Site specific insertion of a transgene into the murine α-casein (CSN1S1) gene results in the predictable expression of a recombinant protein in milk

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Abstract

Gene loci of highly expressed genes provide ideal sites for transgene expression. Casein genes are highly expressed in mammals leading to the synthesis of substantial amounts of casein proteins in milk. We have assessed the α-casein (CSN1S1) gene as a site of transgene expression in transgenic mice and a mammary gland cell line. A transgene encoding an antibody light chain gene (A1L) was inserted into the α-casein gene using sequential homologous and site-specific recombination. Expression of the inserted transgene is directed by the α-casein promoter, is responsive to lactogenic hormone activation, leads to the synthesis of a chimeric α-casein/A1L transgene mRNA and secretion of the recombinant A1L protein into milk. Transgene expression is highly consistent in all transgenic lines, but much lower than that of the α-casein gene (4%). Recombinant A1L protein accounted for 0.5% and 1.6% of total milk protein in heterozygous and homozygous transgenic mice, respectively. The absence of the α-casein protein in homozygous A1L transgenic mice leads to a reduction of total milk protein and delayed growth of the pups nursed by these mice. Overall, the data demonstrate that the insertion of a transgene into a highly expressed endogenous gene is insufficient to guarantee its abundant expression.

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