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Ovarian cancer as a genetic disease

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1. ABSTRACT

Ovarian cancer is characterized by the highest mortality rate among gynecologic malignancies. Therefore, there is a growing need for innovative therapies and techniques for monitoring and prevention of this disease. The exact cause of most ovarian tumors usually remains unknown. Ovarian cancer is believed to be caused by a range of different variables. This review is an attempt to summarize some genetic factors involved in the disruption of certain signaling pathways responsible for ovarian tumor transformation and development. Those factors considerably contribute to accurate diagnostics, treatment and prognosis in ovarian cancer.

2. INTRODUCTION

Based on the SEER 1975-2007 report (The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute), ovarian cancer is the fifth most common cancer in women, with an incidence rate of 12.9 per 100,000 women per year. It is a malignant transformation of different tissues of the ovary. Depending on the subtype of affected tissues, ovarian tumors are classified as: 1. ovarian epithelial carcinoma, which is the most common type of ovarian cancer affecting the epithelial surface of the ovary, 2. sex cord-stromal tumors affecting estrogen-producing granulose cells and virilizing Sertoli-Leydig cells, 3. germ cell tumors (teratomas) cancers.

Table 1. Molecular classification of epithelial ovarian

CARCINOMA	CARCINOMA'S PRECURSORS	CRUCIAL MUTATIONS
Serous high-grade	surface epithelial inclusion glands	TP53 BRCA1 and/or BRCA2
Serous low-grade	adenoma-borderline tumor-carcinoma	KRAS BRAF
Mucinous	adenoma-borderline tumor-carcinoma	KRAS
Low-grade endometroid	endometriosis and endometrial-cell like – hyperplasia	CTNNB1 PTEN PIK3CA
High-grade endometrioid	surface epithelial inclusion glands	TP53 BRCA1 and/or BRCA2
Clear cell	endometriosis	PTEN PIK3A

originating from the germinal cells, 4. mixed tumors, affecting a number of ovarian tissues. Epithelial ovarian cancer comprises the majority of malignant ovarian tumors in adult women. Based on the appearance of the epithelium, these neoplasms are classified into distinct morphologic categories of tumors: Serous, Mucinous, Endometriod, Clear cell, Transitional, Squamous, Mixed, and Undifferentiated.

Ovarian cancer can also be a secondary cancer resulting from metastasis from a primary cancer elsewhere in the body**.** In these patients, common primary cancers are breast cancer, peritoneal cancer and gastrointestinal cancer.

3. REASONS

3.1. Ovarian cancer as an effect of multiple factors

Ovarian carcinoma is believed to be caused by various groups of factors: environmental, individual and genetic. Family history is the strongest risk factor for ovarian cancer. The risk is greater in older women and women whose first or second degree relative has suffered from this type of malignancy. Patients with a history of breast cancer or a family history of breast and/or ovarian cancer may also fall into this risk group. Some data suggest that hereditary forms of ovarian cancer can be caused by mutations in BRCA1 on chromosome 17q and in BRCA2 on chromosome 13q (1-7). Ovarian carcinoma belongs to estrogen-dependent cancers. Infertile women, women with endometriosis and women using postmenopausal estrogen replacement therapy are at an increased risk. It is a generally accepted view that risk factors for ovarian carcinoma are related to the general phenomenon of "incessant ovulation." Thus, women who have never been pregnant are exposed to a higher risk. Factors that interrupt ovulation, such as pregnancy and contraception, lower the risk. Consequently, the risk is reduced for women with more than one child. Early or late pregnancy and the use of contraceptive pills also have a protective effect, as does tubal ligation (8, 9).

3.2. Ovarian cancerogenesis as an effect of genetic changes in precursor lesions

Current data indicate that each histological subtype of ovarian cancer is associated with distinct molecular and morphologic changes. What is significant is the fact that genetic alterations characteristic for particular types of carcinoma are commonly present in precursor structures of that cancer (10, 11). This data suggest that cancerogenesis is induced by specific mutations in precursor lesions. There are at least 2 pathways of ovarian cancerogenesis: 1) arising stepwise from benign and borderline tumors or structures such as endometriosis; 2) starting de novo from surface epithelium or its alterations (surface epithelial inclusion glands) (10). Each pathway comprises crucial mutations in the precursor lesions (Table 1). High-grade serous carcinoma probably derives from surface epithelial inclusion glands with TP53 mutations and dysfunction of BRCA1 or/and BRCA2 (12-15). Low-grade serous carcinomas possibly develop in a stepwise manner in an adenoma-borderline tumor-carcinoma sequence via activation of the RAS-RAF signaling pathway due to mutations in KRAS and BRAF (16-18). Mucinous carcinomas possibly develop via an adenoma-borderline tumor-carcinoma sequence with a mutation in KRAS (19-21). Low-grade endometrioid carcinomas develop most probably from endometriosis via mutations in CTNNB1 (22, 23), PTEN (24, 25) and PIK3CA (11). High-grade endometrioid carcinomas have demonstrated genetic alterations similar to those in high-grade serous carcinomas (14). Clear cell carcinomas possibly derive from endometriosis. The molecular background of this phenomenon is still not known. Some evidence suggests that the decisive factors for this type of carcinoma are mutations in PTEN and PIK3A (24, 26).

3.3. Other genetic factors

Not all the reports concerning ovarian carcinoma take into account its histological type. Genetic alterations (mutation, deletion, translocation, overexpression or amplification) in ovarian cancer have been confirmed for genes: ERBB2, ERBB1 (EGFR), FOLR1, CDKN1A, CDKN1B, AKT2, MYC, TFAP2A, BCL-2, IL6, SPARC, VEGT, p16, p15, RB, XIAP and STAT3. Microsatellite instability has been described in ovarian neoplasms, particularly in the early stages (stage I: 75%; stages II-IV: 11-15%) (27, 28). A large set of data concerning changes in gene expression levels has been obtained using microarrays techniques. This method allowed identification of genes which are up- and downregulated in ovarian cancer and those whose expression allows the distinguishing of different histological types of cancer. Functional interpretation of these results remains a challenge.

4. THE ROLE OF ALTERED GENES

4.1. BRCA1

BRCA1 (breast cancer 1, early onset), known as a tumor suppressor gene, is involved in a number of important cellular functions, including DNA damage repair, cell cycle checkpoint control, apoptosis, and transcriptional regulation (6). It has been found that the BRCA1 protein is a component of RNA polymerase II transcription complex and activates gene transcription *in vitro* (29-32). The BRCA1 gene consists of 22 coding exons distributed over approximately 100 kb of genomic DNA on chromosome 17q21 (32). To date, about 300 mutations within the BRCA1 gene have been identified, including small insertions, deletions, and nonsense mutations, most of

which lead to a functionally inactive protein (7, 33-35). Thus, mutations in BRCA1 might be expected to affect the expression of other genes, presumably those involved in the regulation of growth or differentiation in breast and ovarian tissues. BRCA1 and BRCA2 are known to conjunct to hRAD51 (RAD51 homolog) protein and form a functional biochemical complex involved in the repair of double-strand DNA breaks and the maintenance of genomic stability. (7). Dysfunction of this complex may be one of the reasons for hereditary breast and/or ovarian cancer (36-38). Many of the functions ascribed to BRCA1 are connected with its E3 ligase activity after binding to BARD1 **(**BRCA1-associated RING domain protein 1) (39). BARD1 interacts with the N-terminal region of BRCA1. The BARD1/BRCA1 interaction is disrupted by tumorigenic amino acid substitutions in BRCA1, which implies that the formation of a stable complex between these proteins may be an essential aspect of BRCA1 tumor suppression. BARD1 may be the target of oncogenic mutations in breast or ovarian cancer. BRCA1 plays an important role in all types of cells and tissues, but its role in hormonally regulated tissues such as breast and ovary is intriguing. The estrogenes: oestrone (E1), estrodiol (E2) and oestriol (E3) exert their effects by binding to the estrogen receptors (ERa and ERh). The BRCA1 level dramatically increases during puberty and pregnancy, when the E2 level increases. Administration of E2 to ovariectomized animals induces expression of BRCA1 (32, 40). The BRCA1 promoter possesses estrogen-responsive elements (ERE), but also other sequences resembling ERE. These similar sequences might not directly interact with or respond to E2, but they may rather interact with different co-factors competing with the binding of E2 to ERE. This competition may be of great importance in the control of cell proliferation after E2 stimulation. Mutations in ERE or sequences resembling ERE may lead to a disruption of the proliferative control and tumorigenesis.

The estrogen receptor alpha (ERa) is a key molecule in breast cancer development, and a predictive marker for anti-estrogen response in clinical practice. After estrogen stimulation, BRCA1 interacts with ERa and inhibits the ERa-mediated transactivation. It has been shown that cotransfection of wild-type BRCA1 with ERa blocked the ability of ERa to transactivate receptor constructs under the control of estrogen-responsive elements. In contrast, most cancer-associated mutated forms of BRCA1 lack the ability to repress ERa signaling (41). This finding suggests that BRCA1 could inhibit ERa-driven proliferation and that mutations in BRCA1 would disrupt this inhibition. It has been shown that BRCA1 may affect ERa transcriptional activation by deregulating the ERa coactivator p300. BRCA1 and p300 compete for the same binding site on ERa and the overexpression of p300 reverses BRCA1-mediated repression of ERa (42). Cyclin D has also been reported to compete with BRCA1 for ERa binding and to reverse BRCA1-mediated repression of ERa transactivation (41). Since ERa is essential for the proliferation and differentiation of breast and ovarian tissue, the blocking of ERa by BRCA1 would reduce the proliferative capacity of estrogens. Approximately 90% of BRCA1-linked tumors are ERa negative and, similar to ERa deficient tumors, have a poor prognosis (43). Many ERa-negative tumors have mutations in BRCA1 and the negative expression of ERa is reported to be a predictor for mutations in BRCA1 (44, 45). In consequence, the loss of BRCA1 function would promote increased ERa signaling, resulting in increased proliferation and malignant transformation. However, as mentioned above, the majority of BRCA1 mutant tumors do not express ERa (44, 46, 47). Preclinical models indicate that the loss of BRCA1 function is accompanied by the loss of ERa expression. In this case, the developing tumor would be hormonally independent (41). This would explain the failure of tamoxifen as a chemopreventative agent in these patients. Why, then, do estrogens exert a carcinogenic effect? One possible explanation is that estrogen metabolites can be genotoxic, and some studies have reported the carcinogenic effect of prolonged exposure to estrogens (48, 49).

4.2. BRCA2

The BRCA2 (breast cancer 2, early onset) gene consists of 26 coding exons distributed over approximately 70 kb of genomic DNA, encoding a transcript of 11 to 12 kb (50). Similarly to BRCA1, BRCA2 is able to function as a transcription factor and activate transcription *in vitro* (51). An “ovarian cancer cluster region” has been identified in exon 11 of the BRCA2 gene. Mutations in this region appear to be linked to a higher incidence of ovarian and breast cancer (52). In ovarian carcinoma with microsatellite instability there has been found a mutated coding poly-A region of the BRCA2 gene (53).

4.3. P53 (TP53)

The tumor protein 53 or p53 is a tumor suppressor protein that in humans is encoded by the TP53 gene, which is located on the short arm of chromosome 17 at position 13.1 (17p13.1) (54-56). The protein it encodes plays an essential role in regulating cell division and preventing tumor formation (57). p53 binds directly to DNA and plays a role in apoptosis, genetic stability, and inhibition of angiogenesis. In its anti-cancer role, p53 works through several mechanisms: It can activate DNA repair proteins when DNA is damaged. It can induce growth arrest by stopping the cell cycle at the G_1/S regulation point when DNA damage is recognized (this allows the repair of the DNA damage and continuation of the cell cycle). It can initiate apoptosis if the DNA damage proves to be irreparable. Activation of p53 prevents the replication of damaged DNA until repair or apoptosis is completed (58).

Mutations of the TP53 gene are the most common mutations in human cancers (59). Most TP53 mutations disrupt the ability of the protein to bind effectively to DNA. TP53 gene mutations have been observed in a high number of ovarian tumors, which confirms the protein’s crucial role in cancer prevention through its action as a checkpoint control for recognizing damaged DNA and the induction of repair or apoptosis (26, 60-63). It has been suggested that alterations in the p53 protein due to missense mutations or absence of the p53 protein due to nonsense or frameshift mutations might play an important role in the clonal expansion of neoplastic cells

(64). Besides mutations, several reports have indicated the importance of polymorphisms in the gene. Most attention has been paid to the codon 72 of the TP53 gene (65-68). Codon 72 encodes either a proline or an arginine residue. Research in a group of ovarian carcinoma patients has revealed a prevalence of Arg/Arg and Arg/Pro in codon 72 (69). Both variants are structurally diverse and seem to act differently in the induction of apoptosis and cell cycle repair (70, 71). Apart from mutations and polymorphisms, alternative p53 splice variants are found in ovarian cancers (72). Activated p53 binds to DNA and activates the expression of several genes, including CDKN1A which encodes p21. p21 binds to the G1-S/CDK (CDK2) and S/CDK complexes and inhibits their activity. These molecules are essential for the G1/S transition in the cell cycle. BRCA1 cooperates with TP53 and regulates TP53-dependent gene expression (73, 74). There is a hypothesis that BRCA1 functions as a caretaker and TP53 as a gatekeeper in BRCA1-associated ovarian cancer (58, 75).

4.4. KRAS

In the 1960s and 1970s, a great deal of research focused on murine and avian viruses which are capable of inducing tumors in those species (76, 77). Ras genes are the family of protooncogenes originally isolated from rats with sarcoma and found in human cancer cells (78-80). In humans there are three prominent members of the Ras gene family: *H-RAS* (Harvey rat sarcoma viral oncogene homolog) and *K-RAS* (Kirsten rat sarcoma viral oncogene homolog), corresponding to the rat sarcoma virus oncogenes, and *N-RAS* (neuroblastoma RAS viral oncogene homolog), which was first isolated and identified in human neuroblastoma cells (81). These three genes are unlinked and mapped to different chromosomes: *H-RAS* to chromosome 11, *K-RAS* to chromosome 12, and N-RAS to chromosome 1 (81, 82). The proteins encoded by Ras family genes are small GTPases involved in cellular signal transduction. Activation of Ras signaling pathways triggers cell division, growth, differentiation and survival. Mutations in the Ras genes can permanently activate signal transduction, which can in consequence lead to cancerogenesis (83). The members of the Ras gene family are among the most common proto-oncogenes associated with human neoplasms and have been found to be mutated in 20% to 30% of all human tumors (84). They have been also reported in adenocarcinomas of the pancreas, colon and lung, thyroid tumors, leukemia and many other types of cancers (84). It is reasonable to speculate that a pharmacological approach that curtails Ras activity may represent a possible method for inhibiting certain cancer types. In ovarian cancer, mutations of the *K-RAS* gene most often occur in codons 12 and 13, in around 90% and 10%, respectively (85-89). It has also been found that tumors in younger patients more frequently contained a *K-RAS* mutation. Sequencing codon 12 revealed that *K-RAS* mutations exist in several histological types of ovarian carcinomas (89). Mutations in codon 61 are rare in ovarian cancers (90, 91). The protein product of *K-RAS* gene is involved primarily in signal transduction regulating cell division and differentiation. It is a part of the signaling pathway of EGFR (epidermal growth factor receptor) and it stays behind the EGFR connected to the cell membrane. Normally the K-RAS protein activates only after the EGFR activation, but when mutation appears in the K-RAS gene, instead of triggering cell growth in response to particular signals from outside the cell, the protein is constantly active, which leads to uncontrolled growth, tumor cell formation and development of many cancers (92). In such cases, the attacking and blocking of EGFR by the targeted therapy is ineffective because the mutated K-RAS gene is not dependent on the EGFR signal. This way anti-EGFR therapy would not have any positive effect because KRAS continue to be active, and the tumor growth would not be stopped. Looking for *K-RAS* mutations before starting anti-EGFR therapy would help oncologists in choosing the right treatment. Patients without mutations in the *K-RAS* gene would benefit from an anti-EGFR target therapy, but in those with mutations in *K-RAS*, such therapy might harm rather than help. For patients under standard therapy, *K-RAS* mutation was not found to have impact on prognostic value, but these mutations might be an important factor for individually tailored anti-EGFR therapies (87).

4.5. PIK3CA

PIK3CA is a gene which codes the catalytic (alpha polypeptide) of the subunits of phosphoinositide-3-kinase. The PIK3 protein is composed of 2 units: an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. It phosphorylates phosphatidylinositols (PI), Phosphatidylinositol 4-phosphate (PI4P) and Phosphatidylinositol 4,5-bisphosphate (PI (4,5)P2). There are three widely expressed catalytic subunits: P110 alpha, beta or delta. The P110alpha is localized in the cytoplasm and has been shown to interact with h-RAS (93). PIK3CA phosphorylates AKT (v-akt murine thymoma viral oncogene homolog 1) and stimulates cell growth. Recent evidence has shown that the *PIK3CA* gene is mutated in a number of human cancers (94). *PIK3CA* has been found in increased numbers of copies in many ovarian cancer cases, and it has been suggested that *PIK3CA* is one of the crucial oncogenes in ovarian cancer (95). Disruption of the PIKC3A/AKT pathway has been proved to play an important role in ovarian malignancy (96). An elevated level of *PIK3CA* transcript has been detected in around 66.6% of stage I and 93.9% of advanced stage ovarian cancer specimens. Transcript levels were significantly higher in invasive carcinomas. Elevated PIK3CA-mRNA level has been positively correlated with the increased proliferation and decreased apoptosis of tumor cells, angiogenesis and cancer progression (97). Furthermore, overexpression of PIK3CA in ovarian surface epithelium has been reported to induce hyperplasia (98). It has been also found that the PIK3CA amplification in ovarian carcinomas is more frequent in tumors with TP53 mutations and associated with high AKT expression. PIK3CA overexpression has been associated with resistance to chemotherapy and has been proposed as a marker predicting response to chemotherapy in ovarian cancer (97, 99). Due to the association between PIK3CA and cancer progression, P110alpha is believed to be a promising drug target. It is found that treatment with the PI3-kinase inhibitor LY294002 decreases proliferation and increases apoptosis (95, 100). Many pharmaceutical companies are currently designing and characterizing

potential P110alpha isoform specific inhibitors (53, 101). Another approach is targeting PIK3CA using siRNA techniques. This strategy allows studying of the function of various PIK3 isoforms and developing the isoform-specific targeting of PIK3 in human cancer (102). Researchers have identified two alternate *PIK3CA* promoters. Moreover, p53 has been shown to directly bind to and cause transcriptional inhibition of one of these promoters. Studies have demonstrated that overexpression of p53 by adenoviral infection or activation of p53 by gamma-irradiation diminished P110alpha protein levels both in normal ovarian surface epithelium and in ovarian cancer cells (103). The information that p53 binds directly to the *PIK3CA* promoter and inhibits its activity reveals a novel mechanism of cell function regulation and the pathophysiology of ovarian cancer (103).

4.6. CTNNB1

Beta-catenin is a protein encoded in humans by the *CTNNB1* gene (104). The protein plays a part in the signaling pathway that is necessary for the creation and maintenance of epithelial cell layers by regulating cell growth and adhesion between cells. Beta-catenin also anchors the actin cytoskeleton and is proposed to be responsible for transmitting the contact inhibition signal that causes cells to stop dividing once the epithelial sheet is complete. Beta-catenin contains armadillo repeats and is able to bind to other proteins: cadherins, transcription factors, axin, EGFR, galectin-3, beta-galactoside-binding protein, HER2/neu (human epidermal growth factor receptor 2), RuvB-like 1 and others (105-110). The ability of beta-catenin to bind to other proteins is regulated by tyrosine kinases and serine kinases such as GSK-3 (glycogen synthase kinase 3) (111, 112). Beta-catenin can be phosphorylated by other kinases such as protein kinase A (PKA). Phosphorylation of beta-catenin by PKA has been associated with increased levels of beta-catenin in the nucleus and interaction of beta-catenin with TCF family transcription factors to regulate gene expression (113). Beta-catenin can function as an oncogene (114). An increase in beta-catenin production has been noted in patients with basal cell carcinoma, leading to an increase in the proliferation of related tumors (115). Mutations in this gene are a cause of colorectal cancer, pilomatrixoma, medulloblastoma, and ovarian cancer (22, 116-118). Reduced or absent expression of beta-catenin in ovarian cancers, compared to the normal ovarian epithelium, probably makes it possible for the catenin associated with membrane proteins in ovarian epithelium to function as tumor suppressors in this epithelium. Therefore, the suppressed expression of main adhesion molecules in the adherens junction might contribute to adherens junctional dysfunction, which might lead to the acquirement of invasiveness and metastatic potential by advanced ovarian cancers (119, 120). The immunohistochemical profile of beta-catenin was shown to be of biological relevance: reduced beta-catenin was correlated with loss of tumor differentiation and serous carcinomas that are known to depict aggressive biological behavior in epithelial ovarian tumors (121). Negative immunoreactivity of beta-catenin in serous ovarian carcinomas and the presence of residual tumor are associated with poor prognosis (122, 123). The expression of beta-catenin in ovarian tumors was related to a good prognosis for the patients. Determination of the beta-catenin expression pattern in early-stage ovarian cancer could prove to be a useful marker for selecting low-risk patients (23).

4.7. PTEN

PTEN (Phosphatase and tensin homologue deleted on chromosome 10), mapped to chromosome 10q23.3, is another tumor suppressor gene involved in ovarian cancerogenesis. It encodes a tyrosine phosphatase which preferentially dephosphorylates PIP3 (Phosphatidylinositol (3,4,5)-trisphosphate) and therefore acts as a negative regulator of the Act signaling pathway. Inactivating mutations of *PTEN* compared to *TP53* are quite uncommon and found only in 3-8% of ovarian carcinomas, which are mostly of the low-grade endometrioid histotype (124). Deactivation of PTEN stimulates the proliferation, migration and invasion of cancer cells, and is known to be involved in peritoneal dissemination. Recent studies demonstrate that enhanced expression of PTEN inhibits ovarian cancer cell migration, suggesting the role of putative *PTEN* gene therapy in suppression of peritoneal dissemination of ovarian cancer (125, 126). Overexpression of PTEN was also shown to suppress ovarian tumor growth and to prolong the survival time of the mice with peritoneal disseminated tumor (125).

4.8. Other genes contributing to ovarian cancer

4.8.1. ERBB2

Another oncogene involved in tumorigenesis is *HER2/neu* (Human Epidermal growth factor Receptor 2), also known as: v-erb-b, ERBB2, CD340 and P185. The ERBB2 gene codes a protein called the ErbB2 growth factor receptor. This receptor is located on the cell surface, where it associates with similar receptors (for example: ErbB3) to form a complex. Growth factors bind to these receptors and trigger the complex to transmit the signals inside the cell. HER2/neu-activated signaling pathways are known to promote cell growth. ErbB2 probably also plays a role in cell adhesion, differentiation, and mobility. Overexpression of ErbB2 is associated with aggressive tumors that are more likely to metastasize to other tissues. The *ERBB2* gene is located on the long arm of chromosome 17 between positions 11.2 and 12 (17q11.2-q12). *ERBB2* encodes a 185-kDa orphan receptor tyrosine kinase, comprised of 1255 amino acids. It consists of three domains: a single transmembrane domain that separates an intracellular kinase domain from an extracellular ligand-binding domain. HER2/neu displays potent oncogenic activity when overexpressed. Approximately 15-20 percent of breast cancers have an amplification of the HER2/neu gene or overexpression of its protein product. Another study has shown the *HER2/neu* oncogene to be amplified and/or overexpressed in 25%-30% of human breast and ovarian cancers, and its overexpression portends a poor prognosis for those patients whose tumors contain this kind of alteration. Overexpression of this receptor in breast cancer is associated with increased disease recurrence and a worse prognosis. HER2 positive tumors are much more aggressive and recur more often than HER2 negative tumors. Overexpression also occurs in other cancer types,

such as ovarian cancer, gastric cancer, and biologically aggressive forms of uterine cancer, such as uterine serous endometrial carcinoma (127). Improved understanding of HER2/neu signal transduction pathways may lead to the identification of novel therapeutic targets in the treatment of carcinomas.

4.8.2. FOLR1

Folate receptor 1 (Folate receptor alpha, Folate-binding protein-FBP, Ovarian tumor-associated antigen-MOv18) is a protein encoded by the FOLR1 gene (128). It is a member of the folate receptor (FOLR) family. Members of this gene family have a high affinity for folic acid and for several derivatives of a reduced folic acid, and mediate delivery of 5-methyltetrahydrofolate to the interior of cells. So far, four family members (FR-alpha, -beta, -gamma, and -delta), have been identified (129). Genes coding FR, FOLR1-4, are located on the long arm of chromosome 11. FOLR1 and FOLR2 code membrane-attached glycoproteins bound to glycosyl phosphatidylinositol anchor, whereas FOLR3 codes 2 forms of secreted protein: FR-gamma and altered FR-gamma' (129, 130). FR family members bind folic acid and its reduced derivatives, and transport 5-methyltetrahydrofolate into cells. Mutations in this gene have been associated with neurodegeneration due to cerebral folate transport deficiency. Separate research groups have reported the overexpression of FBP family proteins in ovarian cancers. The degree of FBP overexpression was significantly associated with parameters of biological aggressiveness, indicating an involvement of FBP in the progression of these neoplasms. The role of high-affinity FBPs in ovarian cancer is intriguing. It is possible that the attachment of FBP by a GPI (Glycosylphosphatidylinisotol) link may act not only as a mean of controlling cell surface expression, but may also be involved in cell activation or communication (131-133). There is an antibody against FBP called MOv10. It recognizes specific epitopes of the glycoprotein, which are present only on ovarian tumors and completely absent on normal ovarian, uterine and vaginal tissues (134). Moreover, it was suggested that folate receptor levels effectively differentiate ovarian carcinoma from other cancers, and that the high expression of folate receptors in ovarian carcinoma supports their validity as molecular therapeutic targets in this disease (135).

4.8.3. CDKN1A and CDKN1B

Cyclin-dependent kinase inhibitors: CDKN1A (p21, Waf1, Cip1) and CDKN1B (p27, Kip1) are potent inhibitors of various cyclin-dependent kinases controlling the cell cycle, the expression of which is regulated at the transcriptional level by p53-dependent and independent mechanisms. Mutations in *CDKN1A* and *CDKN1B* are potentially important in human malignancies because they could affect the control of the cell cycle. P21 and P27 are significant prognostic markers for improved survival in ovarian cancer and novel targets for the therapy (136-153).

4.8.4. AKT2

AKT2 (v-akt murine thymoma viral oncogene homolog 2) is a putative oncogene encoding a 56kDa protein belonging to a subfamily of serine/threonine kinases. AKT protein plays a key role in multiple cellular processes, such as glucose metabolism, cell proliferation, apoptosis, transcription and cell migration. The gene was shown to be amplified and overexpressed in 2 out of 8 ovarian carcinoma cell lines and in 2 out of 15 primary ovarian tumors (154). Overexpression and alterations may contribute to the pathogenesis of ovarian carcinomas and to a malignant phenotype, poor prognosis and aggressiveness (155). It has been demonstrated that AKT2 is activated by several growth factors, including epidermal growth factor, insulin-like growth factor 1, insulin-like growth factor II, basic fibroblast growth factor, platelet-derived growth factor, and insulin, in human ovarian epithelial cancer cells. Moreover, AKT2 activation occurs via Ras and v-Src proteins generating transduce growth factors signals. These findings provide further evidence that AKT2, in cooperation with Ras and Src, is important in the development of some human malignancies (156). The knowledge about the activation of the PI 3-kinase/Akt signaling pathway in human primary ovarian cancer facilitated the search for specific inhibitors. It has been demonstrated that wortmannin or LY294002 inhibits PI 3-kinase/AKT2 activation and induces apoptosis in ovarian cancer cells. These findings demonstrate for the first time that the activation of AKT2 is a common occurrence in human ovarian cancer and that PI 3-kinase/Akt pathway may be an important target for ovarian cancer intervention (157). Mutations of *PIK3CA* and *ATK2* are rare in ovarian serous tumors but amplification of both genes is reported to play an important role in the development of high-grade ovarian serous carcinoma (158-162). Development of potent inhibitors that block the AKT pathway is an attractive therapeutic strategy for treating ovarian carcinoma. 9-methoxy-2-methylellipticinium acetate (API-59-OME) is a non-peptide small molecule compound, which potently inhibits the AKT pathway. Treating of ovarian cancer cell lines with different doses of API-59-OME may be an effective agent to target constitutively activated AKT pathway in ovarian cancer cells (163). Another small molecule called API-1 binds to pleckstrin homology domain of AKT and blocks AKT membrane translocation. Furthermore, API-1 inhibits the kinase activities and phosphorylation levels of the three members of the AKT family. The inhibition of AKT by API-1 has induced the cell cycle arrest and apoptosis selectively in human cancer cells with constitutively activated AKT, but not in those cancer cells in which AKT is not activated. API-1 could be a potential anti-cancer agent for patients with tumors expressing hyperactive AKT (164). Another therapeutic approach is inhibition of AKT2 using siRNA technology (165, 166).

4.8.5. TFAP2A

Transcription factor AP-2 alpha, (Activating enhancer-binding protein 2 alpha, AP2, AP2TF) is a 52-kD transcription factor that recognises and binds to specific DNA GC-rich sequences. There have been various TFAP2A-binding sites identified (167, 168), among them sequences: 5'-GCCN3GGC-3', 5'-GCCN4GGC-3', 5'-GCCN3/4GGG-3' and 5'-CCCCAGGC-3' have been reported to mediate both activation and repression of gene

transcription (169). TFAP2A has been shown to interact with P53 (170). Dysregulation of TFAP2A protein levels alters the cell functions via dysregulation of genes involved in physiological or pathological processes, such as development, cell growth, differentiation, apoptosis and tumorigenesis. Expression of TFAP2A was reported to relate with survival in cases of ovarian cancer. In a study of 303 ovarian carcinomas analyzed for AP-2 alpha expression, it was found that cytoplsamic expression is related to survival, while the nuclear expression combined with low cytoplasmic expression increases the fatality risk. It has been suggested that shifting the expression from cytoplasm to the nuclei in carcinomas is followed by the transcriptional activation of some oncogenes (171). Additionally, overexpression of AP-2alpha has been demonstrated to change cell morphology from spindle to epithelioid type and to suppress cell proliferation and invasion. These data represent the first direct evidence that AP-2alpha plays a tumor suppressive role in ovarian cancer (172). Furthermore, analysis of the expression of the AP-2gamma transcription factor in ovarian tumors has shown a growing percent of nuclear AP-2gamma expression in cases of advanced stage carcinomas. The authors conclude that AP-2gamma expression is upregulated in advanced-stage ovarian carcinoma compared to early-stage carcinomas, borderline tumors, and the ovarian surface epithelium, suggesting a role in tumor progression (173). AP-2gamma has been proposed as an additional diagnostic marker for ovarian carcinomas next to the elevated levels of CA125 (174).

4.8.6. BCL-2

B-cell lymphoma 2 (BCL-2) is a protein inhibiting mitochondria-induced apoptosis. Its name derives from B-cell lymphoma 2, as it was initially described in chromosomal translocations involving chromosomes 14 and 18 in follicular lymphomas (175, 176). BCL-2 is located on the mitochondrial membrane and contains a transmembrane domain and domains named BH1, BH2, BH3 and BH4. BCL-2, in addition to Bak and Bax proteins, is involved in mitochondria-induced apoptosis. When activated, pro-apoptotic Bak and/or Bax form MAC (Mitochondrial Apoptosis-induced Channel) mediates the release of cytochrome c and other apoptogenic factors that trigger apoptosis via activation of the caspases (177). Once activated, anti-apoptotic BCL-2 inhibits Bax and/or Bak and blocks the release of these factors (178). The *BCL-2* gene has been implicated in a number of cancers. It is also suggested to be a reason for the decreased apoptosis in tumors and resistance to conventional cancer treatment. Investigations of BCL-2 as an anti-apoptotic factor and its role in the pathogenesis of ovarian cancer and resistance to chemotherapy have found the expression of BCL-2 to be significantly higher in malignant than in benign ovarian tumors (179). The loss of expression of BCL-2 in ovarian carcinomas is a favorable prognostic factor. It has been found that significantly poorer survival has been observed in patients with BCL-2 positive ovarian tumors than those with negative BCL-2 staining (180). Elevated BCL-2 level correlates with the platinum drug resistance in ovarian carcinomas (181). BCL-2 expression has been found to be a significant independent predictor of responsiveness to chemotherapy (182). Many reports have shown that BCL-2 overexpression contributes to neoplastic transformation and drug-resistant disease, resulting in a poor clinical outcome. The overexpression of the BCL-2 protein or p53 protein plays an important role in the malignant transformation of ovarian endometriosis. Alterations in BCL-2 and p53 may be associated with the malignant transformation of endometriotic cysts (183).

Knowing the molecular mechanism, explaining the overexpression of BCL-2 may help in understanding of mechanisms responsible for chemotherapy resistance. Further studies in this area would help clarify the therapeutic possibilities. A novel finding is the relationship between BCL-2 expression, lymphocyte infiltration and ovarian cancer progression. BCL-2 expression and lymphocyte status may be important for prognostics or as useful targets for therapeutic intervention (184). On the contrary, some most recent data suggest that BCL-2 expression may not be of important clinical value in the treatment of Danish ovarian cancer patients (185).

4.8.7. IL6

Interleukin-6 is cytokine acting as both a pro-inflammatory and anti-inflammatory. It is secreted by T cells and macrophages to induce immune response in reply to trauma and other tissue damage. The anti-inflammatory role of IL-6 is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10. IL-6 is also produced by muscles as a respond to muscle contraction. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and augment substrate delivery (186). Additionally, IL-6 is known to be secreted by osteoblasts to stimulate osteoclast formation.

IL-6 is one of the key mediators of the acute phase response. It is relevant to many disease processes, including cancerogenesis. Advanced and metastatic cancer patients have higher levels of IL-6 in their blood. There have also been reports that single nucleotide polymorphism (G/C) at position -174 in IL6-gene promoter is associated with the biological phenotype of ovarian cancer and overall survival (187, 188). Hence, there is an interest in developing anti-IL-6 agents as therapy against ovarian cancer (189, 190). Expression of the interleukin-6 receptor (IL6R) has been found increased in malignant ovarian tumors and localized in epithelial cells. Additionally, expression of a soluble splice variant of IL6R was also increased in malignant tumors. Soluble IL6R may be an efficacious target for reducing IL6-mediated ovarian tumor progression (191). IL-6 signaling pathways and IL-6-induced gene expression are effectively blocked by siltuximab. Blockage of IL-6 signaling may provide benefits for the treatment of ovarian cancer (192).

4.8.8. SPARC

SPARC is a calcium-binding bone glycoprotein coded by the *SPARC* gene. It is a component of the extracellular matrix secreted by osteoblasts during bone formation, initiating mineralization and promoting mineral crystal formation. It is a regulated directly by progesterone

and dexamethasone and indirectly by cytokines. Osteonectin stimulates the production and the activity of matrix metalloproteinases, which are essential agents in the process of cancer cell invasion and metastasis. Additionally, osteonectin is known to stimulate angiogenesis, proliferation and migration, which is beneficial to tumor cells. Some current research shows a correlation between osteonectin overexpression and ampullary cancers and chronic pancreatitis. Overexpression of osteonectin has been reported in many human cancers, such as breast, prostate, pancreas, colon and ovary cancer (193). In one of the studies, SPARC protein was found in 63% of investigated ovarian carcinomas. The expression was restricted to the stroma of neoplastic ovaries and suggested to be associated with malignant transformation (194). In another study, SPARC expression was up-regulated in reactive stroma and associated with invasive ovarian cancer. It has been suggested that SPARC protein secreted from the stroma may be incorporated by ovarian cancer cells and exert important intracellular effects upon these cells (195). Other data demonstrate a much lower expression of SPARC in ovarian carcinoma than in normal ovarian epithelium (196). Transfection of ovarian carcinoma cells with SPARC reduced cell growth and led to the hypothesis that SPARC functions as tumor suppressor (196). It has been suggested that the function of the tumor suppressor of SPARC is its inhibiting the proliferation of both normal and cancer cells and inducing apoptosis only in cancer cells. This observation indicates that down-regulation of SPARC makes ovarian cells resistant to apoptosis during malignant transformation (197). There is also some evidence that putative SPARC receptors are present on ovarian epithelial cells. Their levels are higher in human ovarian surface epithelial cells than cancer cells. The binding of SPARC to its receptor is likely to trigger tissue-specific signaling pathways that mediate its tumor suppressing functions. A decrease in ligand-receptor interaction by the down-regulation of SPARC and/or its receptor is essential for ovarian carcinogenesis (197). *In vitro* experiments have shown that SPARC significantly suppresses the adhesion and invasion of human ovarian cancer cell lines. Thus, SPARC represents an important candidate in ovarian cancer treatment (198). In addition to its potent antiproliferative and proapoptotic functions, SPARC also abrogates ovarian carcinoma cell adhesion, which is an important step in peritoneal implantation. SPARC significantly inhibits integrin-mediated ovarian cancer cell adhesion to extracellular matrix proteins, as well as to peritoneal mesothelial cells. Moreover, SPARC significantly suppressed activation of AKT and mitogen-activated protein kinase survival signaling pathways in ovarian cancer cells in response to serum and epidermal growth factor stimulation. In summary, researchers have identified a novel role of SPARC as a negative regulator of both integrin-mediated adhesion and grow factor-stimulated survival signaling pathways in ovarian cancer (199). SPARC inhibits mesothelial-ovarian cancer cell crosstalk and represents a potential therapeutic candidate in peritoneal ovarian carcinomatosis (200). SPARC normalizes the microenvironment of ovarian cancer malignant ascites through down-regulation of the VEGF-integrin-MMP axis, decreases the levels and activity of bioactive lipids, and ameliorates inflammation (200). SPARC significantly reduces macrophage chemoattractant protein-1 production and its macrophage chemotactic effect, and decreases macrophage-induced cancer cell invasiveness. Overexpression of SPARC in ovarian cancer cells attenuates macrophage- and mesothelial cell-induced production and the activity of interleukins and prostaglandins, as well as of matrix metalloproteinases and the plasminogen activator. These results indicate that the effects of the tumor SPARC protein as a negative regulator of ovarian cancer are mediated through decreased recruitment of macrophages and downregulation of the associated inflammation (201). Besides its antitumor effect by controlling cell growth, SPARC is reported to impede the efficacy of cisplatin therapy. Therefore, selective inhibition of SPARC may provide an attractive strategy for increasing the efficacy of therapy in platinum-resistant ovarian tumors (202). SPARC is downregulated in ovarian cancer through aberrant promoter hypermethylation. Treatment with the demethylating agent 5-aza-2'-deoxycytidine rescued SPARC mRNA and protein expression. Addition of exogenous SPARC resulted in decreased proliferation of ovarian cancer cell lines. These results implicate *SPARC* promoter methylation as an important factor in the genesis and survival of ovarian carcinomas and provide new insights into the potential use of SPARC as a novel biomarker for this disease (203).

4.8.9. VEGF

VEGFs are a family of growth factors responsible for triggering an angiogenesis. The most important member is VEGF-A, simply called VEGF. Other members are VEGF-B, VEGF-C VEGF-D and placenta growth factor (PlGF). Apart from angiogenesis, VEGF stimulates vascular endothelial cell mitogenesis, migration of particular epithelial cells, neurons, monocytes and macrophages, as well as vascular permeability and vasodilatation. Human VEGF exists in different isoforms that are the result of mRNA splicing of exons 6, 7 and 8. The exclusion or inclusion of some of these exons alters the binding ability of VEGF to their receptors (VEGFRs) and changes their angiogenic function in pro- or anti-angiogenic (204). An imbalance between pro-angiogenic and anti-angiogenic factors is hypothesized to contribute to the pathogenesis of tissue development and tumorgenesis. As a potent mitogen of endothelial and epithelial cells, VEGF is produced in elevated amounts by many tumors, including ovarian carcinomas. Significantly higher VEGF expression in tissues and elevated levels in serum were observed in malignant ovarian carcinomas. Patients with strong VEGF staining had poorer survival rates than those with weak or no immunostaining for VEGF (205). Among the subtypes of VEGF splice variants, 121-, 165- and 189-amino acid types were detected, but 206-amino acid type was not observed in ovarian tumors (206). The expression of VEGF promotes angiogenesis in epithelial ovarian cancers and helps it to grow (207). Angiogenesis in ovarian tumors corresponds to the prevalence of the soluble or membrane form of VEGFR-1 (208). It has also been reported that there is a relationship of some VEGF polymorphisms with serum VEGF levels and progression-

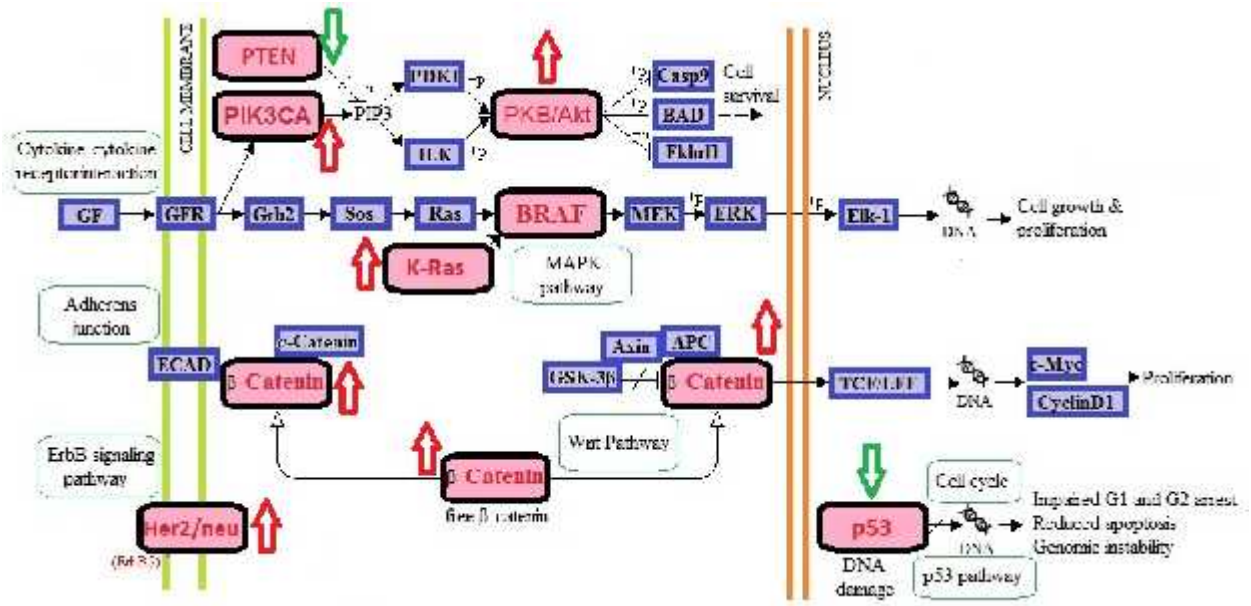

Figure 1. Selected signaling pathways involved in the pathogenesis of ovarian cancer (based on the KEGG database). Proteins crucial for the oncogenesis are marked in red. Arrows indicate changes in the functional protein level in ovarian cancer compared to healthy conditions; red arrow – overexpression/constitutional activation/disruption of inhibiting mechanisms (refers to oncogenes); green arrow – loss of function mutations/ decreased activity/decreased expression (refers to tumor supressors).

free survival in patients with epithelial ovarian cancer (209). Moreover, VEGF is suggested to contribute to peritoneal metastases in advanced ovarian carcinoma (210). It has been found that simultaneous carriage of the three homozygous genotypes of VEGF -634C/C, VEGF -1154G/G, VEGF -2578C/C is associated with shorter overall survival, and is an adverse prognosticator in patients with ovarian cancer (211). The two known human receptors for VEGF, Flt and KDR, are cell surface tyrosine kinases, and are expressed predominantly on endothelial cells (212). They have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a tyrosine-kinase domain. Binding of VEGF members to VEGFR causes receptor dimerisation and transphosphorilation (213). Strong expression of VEGF, Flt-1 and KDR was found in malignant and borderline ovarian tumors, suggesting their role in the angiogenesis associated with ovarian neoplasms (214). It has been proposed that coexpression of VEGF and KDR by tumor cells in ovarian carcinoma raises the possibility of autocrine stimulation and of therapeutic strategies related to this receptor-ligand interaction (212). Some studies indicated VEGF as a serological marker with diagnostic relevance and prognosis in ovarian neoplasms (215, 216). Elevated VEGF serum levels before therapy are correlated significantly with malignancy, poorer prognosis and overall survival. Also high VEGF expression in epithelial ovarian carcinomas has been associated with poor overall survival (217). Serum VEGF levels decreased after the successful removal of tumors and were re-elevated during relapse. Therefore, serum VEGF could be used as a prognostic factor of ovarian cancer (218, 219) and as a marker for monitoring the clinical course of ovarian cancer patients (215, 216, 220). The expression of VEGF may enhance the predictability of patients at high risk for tumor progression who are potential candidates for further aggressive therapy (221-226). Elevated VEGF levels suggest novel therapeutic perspectives by VEGF inhibition. The discovery of a group of inhibiting VEGF splice variants gave rise to the idea of using them as antiangiogenic agents for cancer treatment (227). In addition, target therapy using siRNA-mediated silencing of VEGF or VEGFR might be a promising therapeutic strategy against ovarian cancer by reducing angiogenesis and inducing apoptosis (228, 229). The anti-VEGF antibody bevacizumab has been proposed for treatment of epithelial ovarian cancer (230, 231).

5. CONCLUSIONS

5.1. Genes related to ovarian cancerogenesis

Ovarian carcinoma, like other cancers, occurs as a result of multi-stage interactions of genetic and environmental factors. Ovarian cancer transformation is triggered by mutations in certain genes. The majority of the critical genes are involved in the same signaling pathways, in particular: MAPK signaling pathway, WNT signaling pathway and p53 signaling pathway (Figure 1). Even subtle changes in these pathways might induce cancerogenesis and result in a different morphologic type of cancer and different molecular characteristics. There is also a large group of genes involved in further cancer development, neoangiogenesis, increasing malignancy and peritoneal metastasis formation.

5.2. Genetic-based approaches in managing of ovarian cancer

Ovarian cancer is characterized by the highest mortality rate among gynecologic malignancies. Therefore,

there is a growing need for early detection and diagnosis methods and innovative therapies. Some neoplasms occur as a result of inherited mutations in highly aggressive cancer susceptible genes (e.g., BRCA1, BRCA2). Recognition of individuals and families with inherited cancer predisposition syndromes, and individuals at high risk due to familial cancer clustering is fundamentally important for the management and treatment, and for future prevention, of cancer both in patients and their families. It is essential to choose the optimal treatment for a particular neoplasm. Molecular screening investigating the presence of mutations and protein expression levels allows accurate diagnosis and choosing the right treatment scheme. It may also be used in prevention and monitoring in high risk groups. Identification of additional tumor antigens and biomarkers of ovarian cancer may facilitate the development of screening methods, diagnosis and novel therapies for the disease.

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Abbreviations: PTEN – phosphatase and tensin homolog; GF – growth factor; GFR – growth factor receptor; Grb2 – growth factor receptor-bound protein 2; PI3K – phosphoinositide-3-kinase, catalytic, alpha polypeptide; PIP3 – Phosphatidylinositol (3,4,5)-trisphosphate; PDK1 – pyruvate dehydrogenase kinase, isozyme 1; Sos – son of sevenless homolog (Drosophila); Ras – rat sarcoma viral oncogene homolog; K-Ras – Harvey rat sarcoma viral oncogene homolog; BRAF – v-raf murine sarcoma viral oncogene homolog B1; ILK – integrin-linked kinase; PKB/Akt – v-akt murine thymoma viral oncogene homolog 1; Casp9 – Caspase 9; BAD – BCL2-associated agonist of cell death; MEK – mitogen-activated protein kinase; MAPKK – mitogen-activated protein kinase kinase; ERK – mitogen-activated protein kinase 1; Fkhrl1 – forkhead box O3; Elk-1 – member of ETS (E-twenty six) oncogene family; MAPK – mitogen-activated protein kinase; ECAD – type 1, E-cadherin (epithelial); GSK-3beta – glycogen synthase kinase 3 beta; APC – adenomatous polyposis coli; TCF/LEF – group of transcription factors (transcription factor /lymphoid enhancer-binding factor); c-Myc – v-myc myelocytomatosis viral oncogene homolog; p53 – tumor protein p53; Her2/neu – Human Epidermal growth factor Receptor 2; ErbB2 – v-erb-b2 erythroblastic leukemia viral oncogene homolog

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