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REVIEW

Discovery of Prognostic Factors for Diagnosis and Treatment of Epithelial-Derived Ovarian Cancer from Laying Hens

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Ovarian cancer is a lethal gynecological cancer causing cancer-related deaths in women worldwide. It is difficult to diagnosis at an early stage when more than 90% patients can be cured because of lack of specific symptoms and early detection markers. Most of malignant ovarian tumors are originated from the germinal epithelium of the ovary. For investigation with animal models of epithelial-derived ovarian cancer (EOC), laying hens are the most relevant animal models because they spontaneously develop EOC as occurs in women through ovulating almost every day. As in women, EOC in the hen is age-related and grossly and histologically similar to that in women. However, domesticated animals are inappropriate for research human EOC due to multiple pregnancies and lactating or seasonally anestrous. In addition, the non-spontaneous nature of rodents EOC limits clinical relevance with human EOC. Recent studies have shown that ovarian cancer could arise from epithelium from the oviduct as oviduct-related genes are up-regulated in EOC of hens. Therefore, we showed in the review: 1) characterization and classification of EOC; 2) chicken models for EOC; 3) relationship estrogen with EOC; 4) candidate prognostic factors for EOC including serpin peptidase inhibior, clade B (ovalbumin), member 3 (SERPINB3), SERPINB11, gallicin 11 (GAL11), secreted phosphoprotein 1 (SPP1) and alpha 2 macroglobulin (A2M) in normal and cancerous ovaries of laying hens; 5) biological roles of microRNAs in development of EOC. Collectively, the present reviews indicate that expression of SERPINB3, SERPINB11, GAL11, SPP1 and A2M is clearly associated with the development of ovarian carcinogenesis. These results provide new insights into the prognostic biomarkers for EOC to diagnose and to evaluate responses to therapies for treating EOC of humans. **(J Cancer Prev 2013;18:209-220)**

Key Words: Epithelial-derived ovarian cancer, Prognostic factors, Hen, Estrogen, microRNA

INTRODUCTION

Ovarian cancer is the most fatal gynecological carcinoma even though it is the 8th most commonly diagnosed cancer and the 7th leading cause of cancer-related deaths in women worldwide.[1] There are two hypothesis linked to carcinogenesis of ovaries, which indicate 'incessant ovulation' and 'gonadotropin' hypothesis. Incessant ovulation causes increase of epithelial ovarian cancer with the number of ovulation repeating ovarian rupture and repair.[2] And gonadotropin-related hypothesis provides that incidence rate of the ovarian cancer is increased by high levels of gonadotropin such as FSH and LH through stimulating the ovarian epithelium surface.[3] In a variety of previous studies, the first hypothesis related with spontaneous incessant ovulation has been reported having strong relationship with malignant transformation of ovaries. Recently several studies have suggested alternative theory that aggressive ovarian carcinomas arise from the fallopian tube in women.[4,5]

Ovarian cancer can be classified to three cancerous types, epithelial carcinoma, sex-cord stromal carcinoma and germ cell carcinoma.[6,7] More than 90% of human ovarian cancers are originated from ovarian surface epithelium.

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And there are mainly four subtypes of epithelial-derived ovarian cancer that are serous (70%), endometrioid (10-20%), mucinous (3%) and clear cell (10%) carcinomas based on tumor cell morphology.[8] Furthermore, staging of human ovarian cancer is described by FIGO system from Stage I to IV with presence or absence of metastasis and ascites. Due to the lack of specific symptom and prognostic factors to diagnose ovarian cancer, most patients with this disease present advanced stage (Stage III or IV).[9,10] This fact causes approximately 70% of patients with ovarian cancer to death. Therefore, it is important to develop the valuable early detection marker to diagnosis or treatment for ovarian cancers.

To investigate the mechanisms of target genes to develop as a biomarker, laying hens are relevant models because they spontaneously induce EOC at a high rate after stop egg production as occur in women whereas other animals including mammals and rodents are not develop spontaneous in nature for ovarian cancer.[11] Moreover, commonly used biomarkers to detect ovarian cancer clinically such as CA125 (also known as MUC16), epididymis protein 4 (HE4), proliferation markers including proliferating cell nuclear antigen (PCNA), vimentin, a proto-oncogene (ERBB2), a growth factor receptor (EGFR), a cell cycle inhibitor (p27), oncofetal tumor markers (CEA, Lewis Y and Tag 72) and TGF-α are expressed in chicken ovarian cancer, too.[12-14] In addition, histological appearance of EOC of chicken is similar to those of humans.[15] Therefore, avian model is the best for determination of oncogenic mechanisms.

In this regard, to discover the prognostic factors for diagnosis and treatment of EOC, we reviewed the characteristics, classification and experimental models for EOC and relationship estrogen and genetic regulation including SERPINB3, SERPINB11, GAL11, SPP1, and A2M genes with development of female reproductive tract and those of disease. In addition, we determined the biological roles of microRNA in development of EOC.

CHARACTERIZATION AND CLASSIFICATION OF OVARIAN CANCER

The histologic classification categorized ovarian carcinomas according to derivation from coelomic surface epithelium, germ cells, and sex-cord stromal cells.[6,7] Among the rest, the majority human malignant ovarian cancers are germinal epithelium of the ovary. The etiology of EOC is not well known. The likelihood of developing EOC is associated with several factors such as age, genetics, epigenetics, hormones and others. Previous studies suggest that the major causative factor of EOC is incessant ovulation which contributes to increased risk for genetic aberrations to the ovarian surface epithelium in response to repeated rupture and repair of the epithelial surface of the ovary.[2,16] According to this hypothesis, taking oral contraceptives for more than five years and multiparity can reduce the incidence of ovarian cancer by suppressing ovulation and controlling hormone levels.[17,18]

EOC is classified as follows: serous, endometrioid, mucinous and clear cell tumors based on tumor cell morphology and histology.[8] Serous carcinoma is the most common of EOC with specific characteristics that include multiple cysts, solid areas, glands and parts of papillae. Malignant serous carcinomas account for approximately 30% of ovarian serous carcinomas and nearly 70% of all EOCs. Most serous carcinomas are large and form bilaterally.[19,20] In development of ovarian serous carcinoma, a few gene mutations have been identified. For example, mutations in tumor protein 53 gene is frequently associated with malignant serous carcinomas.[21] And V-KI-RAS2 kirsten rat sarcoma viral oncogene homolog (KRAS) and V-RAF murine sarcoma viral oncogene homolog B1 (BRAF) gene mutations exist in the early grade serous carcinomas and they lead to activation of the mitogen activated protein kinase (MAPK) signaling pathway.[22]

The next most common EOC is endometrioid carcinomas that make up 10-20% of all ovarian cancers. This type of cancer is composed of epithelial and stromal cells that resemble those of the endometrium. These tumors are associated with endometriosis due to genetic alterations and hyperplasia of the endometrium.[23,24] In addition, endometrioid carcinomas have glands, solid masses or a fibrous consistency. The endometrioid carcinomas are related to various alterations in molecular genetics including the mutation of oncogenes, tumor suppressor genes and other genes associated with DNA repair. For example, activating mutations of a key effectors of the wingless-type

MMTY integration site family (WNT) signaling pathway and, catenin beta 1 (CTNNB1), as well as inactivating mutations of tumor suppressor gene, phosphatase and tensin homolog (PTEN), have been detected mainly in endometrioid carcinomas. Both of them are rare in the other types of ovarian cancers.[25,26]

The third most common EOC is the mucinous carcinomas which occur in a small percentage (3%) of primary ovarian carcinomas. Mucinous carcinomas are composed of papillae and solid areas, mucin-riched cytoplasm and large areas of necrosis and hemorrhage. Histologically, mucinous carcinomas are characterized with glands and cysts including abundant cytoplasmic mucins.[27] The mechanism responsible for development of mucinous carcinomas has not been established; however mutations in the KRAS gene are commonly associated with mucinous ovarian tumors. This analysis indicates that KRAS mutations might be early events in the development of mucinous tumors.[28]

Clear cell carcinomas account for approximately 10% of EOC. Most ovarian clear cell carcinomas are malignant, as benign and borderline tumors are uncommon. Clear cell carcinomas are composed of clear cells that develop as tubular, papillary, solid or mixed types and hobnail cells which contain apical nuclei. Most of tumors are solid or cystic masses with one or more nodules protruding into the lumen.[20,29,30] In clear cell carcinomas of the ovary, the following genetic mutations have been found as follows: mutations of PIK3CA (20-25%), TP53 (8.3%), PTEN (8%) and BRAF (6.3%).[31-34] In addition, these type of tumor are associated with over-expression of numerous genes such as HFF1 homeobox 1B (HNF-1B), SPP1, neuraminidase 3 (NEU3) and annexin A4.[35,36]

Recent studies based on clinicopathologic and molecular genetic characteristics have suggested dualistic model for ovarian carcinogenesis, which indicates type I and type II tumors.[37-39] Type I tumor features low-grade serous and endometrioid carcinomas, well-differentiated clear cell and mucinous carcinomas and Brenner tumors. This type of EOC exists in the early stage (stage I) and grows slowly from precursor lesions, such as borderline tumors and endometriosis. In addition, type I tumors are associated with specific genetic mutations, including ARID1A, BRAF, CTNNB1, ERBB2, KRAS, PIK3CA, PPP2R1A, PTEN, Raf, and Ras.[40-44] On the other hand, type II tumors present papillary, glandular, and solid morphologies and consist of high-grade serous and endometrioid carcinomas, malignant mingled mesodermal carcinosarcomas, and undifferentiated carcinomas. Type II epithelial ovarian cancers present in advanced stage (stage II-IV) and grow aggressively occurring to more than 75% of all EOC patients. They show high frequency of TP53 gene mutations, which are indicated rarely in the type I tumors.[45] Furthermore, approximately 50% of high-grade serous carcinomas is related in molecular alteration of BRCA by the gene mutation or by methylation of BRCA promoter.[46]

CHICKEN MODEL FOR EPITHELIAL-DERIVED OVARIAN CANCER

The majority of women diagnosed at an advanced stage of EOC have a high probability of dying from the disease. EOC is associated with complex genetic and epigenetic alterations leading to ovarian cancer. Thus, it is very important to identify mechanism leading to initiation, promotion and progression of EOC. It is difficult to establish etiologies and pathogenesis of EOC in women; therefore, exploitation of animal models for EOC is essential.

The laying hen is a valuable model for investigation of EOC because they develop EOC spontaneously at a high rate after producing eggs when more than two years of age. Similarly, natural menopause usually arises between 40- and 55-years of age in women when production of female steroid hormones, estrogen and progesterone, is decreasing with advancing age of their ovaries. Incessant ovulation in laying hens (almost every day) and women (once a month) is considered the major causative factor of EOC.[11,15,47]

Ovarian carcinomas of the laying hen model presents histopathologically with serous, endometrioid, mucinous and clear cell carcinomas as occurs in women. Furthermore, the stages of ovarian cancer in laying hens are similar to that for EOC in women based on the following FIGO system classifications.[10,15] Stage I of EOC in laying hens indicates tumor growth limited to the ovary, firm nodules and little or no ascites. For stage II EOC in laying hens, ovarian tumors are larger and have metastasized to the

oviduct with moderate ascites. Next, Stage III ovarian cancer in laying hens shows metastasis of the tumor to the pelvic organs, as well as peritoneal and abdominal organs including small and large intestine and mesentery and surface of the liver with copious ascites. Stage IV EOC in laying hens is characterized by severe metastasis to distant organs such as liver, lung and spleen with multiple solid tumors and copious ascites.[15] Therefore, the laying hen is the only animal model that develops EOC spontaneously from surface epithelium of the ovaries at an incidence rate due to incessant ovulations and can be used for investigations to develop therapeutic agents for prevention and or treatment of EOC.

Genetically manipulated rodent models of each subtype of ovarian cancer have been used to improve knowledge of the etiologies and pathogenesis of EOC and confirm effects in preclinical tests of signal transduction inhibitors as potential therapeutic agents.[20,48,49] On the other hand, the fact that EOC does not occur spontaneously in rodent models limits their clinical relevance.[15]

ESTROGEN ACTION IN THE EPITHELIAL-DERIVED OVARIAN CANCER

Estrogen is the most important steroid hormone in the avian female reproductive tract as a primary sex hormone. In general, estrogen plays crucial roles in the modification of several cell-types with respect to development and differentiation, altering expression of specific genes in a variety of organs, and regulation of various biological events including protection against apoptosis, osteoporosis, diabetes and Alzheimer's disease.[50-52] For these biological actions, estrogen binds two classical nuclear receptors, estrogen alpha (ESR1) and beta (ESR2).[53]

Reproductive hormones, including gonadotropins and steroids hormones, affect the risk for development of ovarian cancer.[54] Estrogen, in particular, has long been implicated as a factor inducing ovarian cancer. For instance, menopausal women who have taken estrogen as hormone replacement therapy have an increased risk of ovarian cancer[55] whereas women who have taken oral contraceptives for more than 5 years have a reduced incidence of ovarian cancer during premenopausal years. [56,57]

High levels of estrogen can change immune response, phagocytic activity, growth factor levels and differentiation of cancer cells.[58] For example, estrogen increases angiogenesis that is one key feature of cancer development by promoting secretion of vascular endothelial growth factor (VEGF) and endothelial cell migration.[59,60] In addition, estrogen regulates expression of hepatocyte growth factor (HGF)[61] and epidermal growth factor (EGF), both of which activate proliferation of ovarian surface epithelial cells.[62] In animals, incessant exposure of the reproductive tract and mammary glands to estradiol induces development of papillary ovarian carcinomas in guinea pigs and rabbits that are similar to human benign serous carcinomas.[63,64] Also, estrogen can increase proliferation of ovarian surface epithelial cells in ewes.[65]

Both ESR1 and ESR2 have been reported to be expressed in human ovarian cancers.[66] In the four subtypes of EOC, ESR1 was expressed abundantly in endometrioid carcinomas (100%) and detected in serous (97%) and mucinous (70%) carcinomas by immunohistochemal analysis. Moreover, expression of ESR1 was higher in malignant EOC than in ovaries with benign tumors and normal ovaries.[16,67] In contrast, ESR2 is expressed in all types of EOC in sequence as follows: endometrioid, serous, clear cell, mucinous carcinomas.[67,68]

On the other hand, the exact mechanisms of estrogen action are unknown regarding development of ovarian cancer. Therefore, advanced studies are required to verify the relationship between estrogenic activity and expression of its receptors and the etiology and pathogenesis of EOC.

CANDIDATE BIOMARKERS FOR EPITHELIAL-DERIVED OVARIAN CANCER

1. A2M

The alpha 2 macroglobulins (A2M) function as protease inhibitors in serum of mammals and are able to bind a variety of cytokines and growth factors.[69-72] Proteases and their inhibitors take part in various biological events such as oncogenesis and metastasis because of their capacity to degrade extracellular matrix proteins.[73] Similar to other protease inhibitors, A2M is increased in plasma of women

with inflammatory and neoplastic lesions of the ovary.[74] In addition, A2M increases in blood of laying hens more than 6 months prior to detection of advanced-stage EOC whereas A2M suppresses DNA synthesis in mouse ovarian tumor cells as a cytotoxic factor in serum.[75-77] These results suggest that increased levels of A2M in plasma of laying hens develop in the late-stages of ovarian cancer as compared with its concentration in serum of normal laying hens.[77] According to various lines of evidence, A2M might be a novel biomarker for improvements in early detection of ovarian cancer.

2. GAL11

GAL11 (also known as beta-defensin 11; DEFB11) belongs to avian defensins that are members of the beta-defensin subfamily members that exhibit antimicrobial activity against microbes including gram-positive/-negative bacteria or fungi.[24,78-80] Avian beta defensing genes identified in chicken leukocytes can be subdivided into 14 classes.[81] Among them, GAL11 expression increases significantly in response to lipopolysaccharides[82] and DES[83] in chicken.

In mammals, there are several reports on identification of the role of beta-defensins in carcinogenesis. First of all, the low expression of human beta-defensin 1 (DEFB1) is involved in renal cell carcinomas, prostate cancer, basal cell carcinomas and oral squamous cell carcinomas as a tumor suppressor.[84-86] And overexpression of DEFB3 increases development of oral cancer through recruitment of macrophages via EGF that induces DEFB3 expression.[87] In addition, DEFB2 and DEFB3 function as proto-oncogenes in oral squamous cell carcinomas, whereas DEFB1 works as a tumor suppressor gene.[88] Moreover, GAL11 was induced in the cancerous ovaries compared with normal ovaries of chicken. With these results, it is possible to suggest that beta-defensins influence carcinogenesis through alteration of inflammation and cytokine production.

3. SERPINB3

SERPINB3, also known as squamous cell carcinoma 1 (SCCA1), was discovered originally in squamous cell carcinoma of the cervix.[89] It belongs to the serpin superfamily of protease inhibitors related to apoptosis, immune response, blood coagulation, cell migration and invasiveness of cells.[90,91] SERPINB3 regulates programmed cell death through different biological process in diverse cancer types and over-expression of this gene is one characteristic of epithelial-derived cancerous cells. SERPINB3 decreases apoptosis mediated by carcinostatis substances and by TNFA -induced cell death by suppressing cytochrome c release from the mitochondria.[92,93] In addition, in apoptosis mechanisms, SERPINB3 is upstream of caspase-3, one of its molecular targets, which attenuates caspase-3 activity and apoptosis.[94] Moreover, SERPINB3 specifically modulates activity of c-Jun NH2-terminal kinase-1 (JNK-1).[95] In chicken ovarian cancer, *SERPINB3* mRNA and protein were localized in the glandular epithelium of cancerous ovaries. And it was abundant in the nucleus of both chicken and human ovarian cancer cell lines. Moreover, in 109 human patients with EOC, SERPINB3 protein was showed weak (13.8%), moderate (60.6%), and strong (25.7%) expression respectively.[96] Therefore, SERPINB3 may play a crucial role in EOC and be a novel biomarker for prognosis for EOC.

4. SERPINB11

SERPINBs are one of group in the serpin superfamily of serine and cysteine proteinase inhibitors having crucial roles in various biological events such as blood coagulation, angiogenesis, inflammation and fibrinolysis.[97] Most clade B serpin genes are intracellular proteins that primarily suppress target proteases whereas SERPINB5 and SERPINB11 are intracellular non-inhibitory proteins.[97-99] SERPINB5 is a class II tumor suppressor gene called as maspin (mammary serine protease inhibitor). This gene was demonstrated to induce apoptosis of breast and prostate cancer cells.[99,100] Moreover, methylation of the 5' flanking region of SERPINB5 causes gene silencing in colorectal, ovarian, skin and thyroid carcinomas.[101-103] Unlike SERPINB5, SERPINB11 functions as an inhibitor of angiogenesis through repressing endothelial cell migration and controlling mitogenesis.[104] SERPINB11 expression was induced in cancerous ovaries in chickens. And in human ovarian cancer cells such as OVCAR-3, SKOV-3 and PA-1 cells, immunoreactive SERPINB11 protein was predominant in the cytoplasm and had a similar expression pattern to that in chicken ovarian cancer cells. These results sug-

gest that SERPINB11 is a biomarker for chicken ovarian endometrioid carcinoma that could be used for diagnosis and monitoring effects of therapies for the disease in women.[105]

5. SPP1

SPP1 (also called as osteopontin), is a highly phosphorylated integrin-binding ligand and N-linked glycoprotein originally isolated from bones of rats.[106] This gene has crucial functions in a variety of physiological processes including cell to cell interactions, inflammatory responses, wound healing, calcification, morphogenesis of organs and tumorigenesis.[107] In blood, increases in SPP1 are associated with several types of cancers.[108,109] Especially, in development of ovarian cancer, SPP1 expression increased abundantly as compared with normal ovaries. In addition, its expression was localized predominantly to serous carcinoma which is one of subtype of EOC.[110] Results of clinical experiments with postoperative patients also indicated that SPP1 is a biomarker for not only detecting specific types of ovarian cancer, but also a marker for examination of responses to primary treatments for cancer in place or in addition to the use of CA125 as a biomarker for cancer.

BIOLOGICAL ROLEES OF MICRORNAS IN DEVELOPMENT AND DIFFERENTIATION

MicroRNAs (miRNAs) are small and non-coding single stranded RNAs. They consist of 18-23 nucleotides that are post-transcriptional regulators and transform cell fate through modulation of target-mRNA translation in various cells and tissues by binding partial sequences in the 3' untranslated region of target genes. In other words, miRNAs are known to control a variety of biological events such as growth, development, differentiation, oncogenesis, angiogenesis and cell cycle by regulating gene expression. They function through diverse mechanisms including inhibition of translation elongation and degradation of target mRNAs.[111-114]

Mechanisms of oncogenesis are very complex with genetic and epigenetic processes changing expression of oncogenic and tumor suppressor genes via various mechanisms. An example of one epigenetic factor is miRNAs involved in the initiation and progression of tumors through effects on oncogenes and tumor suppressor genes.[115,116] For example, the deletion and down-regulation of *miR-15a* and *miR-16-1* causes overexpression of BCL2 gene that is frequently shown to increase in level of expression in various human cancers through actions as an anti-apoptotic gene.[117] In addition, *let-7* family members, first demonstrated to be onco- miRNAs, regulate the expression of the RAS oncogene that usually shows highly increased levels in lung cancer cells as compared to normal cells due to mutations in RAS genes.[118] So, transfection of *let-7* in lung cancer cells can protect from development of lung cancer or reduce tumor size if cells have RAS mutations.[116] Moreover, the MYC oncogene which regulates cell proliferation and apoptosis induces B-cell cancer through correlation with *miR-155*.[119,120] Also collaboration between MYC oncogene and *miR-17-92* causes amplification of B-cell tumorigenesis.[121] Furthermore, it is remarkable that several miRNAs (*miR-20, miR-92a, miR-93, miR-126, miR-132, miR-218* and *miR-221*) control intracellular signaling pathways downstream of vascular endothelial growth factors (VEGFs) that are remarkable regulators of vascular development and maintenance of carcinogenesis.[114]

The miRNAs also regulate gene expression at post-transcription levels in EOC. Compared with normal ovaries, abnormal expression of miRNAs has been demonstrated in human EOC. For example, *miR-200a, miR-200b, miR-200c* and *miR-141, miR-429* are expressed in the epithelial phenotype of cancer cells by targeting ZEB1 and ZEB2 that are E-cadherin repressor proteins and overexpressed in human endometrioid ovarian tumors.[122,123] In addition, the expression of *miR-21, miR-203* and *miR-205* is up-regulated in EOC as compared to normal ovaries of women and the abundance of these miRNAs increase considerably after treatment of 5-aza-2'-deoxycytidine to demethylate OVCAR3 cells. These results suggest that DNA hypomethylation might be involved in the mechanism for over-expression of oncogenic miRNAs.[123-125] On the other hand, there are down-regulated miRNAs leading to an increase in cellular events. For instance, *miR-9, miR-15a, miR-22, miR-152* are suppressed in ovarian cancer cell lines and this repression is associated with increases

invasion, migration and proliferation of the cancer cells.[126-129] In chickens, several microRNAs were reported to regulate expression of their target genes that are related in the development of EOC (Table 1).[130-132]

In accordance with previous studies, the cancer-related miRNAs expressed aberrantly or mutated in various cancers might have crucial roles as modifiers of expression of oncogenes or tumor suppressor genes that regulate their target genes.

CONCLUSION

Ovarian carcinogenesis leads to dynamic alterations in morphology, physiology and function of the female reproductive tract. Present review demonstrates general characteristics and animal model of EOC, and the function of prognostic factors (SERPINB3, SERPINB11, GAL11, SPP1 and A2M) which are associated with and may be essential for development of EOC in women and laying hens. In addition indicated genes might be regulated by mechanisms affecting both the genome and epigenome including post-transcriptional regulation via miRNAs and methylation or demethylation of CpG sites of target genes. In addition, most suggested genes for detection of ovarian cancer are also related in the development of the chicken oviduct in response to estrogen which can act via its receptors to induce malignant transformations in cells of the ovaries. These results support the recently suggested hypothesis that oviduct developmental regulatory genes are critical regulators for development and differentiation of epithelial cells of the ovaries as they transition from the normal to the cancerous state during oncogenesis in women and laying hens. Collectively, present study revealed regulation of expression and function of five selected genes during progression of development of EOC and that their expression depends on transactivation of estrogen via

Table 1. Post-transcriptional regulatory microRNAs for prognostic factors in epithelial-derived ovarian cancer in chickens

Gene	Target miRNA	Gene ID	Accession No.
GAL11	gga-mir-1615	100315962	NR_035103.1
SERPINB3	gga-mir-101	777874	NR_031494.1
	gga-mir-1668	100315917	NR_035161.1
	gga-mir-1681	100315975	NR_035174.1
SPP1	gga-mir-140	777833	NR_031453.1

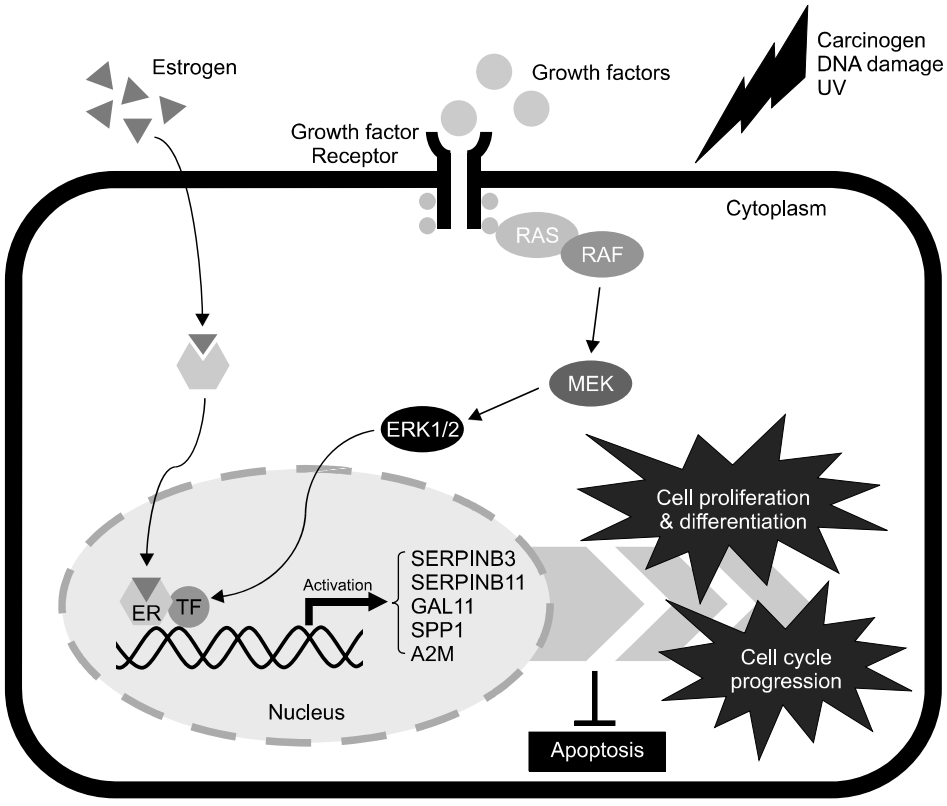

Fig. 1. Schematic illustrating mechanism for expression and function of regulatory genes for development of the oviduct and for development of epithelial-derived ovarian cancer. Carcinogens, DNA damage, estrogen and ultra-violet light (UV) likely activate estrogen- and MAPK cascade signaling pathway that regulate cell proliferation and differentiation, cell cycle progression and apoptosis in EOC through stimulation of expression of SERPINB3, SERPINB11, GAL11, SPP1 and A2M genes. Legend: RAS, synaptic Ras-GTPase-activating protein; RAF, mitogen-activated protein kinase (MAPK) kinase kinase; MEK, MAPK kinase; ERK1/2, extracellular signal-regulated kinase; ER, estrogen receptor; TF, transcription factor.

estrogen receptors as shown in Fig. 1.[133] However, further studies are required to elucidate the clinical application of discoveries of these target genes in the diagnosis and treatment of EOC.

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