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Regulatory mechanism of tissue-specific expression of aromatase (estrogen synthetase) and its physiological significance

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Aromatase catalyzes a key step in the biosynthesis of estrogens which take part in biologically important processes such as reproductive function. This enzyme has been known to be mainly localized in the ovary and placenta of gonadal tissues. Recently, sensitive assays for aromatase activity and mRNA have revealed that it is also present in extra-gonadal tissues, and is tissue-specifically regulated by various factors. This tissue-specific regulation of human aromatase gene is realized by alternative utilization of multiple exons 1, exons 1a, 1b, 1c, 1d, 1e, and 1f specific for expression in the placenta, skin fibroblasts/fetal liver, ovary, ovary/prostate/testis, placenta, and brain, respectively. Each of tissue-specific exons 1 is flanked by a unique promoter region containing basic and regulatory promoter or enhancer sites. To further elucidate tissue-specific regulation of the gene, we analyzed transcriptional elements on the promoter regions of multiple exons 1. The analyses using CAT, foot printing, and gel shift assays indicated two trophoblast-specific elements (TSE) tandem located on the proximal promoter region of exon 1a in addition to TATA and CAT boxes. The facts that TSE sequence is essential for transcription from exon 1a and furthermore, a binding protein for TSE is only present in the placenta agree well with the high tissue-specificity of transcription from exon 1a. On the other hand, there are two cAMP-responsive elements and two AP-1 (TPA-responsive element) sites for PKA and PKC signals as well as TATA and CAT boxes on the proximal promoter region of exon 1c/1d. This is also well consistent with transcriptional regulation from exon 1c/1d in the ovary and testis, in which transcription was drastically regulated by various factors such as gonadotropins, bioactive lipids, and cytokines according to reproductive cycles. In contrast, exon 1b was widely utilized in the aromatase transcripts of extra-gonadal tissues and there are no typical TATA box and no typical DNA motifs for inductive responses on the proximal promoter region of exon 1b. So, a transcriptional machinery from exon 1b seems to be loose, and in fact, several transcriptional start sites was found in the transcripts from exon 1b. Furthermore, a switching from exon 1b to exon 1c was observed in the aromatase transcripts of breast cancer and vascular tissues. Such a switching may cause aberrant expression of aromatase in adipose, bone, and vascular tissues and play an important role in the carcinogenesis of estrogen-dependent breast and endometrial cancers and pathogenesis of osteoporosis and atherosclerosis.

References

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