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Dna Methylation is Involved in the Regulation of Mouse Cyp1A2 Expression

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Cytochrome P450 1A2 (CYP1A2) is constitutively and inducibly expressed preferentially in liver of mice, but the molecular mechanisms underlying the expression of CYP1A2 have not yet been fully clarified. In this study, CpG sites of the Cyp1a2 promoter in liver were found to be hypomethylated in a site-specific pattern compared to those in lung and kidney. A pattern of CpG methylation that is similar to its wild type was observed in liver of aryl hydrocarbon receptor (AhR) null mice, indicating that the tissue-specific demethylation of the Cyp1a2 promoter is independent of AhR. While the expression of hepatic CYP1A2 increased until 4 weeks after birth, the Cyp1a2 promoter was gradually demethylated. Compared to mouse liver, the Cyp1a2 promoter were hypermethylated in a site-specific pattern in mouse hepatoma Hepa1c1c7 cells that do not constitutively express CYP1A2. Treatments with a demethylating agent 5'-aza-2'-deoxycytidine (AzaC) and a direct inhibitor of histone deacetylases trichostatin A (TSA), however, did not activate CYP1A2 expression in Hepa1c1c7 cells, even in the presence of strong inducers such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In primary hepatocytes, constitutive CYP1A2 expression was found to decrease to an undetectable level at 48 hours in culture and the extent of methylation in the Cyp1a2 promoter was observed to increase, but only in a delayed manner. By contrast, primary hepatocytes incubated in a media with TCDD contained induced levels of CYP1A2 mRNA, with the Cyp1a2 promoter hypomethylated compared to untreated control, suggesting that the Cyp1a2 promoter may be methylated only when it is in an inactive state. Taken together, these findings indicate that DNA demethylation is involved in the tissue-specific and developmental regulation of CYP1A2 expression, but other factors, mostly unknown, are probably needed for the expression of hepatic CYP1A2.

Keyword : DNA methylation, liver, CYP1A2