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Response to Zhou et al.

Jean-Marc Pascussi, … , Patrick Maurel, Marie-José Vilarem

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Letter

Osteomalacia is a frequent complication resulting from long-term therapy with drugs such as phenytoin, carbamazepine, and phenobarbital. We have investigated the crosstalk between pregnane X receptor (PXR) and vitamin D receptor (VDR) and have reported that (a) PXR binds to and transactivates vitamin D–responsive elements in the 25-hydroxyvitamin D3-24-hydroxylase (CYP24) promoter, and (b) PXR agonists increase CYP24 mRNA expression in human hepatocytes and mouse kidney (1). Since the CYP24 enzyme converts 1,25-dihydroxyvitamin D3 to inactive metabolites, these observations provide an objective explanation for the induction of osteomalacia by PXR agonists. In their report on this crosstalk in the June issue of the JCI, Zhou et al. (2) concluded instead that CYP24 is not induced but rather downregulated by PXR agonists. These authors observed neither binding to nor transactivation of the CYP24 promoter by PXR, nor did they find induction of CYP24 mRNA in human hepatocytes. As soon as we became aware of this work, we repeated key experiments using extracts from new hepatocyte cultures and new inducers (SR128123 and CITCO). Moreover, we evaluated the constitutive androstane receptor–VDR (CAR-VDR) crosstalk. Our new results fully confirm our previous findings. In human hepatocyte cultures, the CYP24 mRNA level was increased by rifampicin and 2 other PXR agonists, phenobarbital and SR128123. EMSA not only confirmed the binding of PXR to vitamin D–responsive elements–I and […]

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Jean-Marc Pascussi, Patrick Maurel, and Marie-José Vilarem
INSERM U632, Université Montpellier, Montpellier, France.

Conflict of interest: The authors have declared that no conflict of interest exists.

Address correspondence to: Jean-Marc Pascussi, INSERM U632, 1919 route de Mende, Montpellier 34293, France. Phone: 33-4-67-61-33-69; Fax: 33-4-67-52-36-81; E-mail: pascussi@montp.inserm.fr.

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