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ALLEVIATION OF TAMOXIFEN RESISTANCE BY MODULATING ER α ALTERNATIVE SPLICING

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The estrogen receptor alpha (ER α) gene has been extensively studied in breast cancer, however, the function as well as regulation of its splice variants are poorly understood. During our study of HMGA1a (formerly termed HMGI), which is known as a DNA-binding transcription factor, we found it regulates alternative splicing of ER α pre-mRNA as a sequence-specific RNA-binding protein. We searched for HMGA1a RNA-binding sites we previously identified (1,2) and found one in ER α exon 1. HMGA1a binds to this sequence (detected by RNA-EMSA) that resulted in a splicing switch of two alternatively spliced isoforms, ER α 66 (full length) and ER α 46 (truncated). ER α 46 is known to inhibit AF-1 activity of ER α 66. Psoralen-mediated UV crosslinking showed HMGA1a anchored U1 snRNP to the adjacent pseudo-5' splice site. MCF-7 cells transfected with expression plasmids of HMGA1a and its RNA-decoy could induce and repress ER α 46 expression, respectively. The in vivo effect of the HMGA1a RNA-decoy were checked by transplanting its stable transfectants into nude mice, showing that they increased estrogen-dependent proliferation. In tamoxifen-resistant MCF-7 TAMR1 cells, the HMGA1a RNA-decoy improved tamoxifen-responsiveness by inhibiting estrogen-dependent cell proliferation. We conclude that this HMGA1a RNA-decoy would be implicated in novel therapeutic application to improve tamoxifen effectiveness in breast cancer patients.

Biography

Kenji Ohe has graduated from Kyushu University School of Medicine, Japan, with the specialties in Internal Medicine, especially Endocrinology. He completed his PhD at Kyushu University, Japan, and started working as a postdoctoral fellow at Paolo Sassone Corsi's lab when it was at IGBMC, France, and Akila Mayeda's lab when it was at Miami, FL, U.S.A. He is now working on therapeutic tactics on manipulating alternative splicing as an associate professor at Faculty of Pharmaceutical Sciences, Fukuoka University, Japan.

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