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

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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 α- and specific β-subunits. The β-subunits provide the biological specificity for each hormone. The regulation of TSH β-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 β-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 β-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 (βF13) and five pTTP-5 transgenic mice (No. 6, 7, 9, 16 and 26) were identified by Southern blot analysis. One pTTP-1 transgenic mouse (βF13) 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 (βF13, 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, kindney, 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 β-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 β-subunit gene 5′-flanking sequences is required for the stringent expression of the human thyrotropin β-subunit gene in thyrotropic cells.