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PAX3 and FOXO1 in High-Grade Serous Ovarian Carcinoma: Biological Roles, Immunohistochemical Expression, Emerging Biomarkers, and Clinical Implications – A Comprehensive Review

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ABSTRACT

High-grade serous ovarian carcinoma remains the most lethal gynecologic malignancy. Transcription factors PAX3 and FOXO1 regulate cellular differentiation, apoptosis, DNA repair, and survival pathways implicated in tumor progression and treatment resistance. A narrative review of the literature was conducted using PubMed and related databases to summarize and critically evaluate current evidence on the biological and potential clinical relevance of PAX3 and FOXO1 in HGSOC. Available studies indicate that PAX3 and FOXO1 participate in regulatory networks including AKT–FOXO signaling, MET activation, and epithelial–mesenchymal transition, contributing to tumorigenesis and cellular plasticity. Immunohistochemical analyses suggest increased expression of both proteins in HGSOC, with variable associations with clinicopathological parameters and patient outcomes. Mechanisms of chemoresistance—such as BRCA reversion mutations, replication fork stabilization, and tumor microenvironmental influences—may intersect with PAX3- and FOXO1-mediated pathways. In conclusion PAX3 and FOXO1 appear to be involved in key biological processes underlying HGSOC progression and therapeutic resistance, but their independent prognostic significance remains unproven. Further mechanistic and translational studies are required to clarify their potential as biomarkers or therapeutic targets.

Keywords: PAX3; FOXO1; high-grade serous ovarian carcinoma; chemoresistance; immunohistochemistry

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INTRODUCTION

High-grade serous ovarian carcinoma (HGSOC) is the most lethal form of epithelial ovarian cancer, responsible for approximately 70% of ovarian cancer deaths on a global scale (1). The aggressive nature of this condition is attributable to three factors: early dissemination, genomic instability, and a near-universal presence of TP53 mutations (2). HGSOC frequently presents at an advanced FIGO stage, thereby limiting available curative options. Despite significant advances in cytoreductive surgery, platinum-based chemotherapy, and targeted therapies such as PARP inhibitors, overall survival remains unsatisfactory, with only modest improvement over the last three decades (3).

The quest for novel biomarkers that can enhance risk stratification, facilitate early detection, predict response to therapy, and identify new therapeutic targets remains a top priority. Transcription factors have recently been the focus of considerable interest due to their role in regulating fundamental biological processes, including proliferation, apoptosis, differentiation, DNA repair, stress adaptation, and epithelial–mesenchymal transition (EMT). Among these, PAX3 and FOXO1 are emerging as potentially relevant transcription factors in tumor progression, yet their roles in ovarian cancer remain insufficiently characterized (4, 5).

Existing immunohistochemical studies of PAX3 and FOXO1 in ovarian carcinoma are limited, including recent work examining their expression in HGSOC (6). These preliminary findings suggest that both transcription factors may be variably expressed and possibly associated with biological behavior, but comprehensive evidence is lacking. Concurrently, major therapeutic trials in ovarian cancer, including ICON7, SOLO-1, PRIMA, PAOLA-1, and VELIA, have transformed management and accentuated the importance of molecular profiling. This encompasses the status of the breast cancer susceptibility gene (BRCA), the homologous repair (HR) score, and other emerging biomarkers, including circulating tumor DNA (ctDNA) and folate receptor alpha (FRα) (7–11).

The exploration of transcription factors such as PAX3 and FOXO1 in the context of contemporary HGSOC biology has the potential to expand the range of biomarkers utilized in clinical practice and to enhance our comprehension of the molecular mechanisms that underpin chemoresistance, metastasis, and tumor evolution.

METHODS

This article is a narrative review of the literature focusing on the biological and potential clinical relevance of the transcription factors PAX3 and FOXO1 in high-grade serous ovarian carcinoma. A literature search was conducted using PubMed and related biomedical databases to identify relevant experimental, translational, and clinical studies published in English. Search terms included combinations of “PAX3,” “FOXO1,” “high-grade serous ovarian carcinoma,” “ovarian cancer,” “chemoresistance,” “epithelial–mesenchymal transition,” and “immunohistochemistry.”

Original research articles, review papers, and key clinical trial reports relevant to ovarian cancer biology and biomarker development were considered. Priority was given to studies addressing molecular mechanisms, immunohistochemical expression patterns, associations with clinicopathological features, and therapeutic implications. Major phase III clinical trials shaping contemporary management of HGSOC were also reviewed to provide clinical context.

Study selection and interpretation were based on relevance to the topic rather than formal systematic criteria. No quantitative meta-analysis was performed.

THE BIOLOGICAL ROLES OF PAX3

PAX3 (Paired Box Gene 3) is a transcription factor that is essential for embryonic development, particularly in regard to neural crest migration, melanocyte differentiation, myogenesis, and organogenesis (12). As a constituent element of the PAX family, it has been demonstrated to regulate gene expression through its capacity to bind DNA through a paired domain and homeodomain. During normal development, PAX3 is responsible for maintaining progenitor cell viability, preventing apoptosis, and supporting lineage specification.

Regulation of PAX3 signaling

PAX3 is subject to regulation by a variety of upstream pathways, including Wnt/β-catenin, MAPK, and FGF signaling (13). These pathways modulate PAX3 expression in regions requiring rigorous control of migration and differentiation. In adult tissues, PAX3 expression is generally low or absent, though it may be reactivated in pathological states.

The role of PAX3 as an oncogene

PAX3 has been implicated in the development of cancer, particularly tumors of neural crest origin. In the context of melanoma, the PAX3 gene has been shown to enhance survival by suppressing apoptosis and promoting melanocyte stemness via MITF regulation (14). Furthermore, PAX3 has been demonstrated to augment metastatic potential through upregulation of CXCR4 and MET, thereby facilitating motility and invasion (15).

The most striking illustration of PAX3's oncogenic capabilities is perhaps the PAX3–FOXO1 fusion gene in alveolar rhabdomyosarcoma, which displays remarkably strong transcriptional activation, resulting in uncontrolled proliferation, resistance to apoptosis, and augmented invasion (16).

PAX3 has also been implicated in epithelial–mesenchymal transition (EMT) through modulation of transcription factors such as Snail and Twist, thereby promoting migratory and invasive phenotypes. This mechanism is particularly relevant in ovarian cancer, where EMT contributes to peritoneal dissemination, a hallmark of HGSOC spread (17).

Despite the paucity of research conducted on PAX3 in the context of ovarian cancer, the available evidence suggests a potential role for this mechanism in the aggressiveness of tumors, their dissemination, and chemoresistance in HGSOC.

THE BIOLOGICAL ROLES OF FOXO1

FOXO1 (Forkhead box O1) is a member of the FOXO family of transcription factors that regulate a broad range of cellular processes, including apoptosis, oxidative stress response, autophagy, metabolic homeostasis, and DNA repair (18).

Regulation by the PI3K/AKT pathway

FOXO1 is subject to regulation by the PI3K/AKT pathway, which is among the most frequently dysregulated pathways in cancer (19). The process of AKT-mediated phosphorylation of FOXO1 results in its subsequent inactivation, which is characterized by nuclear export and the initiation of proteasomal degradation within the cell. Conversely, a reduction in AKT signaling results in the nuclear accumulation and activation of FOXO1, thereby enabling the transcription of pro-apoptotic and anti-proliferative genes.

FOXO1 as a tumor suppressor

In a multitude of cancers, FOXO1 functions as a tumor suppressor by activating genes such as BIM, p27, and FASL. The loss of nuclear FOXO1 is frequently associated with a poor prognosis, a higher grade, and an increased proliferative index (20).

Context-dependent roles of FOXO1

FOXO1 has been identified as a context-dependent survival factor. In certain contexts,

FOXO1 has been observed to enhance tumor survival under hypoxic or metabolic stress by regulating autophagy, redox balance, and metabolic pathways (21). Such paradoxical behavior has been reported in breast, endometrial, and ovarian cancers, suggesting that FOXO1's function depends heavily on microenvironmental cues and upstream oncogenic signaling.

PAX3 AND FOXO1 IN SOLID TUMOURS: CONVERGENT AND DIVERGENT ROLES

In the context of malignancies, the PAX3 gene has been observed to exhibit a pattern of expression that is consistent across different tumor types. This expression has been found to be associated with increased invasiveness, poor differentiation, and an elevated potential for metastasis. It has been demonstrated that this confers resistance to apoptosis and facilitates adaptation to harsh microenvironments (22). The activation of PAX3 in MET–AKT signaling has been demonstrated to directly link it to pathways that are relevant to the progression of ovarian cancer.

In the context of various malignant neoplasms, FOXO1 is inactivated via the process of PI3K/AKT hyperactivation. This loss has been demonstrated to contribute to unrestrained proliferation. However, in cancers where metabolic and oxidative stress are high, FOXO1 may paradoxically support survival by enhancing cellular resilience (23).

Despite their independent nature, both molecules have been shown to influence a range of biological processes, including apoptosis, differentiation, proliferation, and stress responses. These processes are all core to the biology of HGSOC. The expression of these genes may reflect distinct biological phenotypes, which may have prognostic and predictive implications.

IMMUNOHISTOCHEMICAL EXPRESSION IN OVARIAN CANCER

FOXO1

Immunohistochemical studies in ovarian carcinoma report variable FOXO1 expression. Cytoplasmic accumulation is frequently associated with activation of PI3K/AKT signaling and suppression of FOXO1 tumor-suppressor activity. Nuclear expression may correlate with cell-cycle regulation, DNA damage response, and apoptosis (24).

Some evidence suggests that FOXO1 downregulation contributes to platinum resistance via impaired induction of apoptotic programs. FOXO1-mediated transcription of BIM and FASL is critical for chemotherapy-induced cell death (25).

PAX3

Research on PAX3 expression in ovarian cancer is sparse. Available studies show detectable expression in subsets of epithelial ovarian cancers, suggesting possible involvement in EMT, invasiveness, or stem-like phenotypes (26).

Existing IHC studies evaluating both markers

Recent immunohistochemical analyses, including research examining expression patterns of both PAX3 and FOXO1 in high-grade serous ovarian carcinoma, have demonstrated that these proteins are variably present in tumor cells (6). Although statistically significant correlations with clinical parameters were not consistently observed, these findings highlight the potential importance of studying transcription factors in HGSOC biology.

MAJOR CLINICAL TRIALS SHAPING HGSOC BIOLOGY AND BIOMARKERS

ICON7

ICON7 was a landmark study evaluating bevacizumab in first-line treatment. It demonstrated improved progression-free survival (PFS), particularly in patients with high-risk features such as stage IV disease or suboptimal debulking (7). This trial established angiogenesis as a therapeutic target and emphasized variability in treatment response.

SOLO-1 and SOLO-2

SOLO-1 demonstrated unprecedented survival benefits using olaparib maintenance therapy in BRCA-mutated HGSOC, essentially changing the prognosis for this molecular subgroup (8). SOLO-2 confirmed efficacy in recurrent settings.

PRIMA (Niraparib)

PRIMA showed that niraparib maintenance therapy improved PFS across all subgroups, though the greatest effect was again seen in HRD-positive tumors (9).

PAOLA-1 (Olaparib + Bevacizumab)

PAOLA-1 investigated combination maintenance therapy and demonstrated significant improvement in HRD-positive tumors, confirming HRD as a critical biomarker in modern ovarian cancer management (10).

MIRASOL and folate receptor alpha (FRα)

The MIRASOL trial demonstrated that mirvetuximab soravtansine, an FRα-targeted antibody–drug conjugate (ADC), significantly improved progression-free and overall survival in platinum-resistant ovarian cancer with high FRα expression (30). This established FRα as a validated predictive biomarker and highlighted ADCs as a new therapeutic class.

THE MECHANISMS UNDERLYING CHEMORESISTANCE IN HGSOC

Platinum resistance is a major contributor to poor outcomes in HGSOC. The following mechanisms have been identified:

BRCA reversion mutations

Secondary mutations restore BRCA function, enabling homologous recombination repair and resistance to both platinum agents and PARP inhibitors (25).

Replication fork protection and HRD escape

Tumors stabilize replication forks to bypass PARP inhibitor synthetic lethality (26).

Efflux pumps

Upregulation of ABC transporters, such as ABCB1, reduces intracellular drug accumulation (27).

Tumor microenvironment

Hypoxia, neutrophils, tumor-associated macrophages, and cytokines within the tumor microenvironment collectively contribute to therapeutic resistance (28).

Transcription factors

PAX3 and FOXO1 regulate processes implicated in chemoresistance, including apoptosis, metabolic stress response, cell-cycle progression, and EMT. Despite limited direct evidence, their involvement in resistance-related pathways renders them candidates for future predictive biomarkers.

EMERGING BIOMARKERS RELEVANT TO HGSOC

Circulating tumor DNA

Circulating tumor DNA enables non-invasive detection of minimal residual disease, earlier prediction of recurrence, and monitoring of PARP inhibitor response (29).

Folate receptor alpha

FRα expression is frequently elevated in platinum-resistant tumors. The success of mirvetuximab soravtansine in the MIRASOL trial has validated FRα as a clinically actionable biomarker in ovarian cancer (30).

HRD and BRCA

HRD remains the strongest predictor of benefit from PARP inhibitors. Treatment selection is guided by genomic scar assays, RAD51 foci formation, and BRCA mutation testing (31).

Immune biomarkers

Tumor-infiltrating lymphocytes, PD-L1 expression, and immune transcriptomic signatures demonstrate prognostic potential, although results remain inconsistent (32).

FUTURE RESEARCH DIRECTIONS

Future studies should focus on comprehensive multi-omic profiling of PAX3 and FOXO1 expression, integration of transcription factor expression with HRD status and immune phenotype, evaluation of correlations with platinum and PARP inhibitor response, exploration of synergy with FRα-targeted agents or antibody–drug conjugates, longitudinal ctDNA monitoring in relation to transcriptional states, functional assays investigating the roles of PAX3 and FOXO1 in apoptosis, EMT, and metabolic plasticity.

Such research may enable more precise stratification of HGSOC and identification of novel therapeutic vulnerabilities.

CONCLUSION

PAX3 and FOXO1 are transcription factors with significant biological relevance in development and cancer. Their roles in HGSOC are not yet fully defined, but early evidence suggests involvement in pathways central to tumour progression, EMT, metabolic adaptation, and stress response. Integrating these markers with modern molecular profiling tools—including HRD scoring, FRα testing, ctDNA analysis, and immune biomarkers—may yield new insights into tumor heterogeneity, therapeutic vulnerabilities, and mechanisms of resistance. As ovarian cancer treatment continues to evolve, improved characterization of transcriptional regulators such as PAX3 and FOXO1 may contribute to the next generation of biomarkers and targeted therapies.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS
DT, BGT, DS contributed equally to all aspects of the preparation of this manuscript and meet the ICMJE criteria for authorship.

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