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Inhibitory Effect of PXR on Ammonia-induced Hepatocyte Autophagy via P53

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Highlights

- PXR interferes with ammonia-induced hepatocyte autophagy.
- PXR inhibits ammonia-induced AMPKβ1 accumulation and activation.
- P53 binds to the AMPKβ1 promoter (−253 to −19) and transactivates its expression.
- Interaction of PXR and P53 affects AMPKβ1 expression.

Abstract

Pregnane X Receptor (PXR), a nuclear receptor transcription factor, participates in a wide range of physiological activities, but the regulation of ammonia-induced hepatocyte autophagy by PXR is not yet clear. In this study, the levels of down-regulated LC3B-II and up-regulated SQSTM1 were found in ammonia-induced PXR-overexpressing (PXR+) liver cells, but the opposite appeared in PXR-knockdown (PXR−) liver cells. Rifampicin, a PXR-activating agent, elicits a similar effect as PXR+ cells. The mechanism analysis reveals that the levels of the energy-sensitive molecule AMPKβ1 and phosphorylated AMPKβ1 (p-AMPKβ1) in PXR− cells are higher than those in control cells, whereas the levels of this molecule in PXR+ cells are lower than those in control cells. Two active sites that bind to P53 exist in −253 to −19 at the promoter region of AMPKβ1, and their mutation can reduce the transactivating effect of AMPKβ1 that P53 relies on. A protein interaction also exists between PXR and P53. These findings indicate that PXR is a factor