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EHT

Judging Dept.

Yuan Wei

Student

EHT

5

Xinxin Ding

Dept or Program Years in program

Mentor

Generation of a Mouse Model with a Reversible Hypomorphic NADPH-Cytochrome P450 Reductase Gene

Author (s)

Yuan Wei, Kerri Kluetzman, Xinxin Ding

A mouse model known as “Cpr-low” was recently generated, in which the expression of the cytochrome P450 reductase (Cpr) gene was globally down regulated. The decreased CPR expression was accompanied by phenotypical changes, including reduced embryonic survival, female infertility, and decreases in circulating cholesterol. The aim of this study was to generate a complementary mouse model (named rescue Cpr-low, or rCpr-low), in which the reduced CPR expression can be reversed in an organ-specific fashion, so that the specific contributions of a given organ, such as the liver, to the phenotypical changes seen in the Cpr-low mice can be determined. The hypomorphic expression of CPR in the Cpr-low mouse was hypothetically due to the insertion of a neo gene in the last Cpr intron. In the rCpr-low mouse, the neo marker, flanked by two loxP sites, is still present, but an additional loxP site in Cpr intron 2 was deleted, thus allowing neo to be removed by Cre recombinase, without concomitant deletion of the Cpr exons. Structure of the rCpr-low allele has been confirmed by PCR and Southern blot analysis. As was found for the Cpr-low mouse, CPR expression in the rCpr-low mouse was greatly decreased in all tissues examined. Studies are underway to determine whether hepatic CPR levels are normalized in a tissue-specific manner in rCpr-low mouse that expresses the albumin-Cre transgene in the liver, which represents a new mouse model that would allow us to test the specific function of CPR and CPR-dependent enzymes in extrahepatic tissues.