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Generation And Characterization Of A Cyp2a13 Transgenic Mouse Model

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The aim of this study was to prepare and characterize a CYP2A13-transgenic mouse model for studies on the in vivo role of this human P450 monooxygenase in the toxicity of xenobiotic compounds. CYP2A13 is predominantly expressed in the respiratory tract in humans, and heterologously expressed CYP2A13 is highly efficient in the metabolic activation of NNK, a tobacco-specific carcinogen, as well as other chemical compounds. A genomic fragment containing the full-length CYP2A13 gene, obtained from a bacterial artificial chromosome clone, was isolated, and used for transgenic mouse production. A positive transgenic founder was identified through PCR and Southern blot analysis of tail DNA. Further Southern blot analysis indicated that the CYP2A13 transgene, with approximately 200 kilobase pairs of flanking sequences, was intact, with the transgene present in multiple copies in the mouse genome. Initial characterization of F1 heterozygotes indicated that the CYP2A13 transgene mRNA as well as 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 found in the nasal mucosa. The CYP2A13 mRNA was also 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. Further characterization of the transgenic mouse is underway to demonstrate the activity of the transgenic CYP2A13 in the metabolism and toxicity of known nasal toxicants. (Supported in part by NIH grant ES-013337)