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## The Tangle of Nuclear Receptors that Controls Xenobiotic Metabolism and Transport: Crosstalk and Consequences.

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**Table 1** Crosstalk between CAR/PXR and other signaling pathways and consequences

<b>Crosstalk</b>	<b>Mechanisms</b>	<b>Consequences</b>	<b>References</b>
AhR/HIF	sharing of ARNT partner	perturbation of AhR target genes by hypoxia	48-51
AhR/ER	AhR binding to EREs; activated AhR behaves as a coactivator of ER; inhibitory XRE elements in ER target genes ; sharing of coactivators; AhR-mediated increased ER degradation by the proteasome; activated AhR-mediated RIP140 expression	control of ER target genes by xenobiotics in liver and extrahepatic tissues	54,57-61
CAR/ER	estrogen metabolism by PXR/CAR controlled XMTS; squelching of p160 coactivators	decrease of estrogen levels; repression of ER target genes by xenobiotics	65,66
CAR-PXR/FXR	FXR and PXR share agonists; FXR transactivates CAR-PXR target genes; FXR controls PXR gene expression (mouse)	increase of xenobiotic metabolism by bile acids ; control of bile acids homeostasis by xenobiotics	79,80,92-98 101,103,
CAR-PXR/SHP	inhibition of CAR-PXR transcriptional activity by SHP; PXR controls SHP expression in HepG2 cells	control of xenobiotic metabolism by bile acids control of bile acids homeostasis by xenobiotics	104,110,111
CAR-PXR/LXR	inhibition of CAR-PXR transcriptional activity by activated LXR	decrease of xenobiotic metabolism by oxysterols	96
CAR-PXR/HNF-4	inhibition of HNF-4 transcriptional activity by PXR and CAR through competitive binding with PGC-1 $\alpha$ on HNF-4 and by CAR through binding to HNF-4 (DR1) response elements	control of gluconeogenesis, and bile and fatty acid homeostasis by xenobiotics	43,87,88,96

CAR-PXR/FoxO1	activation of CAR-PXR transcriptional activity by FoxO1 ; inhibition of FoxO1 transcriptional activity by activated CAR-PXR	xenobiotic-gluconeogenesis reciprocal interaction	123
PXR/FoxA2	inhibition of FoxA2 transcriptional activity by activated PXR	decreased hepatic fatty acid metabolism by xenobiotics	135
PXR/PPAR $\gamma$	Induction of PPAR $\gamma$ by activated PXR	hepatic steatosis	126
LKB1-AMPK-CAR	Phenobarbital activates LKB1 and AMPK; AMPK controls CYP induction by phenobarbital	phenobarbital controls cell energy	140-142
CAR-PXR/GR	GR controls CAR, PXR and RXR gene expression	control of xenobiotic metabolism by glucocorticoids	143-146
CAR-PXR/TR	CAR/PXR and TR share response elements; catabolism of thyroid hormones by XMTS	decreased thyroid hormone levels by xenobiotics	a,162 163,164
PXR-CAR/VDR	CAR/PXR and VDR share response elements; vit D hormones catabolism by CYP3A4	control of xenobiotic metabolism by vit D; decreased level of vit D and active metabolites; perturbation of VDR target genes by xenobiotics	168-170, 173,174,b 175,176
PXR-CYP3A4-AhR	CYP3A4 converts AhR antagonist to activator	PXR agonists control AhR target genes	185

a : JM Pascussi et al. unpublished data

b : M Ellfolk et al., Abstract. 15<sup>th</sup> International Conference on Cytochromes P450, Bled Slovenia 2007.