S8. CLINICAL IMPLICATIONS OF OESTROGEN-RELATED RECEPTOR (ERR) EXPRESSION LEVELS IN ENDOMETRIAL CANCERS

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Introduction: Endometrial cancer has been recognised as being an oestrogen-dependent tumour. However, oestrogen dependency related to growth is lost during its advancement. Orphan receptors, oestrogen-related receptors (ERR) α, β, and γ, may interact with oestrogen receptor (ER) α and β and may compete for the use of common ER transcriptional cofactors. This prompted us to study the expression pattern of the novel orphan receptors, ERR α, β, and γ, as well as ER α and β in endometrial cancer tissues.

Patients and methods: *Patients* Consent for the following studies was obtained from all patients and the Research Committee for Human Subjects, Gifu University School of Medicine, Japan. Tissue samples from endometrial cancers were collected from 50 patients (stage I, 21 cases; stage II, 16 cases; and stage III, 13 cases; and well-differentiated endometrioid adenocarcinoma of the endometrium [G1], 25 cases; moderately differentiated endometrioid adenocarcinoma [G2], 17 cases; and poorly differentiated endometrioid adenocarcinoma [G3], 8 cases).

Reverse transcription-real time polymerase chain reaction (RT-PCR) to amplify ERR and ER mRNAs.

Total RNA was extracted from tissue specimens using the acid-phenol guanidinium method (ISOGNE, Nippon Gene, Tokyo, Japan). PCR reaction were in a final volume of 25 l containing PCR buffer (2 mM Tris–HCl, pH 8.0, 10 mM KCl, 10 M ethylenediamine tetraacetic acid, 0.1 mM dithiothreitol, 0.05% Tween 20, 0.05% Nonidet P-40, 5% glycerol, 3 mM $MgCl_2$), SYBR Green I (1:30 000 dilution, BioWhittaker Molecular Applications, Rockland, ME, USA), 0.3 mM deoxyribonucleoside triphosphates (dNTPs), 0.3 M each of the PCR primers (based on each cDNA sequence) and 1.25 units of Takara Ex TaqTM R-PCR Version (Takara Suzo, Otsu, Japan). The mixture was amplified for 45 PCR cycles (94 °C for 10 s (denaturing step), 55 °C for 5 s (annealing step) and 72 °C for 20 s (extension step)) in a Smart Cycler (Cepheid, Sunnyvale, CA, USA).

Results: ER α and β mRNA levels decreased with increasing clinical stage, myometrial invasion and dedifferentiation (Fig. 1). ERR α mRNA levels increased with clinical stage and myometrial invasion, regardless of dedifferentiation. ERR β mRNA levels did not show any specific relationship with clinical stage, myometrial invasion or dedifferentiation. ERR γ mRNA levels increased with myometrial invasion, regardless of the clinical stage and dedifferentiation.

Discussion: In the present study, ER α and β expressions were downregulated in more advanced tumours and with dedifferentiation and myometrial invasion. By contrast, ERR α and γ expression levels were upregulated with myometrial invasion. The pattern of ERR α and ER α gene expression levels might be due to competition for the use of common cofactors [1] and loss of oestrogen dependency. It is speculated that the upregulation of ERR α and β might be related to tumour growth and invasion in endometrial cancers. ERRs can bind to the steroid receptor coactivator family without any ligands, and drive transcriptional activity of the target genes [2]. Transcriptional target genes for ERR α, including lactoferrin, medium-chain acyl coenzyme A dehydrogenase and osteopontin have been detected [3,4]. Although expression levels of ERRs are not directly related to the growth of endometrial cancers, ERR α and γ are candidate prognostic factors in endometrial cancer.

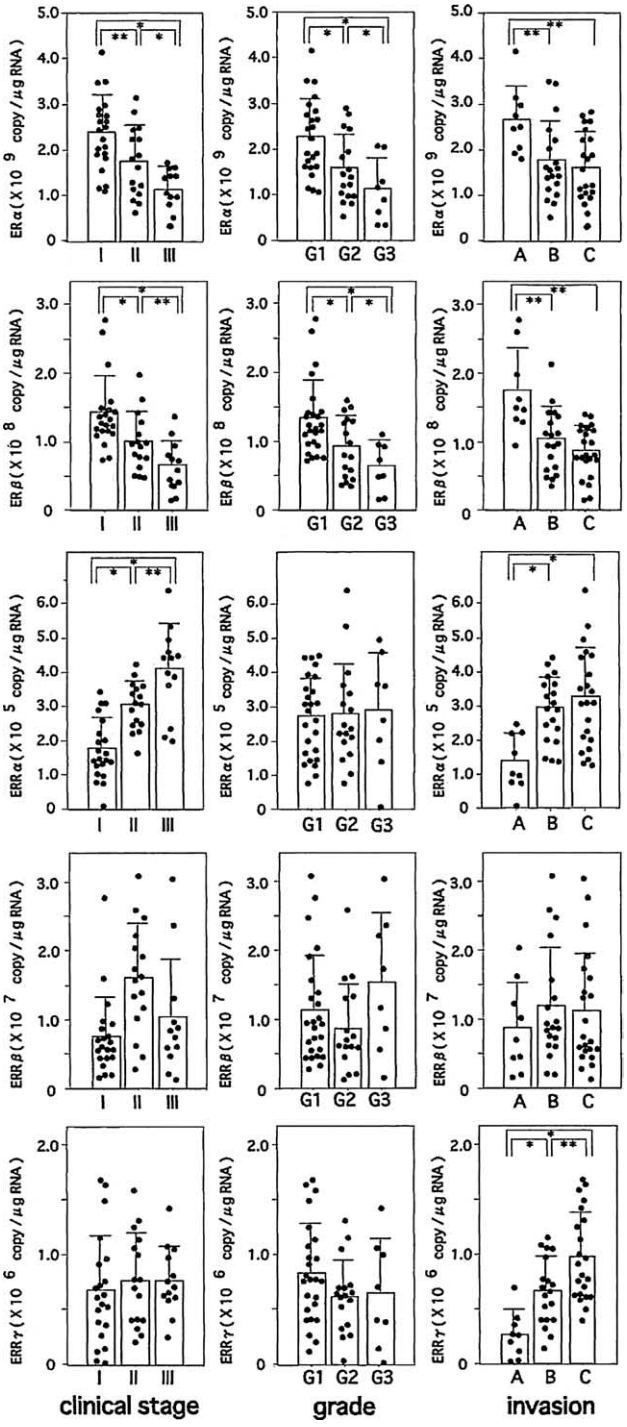

Fig. 1. Levels of oestrogen receptor (ER) α and β, and oestrogen-related receptor (ERR) α, β and γ mRNAs: A: Tumor limited to endometrium; B: tumor invades up to less than one half of the myometrium; C: tumor invades more than one half of the myometrium. *, $P < 0.001$, ** < 0.05.

References

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