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5'-FLANKING SEQUENCES OF HUMAN THYROTROPIN BETA  
CHAIN-SIMIAN VIRUS 40 LARGE T ANTIGEN FUSION GENE  
PRODUCED CARCINOMA OF THE ANTERIOR  
PITUITARY IN TRANSGENIC MICE

Kazushige MAKI

*Department of Laboratory Animal Science,  
Faculty of Veterinary Medicine,  
Hokkaido University, Sapporo 060, Japan*

Thyrotropin (TSH) is a major regulator of thyroid gland function. This hormone, together with lutropin (LH) and follitropin (FSH), is one of three pituitary glycoprotein hormones. Each of these hormones consists of common  $\alpha$ - and specific  $\beta$ -subunits. The  $\beta$ -subunits provide the biological specificity for each hormone. The regulation of TSH  $\beta$ -subunit gene expression has been studied in detail *in vitro*. However, the regulatory sequence concerning the tissue-specific expression still remains unknown *in vivo*. To analyze the control region of human TSH  $\beta$ -subunit gene expression *in vivo*, I have generated two types of transgenic mice that express SV40 large T antigen under the control of ~1200 base pairs and of ~5200 base pairs of human TSH  $\beta$ -subunit gene 5' flanking sequences, which are referred to as pTTP-1 and pTTP-5, respectively.

These recombinant genes were microinjected into fertilized mouse eggs (C57BL/6J), and one pTTP-1 transgenic mouse ( $\beta$ F13) and five pTTP-5 transgenic mice (No. 6, 7, 9, 16 and 26) were identified by Southern blot analysis. One pTTP-1 transgenic mouse ( $\beta$ F13) and two pTTP-5 transgenic mice (No. 6 and 16) carried complete transgenes, but some rearrangement of the transgenes such as recombination or deletion occurred in other transgenic mice. Both pTTP-1 and pTTP-5 transgenic mice ( $\beta$ F13, No. 6 and 16) developed pituitary tumors, but other organs were normal. Histochemical and immunohistochemical analyses showed that the pituitary tumors of pTTP-5 transgenic mice were composed of well differentiated cells and those of pTTP-1 transgenic mice of poorly differentiated cells, compared with the anterior pituitary of normal mice. To examine the tissue specificity of transgene expression, mRNA of SV40 large T antigen was monitored in various tissues (brain, pituitary, lung, heart, liver, spleen, kidney, testis, ovary and muscle) from pTTP-1 and pTTP-5 transgenic mice by RT-PCR analysis. In each transgenic mouse, mRNA of SV40 large T antigen was detected in pituitary. In pTTP-5 transgenic mice, however, transgene expression was unexpectedly observed in testis.

In this paper, I show that 1200 base pairs of the human TSH  $\beta$ -subunit gene 5'-flanking sequence are capable of directing pituitary expression. But the results of histochemical and immunohistochemical analyses using transgenic mice suggest that the *cis*-acting regulatory domain located from -5200bp to -1200bp of human thyrotropin  $\beta$ -subunit gene 5'-flanking sequences is required for the stringent expression of the human thyrotropin  $\beta$ -subunit gene in thyrotropic cells.