors for a steroid hormone (Rao and Slotman, 1991). It is evident that androgens and oestrogens do stimulate (with the probable involvement of growth factors) growth-promoting genes in subsets of ovarian cancer cells. Postmenopausal oestrogen replacement therapy increases the risk of ovarian cancer mortality (Rodriguez et al., 2001), whereas progesterone appears to render protection (Risch, 1998). Secretion of uPA (shedding of exocytotic vesicles) and the invasiveness of SKOV-3 ovarian cancer cells were inhibited by progesterone (McDonnel and Murdoch, 2001).

Paracrine–autocrine factors. Growth factors and cytokines have been implicated in the progression of epithelial ovarian carcinomatosis. Epidermal growth factor, transforming growth factor α (TGF-α), platelet-derived growth factor, basic fibroblast growth factor, hepatocyte growth factor, keratinocyte growth factor–kit ligand, insulin-like growth factor I, macrophage colony-stimulating factor, interleukin 1 (IL-1) and IL-6, TNF-α, steroidogenesis-inducing protein, and lysosphathidic acid (LPA) promote loss of contact inhibition, cellular proliferation or protease secretion in vitro (TGF-β, interferons α and γ, high-dose TNF-α, and GnRH were negative effectors) (Berchuck et al., 1993; Nash et al., 1999). Activation of dominant transforming mitogenic oncogenes (c-myc, k-ras, HER-2/neu) by growth factors and cytokines appears to be causally related to ovarian tumour formation (Aunoble et al., 2000; Auersperg et al., 2001). Vascular endothelial growth–permeability factor (VEGF) is secreted by ovarian cancer cells and has been related to ascites formation and metastasis (Auersperg et al., 2001).

Diagnosis

The main reason that ovarian cancer is so lethal is that it usually remains clinically silent until it becomes well established (that is, reaches stage III or IV). Detection of early-stage and recurrent disease continues to be a major problem. Diagnostic approaches have generally hinged on the principle that specific cell-surface antigens are shed from the tumour. The most thoroughly studied ovarian cancer antigen (CA) is the glycoprotein CA-125. Approximately 80% of patients with overt symptoms demonstrate an increase in immunoreactive serum CA-125. Individuals with mucinous tumours usually test negative. Problems with measuring CA-125 are the lack of specificity and insensitivity of tests. False positive results are common in pregnancy and occur in non-malignant premenopausal conditions of pelvic inflammatory disease, uterine fibroids, endometriosis, peritonitis, pancreatitis, renal failure and alcoholic hepatitis (Bast et al., 1998). Other ostensible indicators of ovarian cancer include mucins, soluble IL-2 receptor, VEGF, inhibin, galactosyltransferase, CA-72-4 and LPA (Menon and Jacobs, 2000).

Transvaginal sonography has been beneficial in identifying asymptomatic women with stage I ovarian cancer (Oram and Jeyarajah, 1994). Second-look laparotomy is sometimes used to assess disease status after completion of primary therapy (typically, cytoreductive surgery used in combination with platinum-containing drugs, alkylating agents or taxol) (Ozols, 1999), yet nearly 50% of patients deemed negative relapse and die of diffuse disease (Podratz and Kinney, 1993).

The reality is that there is no combination of diagnostic tools available that have proven effective in reducing the mortality from ovarian cancer. Furthermore, it is not practical to screen the general population for a malignancy of relatively low incidence that necessitates surgical
intervention. Applications of tests for early detection will probably be restricted principally to individuals designated as at high risk.

Conclusion

Recent research in sheep indicates that the ovarian surface epithelium plays an active role in the mechanism of ovolitary follicular rupture, and that damage to DNA imposed upon surface epithelial cells that survive the process of ovulation (and proliferate to repair the rupture wound), could be a predisposing (that is, potentially mutagenic) factor in ovarian cancer. Nevertheless, cause–effect associations between ovolatory disturbances to DNA and ovarian epithelial carcinogenesis have not been established. Future studies, to include additional species, are needed to resolve the pathophysiological relevance of the ovarian surface epithelium.

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