Regulation of Genes that Mediate Fatty Acids and Cholesterol Synthesis in Humans through Selective Activation of the Ah Receptor

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II. Abstract

The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor. Activation of AHR has been associated with toxicity through its binding to dioxin response element (DRE) sequences in its target genes (e.g. *CYP1A1).* We have previously performed a microarray analysis on liver isolated from ligand-treated transgenic mice expressing a wild-type *Ahr* or a DRE-binding mutant *Ahr* (A78D). The results revealed that AHR DRE-binding is not required for suppression of genes involved in cholesterol synthesis following activation. In order to confirm this finding in humans, primary human hepatocytes were administered an AHR ligand and subsequent analysis of mRNA levels revealed a significant trend of repression in fatty acid and cholesterol synthesis genes. Our lab has established the ability of the ligand SGA360 to activate AHR without inducing its DRE-binding. Since the toxicity associated with AHR is a DRE-mediated event and our microarray data revealed that DRE-binding is not essential for the regulating of our genes of interest, we propose to test the effect of SGA360 in primary human hepatocytes. The discovery of AHR as a regulator of fatty acid and cholesterol biosynthesis gene expressions independently of its DRE-binding would suggest that AHR may be a previously unrecognized therapeutic target.