Review

Molecular Landscape of Borderline Ovarian Tumors: A Systematic Review

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Review

Molecular Landscape of Borderline Ovarian Tumors: A Systematic Review

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Abstract: Borderline ovarian tumors (BOTs) show intriguing characteristics distinguishing them from other ovarian tumors. This unique type of non-invasive neoplasms is characterized by atypical growth of epithelial cells, nuclear atypia, and a moderate-level mitotic activity that places BOTs between benign tumors and invasive cancers. Similar to invasive carcinomas, BOTs can be categorized into six histological subtypes based on the type of epithelial cells present. The most prevalent subtypes are serous and mucinous BOTs, whereas endometrioid, clear cell, seromucinous, and borderline Brenner tumors are diagnosed less often. Noticeably, molecular changes found in BOTs can vary on a case-by-case basis, which warrants further research on the molecular landscape of these tumors. Identifying carcinogenic mutations through molecular analysis and developing targeted therapies represent significant advancements in the diagnosis and treatment of ovarian malignancies. A growing body of evidence indicates that BOTs often remain clinically dormant for extended periods before a molecular trigger initiates increased cell replication, potentially leading to carcinoma development or recurrence. Continued research in this area is crucial for improving risk assessment and developing personalized treatment approaches. While molecular studies have contributed significantly to our understanding of BOT pathogenesis, substantial research is still required to elucidate the relationship between ovarian neoplasms and extraneous disease, identify accurate prognostic indicators, and develop targeted therapeutic approaches. The aim of the present systematic review was to analyze the spectrum of molecular changes found in BOTs and discuss their significance in the context of the overall therapeutic approach.

Keywords: borderline ovarian tumors; molecular features; mutations; genetic mutations; *BRAF; KRAS; NRAS; ARID1A; CADM1; PIK3CA*; *CHEK2; CLAUDIN-1; ERBB2;* loss of heterozygosity; *PTEN;* microsatellite instability; B-CATENIN; E-CADHERIN; *BRCA 1; BRCA 2*

Introduction

Borderline ovarian tumors (BOTs) show intriguing characteristics distinguishing them from other ovarian tumors. Despite their unusual cellular structure and potential to spread, BOTs exhibit less aggressive behavior than low- (LGSC) and high-grade serous ovarian cancers (HGSC). This discrepancy has been observed since BOTs were first described by Taylor in 1929 [1]. In 2003, BOTs were officially recognized as a distinct group, and their most recent classification was published in 2014 by the World Health Organization (WHO) [2]. BOTs occur in 1.8-4.8 per 100,000 women annually, constituting 10% to 20% of all epithelial ovarian cancers, with a tendency towards higher prevalence within this group [3,4]. This unique type of non-invasive neoplasms is characterized by atypical growth of epithelial cells, nuclear atypia, and a moderate-level mitotic activity that places BOTs between benign tumors and invasive cancers [5]. Notably, BOTs do not exhibit destructive stromal invasion, which differs them from other types of ovarian neoplasms. Although BOTs do not display destructive stromal invasion, they can be associated with microinvasion, lymph node implantation, and non-invasive or invasive peritoneal implantation [5]. BOTs display molecular and genetic alterations similar to those found in LGSCs. In some cases, a gradual progression has been observed from cystadenomas and BOTs to LGSCs [6]. Similar to invasive carcinomas, BOTs can be categorized into six histological subtypes based on the type of epithelial cells present. The most

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prevalent subtypes are serous (50%) and mucinous (45%) BOTs, whereas endometrioid, clear cell, seromucinous, and borderline Brenner tumors are diagnosed less often [5,7].

BOTs are managed like invasive ovarian cancers, with a comprehensive staging guiding the choice of the most appropriate surgical intervention. The management typically involves a series of procedures, such as peritoneal washing cytology, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and complete removal of visible peritoneal lesions. BOTs often affect women in their reproductive years, so preserving fertility is a critical factor during treatment planning. In a traditional approach, fertility-sparing surgery was primarily offered to patients with BOTs localized within the ovary. However, recent evidence suggests that some appropriately selected patients with advanced disease may also be eligible for fertility-sparing procedures without compromising their safety [8]. If a patient with BOT is eligible for a fertility-sparing treatment, a choice between cystectomy and unilateral salpingo-oophorectomy needs to be made in the case of unilateral tumors or between bilateral cystectomy and unilateral salpingo-oophorectomy with contralateral cystectomy in the case of bilateral tumors [9]. While most patients with BOTs are usually diagnosed at early stages, the prognosis is still favorable even if the diagnosis is delayed [10].

Although the prognosis in patients with BOTs is typically favorable, the risk of recurrence needs to be considered. The overall recurrence rate for BOTs is approximately 30%, but it may increase to 50% in patients diagnosed at advanced clinical stages. Prognostic factors for recurrent and/or progressive disease include BOT type, patient age, FIGO stage, presence of invasive implants, microinvasion in the primary tumor, and micropapillary architecture [11]. Notably, however, no single clinical or pathological feature, or a combination thereof, can be considered an accurate predictor of unfavorable outcomes. Several prognostic factors were shown to increase the risk of recurrence, including the advanced stage of the disease at diagnosis, invasive peritoneal implants, and specific pathological features, such as intraepithelial carcinoma and a micropapillary growth pattern [12–14]. Unfortunately, treatment choices in patients with persisting or progressive disease are limited. Currently available chemotherapy schemes for invasive ovarian cancers have shown limited activity in treating BOTs [11], and given the lack of effective treatment, managing persisting or progressive BOTs constitutes a challenge.

Noticeably, molecular changes found in BOTs can vary on a case-by-case basis, which warrants further research on the molecular landscape of these tumors. Identifying carcinogenic mutations through molecular analysis and developing targeted therapies represent significant advancements in the diagnosis and treatment of ovarian malignancies. However, identifying patients with an increased risk of recurrence remains challenging. Continued research in this area is crucial for improving risk assessment and developing personalized treatment approaches. The aim of the present systematic review was to analyze the spectrum of molecular changes found in BOTs and discuss their significance in the context of the overall therapeutic approach.

Methods

The following systematic review was carried out in line with the international standards and guidelines for systematic reviews (PRISMA). Detailed review protocol can be obtained from the author upon request. PubMed, EMBASE and Cochrane databases were searched for articles published between 2000 and 2023. Eligible studies were found using a combination of the following keywords: borderline ovarian tumors, molecular features, mutations, genetic mutations. Searches were conducted on 30.09.2023 where screening, data extraction, and quality assessment were performed. The language of publications was limited to English; duplicated articles and papers without full text available were excluded from further analysis. Peer-reviewed observational studies and retrospective analyses were considered. The results were restricted to publications concerning the specific molecular features. The Newcastle-Ottawa Scale was implemented to assess the quality of the included studies. A secondary search included examining the reference lists of all included articles. After careful consideration, some specific publication types, such as editorials, comments, conference abstracts, case reports, abstracts, validation and animal studies, were excluded from the analysis. A flow diagram illustrating the study selection process is presented in Figure 1.

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Results

After the first round of search, a total of 854 studies were identified after excluding duplicates 427 studies were included for further analysis. The analysis was limited to the following fifteen molecular characteristics: *BRAF*, *KRAS*, *NRAS*, *ARID1A*, *CADM1*, *PIK3CA*, *CHEK2*, *CLAUDIN-1*, *ERBB2*, loss of heterozygosity, *PTEN*, microsatellite instability, B-CATENIN, E-CADHERIN and *BRCA 1/2* mutation. Further analysis included solely English full-text articles presenting the results of studies in humans. Eventually, 76 out of 854 published studies were found to satisfy the inclusion criteria of this review and included in the final analysis.

Discussion

BRAF

The *BRAF* oncogene is a well-known proto-oncogene present in normal cells, capable of transforming into an oncogene under various stimuli. The transformation leads to changes in the oncoprotein's quantity or quality, disrupting normal metabolic processes and promoting the shift towards cancerous cells [15]. Proto-oncogenes can be activated through diverse mechanisms, with point mutations being a primary contributor. Other pathways include DNA rearrangement and the insertion of promoter or enhancer sequences. The activation of proto-oncogenes, including *BRAF*, can trigger cancer development [15]. Mutations in the *BRAF* gene are commonly observed across multiple cancers, with around 95% of the anomalies being T1799A point mutations, known as BRAFV600E [15]. *BRAFV600E* is associated with abnormal activation of the protein encoded by the *BRAF* gene, initiating downstream signal transduction pathways that enhance cell proliferation and alter differentiation [16]. The *BRAFV600E* mutation has been identified as a prevalent genetic alteration in serous borderline tumors (SBOTs) and LGSCs, found in up to 40% and 5-10% of these tumors, respectively [17]. Interestingly, patients with *BRAFV600E*-mutated SBOTs were shown to have a lower risk of progression to invasive serous carcinoma, which implicates a possible protective role of this mutation in the transition to more aggressive ovarian cancers [16]. Additionally, SBOTs harboring *BRAFV600E* mutations were demonstrated to have a distinct cellular morphology, potentially representing cellular senescence, namely a state of growth arrest in response to stress [18]. Intriguingly, LGSCs, more advanced malignant tumors than SBOTs, often do not display this senescence-associated morphology, which points to a potential mechanism for their aggressive behavior and progression. These findings highlight the significance of *BRAF* mutations, especially *BRAFV600E*, in the development and progression of SBOTs and LGSCs [19]. Understanding molecular characteristics associated with *BRAF* mutations may provide a better insight into the biology of those ovarian cancer subtypes and help establish prognosis and targeted therapeutic interventions. The discovery of recurrent non-*V600 BRAF* driver mutations in various tumor types has led to a new classification system based on the results of preclinical studies [20]. In this system, *BRAF* mutations are divided into three classes: Class I, including V600E, V600D, V600K, and V600R mutations, with high kinase activity and RAS-independent monomer signaling; Class II mutations with intermediate kinase activity and RAS-independent dimer signaling; and Class III mutations with lacking or impaired kinase activity, relying on RAS-dependent heterodimer formation for downstream signaling. This classification system reflects the tumor's response to MAPK pathway inhibitors, commonly used in treating malignancies with *BRAF* mutations. While Class I mutations are more sensitive to MAPK pathway inhibitors, Class II and Class III mutations may show a varying degree of resistance or reduced sensitivity [21]. In conclusion, the knowledge of specific *BRAF* mutations and their clinical implications may facilitate the selection of personalized treatment strategies for patients with *BRAF*-mutated tumors. Accurate molecular classification and profiling are crucial for tailoring effective therapeutic approaches.

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KRAS

Mutations in *BRAF* and *KRAS* genes are the most common genetic abnormalities found in SBOTs and LGSCs [22]. Interestingly, LGSCs with *KRAS* mutations tend to exhibit higher aggressiveness and are more likely to recur than malignancies with *BRAF* mutations [22]. According to the literature, *KRAS* and *BRAF* mutations are detected in approximately one-third of BOTs and one-third of LGSCs. However, the co-occurrence of *KRAS* and *BRAF* mutations has never been observed within the same tumor, which implies that those malignancies harbor either *KRAS* or *BRAF* anomalies [23]. Both *KRAS* and *BRAF* play crucial roles in the RAS-RAF-MEK, ERK, and MAPK signaling pathways, which are pivotal for the regulation of cell proliferation [24]. The *RAS* oncogene family comprises three principal members: *KRAS*, *HRAS*, and *NRAS*, all of which have been linked to the development of various human malignancies [24]. *KRAS*, located on chromosome 12p12, encodes a 21-kD protein (p21RAS) essential for MAP-kinase signal transduction, responsible for controlling cellular proliferation and differentiation [25]. Mutations in *KRAS* lead to constitutive activation of this signal transduction pathway, resulting in uncontrolled cell proliferation and differentiation [26]. The incidence of *KRAS* mutations in SBOTs is similar to that in LGSCs, between 19% and 54.5% [27]. SBOTs without a *BRAF* mutation may progress to LGSCs because of *KRAS* mutation or other genetic alterations. Knowledge of those genetic aberrations is crucial for a better understanding of SBOT biology and perhaps for developing more effective targeted treatment strategies. Another intriguing observation is finding that patients with the *KRAS G12V* mutation had shorter overall survival than those without this mutation. This suggests that SBOTs with the *KRAS G12V* mutation might be a more aggressive phenotype of BOTs that may recur as LGSC [25]. This notion is supported by the results of a study including over 3,000 colorectal cancer samples; in that study, *the KRAS G12V* mutation was the only one among 12 different mutations in *KRAS* codons 12 and 13 associated with poor overall survival. While surgery remains a cornerstone in SBOT treatment, one direction of ongoing research is the identification of molecular alterations that would facilitate the choice of other therapeutic options. Unfortunately, published data on the influence of molecular characteristics on the outcomes of SBOT treatment are limited. Nevertheless, sparse available evidence suggests that SBOT cell lines with *KRAS G12V* mutations might be more responsive to AZD6244 (selumetinib) compared with cell lines with wild-type *KRAS* [28].

NRAS

NRAS, a well-known oncogene implicated in some malignancies, such as leukemia and melanoma, is a part of the human *RAS* gene family, along with *HRAS* and *KRAS* [29]. The family, including two *KRAS* variants, *KRAS4A* and *KRAS4B*, encodes closely related proteins consisting of approximately 188-189 amino acids [30]. Those Ras proteins serve as GDP/GTP-regulated switches on the inner cell membrane, crucial for transmitting extracellular signals and governing vital intracellular signaling pathways. The latter pathways play pivotal roles in fundamental cellular processes, such as cell polarity, proliferation, differentiation, adhesion, migration, and apoptosis [31]. Mutations in the *NRAS* gene result in the constant activation of intracellular signaling through some pathways, such as RAS–RAF–MAPK and PI3K–AKT [31]. Regarding cancers, some shared mutations, specifically *KRAS*/*BRAF* and *TP53*/*BRCA* mutations, are found in low- and high-molecular grade tumors, respectively [32]. However, not all tumors harbor those mutations, implying that other, yet not fully defined, pathway-related events, including *NRAS* mutations, could be involved. A study of serous ovarian tumors demonstrated that the presence of Ras pathway mutations might be associated with variable pathogenic effects. Early occurrence of co-mutations implies that *KRAS* and *NRAS* might be involved in regulating distinct cellular functions, potentially producing a synergistic effect, as *KRAS* impacts proliferation, whereas *NRAS* influences cell survival [33]. Mutations in either *KRAS* or its homologue, *NRAS*, were found in 21% and 26% of LGSCs, respectively. Notably, *NRAS* mutations are present in SBOTs that show traits of transformation to ovarian cancer but are absent in those lacking the transformation features [34]. *KRAS* and *BRAF* mutations can be found in early-stage ovarian malignancies, even before the SBOTs stage. Additional driving events, including *NRAS* mutations, are thought to expedite the disease progression [34]. Those findings suggest that *NRAS*

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might act as a significant oncogenic driver in the progression of SBOTs to more invasive forms. The occurrence of *NRAS* mutations in SBOTs with invasive characteristics highlights the potential role of this gene in ovarian cancer pathogenesis and warrants further research in this matter. According to some authors, *NRAS* might play a crucial role in the transformation of SBOTs towards more invasive forms [35]. The early occurrence of *KRAS* and *NRAS* co-mutations points to the distinct role of these genes in cellular function and ovarian cancer progression [34]. Further research is needed to understand the exact roles of those mutations and their potential synergistic effect in ovarian cancer development, especially in the context of potential personalized therapies targeting *NRAS* or its downstream effectors.

ARID1A

ARID1A is a tumor suppressor gene that is frequently altered in ovarian neoplasms linked to endometriosis, such as clear cell and endometrioid carcinoma [36]. Previous studies documented the presence of somatic *ARID1A* mutations in 46-57% of ovarian clear cell carcinomas, 30% of ovarian endometrioid carcinomas, and 40% of uterine endometrioid carcinomas [37]. Molecular alterations found in seromucinous borderline tumors (SMBOTs) strikingly differ from those observed in other borderline (serous and mucinous) ovarian tumors. In a study involving 24 SMBOTs, the loss of *ARID1A* expression was found in approximately 33% of the cases (8 out of 24), including one case with synchronous endometriosis [38]. *ARID1A* encodes the BAF250a protein critical for forming switch/sucrose nonfermentable chromatin remodeling complexes [39]. Most *ARID1A* mutations are nonsense, frameshift, or in-frame mutations that lead to BAF250a expression loss. Thus, the absence of BAF250a immunoreactivity is indicative of *ARID1A*-inactivating mutations in preserved tissues [40]. According to Ayhan et al., 66% of ovarian endometrioid and clear cell carcinomas presented with *ARID1A* (BAF250a) expression loss [41]. Seromucinous tumors are not often associated with endometriosis, and limited WT1 expression does not link them to serous neoplasms [42]. Meanwhile, the available evidence points to the loss of *ARID1A* expression as a potential link between seromucinous tumors and endometrioid/clear cell neoplasms [43]. This feature differentiates seromucinous tumors from serous tumors, as the latter do not present with *ARID1A* expression loss nor harbor mutation of this gene. The results of morphological, immunohistochemical, and genetic analyses confirm that seromucinous tumors are not composed solely of serous and mucinous epithelium, debunking prior misconceptions [43]. To summarize, seromucinous tumors differ from serous tumors and appear to be linked more closely to endometrioid and clear cell neoplasms through the loss of *ARID1A* expression and other molecular traits.

CADM1

CADM1, an adhesion molecule from an immunoglobulin superfamily, is recognized as a tumor suppressor that plays a significant role in the progress and spread of various epithelial malignancies, especially in squamous cell carcinomas of the lungs, head, neck, esophagus, and cervix [44]. CADM1's extracellular domain engages with HER2 on the cell surface, thereby regulating downstream STAT3 activity. This interaction effectively restrains tumor growth and diminishes the potential for metastatic spread [45]. However, alterations within the CADM1/HER2/STAT3 axis in breast and lung adenocarcinomas were shown to be linked to more aggressive phenotypes of these malignancies [46]. According to the literature, CADM1 is expressed in all serous cystadenomas and up to 83.33% of SBOTs. While benign serous cystadenomas and SBOTs show the overexpression of CADM1, the expressions of HER2 and STAT3 in these tumors are reported to be either scant or low [47]. Interestingly, an opposite expression pattern, with reduced CADM1 expression and overexpression of HER2 and STAT3, is observed in malignantly transformed LGSCs and HGSCs [47]. Notably, the expression of CADM1 was shown to be weaker or absent in malignant LGSCs and HGSCs. The expression of CADM1 was also demonstrated to correlate inversely with HER2 and STAT3 expressions in serous ovarian tumors. Furthermore, the loss of CADM1 expression was associated with aggressive tumor behavior and lymph node metastases [47]. Those findings highlight a potential role of CADM1 expression loss in the pathogenesis of serous ovarian tumors, implying that this

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parameter could serve as a novel molecular marker for identifying the disease and monitoring its progression. Furthermore, a better understanding of the CADM1/HER2/STAT3 axis and its implications for tumor pathogenesis might open a new perspective for more effective, targeted therapeutic interventions.

PIK3CA

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway was shown to be activated in multiple cancers and is recognized as an essential regulator of cell growth, metabolism, proliferation, survival, mobility, and invasion [48]. The *PIK3CA* oncogene was identified as the most frequently mutated gene in uterine endometrioid and breast carcinomas. The presence of *PIK3CA* mutations has also been described in borderline ovarian tumors, whether serous, seromucinous or endometrioid [49]. The role of *PIK3CA*, *BRAF*, and *ERBB2* mutations in the pathogenesis of LGSCs with synchronous SBOTs was the subject of a comprehensive study. In one patient, *PIK3CA*, *BRAF*, and *ERBB2* mutations were found solely in LGSC but not in synchronous SBOT, whereas in another one, *PIK3CA* mutations were detected in both LGSC and SBOT. The results of that study imply that *PIK3CA* and *ERBB2* mutations are significant events occurring during the transformation of serous cystadenoma to SBOT and further to LGSC [50]. Interestingly, the frequency of *PIK3CA* mutations in LGSCs/SBOTs in the Japanese population appears notably higher than in Western patients [50]. This implies that *PIK3CA* mutation might play a primary role in developing LGSCs in Japanese patients, with *BRAF* or *ERBB2* mutations acting as secondary factors [50]. Considering all the findings mentioned above, targeting the PIK3CA/AKT pathway through molecular therapies appears to be a potentially promising treatment for LGSC in Japanese patients. Understanding mutational patterns and their roles in LGSC progression might open perspectives for more effective, personalized therapeutic approaches [51].

CHEK2

CHEK2 (checkpoint kinase 2), located at 22q12.1, is a critical tumor suppressor gene encoding a serine-threonine kinase called CHEK2 protein [52]. The latter, acting as an anti-oncogene, interacts with other proteins, including P53, to control the cell cycle and to avert uncontrolled cellular proliferation. CHEK2 plays a crucial role in DNA repair and triggers cell cycle halt or apoptosis in response to DNA damage. The presence of mutations within the CHEK2 gene was shown to be associated with a plethora of malignancies, both hereditary and non-hereditary [53], including breast, prostate, lung, colon, kidney, and thyroid cancers. Furthermore, available evidence points to the potential involvement of CHEK2 mutations in BOTs. One study demonstrated that patients with BOTs carried a common missense mutation (c.470T>C) within the CHEK2 gene [54]. The role of that mutation was further analyzed in patients with ovarian cystadenomas, BOTs, and ovarian cancers. The study showed a substantial link between the presence of the mutation and the risk of non-invasive tumors, along with a borderline significant correlation with LGSC risk. Interestingly, the link with the CHEK2 missense mutation (c.470T>C) was confirmed to be statistically significant in the case of BOTs but not ovarian cancer. The fact that the study included a higher number of low-grade ovarian cancer cases than tested previously might explain a discrepancy with the results of previous research and implies that the CHEK2 missense mutation (c.470T>C) might, in fact, not contribute to ovarian cancer risk. This notion is in pair with the results of other studies in which CHEK2 mutations were shown to be associated with increased risks of prostate and breast malignancies but not ovarian cancer risk [55]. Furthermore, available evidence suggests that the CHEK2 missense mutation might be associated with a two-fold increase in BOT risk. Additionally, a link has been found between the presence of the CHEK2 missense mutation (c.470T>C) and an earlier age at the diagnosis of BOT [54]. While overall survival rates in BOT patients are generally more favorable than in those with ovarian cancer, the 10-year survival rates in the mutation carriers were shown to be approximately 10% lower than in non-carriers. In summary, available evidence suggests that the CHEK2 missense mutation (c.470T>C) might be involved in BOT pathogenesis but does not significantly influence the development of low-grade ovarian cancer. The mutation appears to be

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associated with an earlier age at the BOT diagnosis and a somewhat diminished 10-year survival rate [In summary, available evidence suggests that the CHEK2 missense mutation (c.470T>C) might be involved in BOT pathogenesis but does not significantly influence the development of low-grade ovarian cancer. The mutation appears to be associated with an earlier age at the BOT diagnosis and a somewhat diminished 10-year survival rate [54]. However, more research is needed to fully understand the implications of CHEK2 mutations for ovarian cancer and BOTs.

CLAUDIN-1

Claudins are a family of integral membrane proteins situated within tight junctions, crucial for signal transmission and cellular transport [56]. Compromised integrity of tight junctions was shown to play a role in the pathogenesis of solid tumors. Notably, the expression of claudin protein in tumor cells was demonstrated to be different than in adjacent normal cells; while some malignancies showed a decrease in claudin protein expression, the expression of this protein in other tumor types was increased or mislocalized. Over 20 various claudins have been identified and characterized thus far. The role of those proteins in cancer pathogenesis is intricate, as they can either facilitate or inhibit tumor growth [57]. Claudin expression was shown to have prognostic value in various malignancies, which points to those proteins as potential therapeutic targets. In particular, claudin-1 was identified as a prognostic factor in multiple cancer types. One study analyzed a link between claudin-1 and clinicopathological parameters in BOTs [58], showing a significant association between a robust expression of that protein and some histological characteristics [58]. Specifically, the overexpression of claudin-1 was demonstrated to correlate with the presence of peritoneal implants and a micropapillary pattern, both being recognized as unfavorable prognostic factors in BOT. Moreover, claudin-1 overexpression in BOT appears to be associated with activating the mitogen-activated protein kinase pathway [59]. The latter observation justifies further research on the prognostic value of claudin-1 in BOT and its role as a potential therapeutic target interfering with the mitogen-activated protein kinase pathway.

ERBB2

The family of Epidermal Growth Factor Receptor (EGFR) proteins includes four proteins: ERBB1 (EGFR), ERBB2, ERBB3 and ERBB4. The ERBB family receptors have been studied extensively, given their role in the normal development of ovarian follicles and regulation of the growth of the ovarian surface epithelium [60]. ERBB2, a member of the epithelial growth factor receptor (EGFR) family, activates the PI3K/AKT and MAPK/ERK pathways to regulate cell proliferation, migration, and differentiation [61]. The overexpression of the ERBB2 proto-oncogene occurs in 11–30% of epithelial ovarian cancers (EOC) [62]. The expression of ERBB2 has traditionally been evaluated by immunohistochemistry, with inconsistent prognostic results for epithelial ovarian cancer [62]. While increased ERBB2 expression intensity was shown to be associated with decreased median and overall survival in EOC in some studies, other authors found no significant relationship between the expression of this protein and survival. *ERBB2* mutations were described in SBOTs, SMBOTs and mucinous BOTs (MBOTs) [63], and *ERBB2* was even identified as one of the most prevalent mutant oncogenes in SMBOTs in the Japanese population [64]. *ERBB2* mutations are found in approximately 6% of SBOTs and typically do not co-exist with *KRAS* or *BRAF* mutations. According to the most widely accepted hypothesis, alterations in any of those three genes, all serving as upstream regulators of the MAPK pathway, can activate the latter pathway with the resultant uncontrolled cell proliferation. Thus, available evidence suggests that each BOT might have its distinct molecular mechanism of carcinogenesis.

Loss of Heterozygosity

The origin of additional diseases associated with ovarian tumors, specifically, whether they result from tumor spread (monoclonal origin) or develop independently (multifocal origin), is a matter of ongoing debate. Previous research on the loss of heterozygosity (LOH) in ovarian cancer

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identified multiple regions with a high frequency of LOH, suggesting potential involvement of tumor-suppressor genes [65]. LOH has been observed across various chromosome arms at varying frequencies. Given that some benign and borderline tumors may represent early stages of ovarian carcinogenesis, research on these precursor lesions could provide an insight into the genetic events the accumulation of which is necessary for the transformation of normal ovarian epithelium to benign, borderline, malignant, or metastatic tumors [66]. The presence of LOH at D11S860 and D7S522 in borderline cystadenomas and stage II invasive tumors suggests that these somatic genetic events might occur relatively early in ovarian carcinogenesis. Additionally, a frequent occurrence of LOH in *BRCA1*-containing loci in invasive tumors raises a question about the potential role of benign and borderline lesions with LOH at those specific loci as precursors of the invasive disease; specifically, it has been implied that 17q and 18q LOH in benign tumors might serve as a risk factor for malignant transformation [67]. However, the results of research on X-chromosome inactivation and LOH studies are inconclusive, complicating the determination of clonality. In some cases, disparities in LOH and X-inactivation patterns have been attributed to methodological limitations, including aneuploidy and abnormal methylation affecting X-chromosome inactivation, as well as inadequate markers for LOH detection, impeding accurate clonality assessment. Mutational analysis, which was expected to clarify whether extra-ovarian diseases have a monoclonal or multifocal origin, has not provided a definitive answer. Given the discrepancies between the results of X-chromosome inactivation research and LOH studies and the inherent limitations of these methods, alternative approaches are needed to address the issue of ovarian tumor clonality definitively.

PTEN

PTEN, functioning as a tumor suppressor gene, has often been reported to be lost in endometrioid carcinoma [68]. Genomic alterations or mutations within the *PTEN* can emerge prior to the malignant transformation of endometroid foci, potentially disrupting the inhibitory function of this gene and initiating antiapoptotic pathways [69]. Located on chromosome 10q23, *PTEN* encodes a lipid phosphatase that acts as a negative regulator of phosphoinositide 3-kinase (PI3K) by dephosphorylating phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3]. Phosphorylated PI(3,4,5)P3 triggers the activation of proto-oncogene protein kinase B (PKB/AKT), which in turn inhibits apoptotic pathways, activating mechanistic target of rapamycin or deactivating forkhead family proteins [70]. The PTEN-mediated dephosphorylation of PI(3,4,5)P3 leads to the activation of the apoptotic pathway, with the resultant restrain of the PI3K/AKT signaling. *PTEN* mutations are found frequently in endometrial and ovarian cancers, especially endometrioid subtype, often in early-stage tumors. The mutations are commonly detected in endometrioid borderline ovarian tumors (EBOTs) or even in the areas of non-atypical endometriosis. *PTEN* mutations were reported in approximately 12% of EBOTs [71]. Importantly, EBOTs are also the tumors in which PI3K/AKT pathway activation is observed particularly often, implying that early-occurring *PTEN* mutations might be involved in developing these lesions [72]. However, the formation of an invasive carcinoma may require additional genetic changes to activate the PI3K/AKT pathway. Indeed, ovarian endometrioid carcinomas, genetically stable and originating from EBOTs, exhibit mutations not only in *PTEN* but also in other genes, such as *ARID1A*, *PIK3CA*, and *TP53*. Available evidence indicates that although LOH at the *PTEN* locus is infrequent in endometriosis, somatic *PTEN* gene mutations can be quite common in solitary endometriotic cysts [73]. Indeed, reduced PTEN protein expression was reported in some cases of endometriosis [73. In conclusion, available data on the role of *PTEN* as a tumor suppressor and its mutation dynamics within endometrioid carcinomas and EBOTs highlight the importance of this gene in ovarian carcinogenesis. Thus, a better understanding of molecular events associated with functional loss of *PTEN* might open new perspectives for targeted therapies in ovarian malignancies.

Microsatellite Instability

Microsatellites, i.e., short repeating sequences of DNA bases found across the genome, can vary in length from tens to hundreds of bases. Those regions are particularly susceptible to mutations,

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such as the insertion or deletion of repeating units, during DNA replication [74]. The alteration in microsatellite length is referred to as microsatellite instability (MSI). MSI occurs due to defects in DNA mismatch repair mechanisms; these defects cause DNA replication disruption, resulting in increased mutation rates and contributing to the development of tumors with replication errors [75]. The examples of tumors with the replication error phenotype are colon and endometrial carcinomas that exhibit minimal chromosomal abnormalities yet display MSI, indicating defects in mismatch repair [76]. It is still unclear whether MSI could also be involved in the pathogenesis of BOTs. The results of research on microsatellite instability in BOTs vary considerably, with the MSI rates ranging from 0% to 30%; these discrepancies may be caused by a plethora of factors, among them the type and number of markers used for detecting MSI and the criteria for defining the latter [77]. BOTs typically display limited chromosomal abnormalities, but the extent to which MSI plays a role in the development of these lesions remains unclear. Some authors detected MSI in up to 27-30% of BOTs, whereas others found no evidence of microsatellite instability [6]. Those results seem to support the dualistic model concept in which BOTs and invasive ovarian cancers follow distinct pathways, possibly originating from different cell clones with unique genetic modifications [78]. Moreover, research showed significant differences in MSI found in serous BOTs and serous invasive epithelial ovarian cancers, especially on chromosome 3 [79]. Instead of a gradual increase in allelic imbalance, observed during the progression of non-invasive to invasive micropapillary serous carcinomas in BOTs, HGSCs present with higher levels of allelic imbalance, found even in smaller primary tumors [80]. Those findings suggest that MSI and chromosomal instability may play pivotal roles in forming BOTs and their progression from normal ovarian epithelium. While shared chromosomal aberrations are common in both BOTs and high-grade tumors, their exact role in these two types of lesions remains unclear.

β-CATENIN

β-catenin, a multifunctional protein, plays pivotal roles in two crucial biological processes: cell-cell adhesion and signal transduction involving transcriptional activation. The involvement of β-catenin in cell adhesion is a well-established phenomenon, particularly within the adherens junctions of epithelial cells, where the cytoplasmic domain of E-cadherin orchestrates a peripheral protein complex essential for adhesion [81]. The activation of the Wnt signaling pathway, which includes *CTNNB1* mutations, is associated with fibrotization of the surrounding area, enhances proliferation, and promotes implantation or invasion [82]. This phenomenon was observed in endometriosis, with consequences being proportional to the extent of the protein defect. *CTNNB1* gene mutations were found in various malignancies, such as pulmonary, breast, colorectal, endometrial, and ovarian cancers, the latter including endometriosis-associated ovarian malignant tumors. Immunohistochemistry revealed the expression of β-catenin in 61.2% of epithelial ovarian cancer patients, both endometriosis-free and those with concomitant endometriosis [83]. Mutations of the β-catenin gene and β-catenin overexpression are commonly found in ovarian endometrioid carcinomas, with approximately 50% of these malignancies exhibiting β-catenin alterations [82]. Moreover, up to 90% of EBOTs, among them endometrioid borderline carcinomas, were shown to harbor the β-catenin gene mutations [84]. Those findings suggest that *CTNNB1* mutations may represent an early event in the malignant transformation of certain ovarian tumors. Specifically, mutations of the β-catenin gene appear to be common at early stages of endometrioid ovarian carcinoma development [84]. The fact that most endometriosis-associated tumors are low-grade lesions with relatively favorable prognoses warrants further research on the role of β-catenin as an early marker for endometroid ovarian carcinoma. To summarize, the pattern of β-catenin expression varies across different histological types of ovarian carcinomas. The activation of the APC-B-catenin-Tcf signaling pathway, associated with the presence of an oncogenic β-catenin mutation, is a characteristic feature for a subset of endometrioid carcinomas with nuclear β-catenin expression and a favorable prognosis, many of which originate from benign tumors or BOTs. In turn, endometrioid carcinomas that display the membrane expression of β-catenin solely appear to be a distinct subgroup

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of malignancies not associated with the β-catenin signaling pathway that likely harbor a poorer prognosis.

E-Cadherin

E-cadherin, a calcium-dependent transmembrane glycoprotein (120 kDa), plays a crucial role as a tumor suppressor, preventing the progression and spread of various epithelium-derived carcinomas [85]. E-cadherin is encoded by the cadherin-1 (CDH1) gene located on chromosome 16q22.1. This gene consists of 16 exons interwoven by 15 introns and is primarily localized within the cell membrane of epithelial cells [86]. While the extracellular domain of CDH1 is pivotal for cellular adhesion, its intracellular domain binds with the cytoskeleton via β-catenin, triggering an array of intracellular signaling pathways [85]. A downregulation of E-cadherin has been observed in advanced malignancies, and E-cadherin loss was shown to promote epithelial-to-mesenchymal transition (EMT), thus facilitating metastatic spread. The onset of EMT often marks the beginning of the malignant transformation in epithelial tumors, leading to decreased adherence of epithelial cells and facilitating their attachment to the basal membrane. A vital component of the EMT is the so-called "cadherin switch", wherein reduced E-cadherin expression coincides with the acquisition of N-cadherin expression [85]. This transition promotes the mobility and invasiveness of cancer cells. EMT is associated with the upregulation of CDH2 and metalloproteinases and the downregulation of CDH1 within cancer cells. Those molecular changes are reflected by extracellular matrix remodeling, enhanced migration and invasion, tumor stemness, and metastatic spread, and lead to increased mortality of cancer patients. EMT is pivotal in cancer progression, drug resistance, and tumor stemness, providing a foundation for metastatic spread [86]. Therefore, the strategies to inhibit or prevent EMT are critical for impeding or ameliorating the progression of various human malignancies. Immunohistochemical studies demonstrated membranous E-cadherin expression in benign ovarian tumors and SBOTs. Notably, reduced E-cadherin expression was shown to correlate with microinvasion in serous borderline tumors [87]. The results of recent research involving cultured SBOT cells suggest that the downregulation of E-cadherin contributes to the progression of SBOTs towards invasive LGSCs. Mucinous tumors appear to be more likely to express E-cadherin than serous tumors (62% vs. 4%, $p<0.001$) and have a lower likelihood of N-cadherin positivity (8% vs. 68%, $p<0.001$) [88]. The expression of E-cadherin protein was found in inclusion cysts and benign, borderline and malignant tumors of all stages but is absent in normal ovarian surface epithelium [89]. The loss or decrease of E-cadherin expression is a predictor of poorer overall survival in ovarian cancer and correlates with higher tumor grade [90]. In conclusion, because of its involvement in cellular adhesion, EMT and intracellular signaling pathways, E-cadherin plays an essential role in cancer progression and spread and, as such, is a determinant of clinical outcomes in patients with various malignancies. Thus, pharmacological control of E-cadherin expression and related pathways appears to be a promising option in managing ovarian cancer.

BRCA 1/2

BRCA1 and *BRCA2* mutations are specific genetic changes in tumor suppressor genes that appear in various instances of hereditary and some sporadic breast and ovarian cancers. If ovarian malignancy arises in a *BRCA1* or *BRCA2* carrier, it tends to be a high-grade serous ovarian cancer, demonstrating aggressive behavior and presenting at an advanced metastatic stage [91]. The occurrence of BOTs in women with *BRCA* mutations is uncommon. While BOTs have been identified in some *BRCA* mutation carriers, this occurrence is likely attributed to the prevalence of these anomalies within the broader population [92]. Although mutations in *BRCA1*, *BRCA2*, *RAD51C*, and *PALB2* genes were shown to be associated with an increased ovarian cancer risk, no such clear-cut relationship was found for BOTs. The prevalence of *BRCA* mutations in BOTs can vary among different populations. In-depth research involving specific ethnicities or geographical groups might shed light on the genetic background of BOTs. Nevertheless, several studies demonstrated a link between *BRCA* mutations and BOTs. Specifically, two studies involving patients of Jewish heritage found that the occurrence of founder *BRCA1* and *BRCA2* mutations in women with BOTs was

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significantly lower than in those with early-stage invasive ovarian carcinomas, 2.2% and 4.3% versus 24.2% and 32%, respectively [93]. Those findings are consistent with the results of studies conducted in Norway (including 190 patients with BOTs and 478 with ovarian cancer) and Canada (134 BOTs and 515 ovarian cancers), in which *BRCA1*/2 mutations were detected in 4% and 11.7% of women with invasive cancers, respectively, but in note with BOTs [54]. Also, other smaller-scale studies showed that *BRCA1*/2 anomalies are found only sporadically in BOT patients, with the cumulative prevalence of *BRCA1* and *BRCA2* mutations of 1.3% and 0.2%, respectively [54]. In a Polish study, BOTs were diagnosed at a notably younger age than LGSCs (47.76 vs. 54.25 years). When the results were stratified according to *BRCA1*, *BRCA2*, *RAD51C*, *PALB2*, and *CHEK2* mutational status, carriers of at least one of those anomalies turned out to be diagnosed with BOTs at younger age than non-carriers (45 vs. 49 years) [54]. In conclusion, a growing body of evidence suggests that the occurrence of *BRCA* mutations in patients with BOTs is generally lower than in those with invasive ovarian carcinomas. BOTs tend to be more closely associated with wild-type *BRCA* status, implying that the pathogenesis of most of these tumors is not directly linked with the presence of *BRCA* mutations.

Conclusions

A growing body of evidence indicates that BOTs often remain clinically dormant for extended periods before a molecular trigger initiates increased cell replication, potentially leading to carcinoma development or recurrence. Molecular analyses have uncovered notable similarities in molecular and genetic backgrounds of serous borderline tumors and LGSCs. This molecular shift in BOTs indicates their progression towards low-grade carcinoma through a distinct "low-grade pathway" characterized by mutations in the RAS/RAF/MEK/MAPK pathways. Meanwhile, specific molecular features associated with HGSC can help identify a subgroup of BOTs prone to more aggressive behavior. Conventional histopathological parameters, including previously suggested risk factors, such as micropapillary patterns and microinvasion, have proven unreliable in predicting recurrence risk. As BOTs predominantly affect women of reproductive age, preserving fertility becomes of utmost importance during treatment planning. However, fertility-conserving surgery and incomplete surgical staging have been linked to a heightened risk of recurrence. With the advent of targeted therapies, particular emphasis must be placed on detecting even minute numbers of malignant cells within advanced-stage BOTs that have acquired additional driver mutations or undergone clonal expansion. Notably, different mutations within the same pathway, such as those involving KRAS, NRAS, and BRAF, may not respond uniformly to specific targeted therapies. Consequently, patients with such diverse genetic mutations may need to be subjected to a subset analysis in studies analyzing the effectiveness of targeted interventions. While molecular studies have contributed significantly to our understanding of BOT pathogenesis, substantial research is still required to elucidate the relationship between ovarian neoplasms and extraneous disease, identify accurate prognostic indicators, and develop targeted therapeutic approaches.

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