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Pathway modulations and epigenetic alterations in ovarian tumorbiogenesis

Sabita N. Saldanha^{1,2} and Trygve O. Tollefsbol^{*,3,4,5,6,7}

¹Department of Biology, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

²Department of Biological Sciences, Alabama State University, Montgomery, AL 36104, USA

³Department of Biology, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

⁴Clinical Nutrition Research Center, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

⁵Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

⁶Comprehensive Center for Healthy Aging, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

⁷Nutrition Obesity Research Center, University of Alabama at Birmingham, Birmingham, AL 35294-1170, USA

Abstract

Cellular pathways are numerous and are highly integrated in function in the control of cellular systems. They collectively regulate cell division, proliferation, survival and apoptosis of cells and mutagenesis of key genes that control these pathways can initiate neoplastic transformations. Understanding these pathways is crucial to future therapeutic and preventive strategies of the disease. Ovarian cancers are of three major types; epithelial, germ-cell and stromal. However, ovarian cancers of epithelial origin, arising from the mesothelium, are the predominant form. Of the subtypes of ovarian cancer, the high-grade serous tumors are fatal, with low survival rate due to late detection and poor response to treatments. Close examination of preserved ovarian tissues and *in vitro* studies have provided insights into the mechanistic changes occurring in cells mediated by a few key genes. This review will focus on pathways and key genes of the pathways that are mutated or have aberrant functions in the pathology of ovarian cancer. Non-genetic mechanisms that are gaining prominence in the pathology of ovarian cancer, miRNAs and epigenetics, will also be discussed in the review.

Keywords

Ovarian cancer; Pathways; Epigenetics; miRNA; Cell cycle; Apoptosis; Proliferation

*Author to whom correspondence should be addressed; Dr. Trygve Tollefsbol, Professor of Biology, 175 Campbell Hall, 1300 University Boulevard, University of Alabama at Birmingham, Birmingham, AL 35294-1170, (Tel); 205-934-4573, (Fax); 205-975-6097, trygve@uab.edu.

Conflict of Interest

The authors declare no conflict of interest.

Introduction

Ovarian neoplasms are challenging to detect and their genesis is often considered as *de novo* or sporadic (Scully, 1995; Liu and Ganesan, 2002; Zikan et al., 2007; Weberpals et al., 2008; Weberpals et al., 2011; Sarojini et al., 2012; Wysham et al., 2012). When detected the cancer is often advanced and is at stage III/IV category (Kurman and Shih Ie, 2010). The absence of or poor detection methods of precancerous lesions of the tissue account for the late detection of ovarian cancer (Fleischer et al., 2012; Sarojini et al., 2012). Thus, ovarian cancer is considered to be a very lethal disease of gynecological origin.

In contrast to previous reports, ovarian cancer is not considered a single disease of epithelial origin, but instead covers a group of tumors that are morphologically and genetically distinct (Kurman and Shih Ie, 2010; Kurman and Shih Ie, 2011). The hypothesis however is still highly debated. Some of the reasons include late detection, inability to detect precancerous lesions and therefore insufficient evidence of neoplastic origination. This obscurity in the pathogenesis of the disease requires the understanding of the molecular aspects that influence the cellular pathways of the ovarian tissue. Based on morphology, genetics, and site of origination, ovarian cancers of epithelial-cell origin have been categorized into two groups. The type I group are those that are strictly confined to the ovary and are low- grade serous, endometrial, mucinous, and clear-cell type (Figure 1) (Kurman and Shih Ie, 2010; Kurman and Shih Ie, 2011; Le Page, 2010). These tumors are genetically more stable, have few to rare p53 mutations, are easily diagnosed and have a good prognosis. However, only 25% of the ovarian cancers detected are of this type. The Type 2 group contains tumors that are aggressive and comprise high-grade serous carcinomas, undifferentiated carcinomas and carcinosarcomas (Figure 1) (Le Page, 2010). These tumors constitute 75% of the ovarian cancers with a 90% death rate and the site of origination stems from tissues other than the ovary. These tumors exhibit genetic instabilities with a higher percentage of p53 mutations (Kurman and Shih Ie, 2011).

Since the last 30 years or so, many preclinical and clinical trials have been conducted to determine the therapeutic efficacies of drugs against ovarian tumors. However, the success rates against ovarian cancers have been few. A majority of tumors that are removed through cytoreductive surgery resurface and become aggressive and have been proposed to be mediated in part through the treatment itself (Steffensen et al., 2011a; Modugno and Edwards, 2012; Stathopoulos et al., 2012). Elucidating the underlying factors that govern the genesis, progression and metastasis of this disease would provide valuable information for the development of diagnostic, prognostic and therapeutic approaches of the disease. Further understanding the genes and pathways that become dysregulated either due to loss of heterozygosity, loss of function, amplification or mutation would facilitate progress in managing ovarian cancer. This review will focus on the pathways deregulated and instrumental in the pathogenesis of ovarian tumors and key genes that are involved in these pathways. Genetic and epigenetic factors that contribute to these changes will also be analyzed.

Genes involved in the biogenesis of ovarian cancers

p53

Mutations in cell-cycle regulatory genes, primarily tumor suppressor genes, favor an uninhibited growth of cells and serve as precursors of immortality. Combined mutations in these genes and oncogenes encourage a neoplastic phenotype. How these tight regulations become deregulated through mutations and how these mutations affect important regulatory pathways is important to a diagnostic and prognostic approach for all cancers. Unlike cancers of other origins, a majority of ovarian cancers are of epithelial-cell origin,

commonly designated as epithelial ovarian carcinomas (EOCs). Nonetheless this single layer epithelia morphs to give rise to histologically different types (Kurman and Shih Ie, 2011). The transition is thought to occur through the cell cycle and genes that control metabolic and molecular pathways within the ovarian cell or via changes of the epithelia of surrounding reproductive tissue that find their way into the ovary through the inflammation and repair process of ovulation (Figures 1 and 2). Of the many regulators, tumor suppressor proteins play a pivotal role in the cell cycle process and these proteins are highly deregulated in ovarian cancers (Table 1).

Tumor suppressor genes, proto-oncogenes and cell-cycle proteins cohesively regulate cell growth and division. The primary cyclins and kinase inhibitors that have a major role in ovarian cancer are cyclin D1, p¹⁶INK4a, p27 and p21 (Table 1, Figure 2), (Vikhanskaya et al., 1996; Kusume et al., 1999; Shigemasa et al., 1999; Bali et al., 2004; Barbieri et al., 2004; Hashimoto et al., 2011). The regulation and function of cyclin D1, p¹⁶INK4a, p27 and p21 have been shown to be controlled in part by the tumor suppressor gene *p53*, which is predominantly mutated in high grade ovarian cancers (Shigemasa et al., 1999; Bali et al., 2004). The changes in *p53* as seen in ovarian cancers could be both at the gene and protein level. Point mutations, missense mutations and truncations have been observed, and overexpression of the *p53* protein has been detected in many of the immunohistochemical studies that have been performed (Table 1) (Marks et al., 1991; Liu et al., 1994; Havrilesky et al., 2003). The accumulation of non-functional *p53* has been shown to affect the expression and interaction of pro-apoptotic genes such as BCL2-associated X protein (*BAX*) and B-cell lymphoma 2 (*BCL-2*) (Tai et al., 1998; Schuyer et al., 2001; Ziolkowska-Seta et al., 2009). The aberrations in *p53* result in the accumulation of the altered protein within the cell that has a negative effect on *BAX*, a transcriptional target of *p53* (Ozer et al., 2012). It seems likely that *p53* alterations in high grade tumors reduce *BAX* expression allowing the progression of solid tumors. However, immunohistological studies have not provided a definitive conclusion of a positive correlation with *p53* expression and tumor prognosis and survival (Reles et al., 2001; Rose et al., 2003; Leffers et al., 2008). Contradictions in observations are possible due to the type of ovarian tissue analyzed, the method used and statistical programs employed to determine the correlation (Table 1).

The BCL family of apoptotic proteins along with *p53* can serve as tools for histotyping (Skirnisdottir et al., 2002). The expression of *p53*-*BCL-2* and *BCL-2*-*BAX* have been shown to have a strong association with tumor grade and histopathological subtyping, factors that could be vital for identifying the specific epithelial ovarian carcinoma for adjuvant or combined therapies (Skirnisdottir et al., 2002). What has been observed is that ovarian tumors are initially very responsive to treatment but later become chemoresistant. Possibly the treatment itself may cause a few cells within the tumor mass to harbor mutations in *p53* that, in addition to epigenetic silencing of promoter regions of apoptotic favorable genes such as *p16* or *Rb*, may account for the relapse and progression of the tumor. Ovarian cancers are categorized as low or high-grade tumors of various histological subtypes (Le Page, 2010). These range from well-differentiated, to moderately differentiated to non-differentiated tumors, respectively, and morphologically are identified as benign, borderline or malignant ovarian tumors, (Figure 2) (Le Page, 2010). Studies have shown that in low-grade ovarian tumors, *p53* mutations are absent, but transitioning into the aggressive type, a significant increase in mutations of the gene are observed, with a majority of them being of the serous epithelial type (Marks et al., 1991; Kohler et al., 1993). The factors that contribute to this observed increase in *p53* mutations are still very unclear. *p53* is a quintessential player in the cell cycle and its role in maintaining healthy cell populations is very apparent. Since ovarian cancers are of multi-histological phenotype the alterations of *p53* in tumors of this type may be varied. An altered state of *p53* is observed both at the gene and at the protein level in type 2 ovarian cancers (Yemelyanova et al., 2011; Jones et

al., 2012; Kuhn et al., 2012). Most mutations observed in *p53* gene are point mutations that cause the accumulation of the non-functional protein in the cell due to increased stability. In some instances, the binding domains of *p53* could be altered such that *p53* cannot bind to the DNA binding elements of its target genes hindering subsequent pathways that encourage apoptosis. In other scenarios, the functional role of the non-functional *p53* is based on *p16^{INK4a}*, a cyclin kinase inhibitor within the cell (Leong et al., 2009).

p21 and p27

Cyclin dependent kinase (CDK) inhibitors are major co-regulatory proteins in the cell cycle along with the *p16*, *p53* and retinoblastoma (*Rb*) pathways (Sherr, 1996; Bartkova et al., 2003; Jayasurya et al., 2004). *p21* is a direct transcriptional target of *p53* (Gallagher et al., 2012). In the presence of wild-type (WT) *p53*, *p21* induction ensues followed by the inhibition of cyclin E/CDK2 preventing the G1-S transition, encouraging the apoptotic phenotype of cells (Hindley and Philpott, 2012). CDK inhibitors *p21* and *p27* control various phases of the cell cycle based on the cyclin with which they associate. *p21* association with cyclin D-CDK4/6 inhibits G1-S transition; with cyclin E-CDK2 the late G1-S transition; with cyclin A-CDK2 preventing the S-G2 transition; and with cyclinA-cdc2 the G2-M transition (Cariou et al., 2000; Sandhu et al., 2000). *p27* exhibits the same level of control with cyclins D, E and A from the G1 to the G2 phase (Cariou et al., 2000). Although the roles of *p21* and *p27* have been discussed in many cancers, they appear to have secondary roles in the etiology of ovarian cancer rather than in the genesis (Milde-Langosch et al., 2003; Plisiecka-Halasa et al., 2003; Oudit et al., 2004; Lee et al., 2007). The role of *p27* in ovarian cancer is somewhat contradictory. On examination of the protein level and localization of *p27* in 150 advanced epithelium ovarian cancers (EOCs), lower nuclear *p27* expression was associated with an improved prognosis (Psyrris et al., 2005). However, another study found that negative *p27* expression was associated with poor prognosis (Shigemasa et al., 2001). Possibly, different grading scales, techniques and samples assessed might account for these inconsistencies. Loss of function or accumulation of these proteins in ovarian cancers has not been reported. In some cases, the absence of or low expression of *p21* with *p53* expression appears to place patients at a higher risk for disease recurrence (Anttila et al., 1999b). Studies have also shown that high *p21* expression correlates with early stage ovarian tumors and that only high *p27* expression was necessary for disease free survival (Schmider-Ross et al., 2006). Overall, there appears to be no correlation between *p21* and *p27* expression and in terms of ovarian cancers, as yet these proteins are not especially useful tools for the prognosis of the disease (Baekelandt et al., 1999).

Pathways implicated in the biogenesis of ovarian cancer

***p16^{INK4a}* and *Rb* pathway**

In normal cells, *p16^{INK4a}* regulates cell proliferation by promoting genes of the apoptotic pathways (Leong et al., 2009). However, in ovarian cancer cells, it has been observed that *p16^{INK4a}* is mutated or its promoter region is hypermethylated switching off its expression. Transfection studies using ovarian cancer cell lines have shown that in the absence of WT *p53*, *p16^{INK4a}* is upregulated to rescue the apoptotic pathway (Modesitt et al., 2001; Ramirez et al., 2001). In cells that contain double defects of both *p53* and *p16^{INK4a}*, cell proliferation is rampant and the tumors are more aggressive (Modesitt et al., 2001; Ramirez et al., 2001). Far advanced tumors have been shown to have low expression of *p16^{INK4a}* but higher expressions of retinoblastoma (*Rb*) (Todd et al., 2000). *p16^{INK4a}* is considered to be a direct target of *Rb* expression (Todd et al., 2000). However, some studies have contradicted this finding. It appears that *p16^{INK4a}* and *Rb* mutually regulate the expression of one another. While trying to understand the mechanistic pathways involved in ovarian cancers, the *Rb-p16^{INK4a}* pathway in conjunction with *p53* has been implicated in the genesis of a

majority of cancers and has a pivotal role in the ovarian epithelial specific type (Konecny et al., 2011). The p16^{INK4a} inhibitor of kinase prevents the association of the cyclin D1-CDK4/6 complex necessary for the transition of cells from the G1-S phase, in conjunction with hyperphosphorylated Rb. Studies performed to determine the expression patterns of these key genes have shown that loss of p16^{INK4a} function through promoter methylation is more frequent than mutations and deletions, in comparison to Rb, where hemizygous deletions are more pronounced with few mutations (Todd et al., 2000; Hashiguchi et al., 2001). The level of cyclin D1 necessary for cyclin-CDK complex formation is overexpressed and has been found to be associated with aggressive phenotype and poor prognosis in about 19% of ovarian cancers. (Todd et al., 2000; Konecny et al., 2011). As discussed, although alterations/loss of function appear to be the highlighted changes associated in the Rb-p16^{INK4a} pathway, most ovarian cancers appear to co-express Rb and p16 proteins, with overexpression of Rb found in advanced ovarian tumors (Todd et al., 2000). Post-translational modifications that affect protein function are also an important factor to consider in the analysis of tumor biogenesis. The Rb protein release from the Rb-E2F complex occurs by the hyperphosphorylation of its serine/threonine residues. A further examination of the phosphorylation levels of Rb protein therefore needs to be examined. Post-translational modifications have been found to affect protein function based on the residues phosphorylated as seen in p53 (Smeenk et al., 2011). In addition, epigenetic alterations as seen in the p16^{INK4a} gene, may also regulate Rb and p53 function through CCCTC binding factor (CTCF) (De La Rosa-Velazquez et al., 2007; Soto-Reyes and Recillas-Targa, 2010).

KRAS/MAPK/ERK pathway

Kirsten rat sarcoma oncogene (KRAS) activation triggers a sequence of events through the RAF/MEK and mitogen activated protein kinases (MAPK) pathways, and in conjunction with mammalian target of rapamycin (mTOR), a target of the protein AK strain thymoma (AKT) pathway, control cell proliferation (Table 2) (Janku et al., 2012). Point mutations in *KRAS* provide an advantage for the survival and progression of tumors (Mane et al., 1990; Edkins et al., 2006; Harris and McCormick, 2010; Li et al., 2011; Oliveira-Cunha et al., 2012). *KRAS* mutations have been implicated in the genesis of low-grade ovarian tumors, inducing an overactive proliferative phenotype (Vereczkey et al., 2011; Stewart et al., 2012). In addition to breast cancer associated protein 1 (BRCA1) and 2 (BRCA2) that have familial roles in sporadic germline-based breast and ovarian cancers, *KRAS* is now considered the third player (Kundu et al., 2012; Pilarski et al., 2012). *KRAS* expression levels differ based on the histopathological type of ovarian tissue and the expression levels may help determine the various type of ovarian epithelial cancers (Auner et al., 2009; Steffensen et al., 2011b; Nowak-Markwitz and Spaczynski, 2012). These signatures have a specific pattern in tandem with the expression of RAF/MAPK components, phosphatase and tensin homolog (PTEN) levels and AKT (Table 2) and may help differentiate normal from borderline to early-stage cancers. Determining the signatorial patterns is relatively difficult due to heterogeneity of the tumors.

A mutant form of *KRAS*, called *KRAS*-variant, carries a mutation in its sequence that has the binding site of a micro RNA (miRNA) termed lethal-7 (Let-7), limiting the association of Let-7 with *KRAS* (Ratner et al., 2010). Consequently the levels of *KRAS* rises followed by the induction of the nuclear transcription factor (NF- κ B) that promotes the induction of anti-apoptotic genes. It is quite probable that in late stage ovarian cancers, the earlier mutations in *KRAS* can stimulate and induce the over-activation of NF- κ B in cancer stem cells (CSCs) that survive chemotherapy. However, immunohistochemical-based correlation assessments between the *KRAS* expression and alterations in NF- κ B components and PTEN have not yet been able to confirm a direct association (Laudanski et al., 2011). *KRAS*-

variants have also been shown to target NF- κ B expression independent of the phosphatidylinositide-3 kinase PI3K-AKT pathway (Keane and Ratner, 2010; Ratner et al., 2010; Kinross et al., 2011; Mizumoto et al., 2011; Pharoah et al., 2011; Weidhaas and Slack, 2011; Pilarski et al., 2012; Ratner et al., 2012). The disparities in KRAS expression and association patterns with downstream targets may stem from the type of tissues analyzed. In a study conducted on 489 high grade ovarian adenocarcinomas, Spellman et al. (2011) showed that in 45% cases that contained altered PI3K / RAS signaling, less than 1% was due to mutations and 11% were amplifications. Also, the downstream target, serine/threonine-protein kinase B-Raf (BRAF) was mutated (0.5%). In addition to PI3K/RAS signaling, KRAS induces mitogen activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) through BRAF. Stimulation of KRAS via GTPase activity activates BRAF. The stimulation can be mediated by cytokines, growth factors or proto-oncogenes. The downstream target of BRAF, MEK stimulates ERK when activated. ERK targets transcription factors that are involved in cell proliferation such as Myc (Smolle et al., 2013). In ovarian carcinomas, activation of the ERK pathway stems from hormonal activation of G-protein coupled receptors (Smolle et al., 2013). MAPKs, part of the MAPK/ERK pathway, are involved in the transduction of signals through hormones. MAPKs are of two types, tyrosine protein kinase and G-protein coupled receptor. In ovarian cancers, hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) may participate in signal transduction via MAPKs, and are thought to be responsible for ovarian cancer cell growth in carcinomas that express the receptors (Hilliard et al., 2013).

PI3K/PTEN/AKT pathway

Phosphatidylinositide-3 kinase (PI3K) and phosphatase and tensin homolog (PTEN) proteins influence multiple pathways within the cell that have many effects on the cellular phenotype through protein AK strain thymoma (AKT), also known as protein kinase B (PKB). These genes are crucially required to transcend the input from external stimuli (growth factors) and convey them to AKT. Phosphorylation of key amino acid residues in these proteins triggers the downstream activation processes. PTEN is a tumor suppressor gene and either mutations in the gene or loss of function of the protein is observed in many cancers, including ovarian cancers (Table 2) (Saga et al., 2002; Meng et al., 2006; Yan et al., 2006; Paige and Brown, 2008). Loss of function in this gene is mediated through epigenetic silencing and its role in ovarian cancer needs to be further assessed (Kurose et al., 2001). *AKT* is an oncogene, and its function and activation depends on the function of PTEN (Meng et al., 2006; Blanco-Aparicio et al., 2007). However, when PTEN becomes inactivated, or loss of function is observed, AKT is overexpressed which serves as an impetus for tumor formation by changes in sub-pathways such as NF- κ B, mammalian target of rapamycin (mTOR), and p53, that in turn regulates proliferation, cell division, and cell apoptosis (Tables 1 and 2) (Blanco-Aparicio et al., 2007; Hussain et al., 2012). *PTEN* and *AKT* are genes of a pathway controlled by PI3K phosphorylation of its internal amino acid residues, the signals of which depend on either growth receptors or tyrosine kinase receptors (Xu et al., 2004; Lee et al., 2005; Meng et al., 2006).

PI3K is a heterodimeric protein comprised of a regulatory subunit, p85, and a catalytic subunit, p110 (Berenjeno and Vanhaesebroeck, 2009; He et al., 2010; Folgiero et al., 2012; Hofmann and Jucker, 2012; Li et al., 2012; Takayama et al., 2012). The p110 catalytic subunit exists as isoforms α , β , γ and δ (Li et al., 2012). This enzyme phosphorylates the hydroxyl group of inositol of phosphatidylinositol triggering endocellular pathways from external stimuli. For the activation of PI3K, autophosphorylation of tyrosine kinase receptors (RTKs) is essential (Smith et al., 2002). The p85 subunit of PI3K tethers to the phosphorylated residues of RTKs. Once the docking of its regulatory subunit occurs, p110 begins its phosphorylation of phosphatidylinositol-4,5 biphosphate (PIP)₂ to

phosphatidylinositol-3,4,5- triphosphate (PIP)₃. (PIP)₃ is essential for the activation of AKT (Carnero, 2010). However, AKT activation requires phosphorylation activities of (PIP)₃ and mTOR (Carnero, 2010). PTEN, an intermediate factor of the PI3K/PTEN/AKT pathway, plays an important role in ensuring that the activity of AKT is held in check by dephosphorylating (PIP)₃ (Stocker et al., 2002). While assessing the roles of PI3K/PTEN/AKT in ovarian carcinogenesis, amplifications of PI3K, p110 α subunit, and loss of PTEN function are found (Blanco-Aparicio et al., 2007). When events such as these occur, AKT levels cannot be controlled triggering pathways of survival, progression and invasion through sub-pathways controlled by AKT (Blanco-Aparicio et al., 2007). It has been observed that inhibition of p110 α subunit or AKT, can induce cell cycle regulatory proteins, p21 and p27, inhibit phosphorylation of Rb and reduce the levels of cyclins D1 and CDK4 that essentially serve the apoptotic pathway (Meng et al., 2006). Some of the resistance offered by ovarian tumors to treatment by certain drugs stem from the amplification of *PIK3Ca*, a gene that encodes PI3K p110 α subunit, and AKT expression with reduced PTEN levels (Janku et al., 2011; Yamamoto et al., 2011; Abe et al., 2013). In such instances, cell cycle regulatory functions are impaired, and pro-apoptotic proteins such as Bax translocation is inhibited (Lee et al., 2005). PI3K mutations in ovarian tumors are rare, but an increase in gene copy number has been observed. The amplifications are more pronounced in high grade ovarian tumors than low grade tumors along with AKT phosphorylation contributing to survival, and progression of the disease (Huang et al., 2011; Abe et al., 2013). There does not appear to be a collective association of the three proteins together in ovarian carcinogenesis and are thought to act independently (Carden et al., 2012). However, the alterations in the expression of these proteins have been shown to have a relationship between the resistance offered against therapies and the recurrence of the disease (Dent et al., 2009).

Mammalian target of rapamycin (mTOR) promotes cell growth and proliferation in association with the PI3K/AKT pathway (Dobbin and Landen, 2013). The mammalian target of rapamycin has the ability to phosphorylate AKT at the serine residue 473 through its mammalian target of rapamycin complex 2 (mTORC2) complex. The mammalian target of rapamycin complex 1 (mTORC1), raptor, and mTORC2, rictor, differ in composition by a few elements that make up the respective complexes, in addition to difference in resistant to rapamycin (Mabuchi et al., 2011). mTORC1 promotes cell growth and cell mass by the activation of molecules involved in protein synthesis (No et al., 2011). mTORC2 promotes cell survival and proliferation through AKT activation. Under normal physiological conditions in the ovary, the PI3K/AKT/mTOR pathway protects the primordial follicles from destruction. However, in the presence of environmental toxins, overstimulation of the pathway results in follicular proliferation, depletion of primordial follicles and an induction of a condition called premature ovarian failure (Borman et al., 2000; Sobinoff et al., 2011). Together, PI3K/AKT/mTOR contributes to cell survival, and proliferation. The PI3K/AKT/mTOR pathway is involved in type I and type II ovarian cancers. Single mutations of a member of the pathway coupled with a mutation with members of another pathway promote ovarian hyperplasia, and double mutations within the same pathway are necessary for ovarian tumorigenesis. Mutations in parallel pathways that are involved in cross-talk are found to be mutated in ovarian carcinomas. The integrated genomic analysis study of ovarian carcinomas showed that at least 45% of the cases contained mutations in the PI3K/RAS signaling pathway, where PTEN deletions (7%); mutations (<1%), PIK3CA amplifications (18%); mutations (<1%), AKT isoform amplifications AKT 1 and AKT 2 (3 and 6 % respectively), were observed in conjunction with KRAS amplification (11%) (Spellman et al., 2011). KRAS independently controls survival through BRAF but can also activate PIK3CA that induces AKT and cell cycle progression (Spellman et al., 2011). Similarly, in the PI3K/AKT/mTOR signaling, a study by Kinross et al. (2013) using a mouse model demonstrated that PTEN double deletions with PIK3CA activation was necessary for

ovarian serous adenocarcinomas and granulosa cell tumors (Dobbin and Landen, 2013). Therefore, a single event does not appear to influence ovarian tumorigenesis but multiple hits in the pathways that regulate growth, proliferation, and survival are required for tumorigenesis and progression. Thus, a one cure all for ovarian tumors cannot exist. Rather, ovarian tumor type-pathway specific form of treatment may be more appropriate.

Hedgehog pathway

Hedgehog is a signaling pathway that controls development and is expressed during embryonal development (Chen et al., 2007). Adult tissues have significantly reduced expression of the protein and alterations, either by mutations of mediators of the pathway or overexpression of the ligand receptor, appear to promote ovarian tumorigenesis (Chen et al., 2013a). Sonic hedgehog (SHh), the Indian hedgehog (IHh) and the desert hedgehog (DHh) have distinct biological roles and induce effects through 10-pass transmembrane patch (Ptch) (Chen et al., 2013a). The canonical stimulation of Hh pathway induces the 7-pass transmembrane smoothend (Smo)-triggered Gli activation of Hh targeted genes through Ptch inhibition (Chen et al., 2013a). The hedgehog signaling pathway is important to organ development at early embryonal stages and is selectively expressed during tissue maintenance and repair and in stem cells (Song et al., 2011; Coni et al., 2013). The pathway can be activated by ligand-dependent or independent mechanisms (Ehtesham et al., 2007; Christiansen et al., 2012). Overexpression of the ligand receptor or mutations of the members in the pathway can contribute to cancer progression. Activation through epidermal growth factor receptor (EGFR) constitute the non-canonical mode of Hh signaling (Mangelberger et al., 2012). The expression of Hh in adult ovarian tissue has not been observed. However, the signaling mechanism is likely to be activated within the stem cell population in the ovarian tissue that is necessary for the repair of the ovarian surface epithelium (OSE). Cancers arising from OSE have an epithelial phenotype. They are thought to arise through mutated Hh signaling and produce spheroid like structures with cancer stem cell-like properties (Ray et al., 2011). Suppressor of fused (Su(fu)), a tumor suppressor, is a repressor of the Hh pathway and loss of Su(fu) accounts for increased Hh signaling (Cheng and Yue, 2008). Reports suggest that Hh helps with clonal growth, and that the expression of members of the pathway, Gli1 and patched correlate with poor outcome. The three ligands of Hh signaling have distinct biological functions and yet, it appears that of the three ligands, SHh is the prominent ligand-overexpressed. It remains to be ascertained if the ligand-type overexpressed is ovarian-tumor-type specific or if the overexpression of any one ligand suffices to induce an ovarian tumor phenotype. Studies have shown that using SHh and IHh agonists, the number of spheroid formations increase (Ray et al., 2011). SHh expression has also been found to be expressed in ovarian dermoid and requires the induction of Gli (Sabol et al., 2012). DHh has been shown to correlate with poor prognosis (Chen et al., 2013a). Finally, the role of Hh pathway dysfunction in ovarian carcinogenesis is still not completely understood as its association with other signaling pathways in addition to its non-canonical pathway adds to the complexity.

The Wnt pathway is important to ovarian follicular development (Sarkar et al., 2010). The Wnt pathway is activated downstream of Hh pathway and Gli transcription factors, terminal activators of Hh, induce Wnt ligands. Also, glycogen synthase kinase-3B (GSK-3B) of Wnt pathway regulates molecules of Hh signaling (Sarkar et al., 2010). The Wnt/B-catenin, the canonical pathway of Wnt signaling influences oncogenic Hh signaling. Thus cross-talk activity between the two pathways is apparent. An analysis of 26 and 20 genes of the Hh and Wnt pathway, respectively, of matched fresh frozen and paraffin embedded ovarian endometrial carcinomas showed that the expression of tumor-specific genes associated with Hh and Wnt pathway were not consistent and those that showed statistical significance had varied genetic profiles (Steg et al., 2006). Overexpression of genes *SMO*, *GLI*, *GLI2*, *GLI3*,

and *Wnt7A*, *Frizzled homolog (FRZD1)*, *low-density lipoprotein receptor-related protein 6 (LRP6)*, and *Frizzled related protein (FRZB)* that was detected in both freshly frozen and FFPE tissue, were not statistically significant. Similar observations were seen with genes *DHH*, *IHH*, *SHH*, *PTCH*, *PTCH2*, *GLI*, *GLI3*, and *SMO* specific to the Hh pathway (Steg et al., 2006). For suitable anti-pathway therapies, further studies that determine specific change from inter-individual variations are warranted. From a treatment perspective, an ovarian tumor type-pathway specific form of treatment is therefore more appropriate.

Multiple Drug resistant (MDR) pathway

ATP-binding cassette (ABC) transporters are implicated in multidrug resistance (MDR) of many tumors. Ovarian cancers by far appear to build up resistance to many treatments and ABC upregulation is thought to play a major role in this process (Januchowski et al., 2013). A comparative study analyzing benign versus recurrent ovarian tumors showed that of the 9 ABC transporters, 4 (ABCC1, ABCC2, ABCC3, and ABCB3) of them are significantly elevated in recurrent ovarian tumors (Auner et al., 2010). Analysis of these 4 transporters in recurrent versus primary ovarian lesions transporters showed significant differences but were minor and insignificant with respect to benign tumors. Changes in ABC transporters appear to stem from treatment rather than *in situ* tumor development. Abnormal expression of the transcription factor Gli1, a downstream target of Hh signaling, has been shown to induce MDR resistance in a subset of ovarian cancers and that the promoter regions of ABCB1 and ABCG2 genes contain Gli1 binding specific consensus sequence (Sims-Mourtada et al., 2007; Chen et al., 2013b).

Notch Pathway

Activation of Notch signaling pathway is important to cell fate determination and organogenesis in embryogenesis (Reynaud-Deonauth et al., 2002; Petersen et al., 2006). Downstream targets of Notch signaling such as hairy and enhancer of split-1 (HES1) are expressed in many ovarian cancers indicative of the role of Notch (Schreck et al., 2010; Wang et al., 2010a). Notch pathway is regulated by ligands such as Jagged1, 2 and Delta-like 1, 3, 4 (Fleming et al., 1997; Lendahl, 1998; Gray et al., 1999; Yamaguchi et al., 2002). When Notch receptors are activated by ligand binding, the transmembrane portion of the receptor undergoes posttranslational modifications and a complex cleavage process (Pratt et al., 2011). The cleaved C-terminal domain then translocates to the nucleus and induces downstream targets such as HES1, a transcriptional factor (Schreck et al., 2010). Elements of the Notch pathway are expressed in EOCs (Hopfer et al., 2005). Notch pathway signaling appears to be fundamentally important to cell survival, motility and development of vasculature (Shin et al., 2008; Li et al., 2010). The chemoresistance observed to platinum-based therapy of ovarian cancers stems from the expansion of cancer stem cells that have Notch activated (Notch 3) (McAuliffe et al., 2012). A study analyzing pathway deregulations in ovarian tissue specimens showed that of the tumors analyzed, 22% had altered Notch signaling, mostly as amplifications in the ligand Jagged 1 and 2 and Notch 3 (Spellman et al., 2011). Overactivation of Notch ligands (Jagged 1 and 2) has been shown to be mediated through the stimulation of p73, a member of p53 (Sasaki et al., 2002).

Forkhead Box M1 pathway (FOXO1)

FOXO1 is a transcription factor that regulates genes that control the cell cycle and thus proliferation and tumor progression (Mencalha et al., 2012; Yang et al., 2013) and its role in angiogenesis has also been observed (Li et al., 2009). Serous ovarian cancers express high levels of the protein that correlates with tumor progression (Lok et al., 2011). In the study by Spellman et al. (2011), 85% of the cases studied showed alterations in FOXO1 pathway. Of the important elements of the FOXO1 pathway, baculoviral inhibitor of apoptosis repeat-

containing 5 (BIRC5/survivin) and cell cyclin B1 (CCNB1) were found to be highly up-regulated when compared to aurora kinase-B (AURKB), cell division cycle 25 homolog B (CDC25B) and polo-like kinase 1 (PLK1) (Spellman et al., 2011). Collectively, the proteins are required for regulated cell cycle progression and aberrations lead to deregulated tumor progression. FOXM1 is also involved in the induction of breast cancer type 2 susceptibility protein (BRCA2) a downstream target that regulates DNA repair (Kwok et al., 2010) (Millour et al., 2011). FOXM1 is involved in cell migration/invasion in ovarian cancers via ERK that acts upstream of FOXM1 (Lok et al., 2011) and regulates cell proliferation through a number of elements in the pathway.

Breast cancer type 1/2 susceptibility protein (BRCA1)/(BRCA2) and homologous repair and nucleotide excision repair pathway

BRCA1 and BRCA 2 are tumor suppressors that readily associate with p53 to serve apoptotic functions (Zhang et al., 1998; Abramovitch and Werner, 2003; Navaraj et al., 2009). Most of the mutations seen in ovarian tumors are somatic mutations (Zweemer et al., 1999; Amikura et al., 2006; Usha et al., 2011; Szabova et al., 2012). However, mutations in *BRCA1* and *BRCA2* are heritable germline mutations. Only 10% of the ovarian tumors that arise are heritable, which involve the *BRCA1/2* mutations (Zhou et al., 2013). The remaining 90% arise through somatic mutations affecting proteins such as BRCA1/2 or p53 (Zikan et al., 2008). A study conducted by Zweemer et al. determined the relationship between p53 accumulation and the presence of BRCA1, BRCA2 or both mutations, respectively (Zweemer et al., 1999). When compared alone to the specific mutation itself, it was found that p53 accumulation was more pronounced with *BRCA1* than *BRCA2* mutation (Zweemer et al., 1999). However, similar observations are seen in the absence of BRCA mutations (Cramer, 2012). Thus the correlation between p53 and BRCA mutated genes need further clarification. BRCA1 expression is favored over BRCA2 expression in terms of staging the cancer. p53 accumulation is more apparent with BRCA1 mutations in late stage or stage III ovarian cancers (Johannsson et al., 1997; Kaern et al., 2005; Wysham et al., 2012).

BRCA proteins are associated with DNA repair and exist as a complex with other repair proteins (Brugarolas and Jacks, 1997; Jasin, 2002; Tutt and Ashworth, 2002). Hereditary ovarian cancer involving BRCA requires two-hits for tumor formation. A single BRCA1 affected allele may not be sufficient to promote tumor formation. However, DNA stability is affected as DNA repair is affected that can encourage tumor formation through the loss of function of the second allele or mutations in genes governing the repair pathway. The paradoxical role of BRCA in cancers is apparent (Powell and Kachnic, 2003). Hereditary and somatic mutations in BRCA are responsible for breast and ovarian cancer formation, and yet, cells that carry WT BRCA with other pathway anomalies are less sensitive to treatment or develop chemoresistance. The observations are controversial as some studies point out that the BRCA status (proficient versus absent) of the cells do not have a significant correlation to treatment outcome, whereas others have shown that the absence of BRCA1 enhances the sensitivity to treatment by agents that induce DNA damage, including ionizing radiations (Wiltshire et al., 2007; Johnson et al., 2011). Spellman et al. (2011) showed that the presence of BRCA1 mutations was associated with better survival outcomes as compared to those patients that carried WT BRCA1.

Current therapies against ovarian cancer involve cisplatin treatment (Laios et al., 2013; Song et al., 2013). Patients that are initially responsive become resistant to the treatment. Platinum-based cisplatin therapy involves the induction of DNA damage through inter and intrastrand crosslinking between purines (Basu and Krishnamurthy, 2010). The 1, 3 and the 1, 2-intrastrand crosslinks are excised and removed through nucleotide excision repair

(NER) with the former lesions being easier to remove due to less distortion of the helix (Enoiu et al., 2012). The 1, 3-interstrand lesion are complex and require homologous recombination where double stranded breaks (DSB) are involved (Hinz, 2010). The NER system is robust in terms of lesion recognition and requires a host of various NER components. The up-regulation of these elements by DNA-induced damage could account for the gain of resistance to treatment. In terms of DSBs, Rad51 recombinase is required and acts in conjunction with BRCA2 (Davies et al., 2001). Therefore, loss of function of BRCA2 or mutations that silence the expression of the protein favors sensitivity to treatment and thus women with BRCA1/2 mutations have a better diagnosis and are more responsive to platinum-based therapy. The direct correlation between the expression of NER genes or its members and resistance to therapy does not always hold true. The data obtained from a study analyzing NER efficiency and cisplatin resistance showed that altering the HRR pathway, but not NER member expression, could enhance the sensitivity of cisplatin-resistant tumors to platinum-based agents (Wang et al., 2011). These observations have been corroborated by the Spellman et al. study that showed that of the samples tested 23% carried mutations/epigenetic altered states in BRCA1, while 11% carried mutations in BRCA2 (Spellman et al., 2011) and that 51% of the cases had altered HRR pathway that involved BRCA2 and Rad51C (Spellman et al., 2011).

Epigenetics and ovarian cancer

Histones and DNA are primary targets of epigenetic regulation (Seeber and van Diest, 2012). Genes that harbor CpG islands are susceptible to epigenetic modifications, consisting primarily of DNA methylation (Maradeo and Cairns, 2011). Both types, histone-based and DNA-based methylation marks, are largely known to inhibit gene expression through transcriptional inhibition (Seeber and van Diest, 2012). Of the amino acid residues, lysines are more prone to epigenetic modifications via methylation, acetylation, phosphorylation sumoylation and ubiquitination (Saldanha and Tollefsbol, 2012). However, the well-studied acetylation modifications primarily affect the exposure of the DNA to the transcriptome machinery. In some cases, non-histone proteins like p53 when acetylated affect its cellular functions through its DNA binding interactions and stability (Ito et al., 2002; Scoumanne and Chen, 2008; Pirola et al., 2012; Kim et al., 2013). Alterations to the epigenome have been shown to be instrumental in the genesis of diseased phenotypes. The current status of epigenomic research shows that DNA methylation, histone modifications, miRNA collectively alter epigenetic profiles of tissues that promote tumorigenesis. Epigenetic modifications are promising targets for treatment as the mechanisms can be reversed through epigenetic enzyme targeted therapy.

The role of methylation in cancer formation can be gene or loci specific. In general, hypermethylation of tumor suppressor genes and hypomethylation of oncogenes contribute to pathway deregulations that promote tumor formation. In the genesis of ovarian cancers, overexpression or silencing of members of the pathways that control proliferation and growth promote tumor initiation and progression. In mammalian germ cell-derived ovarian tumor, promotion is associated with the deregulation of pRb pathway where p16 reduction is observed. The reduction is found to be associated with the hypermethylation of *p16 (INK4A)* promoter region that correlates with cell promotion (Kawauchi et al., 2004). Increased methylation of tumor suppressor genes have also been observed in ovarian tumors (Chmelarova et al., 2012; Ozdemir et al., 2012). Increase in promoter methylation of *O⁶-methylguanine DNA methyltransferase (MGMT)*, paired box 5 (*PAX5*), Cadherin 13, H-Cadherin (Rose et al.) (*CDH13*), Wilms tumor 1 (*WT1*), Thrombospondin 1 (*THBS1*), and *GATA5* have been observed in endometrioid ovarian cancer as compared to serous ovarian cancer (Chmelarova et al., 2012). In the same study, surprisingly, commonly deregulated genes in ovarian cancer ataxia telangiectasia mutated (*ATM*), *TP53*, *PTEN*, Von Hippel–

Lindau tumor suppressor (*VLH*), glutathione S-transferase pi (*GSTP1*), *RB1a*, *MGMTb*, and *PYCARD* that encodes apoptosis-associated speck-like protein containing a CARD did not show significant methylation above the cut off value of 15% (Chmelarova et al., 2012). Another study showed that tumor suppressors cyclin-dependent kinase inhibitor 2B (*CDKN2B*), *CDH13* and *RASSF1*, a gene that encodes Ras association domain-containing protein 1 have significant hypermethylation and that *CDKN2B* promoter hypermethylation was observed in clear cell carcinomas as compared to other histological types (Ozdemir et al., 2012). Hypermethylation of *BRCA1* has been shown to be frequent in spontaneous breast and ovarian cancers (Wang et al., 2010b). Demethylation of *BRCA1* appears to decrease chemosensitivity of platinum-sensitive cells associated with partial increase of *BRCA1*. Thus *BRCA1* hypermethylation favors treatment sensitivity and has been shown to function independently of PI3K-Akt pathway (Wang et al., 2010b). Methylation analysis of ovarian tumors of genes involved in the Wnt pathway demonstrated that the naked cuticle homolog 1 (*NKDI*) and disheveled homolog (*DVLI*) methylation increased risk of disease progression (Dai et al., 2011). Hypermethylation of members of SHh pathway, zinc finger protein 1 (*ZIC1*), results in poor progression free survival (PFS) (Huang et al., 2013). In addition to the role in PFS, silencing of SHh members, *ZIC1* and zinc finger protein 4 (*ZIC4*) by methylation correlate with increased proliferation, migration and invasion (Huang et al., 2013). Therefore, methylation shows promise as a marker for PFS. However, studies using larger sample size may be required to support the observation. The relationship between DNA hypermethylation generally favors reduced gene expression. The examination of 1505 CpG sites between ovarian cancer cell lines and primary ovarian tumors showed that ovarian cancer cell lines seem to exhibit distinct methylation profiles as compared to the primary ovarian tumors (Houshdaran et al., 2010). Ovarian cancer cell lines tend to have higher methylation patterns as compared to primary tumors. An explanation may be that ovarian derived cancer cell lines are pure cultures that represent one type of cell population. However, primary tumors are a heterogeneous mass of cells with a mixture of other cells as well. Therefore, careful interpretation is essential as to the use of methylation as a marker for PFS and also in terms of therapeutic treatments with various compounds that target methylation. These studies make it clear that preclinical findings cannot be directly applicable to *in situ* tumors. This may also account for the reason why so many treatments that work successfully *in vitro* fail to show promise *in vivo*.

Methylation of lysine residues takes many different forms; mono, bi and tri valencies (Zhang et al., 2012). However, the position and number of lysines methylated determine the methylation-based gene activity status. Bi- and tri-methylation of histone H3 lysine 27 (*H3K27(me3)*) contributes to gene silencing and tri-methylation of histone H3 lysine 4 residue (*H3K4(me3)*) activates gene expression (Payne and Braun, 2006; Lilja et al., 2013). In ovarian tumors, especially in the case of a subset of cells that escape chemotherapy, these epigenetic alterations are observed (Lotem and Sachs, 2006; Balch and Nephew, 2010; Min et al., 2012). What have been analyzed in studies thus far are comparisons of gene sets at various stages of ovarian cancer to normal tissue. The bivalent marks assessed in these studies are based on comparison of ovarian cancer stem cells to patterns in human embryonic stem cells (hES) (Chapman-Rothe et al., 2012). These findings are important as chemoresistance and recurrence of more aggressive tumors could stem from the population of cancer stem cells that have epigenetic plasticity. The process of ovulation and the stress exerted upon the organ due to ovulation requires the need of continual cell replacement. Continual change and plasticity of tissues are maintained by stem cells and studies have established the presence of such in the endometrium of uterine tissue (Teixeira et al., 2008). In all likelihood a similar scenario could exist in the ovary. Recent findings of the presence of adult stem cells in the ovaries is quite exciting and may provide a key link into how tumors arise in the ovary (Djordjevic et al., 2012; Foster et al., 2012). Linking the methylation patterns to these adult stem cells, normal epigenetic marks may undergo a

change mediated by environmental cues (external/internal) e.g., parity, inflammation, toward a more tumorigenic phenotype by the suppression or loss of tumor suppressor genes. Also, tumor suppressor genes that harbor these specific bi- and tri-methyl marks are more pronounced to gene silencing through epigenetics affecting pathways such as the PI3K pathway (Min et al., 2012; Seeber and van Diest, 2012).

In normal tissues, DNA hypomethylation of tumor suppressor genes is observed, which is reversed in tumorigenic tissues, where hypermethylation of CpG-promoter rich genes and global hypomethylation is predominant (Bammidi et al., 2012; Ozdemir et al., 2012). The patterns can be readily reversed by targeting enzymes that regulate these transient modifications. DNA methyltransferases (DNMTs), histone acetyl transferases (HATs) and histone deacetylases (HDACs) serve as targets for therapies against many cancers (Cherblanc et al., 2012). However, single therapies have been found to be less effective against solid tumors as compared to combined therapy of conventional drugs with epigenetic therapies or combined epigenetic therapies.

There is a possible cross talk between DNA methylation and histone modification that dictates the dynamic states of chromatin and the genes associated with tumor biology. Hypoacetylation of H3 and H4 in association with GATA4 and 6 transcription factors have been found in a variety of ovarian cancer cells (Caslini et al., 2006). Methylation patterns such as trimethylation of H3K27 or dimethylation of H3K4 have been found to exist in carcinogenic ovarian tissue (Marsit et al., 2006; Chapman-Rothe et al., 2012). Hypermethylation of tumor suppressor genes such as *PTEN* and *p16^{INK4a}* have been observed contributing to the loss of function of these proteins in EOCs (Yang et al., 2006; Tam et al., 2007) and the absence of these proteins contribute to deregulated pathways that have been discussed earlier in the review.

Micro RNAs (miRNAs) are tightly controlled in normal cells but become highly deregulated in cancer cells. They are single stranded non-coding RNA molecules about 22 nucleotides in length and regulate the levels of gene expression by performing silencer-like type functions, degrading the mRNA to which they bind (Kuhlmann et al., 2012). They bind either to certain sequences within the mRNA or to the 3'-untranslated region of the gene. The role of some of the miRNAs in the etiology of various cancers have been well established (Kuhlmann et al., 2012). A detailed review of miRNAs and their role in ovarian cancer has been discussed in detail in Chen et al. (Chen et al., 2011). The posttranscriptional modification of genes by miRNA and the presence of varied miRNA expression levels within solid tumors provides a map of miRNA signatures for specific cancers (Baer et al., 2013). Formulating drugs against these miRNAs may provide for a therapeutic approach. Table 3 lists the various miRNAs that play a significant role in ovarian cancers and the targets they affect in the process. For example, p27 is a cell cycle regulatory protein whose post-transcriptional level is altered by the deregulated expression of miRNA 221 and miRNA 222 in ovarian cancers. They inhibit the expression of p27 that is essential to the control of cellular apoptosis thereby promoting cell proliferation (le Sage et al., 2007).

Epigenetic marks may prove useful in the diagnosis, prognosis and prediction of the disease. In the early stages of ovarian cancer, individuals are responsive to the treatment but eventually become chemoresistant, and the presence of cancer stem cells (CSCs) in the tumor mass may be responsible for the observed chemoresistance. Altering the epigenome of these CSCs may prove to be an alternate approach to targeting advanced ovarian cancers and re-sensitizing cells to chemical treatments and regression of tumors.

Future Directions

Ovarian cancers are lethal diseases as they slip detection and are far advanced when detected. Research in ovarian cancer has just scratched the surface in terms of understanding the pathways deregulated in the disease. Clearly, there does not appear to be a strong association between deregulated patterns and the gene specific expression and subcellular correlation patterns. Thus, treatment approaches are still not very effective. This may be due to the fact that most preclinical studies of the disease have been based on the immunohistochemistry of the tissue. Utilizing more quantitative technologies such as microarray systems, western blots, real-time PCR, or whole-genome sequence analysis might provide different insights into the etiology and pathology of the disease. The information generated from these technologies can provide a wealth of information that relates to the mitotic and apoptotic deregulations of cellular pathways, histone signatures, DNA methylation patterns and miRNA expression patterns governing gene expression in ovarian cancer and its subtypes making treatments and therapies more customized.

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Abbreviations

CDK	cyclin dependent kinases
p27kip1	cyclin-dependent kinase inhibitor1B
p16INK4a	inhibitor of kinases 4a
KRAS	Kirsten rat sarcoma oncogene
NF-κB	Nuclear factor kappa B
PI3K	phosphatidylinositide-3 kinase
PTEN	phosphatase and tensin homolog
E2F	transcription factor

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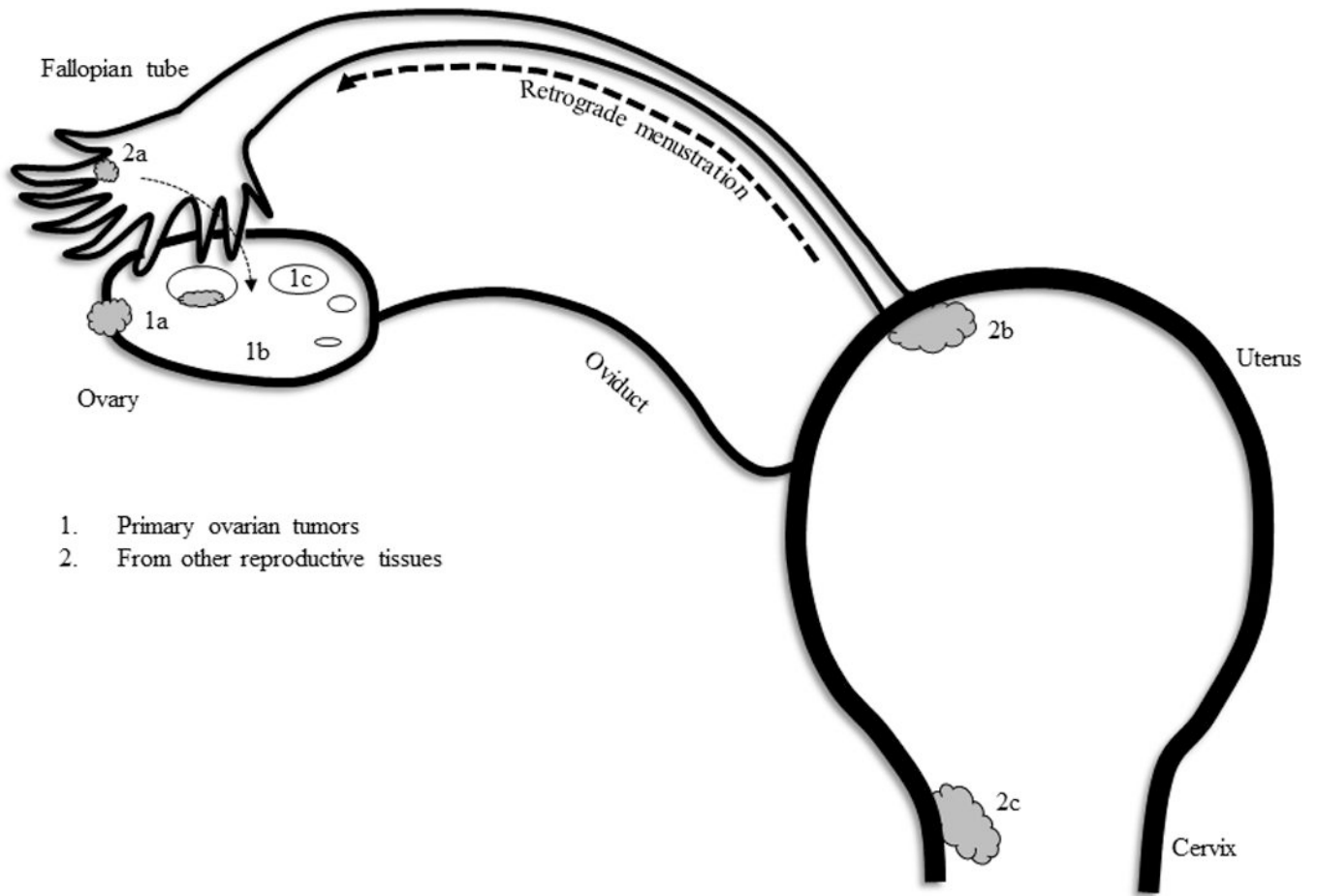
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1. Primary ovarian tumors
2. From other reproductive tissues

Figure 1. Proposed theories of origin of epithelial-cell ovarian cancers (EOCs)

The primary ovarian cancers reside in the ovary tissue itself. However, cells from the endometrium, fallopian tube, stroma can give rise to the histological types of tumors of epithelial-cell origin. As shown in the diagrams, 1a, 1b and 1c denote the commonly seen ovarian tumors - epithelia, stroma and germ-cell tumors, respectively. However, EOCs are the predominant form and closer examination reveals that the origin could stem from other reproductive tissues such as the endometrium lining the uterus, cervical tissue or from the epithelia of the fallopian tube. Retrograde menstruation problems can be a pathway for the transfer of endometrial cells to that of the ovary. Ovulation and encystment of cells can be a mode of travel for cells from the fallopian tube. Therefore, the serous type EOCs arise from the fallopian tube (2a); the endometrioid EOCs arise from the cervical or uterine tissue (2a and 2b); the mucinous and clear-cell tumors could arise from cells of 1b, 1c, (internal environment of the ovary) and 2a (cervical tissue). Hence, ovarian epithelial tumors are of the multi-histological type. Symbols used: grey filled cloud-like structure, tumors; small open oval circles, follicles in the ovary.

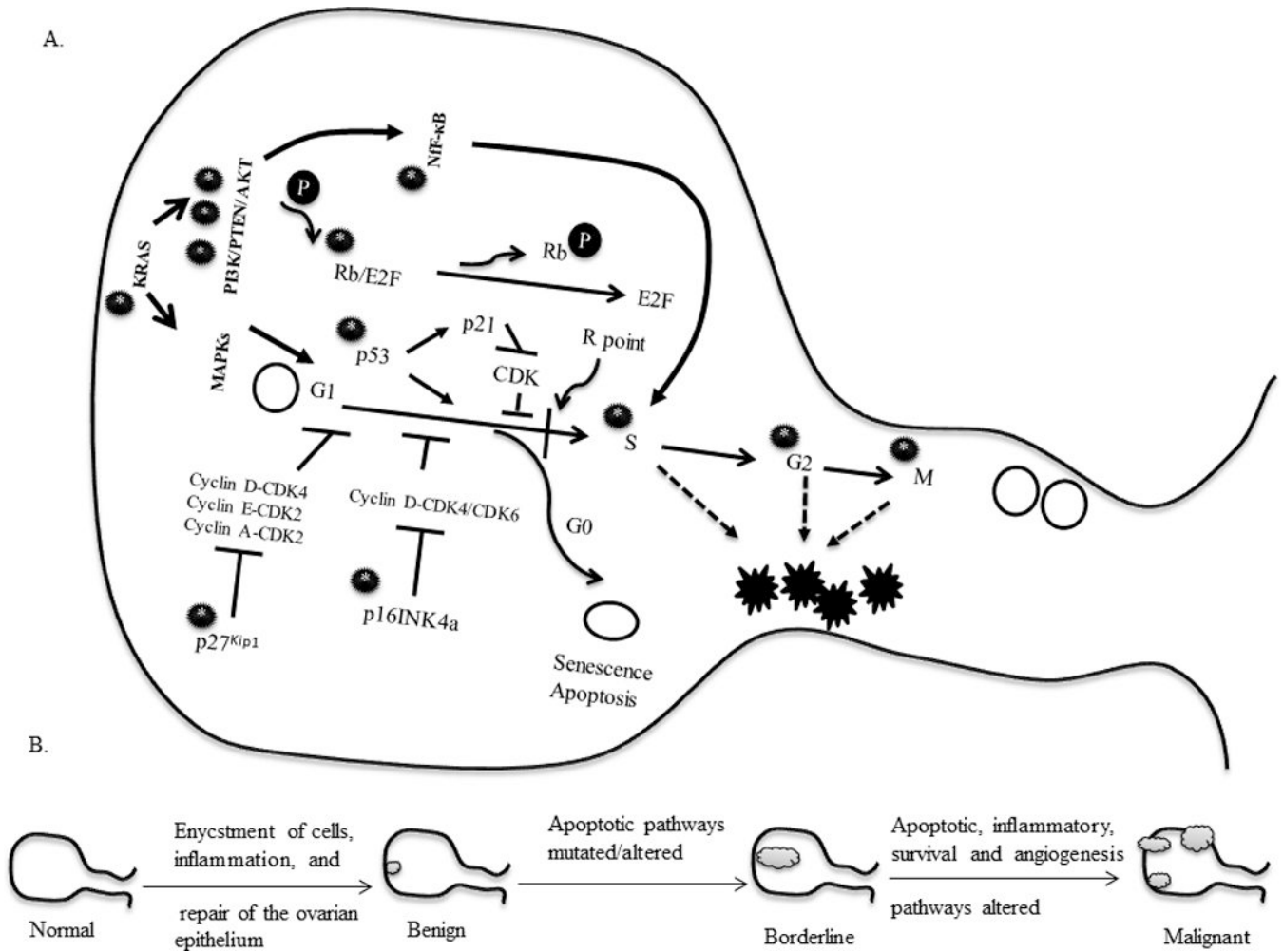


Figure 2. Cell cycle pathways involved in ovarian carcinogenesis

The cell cycle traverses through the G1-S-G2-M phases tightly controlled by check points between each phase through a set of regulatory proteins, primarily cyclins and kinases. The levels and expression of these regulators ensure the fate of the preceding and proceeding phases of the cycle. Cellular destinations, division, differentiation, senescence and apoptosis are controlled by a certain restriction in the late G1 phase termed the restriction (R) point. It is when cells successfully cross this threshold point, that cellular destinations are met.

Various genes involved in tightly regulating the cell cycle in ovarian cancer. A.

Deregulation of the key genes (black circle with a star) initiates aberrant proliferation triggering the development of neoplasms. Single or multiple pathways may be involved in the process. In early stage development there are chances of single gene mutations or epigenetic mechanisms that transform the cell into an immortal phenotype. However, when multiple pathways are hit or crucial genes such as *NF-κB* are mutated, far more aggressive tumors can develop. Symbols used: open circle, normal cell; open oval, cell towards senescence or apoptosis; black jagged star, cancerous cell; black circle with white star, mutated gene/pathway; black circle with 'P', phosphorylated. B. Gradual stages of early to late ovarian tumor development and pathway abnormalities have been highlighted in miniature figures below the main one. Symbol used: grey cloud-like structure, tumor.

Table 1

Alterations in genes and pathways involved in the cell cycle in ovarian carcinomas.

Gene	Cases	Percent	Observations	Ovarian Tissue analyzed	Technique use	Reference
<i>p53</i>	36/46	78.3%	Altered expression	Epithelial	Immunohistochemistry	(Hashiguchi et al., 2001)
<i>p53</i>	79/134	59%	High positive staining	Serous	Immunohistochemistry and disease outcome results	(Bali et al., 2004)
<i>p53</i>	54/107	50.4%	High expression Overexpression	Epithelial	Immunohistochemistry	(Marks et al., 1991)
Nuclear <i>p53</i> protein	15/52 8/52	29% 15%	Point mutations Overexpression	Early-stage Ovarian cancer	Immunostaining and DNA sequencing	(Kohler et al., 1993)
<i>p53</i>	177/284	62.3%	Overexpression	Epithelial (Stage I, II, III and IV)	Immunohistochemistry	(Hartmann et al., 1994)
<i>p53</i>	107/221 193/316 104/136	48.4% 26% 35%	Overexpression Overexpression Mutated	Primary Epithelial (Stages I-IV)	Immunohistochemistry	(Eltabbakh et al., 1997)
<i>p53</i> and cyclin D1	11/18 5/18	61% 27.7%	<i>p53</i> mutation Overexpression of cyclin D1	Primary Epithelial Metastatic tumor	Computer aided image analysis system	(Anttila et al., 1999a)
<i>p53</i> and Cyclin D1	7/18	39%	Absence of <i>p53</i> mutations but increased expression of Cyclin D1	Ovarian tumor	cDNA sequence analysis	(Shigemasa et al., 1999)
<i>p53</i>	42/90	47%	<i>p53</i> expression	Ovarian tumor	cDNA sequence analysis and PCR	(Shigemasa et al., 1999)
	81/125 3/125	74% 3%	Positive staining			
	25/125 55/81	23% 67.9%	Single mutation Two mutations			
<i>p53</i>	7/22	32%	Lacking a mutation exons 2 to 11	Ovarian tumor	cDNA sequence analysis and PCR	(Shigemasa et al., 1999)
	8/25	32%	Overexpression observed with missense mutation	Epithelial	Immunohistochemistry	(Sagarra et al., 2002)

Gene	Cases	Percent	Observations	Ovarian Tissue analyzed	Technique use	Reference
p53	44/82	54%	Overexpression observed with truncations	Frozen Ovarian tumor	cDNA analysis in automated sequencer	(Havrilesky et al., 2003)
	34/66	51.5%	Overexpression in those lacking a mutation in exons 2 to 11	Frozen Ovarian tumor	cDNA analysis in automated sequencer	(Havrilesky et al., 2003)
	33/131	25%	Stained positive Promoter methylated	Frozen Ovarian tumor	cDNA analysis in automated sequencer	(Havrilesky et al., 2003)
Abnormal p53 pathway	nd	80.4%	nd	Epithelial	nd	(Hashiguchi et al., 2001)
Abnormal Rb pathway	nd	60.9%	nd	Epithelial	nd	(Hashiguchi et al., 2001)
pRb	5/46 106/134	10.9% 79%	Protein expression	Epithelial Serous	Immunohistochemistry Immunohistochemistry and disease outcome results	(Hashiguchi et al., 2001; Bali et al., 2004)
p16 ^{INK4a}	16/46	34.7%	Altered expression; no deletions	Epithelial	Immunohistochemistry	(Hashiguchi et al., 2001; Bali et al., 2004)
	74/134	55%	Loss of function	Serous	Immunohistochemistry and disease outcome results	
	7/46	15.2%	Methylated promoter	Epithelial	Immunohistochemistry	(Hashiguchi et al., 2001)
Cyclin D1/CDK4	14/46	30.4%	Overexpression	Epithelial	Immunohistochemistry	(Hashiguchi et al., 2001; Bali et al., 2004)
	25/134 21/27	19% 78%	Overexpression Higher than normal ovarian samples	Serous Ovarian tumors	Immunohistochemistry mRNA expression-PCR analysis	(Shigemasa et al., 1999)
	10/18	56%	Positive immunostaining	Ovarian tumors	Immunostaining	(Shigemasa et al., 1999)
p14ARF mutation	10/46	21.7%	Altered expression	Epithelial	Immunohistochemistry	(Hashiguchi et al., 2001)

Gene	Cases	Percent	Observations	Ovarian Tissue analyzed	Technique use	Reference
p14ARF mutation + methylation	4/46	8.7%	Methylated promoter	Epithelial		

* Nd = not determined

Table 2

Alterations in PI3K/PTEN/AKT pathway in ovarian cancers

Gene	Type of alteration	Frequency found	Cellular Phenotype affected	Pathway affected	Reference
<i>PTEN</i>	Mutation	Less than 1% 20%	Proliferation	RAS/PI3K	(Landen C.N. Jr. et al., 2008; Urlick et al., 2011)
<i>PTEN</i>	Deletion	7%	Proliferation	RAS/PI3K, Homologous repair (HR) altered	(Urlick et al., 2011)
<i>PI3Kα</i>	Amplified	18%	Proliferation	RAS/PI3K	(Urlick et al., 2011)
<i>AKT</i>	Amplified	30%	Proliferation	PI3kinase/AKT	(Landen C.N. Jr. et al., 2008)
<i>AKT1</i>	Amplified	3%	Proliferation	RAS/PI3K	(Urlick et al., 2011)
<i>AKT2</i>	Amplified	6%	Proliferation	RAS/PI3K	(Urlick et al., 2011)
<i>KRAS</i>	Amplified	11% 50%	Proliferation/ survival	RAS alterations	(Landen C.N. Jr. et al., 2008; Urlick et al., 2011)
<i>Rb</i>	Mutation	2%	Cell cycle progression	Rb	(Urlick et al., 2011)
<i>Rb</i>	Deletion	8%	Cell cycle progression	Rb	(Urlick et al., 2011)
<i>BRCA1</i>	Mutated/ hypermethylated	23%	Apoptosis	HR-pathway	(Urlick et al., 2011)
<i>BRCA2</i>	Mutated	11%	Apoptosis	HR-pathway	(Urlick et al., 2011)

Table 3

Effects of miRNA deregulation in ovarian cancer

miRNA	Gene acted on	Phenotype observed	Reference
miR-214	<i>p53</i>	Chemoresistance and metastasis	(Xu et al., 2012a)
miR-31	<i>p14 p16 p53</i>	Inhibits proliferation and induces apoptosis	(Creighton et al., 2010)
miR-214	<i>PTEN</i>	Induces proliferation and cisplatin resistance. Activates AKT pathway	(Yang et al., 2008)
miR-199a*, miR-200a	nd	Tumor progression	(Yang et al., 2008)
miR-182 and miR-96	<i>p27</i> through Forkhead box O3 (<i>FOXO3</i>)	Cancer transformation and progression	(Xu et al., 2012b)
miR-34b/34c	<i>p53</i>	Controls cell proliferation and adhesion-independent growth	(Corney et al., 2007)
miR-101	<i>p21</i>	Inhibits growth, induces p21	(Semaan et al., 2011)
miR- 93	<i>PTEN</i>	Activates AKT; tumorigenesis and cisplatin resistance	(Fu et al., 2012)
miR-146a	<i>NF-κB</i>	Suppression of metastases	(Kayani et al., 2011)
miR-199	<i>IKKβ</i>	Regulates IKK β expression	(Chen et al., 2008)