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芳香族炭化水素受容体リプレッサー (AhRR) によるエストロゲン受容体 (ER) の転写活性の抑制機構

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<Introduction> The aryl hydrocarbon receptor repressor gene (AhRR) is a member of the bHLH-PAS gene superfamily, identified as a new AhR-regulated gene. The function of the AhRR was described as a negative feedback modulator of the AhR pathway by competing with the AhR for Arnt- and XRE-binding, thereby blocking AhR-dependent gene expression. Our previous study reported that AhRR repressed the expression of estrogen-responsive genes, estrogen-mediated cell proliferation in MCF-7 cells, and the transcriptional activity of estrogen receptor alpha (ERα). In the present study, we investigated the repression mechanism of AhRR on the transcriptional activity of estrogen receptor.

<Methods> Full-length cDNAs encoding human AhRR, ERα, and ERβ were inserted into expression vector. DNAs encoding AhRR deletion mutants, truncated from the C- and N-termini, $AhRR_{1-351}$ (AhRRΔC) and $AhRR_{82-697}$ (AhRRΔbHLH), respectively, were prepared by standard PCR and the fragments were cloned, in frame, inserted into expression vectors. HepG2 cells were transiently transfected with the expression plasmids of human AhRR, AhRR deletion mutants, and either ERα or ERβ. The transcriptional activity of ERα or ERβ was determined by luciferase reporter assay. The interaction between ERα and AhRR was analyzed by immunoprecipitation assay.

<Results and Discussion> By ERE-luciferase reporter assay, E2-dependent transcriptional activation of ERα or ERβ was found to be repressed by AhRR. The direct interaction between ERα and AhRR was observed by immunoprecipitation assay. However, AhRRΔC and AhRRΔbHLH were not repressive individually on the E2-dependent transcriptional activition of ERα, suggesting that both C-terminus and bHLH regions of AhRR were required.