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FROM UNDERSTANDING THE MOLECULAR MECHANISM OF ABERRANT ERαPRE-MRNA TOWARD THE THERAPEUTIC APPLICATION IN BREAST CANCER

Kenji Ohe[1], Akila Mayeda[2], Munechika Enjoji[1]

[1]Fukuoka University, Japan
[2]Fujita Health University, Japan

HMGA1a (formerly termed HMGI) is known as a DNA-binding transcription factor with oncogenic properties. We have reported that it also binds to RNA in a sequence-specific manner. HMGA1a anchors U1 snRNP to the 5′ splice site of *presenilin-2* exon 5 to induce its aberrant exon skipping only when the HMGA1a RNA-binding site is adjacent to the 5′ splice site in sporadic Alzheimer's disease. In order to seek for other target genes of HMGA1a, we were prompted to search for HMGA1a RNA-binding sites in the *estrogen receptor alpha (ERα)* gene where both have been extensively studied in breast cancer. We performed a sequence homology search for the *presenilin-2* (PS2) HMGA1a RNA-binding site and found a specific sequence 33-nt upstream of the 5′ splice site of ERα exon 1. Therefore, we examined; (i) HMGA1a-binding to the RNA sequence by RNA-EMSA, (ii) splicing activity in cultured MCF-7 cells that were transfected with HMGA1a-expression and its RNA decoy expression plasmids, (iii) splicing activity *in vitro*. We found it switched two alternatively spliced isoforms, *ERα66 and ERα46*. HMGA1a-mediated U1 snRNP anchoring to the adjacent pseudo-5′ splice site was checked by psoralen-mediated UV crosslinking combined with RNA-EMSA. The effect of the decoy oligonucleotides containing the PS2 HMGA1a RNA-binding site in MCF-7 cells was further checked by transplanting its stable transfectant in nude mice showing increased estrogen-dependent growth. However, in tamoxifen-resistant MCF-7 TAMR1 cells, the HMGA1a RNA-binding decoy oligonucleotides improved tamoxifen-responsiveness by inhibiting estrogen-dependent cell proliferation. We conclude that this HMGA1a RNA-binding decoy oligonucleotides would be implicated in novel therapeutic application to improve tamoxifen effectiveness in breast cancer where tamoxifen lack effect.

Biography

Kenji Ohe has 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, Florida, USA. He is now working on therapeutical tactics on manipulating alternative splicing as an Associate Professor at Faculty of Pharmaceutical Sciences, Fukuoka University, Japan.

ohekenji@fukuoka-u.ac.jp