Letter to Editor

Challenging the Estrogen-Driven Paradigm: ESR1 Gene Mutations in Endometrioid Endometrial Carcinoma

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Dear Sir,

Endometrioid endometrial carcinoma (EEC) is characteristically regarded as an Estrogen-driven malignant neoplasm. It is associated with Estrogen receptor alpha (ERα), encoded by the ESR1 gene, mediating key proliferative and survival pathways. While estrogen dependence has long guided prognostication and therapeutic decision-making, recent molecular profiling has identified a subset of EECs harbouring activating ESR1 mutations. Because of these findings, it is a challenge for the traditional paradigm of Estrogen signalling in endometrial carcinoma and recommend potential implications for disease behaviour and treatment response.

The introduction of molecular classification has transformed the risk stratification of endometrial carcinoma by integrating genomic alterations with histopathologic assessment. Within this evolving framework, ESR1 mutations particularly those affecting the ligand-binding domain have been detected in a small proportion of EECs, with enrichment in advanced or recurrent disease [1]. Large multicentre genomic analyses have reported activating ESR1 mutations in approximately 4% of endometrioid endometrial cancers, occurring more frequently in metastatic or recurrent tumors than in primary lesions. These mutations commonly coexist with alterations in the PI3K/AKT pathway, including PTEN, PIK3CA, and PIK3R1, indicating cooperative oncogenic signalling among Estrogen receptor pathways and intracellular growth cascades [2].

Functional studies have demonstrated that ligand-binding domain mutations in ESR1 can modify ERα transcriptional activity, enabling partial Estrogen-independent signalling. CRISPR/Cas9-based models have shown that mutant ERα alters chromatin accessibility and downstream gene expression patterns distinct from those driven by wild-type receptors, suggesting activation of non-canonical oncogenic programs [3]. These observations provide mechanistic insight into how ESR1 mutations may contribute to tumor progression beyond classical estrogen response pathways.

Clinically, the prognostic and predictive significance of ESR1 mutations in EEC remains incompletely defined. Few of the research studies have recognized hotspot mutations in a minority of cases, with inconsistent associations with clinicopathologic features and survival outcomes [4]. Furthermore, analyses of circulating tumor DNA in advanced hormone-dependent endometrial carcinoma have not consistently linked ESR1 mutations with resistance to aromatase inhibitors or progestin-based therapy, underscoring heterogeneity in biological impact. The current understanding of ESR1 alterations in EEC is summarized in **Table – 1** [1–5].

Table – 1: Clinical and Molecular Implications of ESR1 Gene Mutations in Endometrioid Endometrial Carcinoma.

Aspect	Key Observations	Clinical Relevance
Frequency of ESR1 mutations	Identified in approximately 3–5% of endometrioid endometrial carcinomas, with higher prevalence in recurrent or metastatic tumors [1,4]	Suggests involvement in disease progression rather than early carcinogenesis
Common mutation sites	Predominantly ligand-binding domain hotspot mutations leading to altered receptor activation [1,2]	May result in estrogen-independent or constitutive ERα signalling
Molecular associations	Frequently co-occurs with PI3K/AKT pathway alterations including *PTEN* and *PIK3CA* mutations [1,2]	Supports combined molecular targeting approaches
Effect on estrogen signalling	Mutant ERα demonstrates non-canonical transcriptional activity distinct from wild-type receptor signalling [2]	Challenges the predictive value of ER immunohistochemistry alone
Therapeutic implications	Variable response to progestins and aromatase inhibitors; emerging interest in SERDs and pathway-directed therapy [3,4]	Highlights the need for molecular profiling to guide hormonal treatment
Prognostic significance	ESR1 alterations and overexpression have been linked to relapse risk and aggressive tumor behaviour in select cases [1,5]	May refine prognostic stratification among ER-positive tumors

Remarkably, ESR1 overexpression has been linked with increased relapse risk and adverse disease-specific outcomes in early-stage EEC, highlighting that both qualitative and quantitative ERα alterations may influence tumor behaviour [3]. Collectively, these findings support further evaluation of ESR1 status as a biomarker and raise interest in exploring selective Estrogen receptor degraders or combination endocrine strategies in molecularly selected EECs.

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