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Mapping genetic networks that dictate the mammalian liver phenotype using whole genome microarrays

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Cultured cell culture models have proven to be robust tools by which to understand these regulatory networks in normal development and maintenance of tissue specificity. Two cell model systems that have contributed to our understanding of liver gene regulation include hepatoma x fibroblast cell hybrids (which show complete silencing of hepatic gene expression, a phenomenon termed extinction) and hepatoma variant cells (which have silenced large numbers of liver genes). We have utilized whole genome microarrays to determine the extent of gene silencing in these model systems and to map the interplay of genetic pathways (both activated and repressed) in the rat liver. In both of these cell culture systems, presumed epigenetic alterations result in profound silencing of hundreds of liver enriched genes. We have identified a series of candidate genes, many of which fall into discrete regulatory pathways (including Wnt, HNF, and growth hormone pathways) that may play a role in these silencing phenomena. To test whether this approach is useful in identifying key genetic regulatory pathways, we have over-expressed many of these genes in a hepatoma variant cell line. Results show that over-expression of two of these genes, HNF1A and CREG1 (Cellular Repressor of E1A-stimulated Genes 1), result in partial rescue of hepatic gene expression. These results suggest that the use of whole genome approaches to these cell model systems is highly predictive in identifying key liver-specific genetic pathways as well potentially elucidating combinatorial effects of genetic pathways required to establish and maintain hepatic identity.

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