Supporting Information

Vogel et al. 10.1073/pnas.1215060109

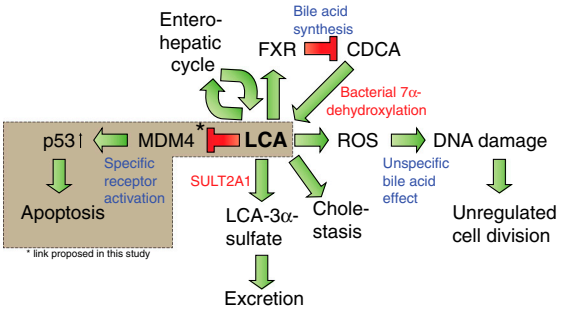
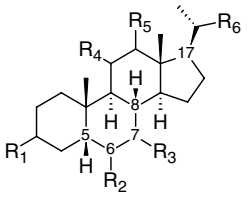
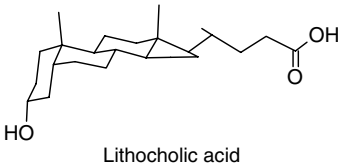


Fig. S1. Regulatory pathway of lithocholic acid (LCA). LCA is a secondary bile acid formed by bacteria in the gut from its precursor chenodeoxycholic acid (CDCA). It is a rare example of a toxic endobiotic that can lead to cholestasis and that is efficiently detoxicated by conjugation with taurine or glycine and sulfation at C-3 by the sulfotransferase SULT2A1. LCA induces its own metabolism by activating nuclear receptors like FXR, thereby inhibiting the synthesis of bile acids and promoting the transcription of genes encoding for sulfotransferases. LCA also activates the vitamin D receptor in a concentration-dependent manner and thereby induces its own detoxification by CYP3A enzymes. Perhaps MDM4 has the role of an intracellular lithocholic acid sensor that initiates programmed cell death at pathological LCA concentrations.

Table S1. Dissociation constants for bile acids and derivatives from MDM4





Lithocholic acid

Common name	R_1	R_2	R_3	R_4	R_5	R_6	Conjugate	Additional feature	K_D [μM]
Lithocholic acid	····OH	H	H	H	H	CH_2CH_2COOH	—	—	12
5β-Cholanic acid-3-one	═O	H	H	H	H	CH_2CH_2COOH	—	—	80
(Acetyloxylithocholic acid)	····OAc	H	H	H	H	CH_2CH_2COOH	—	—	110
Lithocholic acid 3-sulfate	····OSO_3H	H	H	H	H	CH_2CH_2COOH	—	—	210
5,6-Dehydrolithocholic acid	····OH	—	H	H	H	CH_2CH_2COOH	—	Δ^5	400
Ergosterol	—OH	—	—	H	H	CH_2CH_2COOH	—	Δ^5, Δ^7	nb*
Taurolithocholic acid	····OH	H	H	H	H	CH_2CH_2COOH	Taurine	—	200
Taurolithocholic acid-3-sulfate	····OSO_3H	H	H	H	H	CH_2CH_2COOH	Taurine	—	120
Hyodeoxycholic acid	····OH	····OH	H	H	H	CH_2CH_2COOH	—	—	nb*
Hyodeoxycholic acid methyl ester	····OH	····OH	H	H	H	CH_2CH_2COOMe	—	—	nb*
5β-Cholanic acid-3α-ol-6-one	····OH	═O	H	H	H	CH_2CH_2COOH	—	—	nb*
Chenodeoxycholic acid	····OH	H	····OH	H	H	CH_2CH_2COOH	—	—	280
5β-Cholanic acid-3,7-dione	═O	H	═O	H	H	CH_2CH_2COOH	—	—	nb*
Taurochenodeoxycholic acid	····OH	H	····OH	H	H	CH_2CH_2COOH	Taurine	—	280
Glycochenodeoxycholic acid	····OH	H	····OH	H	H	CH_2CH_2COOH	Glycine	—	310
Ursodeoxycholic acid	····OH	H	—OH	H	H	CH_2CH_2COOH	—	—	nb*
Deoxycholic acid	····OH	H	H	H	····OH	CH_2CH_2COOH	—	—	240
8α -Hydroxytaurodeoxycholic acid†	····OH	H	H	H	····OH	CH_2CH_2COOH	Taurine	····OH at C-8	nb*
Taurodeoxycholic acid	····OH	H	H	H	····OH	CH_2CH_2COOH	Taurine	—	250
Glycodeoxycholic acid	····OH	H	H	H	····OH	CH_2CH_2COOH	Glycine	—	300
Cholic acid	····OH	H	····OH	H	····OH	CH_2CH_2COOH	—	—	1,100‡
Dehydrocholic acid	═O	H	═O	H	═O	CH_2CH_2COOH	—	—	nb*
Glycocholic acid	····OH	H	····OH	H	····OH	CH_2CH_2COOH	Glycine	—	1,500‡
Taurocholic acid	····OH	H	····OH	H	····OH	CH_2CH_2COOH	Taurine	—	nb*

Common name	R_1	R_2	R_3	R_4	R_5	R_6	Conjugate	Additional feature	K_D [μM]
7-Oxodeoxycholic acid methyl ester	····OH	H	=O	H	····OH	CH_2CH_2COOMe	—	—	nb*
12-Oxochenodeoxycholic acid	····OH	H	····OH	H	=O	CH_2CH_2COOMe	—	—	nb*
Cholesterol	▬OH	H	H	····OH	H	Isopropyl	—	—	nb*
5β-Pregnane-3α,20α-diol	····OH	H	H	H	H	OH	—	—	nb*
5β-Pregnane-3α,17α,20α-triol	····OH	H	H	H	H	OH	—	····OH at C-17	200

*No binding event detectable by change of fluorescence anisotropy within concentration range.
†Compound AE-562/12222313 from Specs with unknown stereochemistry at C-5, C-9, and C-14.
‡K_D values are calculated from extrapolated IC_{50} values.