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A Transgenic Mouse Model for Studies on the In Vivo Function of a Cytochrome P450 Enzyme CYP2A13 in Xenobiotic-Induced Nasal and Pulmonary Toxicity

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The aim of this study was to prepare and characterize a CYP2A13-transgenic mouse model for studies on the role of this human P450 monooxygenase in the toxicity of xenobiotic compounds. CYP2A13, which is predominantly expressed in the respiratory tract in humans, is highly efficient in the metabolic activation of NNK, a tobacco-specific carcinogen. A genomic fragment containing the full-length CYP2A13 gene was used for transgenic mouse production. A positive transgenic founder was identified; the CYP2A13 transgene was present in multiple copies in the mouse genome. The CYP2A13 transgene mRNA and protein were abundantly expressed in the nasal mucosa. CYP2A13 mRNA and protein were also detected in the transgenic mouse lung, albeit at much lower levels than those found in the nasal mucosa. In addition, the CYP2A13 mRNA was detected by RNA-PCR in small intestine, liver, and testis, but not in heart and kidney, of the transgenic mice. Thus, the tissue distribution of transgenic CYP2A13 expression agreed well with the respiratory tract-selective expression of CYP2A13 in humans, and that of CYP2A5 and CYP2A3 in mice and rats, respectively, suggesting that the regulatory elements for tissue-selective CYP2A13 expression are fully contained in the transgene fragment. In vitro analysis of P450 activities revealed significant increases in the rates of microsomal NNK metabolic activation in the lung and nasal mucosa of the transgenic mice, compared with wild-type mice. Therefore, this mouse model will be valuable for future studies on the in vivo role of CYP2A13 in xenobiotic-induced nasal and pulmonary toxicity.