

**Indirubin potently induces CYP1A1 mRNA expression and is a CYP1A1 substrate**

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Aryl hydrocarbon receptor (AhR) mediates a diverse range of toxic and biological effects of dioxins in a variety of species and tissues, but it remains an orphan receptor since its physiological ligand and functions are unknown. We previously reported that indirubin was a potent AhR ligand and was present in human urine and fetal bovine serum. Here we have addressed whether the amounts of indirubin in these physiological fluids were capable of activating AhR-mediated signalling mechanisms in human cells. We found CYP1A1 and CYP1A2 mRNAs were expressed in the HepG2 cell line by as little as 1 pM indirubin, whereas they were not expressed by the same concentration of the prototypical AhR ligand, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). It is also concluded that indirubin not only induced CYP1A1 mRNA expression, but was also a good substrate for the enzyme from its low dissociation constant to CYP1A1. Our results suggest indirubin regulation system by negative feedback loop, that is, indirubin rapidly activates its own metabolism via AhR-mediated induction of CYP1A1 activity and are consistent with the notion that indirubin is a physiological ligand of AhR.