Abstract

The Carboxyl Ester Lipase, CEL, gene -
Evolutionary implications on structure, organization and transcriptional regulation

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The bile salt stimulated carboxy ester lipase (CEL) is important for the digestion and absorption of dietary lipids, and is highly expressed in the exocrine pancreas and the lactating mammary gland. Low levels of CEL expression are also at hand in the liver, in macrophages, in endothelial cells and in eosinophils.

At the human chromosomal location 9q34.3 both a functional CEL gene as well as a truncated ÏŒ CEL pseudogene are at hand. A 30 kb long cosmid fragment confirms the presence of both CEL genes in close proximity. They are oriented in a head to tail orientation approximately 11 kb apart with the functional CEL gene being the most 5' one. The duplication of the genes is proposed to be the result of an over-replication of an 11719 bp long fragment, followed by a transposition like event. At the insertion site a 364 bp long target site duplication was generated. The duplication of the CEL gene was estimated to have occurred during primate evolution some 23 million years ago. To investigate if the ÏŒ CEL is at hand in other species than man, we decided to analyze the gorilla genome for the presence of two CEL genes. The gorilla genome is shown to comprise one functional gCEL gene and one Ï’ ÏŒ CEL pseudogene, with the same internal orientation as that found in man. The gorilla CEL genes show the same exon distribution as in man, with the functional gene being divided into 11 exons and the pseudogene missing exons 2 through 7 due to a 5 kb deletion. The genomes of chimpanzee, orangutan (Hominoidae), macaque (Old World monkeys) and weeper capuchin (New World monkeys) were also analyzed for the presence of two CEL genes. The truncated form of the CEL pseudogene is shown to be at hand in the, great apes and man only, while macaques and capuchin monkeys are shown to comprise duplicated CEL genes. These findings indicate that the inactivation, through deletion of six exons, rather than the duplication of the original CEL gene occurred after the separation of the Hominoids from Old World monkeys some 23 million years ago.

Previous studies on transcriptional regulation of the CEL gene in mouse and man mainly reveal differences concerning important Ï• regulatory elements, involved in transcriptional activation of CEL. Notwithstanding, we here report on the identification of one common E-box element, in the proximal promoter at -47/-52, that is important for the overall CEL gene expression in monocyteic THP-1 cells, the mouse mammary epithelial cell line HC11 and the rat pancreas tumor AR42J cells. Electrophoretic mobility- shift assays reveal the binding of upstream stimulatory factors 1 and 2 to the E-box.

Keywords: Carboxyl Ester Lipase, gene structure, pseudogene, locus, evolution, duplication, primate, transcriptional regulation, monocyte, mammary gland, USF 1 & 2.

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