Short Communication

Ovarian Cyst Fluid as a Translational Source for Biomarker Discovery and Molecular Target Identification in Ovarian Cancer

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Abstract

Ovarian cyst fluid represents a highly informative but underutilized biological matrix with significant potential for improving diagnostic accuracy and advancing biomarker discovery in ovarian cancer. Traditional diagnostic tools such as imaging and serum markers often fall short in distinguishing benign, borderline, and malignant cystic lesions, especially in early-stage disease. Cytologic evaluation of ovarian cyst fluid - supported by cell-block immunocytochemistry - provides valuable insights into epithelial architecture and atypia, enabling better tumor characterization. Furthermore, cyst fluid is enriched with tumor-derived DNA, circulating tumor DNA, and protein signatures that closely mirror the molecular landscape of the underlying neoplasm. Multi-omic approaches, including targeted sequencing and mass spectrometry–based proteomics, have revealed actionable mutations (e.g., TP53, RAS pathway alterations) and tumor-associated proteins relevant to disease progression and therapeutic stratification. These advancements highlight ovarian cyst fluid as a promising resource for translational research, offering opportunities to refine diagnosis, personalize treatment, and identify novel anticancer targets. However, standardization, validation, and integration of emerging technologies are needed to optimize its clinical utility.

Key words

Ovarian cyst fluid, Ovarian cancer, Biomarker discovery, Proteomics, Circulating tumor DNA, Molecular diagnostics, Precision oncology.

Accurate distinction between benign, borderline, and malignant ovarian cystic lesions remains a clinical challenge, particularly in early-stage disease where conventional tools such as imaging and serum markers (CA-125, HE4) lack optimal sensitivity and specificity [1]. As ovarian cancer continues to rank among the most lethal gynecologic malignancies, improved diagnostic approaches are essential. Ovarian cyst fluid, sampled directly from the tumor microenvironment, provides a unique and underexploited matrix for both diagnostic refinement and anti-cancer molecular target discovery.

Cytologic evaluation of cyst fluid, although historically inconsistent, has shown high specificity for malignancy in contemporary studies. Malignant fluids frequently demonstrate 3D papillary clusters, pronounced nuclear atypia, irregular nuclear membranes, and prominent nucleolifeatures that correlate with aggressive epithelial ovarian tumors [2]. Cell-block preparation further enhances diagnostic value by enabling architectural assessment and immunocytochemistry (ICC) using markers such as PAX8, WT1, CK7, and aberrant p53, which are relevant to both tumor classification and therapeutic stratification.

Cyst fluid also contains abundant tumor-derived DNA and circulating tumor DNA (ctDNA). Targeted sequencing studies show that cyst fluid often reflects the mutational spectrum of the underlying neoplasm, including TP53 alterations, RAS pathway mutations, and cell-cycle gene abnormalitiesmany of which represent established or emerging therapeutic targets for anti-cancer agents [3]. The higher variant allele frequencies in cyst fluid (compared to plasma) highlight its potential for mutation-based triage and personalized oncology.

Proteomic profiling represents a rapidly expanding dimension. Mass-spectrometrybased analyses have identified numerous tumor-associated proteins enriched in cyst fluid, including extracellular matrix regulators, proteases, mucin-domain proteins, and metabolic enzymes implicated in ovarian tumor progression. Certain proteins demonstrate superior discriminatory performance compared to their serum levels, suggesting opportunities for developing novel protein biomarkers or targeted peptide-based anticancer strategies. These molecular signatures may also improve preoperative stratification and help identify patients who need definitive oncologic surgery versus conservative management [4].

An integrated diagnostic approachcombining cytology, cell-block ICC, targeted sequencing, and proteomic profilingclosely aligns with the translational objectives of anti-cancer research [5]. Such multimodal evaluation may support early detection of actionable molecular drivers, guide patient-specific therapeutic decisions, and contribute to the discovery of novel anticancer targets derived from the ovarian tumor microenvironment.

Despite its promise, several challenges persist, including low sensitivity of cytology in sparsely cellular lesions, lack of standardization in proteomic workflows, and the need for large prospective validation studies. Emerging techniques such as extracellular vesicle profiling, single-cell analysis of fluid-derived cells, and machine-learning integration of multi-omic data may significantly advance the clinical utility of cyst fluid in precision oncology.

In conclusion, ovarian cyst fluid is a rich and underused biological resource with significant potential to refine diagnosis, identify molecular targets, and support the development of anti-

cancer agents. Its integration into multimodal evaluation strategies may enhance precision medicine efforts in ovarian cancer and ultimately improve patient outcomes.

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