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Optimizing combination of liver-enriched transcription factors and nuclear receptors simultaneously favors ammonia and drug metabolism in liver cells

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Abstract

The HepG2 cell line is widely used in studying liver diseases because of its immortalization, but its clinical application is limited by its low expression of the urea synthesis key enzymes and cytochromes P450 (CYPs). On the basis of our previous work, we investigated the transcriptional regulation of arginase 1 (Arg1) and ornithine transcarbamylase (OTC) in HepG2 cells. We also screened for the optimal combination of liver enrichment transcription factors (LETFs) and xenobiotic nuclear receptors that can promote the expression of key urea synthases and five major CYPs in HepG2 cells. Thus, recombinant HepG2 cells were established. Results showed that C/EBPβ, not C/EBPα, could upregulate expression of Arg1 and PGC1α and HNF4α cooperatively regulate the expression of OTC. The two optimal combinations C/EBPβ+HNF4α+HNF6+PXR and C/EBPβ+HNF4α+HNF6+CAR were selected. Compared with the control cells, the recombinant HepG2 cells modified by the two optimal combinations exhibited enhanced ammonia metabolism and CYP enzyme activity. Moreover, the HepG2/(C/EBPβ+HNF4α+HNF6+PXR) cells more strongly reduced ammonia