Abstract

The mouse and human carboxyl ester lipase (CEL) genes are mainly expressed constitutively in the exocrine pancreas and in the mammary gland during pregnancy and lactation. By comparing CEL gene promoter elements in mouse and human, as well as the expression levels in the two tissues, we have observed both similarities and substantial differences. The expression levels of the CEL gene in human and mouse pancreas are comparable. However the most important promoter elements in these two tissues differ. In the human CEL gene promoter there is a pancreas-specific enhancer, which is essential for high level tissue-specific expression. In contrast, the mouse CEL gene expression is totally dependent on another pancreas-specific element. This element is identified as a PTF1 (pancreatic transcription factor 1) binding site. These findings provide an example of genetic divergence between species not accompanied by difference in function.

In the mouse mammary gland, the CEL gene is activated at day 13 of pregnancy. This is synchronous with the expression of another milk protein gene encoding the whey acidic protein (WAP). Even though the CEL and the WAP genes are induced at the same time point during mammary gland development, their regulation is different with respect to dependence on the lactogenic hormones. The strong induction of the WAP gene expression due to the activation of STAT5 (signal transducer and activator of transcription 5) by prolactin has not been observed for the CEL gene. Hence, prolactin/STAT5 is not involved in a general activation of milk genes. Instead, high level expression of the mouse CEL gene depends on the binding of the nuclear factor 1-C2 (NF1-C2). Mutation of the NF1-C2 binding site in the CEL gene promoter decreases the activation potential of the promoter down to 15%. We have demonstrated that the NF1-C2 protein interacts with the NF1 binding site with higher affinity than other NF1 family members and that a hyperphosphorylated form of NF1-C2 is present in the mammary gland-specific activating complex. It has earlier been shown that the WAP gene expression is positively regulated by NF1. We have evidence that NF1-C2 is responsible also for this activation, which suggests that there is a connection between induction of the CEL and the WAP genes and the differentiation-related binding of NF1-C2 at about day 13 of pregnancy.

Key words: carboxyl ester lipase, regulation, promoter, enhancer, mammary gland, pancreas, nuclear factor 1

ISBN 91-628-4999-9