ESR1 Mutations

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The *ESR1* gene located at 6q25.1–q25.2 encodes an ER and a ligand-activated transcription factor consisting of several domains involved in hormone binding.

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1. *ESR1* Mutation

Related pathways include the estrogen signaling pathway and signaling by G protein-coupled receptors, the large family of cell surface receptors [1]. Various *ESR1* mutations are implicated in hormone resistance and anti-estrogen therapies, such as tamoxifen, aromatase inhibitors, and fulvestrant, in patients with ER-positive breast cancer [2][3][4]. Resistance to endocrine therapy derived from *ESR1* can be classified into acquired and de novo patterns. *ESR1* expression changes over time; thus, negative results at a point of disease evolution can become detectable at another time [5]. According to studies investigating *ESR1* mutations, there is persistent activation of ER regardless of its ligand. A shift in helix 12 of *ESR1*, leading to the similarity to the estrogen-bound activated state of ER, was suggested as a mechanism for this ligand-independent ER activity. Coactivators may be able to bind and activate ER because of a change in ER configuration conferring resistance to endocrine therapy [6]. This mutational mechanism found in approximately 40% of patients with metastatic breast cancer who were pretreated with aromatase inhibitors [7][8]. Various *ESR1* alterations, amplification, genomic rearrangement, and point mutations contribute to the therapeutic resistance and metastasis of ER-positive breast cancer.

2. *ESR1* Amplification

ESR1 amplification is identified in approximately 30% of patients with ER-positive breast cancer depending on detection techniques and scoring systems [9][10][11][12][13]. A positive association between *ESR1* amplification and ER protein expression demonstrated in several studies suggests that amplification results in the increased production of oncogenic ER proteins [12][14][15]. In terms of the clinical significance of *ESR1* amplification, the link between the presence of *ESR1* amplifications in breast malignancy and resistance to endocrine therapy leading to metastasis is not clear and needs further investigation. *ESR1* amplification in a subset of ER-positive breast cancers was correlated with tamoxifen resistance and poor prognosis of patients [16][17]. In contrast, *ESR1* amplification was suggested as an indicator of longer disease-free survival and elevated sensitivity to endocrine therapy in contradicting studies [13][18]. Further studies are necessary to fully understand the clinical implications of *ESR1* amplifications owing to these controversial results.

3. *ESR1* Rearrangements and Fusion

The genomic rearrangements of *ESR1* have also been investigated. Diverse *ESR1* gene fusion transcripts have been identified in luminal breast cancer cases [19][20]. According to a previous study, RNA-sequencing data from primary TCGA breast samples demonstrated that 2.1% of all luminal B subtype samples harbored recurrently fused transcripts. The identified transcripts involved in the first two non-coding exons of *ESR1* fused to various C-terminal sequences from the coiled-coil domain containing 170 genes (*CCDC170*) (*ESR1*-e2 > *CCDC170*). These fusion transcripts generate truncated forms of CCDC170 proteins, which cannot complete chimeric ER fusion proteins. Therefore, exogenous expression of these truncated CCDC170 proteins in ER-positive breast cancer cells results in overgrowth and decreased sensitivity to tamoxifen [20]. This study presented a representative role for *ESR1*-e2 > *CCDC170* in endocrine therapy resistance. In terms of metastatic ER-positive breast cancer, *ESR1* fusions follow a similar fusion pattern harboring the first six exons of *ESR1* (*ESR1*-e6) fused to the C-terminus of various gene partners. Therefore, this pattern is considered important for endocrine therapy resistance based on *ESR1* fusion structural studies. However, detailed functional characterization and evidence supporting a causal role for *ESR1* fusions have been lacking. Moreover, the incidence of *ESR1* fusions is estimated at approximately 1%, and the exact value has not yet been established [21]. Additional studies that provide

evidence for the causal role of *ESR1* fusions, as well as their significant diagnostic and clinical implications need to be performed. A recent study [22] showed a novel mechanism that *ESR1-CCDC170* bound to HER2/HER3/SRC and activated SRC/PI3K/AKT signaling. Therefore, treatment regimens combining endocrine agents with the HER2 inhibitor lapatinib and/or the SRC inhibitor dasatinib might be applied to patients with *ESR1-CCDC170* gene fusions. Furthermore, kinase fusions in breast cancer analyzed by Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets seemed to be enriched in hormone-resistant, metastatic carcinomas and mutually exclusive with *ESR1* mutations [23]. Based on these results, fusion testing as a molecular testing at progression after endocrine therapy was suggested in an effort to identify additional therapeutic options which may provide substantial clinical benefit.

4. ESR1 Point Mutation

Among several mechanisms of *ESR1* mutation, the acquisition of activating point mutations, which cluster within the ligand-binding domain (LBD) of *ESR1,* is a well-known mechanism for acquired endocrine therapy resistance. Substitution of tyrosine at position 537 to serine (Y537S) in the LBD of *ESR1* conferring constitutive, ligand-independent activity of ER was first reported in experimental breast cancer models [24]. Regarding human tumors, Y537N was found in a metastatic specimen from a patient with breast cancer who experienced disease progression while on endocrine therapy [25], suggesting its ability to drive resistance to tamoxifen. The three most frequently identified *ESR1* point mutations were D538G, Y537N, and Y537S [4][5]. *ESR1* LBD point mutations mostly affect Y537 and D538 residues [26][27]. Samples from patients with ER-positive breast cancer treated with endocrine therapy rather than those from treatment-naïve patients revealed these mutations [27], supporting a role for *ESR1* mutations in acquired resistance to endocrine therapy and metastasis [28].

In vitro studies have been performed to characterize the functional, transcriptional, and pharmacological properties of *ESR1* LBD point mutations. Cell line models expressing *ESR1* mutants showed that these mutants contribute to hormone-independent proliferation resistant to endocrine treatment [4][26][29][30]. These mutations are in an apo-receptor conformation, which are constitutively active, even upon antagonist binding [4][31]. Changes in protein structure derived from these *ESR1* mutations resulted in reduced ligand affinity and ligand-independent activity. Although fulvestrant inhibited the growth of point mutation-containing cells in a dose-dependent manner, growth was not reversed to the levels of wild-type *ESR1*-expressing cell lines [26][32]. When bound to fulvestrant, the *ESR1* mutant also showed enhanced protein stability compared to the wild-type receptor. Moreover, these *ESR1* LBD mutations also recruited coactivators that further potentiated ER transcription [33][34]. In terms of metastatic biology, *ESR1* mutant cell lines, including Y537S and D538G, presented a substantial enrichment of metastasis-associated gene sets. The Y537S mutant showed remarkably potentiated tumor growth and metastasis in patients treated with tamoxifen or fulvestrant compared to the D538G mutant because of different cistromes and transcriptomes [28]. Regarding signaling pathways activated by *ESR1* mutants, interactions between ERs and receptor tyrosine kinases, including EGFR, HER2, and insulin-like growth factor receptor, activate downstream kinases. Particularly, co-localization and crosstalk between mutant ER and the insulin-like growth factor receptor pathway were revealed using ER immunoprecipitation and proximity ligation assays [35]. This upregulated insulin-like growth factor receptor pathway was demonstrated in *ESR1* mutant overexpression models [36][37]. These related pathways induce phosphorylation of multiple transcription factors, such as ERs and co-factors, leading to gene expression in a hormone-independent manner [38], suggesting a role for mutant ERs in promoting a metastatic phenotype [28][39]. With respect to the therapeutic strategy for preventing *ESR1* mutant-driven breast tumors, targeting these signaling pathways could be considered. According to a recent study [40], the emergence of circulating *ESR1* mutations was related to the risk of early progression during aromatase inhibitor treatment in patients with metastatic breast cancer, which suggested the potential role of *ESR1* mutations as a useful biomarker. In addition, the immunogenicity of epitope derived from the most common *ESR1* mutations including D538G and Y537S was suggested as novel targets for breast cancer immunotherapy [41].

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