

ELECTRONIC SUPPLEMENTARY MATERIAL

Table S1. Cytokines and chemicals used in-vitro, assays applied for RT-qPCR, and antisera used for immunodetection.

TREATMENT AGENTS			
Agent	Concentration used in-vitro	Solvent	Supplier
Recombinant human EGF (epidermal growth factor)	10 ng/ml	Culture medium	Sigma, St. Louis, MO
Recombinant human TGF α (transforming growth factor alpha)	10 ng/ml	Culture medium	UBI, Lake Placid, NY
Recombinant human HBEGF (heparin-binding EGF-like growth factor)	1-50 ng/ml	Culture medium	Sigma, St. Louis, MO
Recombinant human FGF1 (fibroblast growth factor 1)	10 ng/ml	Culture medium	Biovision, Old Middlefield, CA
Recombinant human FGF2 (fibroblast growth factor 2)	10 ng/ml	Culture medium	Pepto Tech, Rocky Hill, NJ
Recombinant human FGF4 (fibroblast growth factor 4)	10 ng/ml	Culture medium	Biosource, San Diego, CA
Recombinant human FGF7 (fibroblast growth factor 7)	10 ng/ml	Culture medium	Sigma, St. Louis, MO
Recombinant human FGF9 (fibroblast growth factor 9)	10 ng/ml	Culture medium	R & D Systems, Minneapolis, MN
Recombinant human FGF18 (fibroblast growth factor 18)	10 ng/ml	Culture medium	BioVision, Old Middlefield, CA
Recombinant human HGF (hepatocyte growth factor)	1-20 ng/ml	Culture medium	Sigma, St. Louis, MO
Recombinant human HDGF (hepatoma derived growth factor)	1-50 ng/ml	Culture medium	Abcam, Cambridge, GB
Recombinant human CTGF (Connective tissue growth factor)	1-100 ng/ml	Culture medium	Pepto Tech, Rocky Hill, NJ
Recombinant human GDF15 (Growth and differentiation factor 15)	1-100 ng/ml	Culture medium	R&D Systems, Minneapolis, MN
Recombinant human TNF α (Tumor necrosis factor alpha)	1-200 ng/ml	Culture medium	R&D Systems, Minneapolis, MN
Recombinant human IL6 (Interleukin 6)	10-30 ng/ml	Culture medium	Strathmann, Hamburg, Germany
Recombinant human PGA2 (Prostaglandin A2)	17.5 μ g/ml	Ethanol	Biomol, Plymouth Meeting, PA
Recombinant human PGJ2 (Prostaglandin J2)	5 μ g/ml	Ethanol	Biomol, Plymouth Meeting, PA
Recombinant human PGE2a (Prostaglandin E2a)	17.5 μ g/ml	Ethanol	Biomol, Plymouth Meeting, PA
Recombinant human PGF2a (Prostaglandin F2a)	17.5 μ g/ml	Ethanol	Biomol, Plymouth Meeting, PA
Recombinant TGF β 1 (transforming growth factor β 1)	1ng/ml	Culture medium	Pepto Tech, Rocky Hill, NJ
Phenobarbital (PB; 5-ethyl-5-phenylbarbituric acid)	0.5 mM, 1 mM	Culture medium	Sigma, St. Louis, MO
Cyproterone acetate (CPA)	10 μ M	DMSO	Sigma, St. Louis, MO
ASSAYS/PRIMERS USED FOR RT-qPCR			
Transcript to be measured	Assay Number	Supplier	
β 2M (beta2-microglobulin)	Rn00560865_m1	Applied Biosystems, Foster City, CA	
EGF	Rn00563336_m1	Applied Biosystems, Foster City, CA	
TGF α	Rn00562037_m1	Applied Biosystems, Foster City, CA	

HBEGF	Rn01637090_g1	Applied Biosystems, Foster City, CA
EREG	Rn01413923_m1	Applied Biosystems, Foster City, CA
FGF1	Rn00563362_m1	Applied Biosystems, Foster City, CA
FGF2	Rn00570809_m1	Applied Biosystems, Foster City, CA
FGF4	Rn00709726_m1	Applied Biosystems, Foster City, CA
FGF7	Rn00573319_m1	Applied Biosystems, Foster City, CA
FGF9	Rn00564116_m1	Applied Biosystems, Foster City, CA
FGF18	Rn00433286_m1	Applied Biosystems, Foster City, CA
HGF	Rn01537279_g1	Applied Biosystems, Foster City, CA
HDGF	Rn00678055_g1	Applied Biosystems, Foster City, CA
CTGF	Rn00566673_m1	Applied Biosystems, Foster City, CA
GDF15	Rn00570083_m1	Applied Biosystems, Foster City, CA
IL1 β	Rn00580432_m1	Applied Biosystems, Foster City, CA
TNF α	Rn99999017_m1	Applied Biosystems, Foster City, CA
IL6	Rn99999011_m1	Applied Biosystems, Foster City, CA
COX2 (Cyclooxygenase 2)	Rn01483828_m1	Applied Biosystems, Foster City, CA
ANTISERA APPLIED FOR IMMUNODETECTION		
Protein to be detected	Antibody number	Supplier
Rabbit anti-rat GST-Yp	BIO23YPr	Biotrin Int., Dublin, Ireland
Goat-anti-rabbit biotin	E0432	Dako, Glostrup, Denmark
Rabbit anti-panEGFR	#2232	Cell Signalling Technology, Cambridge, GB
Rabbit anti-EGFR, phosphorylated at Tyr1173	#4404	Cell Signalling Technology
ELISA		
Protein to be detected	Number	Supplier
GDF15	MGD150	R&D Systems, Minneapolis, MN
HGF	MHG00	R&D Systems, Minneapolis, MN
TNF α	88-7340	eBioscience, Santa Clara, CA
IL6	BMS625MST	Bender MedSystems, Vienna, Austria
PGE2a	ABIN1116703	Antibodies Online, Aachen, FRG
HBEGF	Sc 74441	Santa Cruz Biotechnology Inc., , Santa Cruz, CA
NEUTRALIZING ANTIBODIES		
Anti-HGF	AF 294-NA	R&D Systems, Minneapolis, MN
Anti-HBEGF	AF 259-NA	R&D Systems, Minneapolis, MN

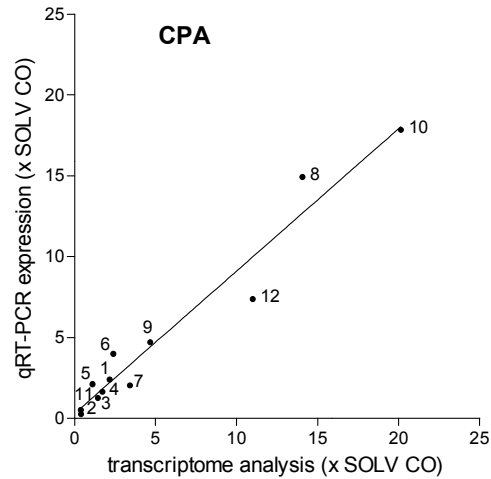


Figure S1. Validation of transcriptome data by quantitative RT-PCR (RT-qPCR). HC and MC were isolated from untreated and CPA-treated rats and were subjected to the analysis. Each data point represents the expression level of a given gene expressed as fold solvent CO, and is the mean of ≥ 3 independent determinations per method applied. Symbols: 1, CCL4; 2, CTGF; 3, FGF21; 4, GADD45G; 5, GDF15; 6, HDGF; 7, HGF; 8, INHBB; 9, PLK4; 10, LPL; 11, ID4; 12, TUSC3. Genes identified by symbol No 1-10 were determined in MC and No 11+12 in HC. Correlation of the relative expression of the selected genes, as determined by the two independent methods, was calculated by GraphPad Prism (Version 5.0): $R^2=0.9529$; $p<0.0001$. Please note that data on the transcriptome validation of HC and MC, obtained from PB-treated animals, have been shown by Riegler et al. 2015.

ELISA for HBEGF. Microtiter ELISA plates (Costar, Corning, NY) were coated with the cell supernatants (100 μ l, 1:1 diluted in 1xPBS (1.44g Na₂HPO₄*2H₂O, 2.62g NaH₂PO₄*H₂O, 5.86g NaCl/1000ml, pH7.4)). The standard calibration row was created with recombinant human HBEGF at a concentration range between 0 and 2500pg/ml. The plate was incubated at 4°C overnight. On the next day, the plate was blocked with 250 μ l PBST (500 μ l tween 20/1000ml PBS) + 0.5% BSA at room temperature for one hour and was washed twice with PBST (200 μ l). Then, the monoclonal HBEGF antibody (100 μ l, 1:50 diluted in PBST + 0.5% BSA, Santa Cruz Biotechnology, Santa Cruz, CA, USA) was applied as primary antibody at room temperature for two hours. After four times washing with PBST, the plate was incubated with the secondary antibody, a biotin labeled anti-mouse antibody (100 μ l, 1:5000 diluted in PBST + 0.5% BSA, DAKO, Glostrup, Denmark) for 2 hours. After the plate had been washed four times with PBST, the streptavidin conjugated horseradish peroxidase (100 μ l, 1:5000 diluted in PBST + 0.5% BSA, DAKO) was applied for one hour. Finally the plate was washed with PBST and the reaction was detected with 100 μ l of the TMB substrate (Thermo Scientific, Rockford, IL). The reaction was stopped with 1M H₃PO₄ when the highest standard became dark blue. The absorbance was measured in a microplate reader at a wavelength of 450nm and a reference wavelength of 620nm.

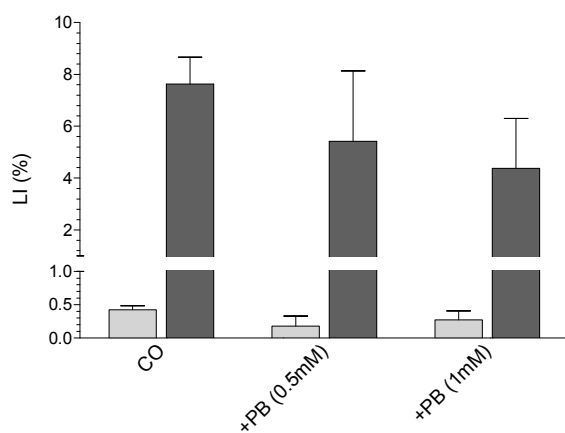


Figure S2. PB suppresses weakly DNA replication in unaltered (HC) and preneoplastic hepatocytes (HC_{PREN}). NNM was applied to induce the formation of HC_{PREN}. Twenty-one days later HC and HC_{PREN} were isolated and cultured in serum-free medium. Stock solutions were prepared of PB (PB sodium salt, dissolved in medium). Aliquots were added to the medium to provide final concentrations of 0.5 or 1mM of PB. Treatments started 2hrs after seeding of HC, were renewed at 48hrs and lasted for 72hrs. Autoradiography served to determine the percentage of nuclei with incorporated ³H-thymidine (LI %). Data are means \pm SEM from ≥ 3 independent experiments. Symbols: light grey bars, HC; dark grey bars, HC_{PREN}

Table S2. Significantly deregulated pathways in rat hepatocytes (HC) and mesenchymal liver cells (MC), treated in-vivo with CPA 1x or 6x on 6 consecutive days. Pathway enrichments were computed against the databases BiobaseTransPath (www.biobase-international.com), Ingenuity Knowledge Base (www.ingenuity.com), and KEGG (www.genome.jp/kegg) using a hypergeometric test. Enrichment analyses were performed separately for upregulated and downregulated genes, respectively. The resulting p-values were corrected for multiple testing using the Benjamini-Hochberg method. Pathways were considered to be significantly deregulated in case of p-value of < 0.05. Please note that data on the pathway analyses in HC and MC, obtained from PB-treated animals, have been shown by Riegler et al, 2015.

Cell type/ time point	Data-base	Pathway	corr. P-value	Regulation	Sample ratio	Back-ground ratio	Gene symbols
HC/1x	KEGG	BASE_EXCISION_REPAIR	0,000	up	10/210	26/3825	PCNA, FEN1, LIG1, POLB, POLD1, POLD2, POLD3, APEX1, XRCC1, POLE2
HC/1x	KEGG	BLADDER_CANCER	0,001	up	9/210	34/3825	MYC, RAF1, KRAS, CCND1, MAPK1, RASSF1, E2F1, MDM2, CDKN1A
HC/1x	KEGG	CELL_CYCLE	0,000	up	41/210	110/3825	PCNA, YWHAH, CDK1, PTTG1, MYC, GADD45A, CDKN2C, CDC20, CCNB1, WEE1, MCM6, CCND1, GADD45B, MCM3, CCNE1, MCM4, MCM2, MAD2L2, CCNE2, MCM5, ESPL1, ORC6, MAD2L1, CDC45, TTK, CCNA2, RBL1, E2F1, CDC27, MDM2, BUB1B, BUB1, ORC1, YWHAG, CDKN1A, E2F5, MCM7, CCNB2, S
HC/1x	KEGG	DNA_REPLICATION	0,000	up	20/210	33/3825	PCNA, FEN1, LIG1, POLD1, RFC2, MCM6, MCM3, MCM4, POLD2, MCM2, MCM5, RFC5, POLD3, POLA2, RPA2, PRIM1, RFC4, MCM7, RFC3, POLE2
HC/1x	KEGG	GLIOMA	0,033	up	9/210	55/3825	RAF1, KRAS, PDGFA, CCND1, MAPK1, SHC1, E2F1, MDM2, CDKN1A
HC/1x	KEGG	GLUTATHIONE_METABOLISM	0,000	up	14/210	42/3825	SRM, GGT1, GSR, GSTM3, GSS, GCLC, GSTM5, GSTM2, GSTA5, RRM1, GPX2, GSTM4, GSTM1, RRM2
HC/1x	KEGG	HOMOLOGOUS_RECOMBINATION	0,000	up	8/210	22/3825	POLD1, POLD2, RAD51, POLD3, RPA2, RAD51C, XRCC2, RAD54L
HC/1x	KEGG	METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0,027	up	7/210	34/3825	GSTM3, GSTM5, GSTM2, GSTA5, GSTM4, GSTM1, EPHX1

HC/1x	KEGG	MISMATCH_REPAIR	0,000	up	11/210	21/3825	PCNA, LIG1, POLD1, RFC2, POLD2, RFC5, POLD3, EXO1, RPA2, RFC4, RFC3
HC/1x	KEGG	NUCLEOTIDE_EXCISION_REPAIR	0,000	up	12/210	42/3825	PCNA, LIG1, POLD1, RFC2, GTF2H1, POLD2, RFC5, POLD3, RPA2, RFC4, RFC3, POLE2
HC/1x	KEGG	OOCYTE_MEIOSIS	0,000	up	19/210	97/3825	YWHAH, CDK1, PTTG1, PPP2CB, CDC20, CCNB1, MAPK1, CCNE1, MAD2L2, CCNE2, AURKA, ESPL1, MAD2L1, CDC27, FBXO5, BUB1, YWHAG, CCNB2, PKMYT1
HC/1x	KEGG	P53_SIGNALING_PATHWAY	0,000	up	16/210	53/3825	CCNG1, CDK1, GADD45A, BID, CCNB1, CCND1, GADD45B, CCNE1, CCNE2, MDM2, CDKN1A, CASP3, RRM2, CCNB2, SESN3, PIDD
HC/1x	KEGG	PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0,007	up	12/210	72/3825	CDK1, RAF1, KRAS, CCNB1, MAPK1, MAD2L2, MAD2L1, CCNA2, CDC27, BUB1, CCNB2, PKMYT1
HC/1x	KEGG	PURINE_METABOLISM	0,021	up	16/210	128/3825	PPAT, ATIC, POLD1, RRM1, POLD2, POLR1E, ADSL, ENTPD5, POLR3G, DCK, POLD3, POLA2, PRIM1, IMPDH2, RRM2, POLE2
HC/1x	KEGG	PYRIMIDINE_METABOLISM	0,000	up	21/210	79/3825	TYMS, POLD1, RRM1, TK1, POLD2, POLR1E, CDA, ENTPD5, POLR3G, DTYMK, CMPK2, DCK, POLD3, TXNRD1, POLA2, DUT, PRIM1, RRM2, UMPS, CTPS, POLE2
HC/1x	KEGG	BUTANOATE_METABOLISM	0,016	down	7/197	29/3825	ACAT1, HMGCS1, AACS, EHHADH, ACSM2A, BDH2, ALDH1B1
HC/1x	KEGG	COMPLEMENT_AND_COAGULATION_CASCADES	0,000	down	16/197	61/3825	A2M, TFPI, PLG, C9, CPB2, C4BPA, F10, FGA, F5, C5, PROC, CFH, C1S, CFB, MASP1, F12
HC/1x	KEGG	PROPANOATE_METABOLISM	0,001	down	9/197	29/3825	ACADM, ACAT1, EHHADH, ACACA, PCCA, SUCLG2, ACSS2, MUT, ALDH1B1
HC/1x	KEGG	TERPENOID_BACKBONE_BIOSYNTHESIS	0,001	down	6/197	12/3825	FDPS, ACAT1, HMGCS1, MVD, IDI1, PDSS2
HC/1x	KEGG	VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0,001	down	10/197	40/3825	ACADM, ACAT1, HMGCS1, EHHADH, ACADSB, BCKDHB, PCCA, MCCC2, MUT, ALDH1B1
HC/1x	BIOARTA	CELLCYCLE_PATHWAY	0,001	up	9/85	22/1118	CDK1, CDKN2C, CCNB1, CCND1, CCNE1, RBL1, E2F1, CDKN1A, CDKN2D

HC/1x	BIOCA RTA	G2_PATHWAY	0,004	up	8/85	21/1118	YWHAH, CDK1, GADD45A, CCNB1, WEE1, MDM2, CDKN1A, CDKN2D
HC/1x	BIOCA RTA	MCM_PATHWAY	0,000	up	10/85	17/1118	MCM6, MCM3, CCNE1, MCM4, MCM2, MCM5, ORC6, CDT1, ORC1, MCM7
HC/1x	BIOCA RTA	P53_PATHWAY	0,002	up	7/85	14/1118	PCNA, GADD45A, CCND1, CCNE1, E2F1, MDM2, CDKN1A
HC/1x	BIOCA RTA	EXTRINSIC_PATHWAY	0,025	down	5/62	12/1118	TFPI, F10, FGA, F5, PROC
HC/1x	BIOCA RTA	INTRINSIC_PATHWAY	0,025	down	6/62	19/1118	F10, FGA, F5, COL4A5, PROC, F12
HC/1x	REACT OME	ACTIVATION_OF_ATR_I N_RESPONSE_TO_REP PLICATION_STRESS	0,000	up	17/267	29/4186	RFC2, MCM6, MCM3, MCM4, MCM2, MCM5, ORC6, RAD1, CDC45, MCM8, RFC5, RAD17, ORC1, RPA2, RFC4, MCM7, RFC3
HC/1x	REACT OME	CELL_CYCLE	0,000	up	106/267	309/4186	PCNA, CDK1, PTTG1, PPP2CB, FEN1, LMNA, LIG1, AURKB, MYC, CENPI, TYMS, CDKN2C, POLD1, CDC20, CCNB1, WEE1, MAPRE1, ZWINT, TUBG1, RFC2, MCM6, CCND1, NHP2, PSMD13, CDCA8, PSMD5, MCM3, HJURP, LIN37, CCNE1, MCM4, KIF20A, LMNB1, POLD2, MCM2, CCNE2, XPO1, KIF2C,
HC/1x	REACT OME	CELL_CYCLE_CHECKP OINTS	0,000	up	33/267	99/4186	CDK1, CDC20, CCNB1, WEE1, RFC2, MCM6, PSMD13, PSMD5, MCM3, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, MAD2L1, RAD1, CDC45, MCM8, RFC5, CDC27, MDM2, PSMD14, BUB1B, RAD17, ORC1, CDKN1A, RPA2, RFC4, UBE2C, MCM7, RFC3, CCNB2
HC/1x	REACT OME	CELL_CYCLE_MITOTIC	0,000	up	95/267	266/4186	PCNA, CDK1, PTTG1, PPP2CB, FEN1, LIG1, AURKB, MYC, CENPI, TYMS, CDKN2C, POLD1, CDC20, CCNB1, WEE1, MAPRE1, ZWINT, TUBG1, RFC2, MCM6, CCND1, PSMD13, CDCA8, PSMD5, MCM3, LIN37, CCNE1, MCM4, KIF20A, POLD2, MCM2, CCNE2, XPO1, KIF2C, CENPT, AURKA, MCM5, GINS1,
HC/1x	REACT OME	CHROMOSOME_MAINT ENANCE	0,000	up	28/267	69/4186	PCNA, FEN1, LMNA, LIG1, CENPI, POLD1, RFC2, NHP2, HJURP,

							LMNB1, POLD2, TINF2, RFC5, CENPK, POLD3, POLA2, RPA2, PRIM1, RFC4, RFC3, H2AFX, CENPQ, CENPN, MLF1IP, POLE2, CASC5, MIS18A, RBBP7
HC/1x	REACTOME	DNA_REPLICATION	0,000	up	68/267	165/4186	PCNA, PPP2CB, FEN1, LIG1, AURKB, CENPI, POLD1, CDC20, MAPRE1, ZWINT, RFC2, MCM6, PSMD13, CDCA8, PSMD5, MCM3, MCM4, KIF20A, POLD2, MCM2, XPO1, KIF2C, CENPT, MCM5, GINS1, ORC6, MAD2L1, CDT1, GMNN, CDC45, CCNA2, MCM8, RFC5, CENPK, E2F1, DSN1, PSMD14, BUB1B,
HC/1x	REACTOME	DNA_STRAND_ELONGATION	0,000	up	23/267	29/4186	PCNA, FEN1, LIG1, POLD1, RFC2, MCM6, MCM3, MCM4, POLD2, MCM2, MCM5, GINS1, CDC45, MCM8, RFC5, POLD3, POLA2, RPA2, PRIM1, RFC4, MCM7, GINS4, RFC3
HC/1x	REACTOME	G1_S_TRANSITION	0,000	up	34/267	97/4186	PCNA, CDK1, PPP2CB, MYC, TYMS, CCNB1, WEE1, MCM6, PSMD13, PSMD5, MCM3, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CDT1, CDC45, CCNA2, MCM8, E2F1, PSMD14, FBXO5, ORC1, CDKN1A, POLA2, RPA2, PRIM1, MCM7, RRM2, SKP2, PKMYT1, POLE2
HC/1x	REACTOME	G2_M_CHECKPOINTS	0,000	up	21/267	34/4186	CDK1, CCNB1, WEE1, RFC2, MCM6, MCM3, MCM4, MCM2, MCM5, ORC6, RAD1, CDC45, MCM8, RFC5, RAD17, ORC1, RPA2, RFC4, MCM7, RFC3, CCNB2
HC/1x	REACTOME	MITOTIC_G1_G1_S_PHASES	0,000	up	41/267	118/4186	PCNA, CDK1, PPP2CB, MYC, TYMS, CDKN2C, CCNB1, WEE1, MCM6, CCND1, PSMD13, PSMD5, MCM3, LIN37, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CDT1, CDC45, CCNA2, RBL1, MCM8, E2F1, PSMD14, FBXO5, ORC1, LIN9, CDKN1A, POLA2, RPA2, E2F5, PRIM1, MCM7, RRM2, SKP2, PKMYT1,
HC/1x	REACTOME	MITOTIC_M_M_G1_PHASES	0,000	up	54/267	146/4186	PPP2CB, AURKB, CENPI, CDC20, MAPRE1, ZWINT, MCM6, PSMD13, CDCA8, PSMD5, MCM3, MCM4,

							KIF20A, MCM2, XPO1, KIF2C, CENPT, MCM5, ORC6, MAD2L1, CDT1, GMNN, CDC45, MCM8, CENPK, E2F1, DSN1, PSMD14, BUB1B, NUF2, FBXO5, BUB1, ZWILCH, ORC1, ERCC6L, NUP107, POLA2, RP
HC/1x	REACTOME	MITOTIC_PROMETAPHASE	0,000	up	31/267	74/4186	PPP2CB, AURKB, CENPI, CDC20, MAPRE1, ZWINT, CDCA8, XPO1, KIF2C, CENPT, MAD2L1, CENPK, DSN1, BUB1B, NUF2, BUB1, ZWILCH, ERCC6L, NUP107, CKAP5, NUP43, SPC25, NUP85, SKA1, KIF18A, CENPQ, CENPN, MLF1IP, CLIP1, CASC5, CENPL
HC/1x	REACTOME	S_PHASE	0,000	up	38/267	100/4186	PCNA, FEN1, LIG1, MYC, POLD1, WEE1, RFC2, MCM6, CCND1, PSMD13, PSMD5, MCM3, CCNE1, MCM4, POLD2, MCM2, CCNE2, MCM5, GINS1, ORC6, CDT1, CDC45, CCNA2, MCM8, RFC5, PSMD14, POLD3, ORC1, CDKN1A, POLA2, RPA2, PRIM1, RFC4, MCM7, GINS4, RFC3, SKP2, POLE2
HC/1x	REACTOME	SYNTHESIS_OF_DNA	0,000	up	32/267	84/4186	PCNA, FEN1, LIG1, POLD1, RFC2, MCM6, PSMD13, PSMD5, MCM3, MCM4, POLD2, MCM2, MCM5, GINS1, ORC6, CDT1, CDC45, CCNA2, MCM8, RFC5, PSMD14, POLD3, ORC1, CDKN1A, POLA2, RPA2, PRIM1, RFC4, MCM7, GINS4, RFC3, POLE2
HC/1x	REACTOME	UNWINDING_OF_DNA	0,000	up	10/267	10/4186	MCM6, MCM3, MCM4, MCM2, MCM5, GINS1, CDC45, MCM8, MCM7, GINS4
HC/1x	REACTOME	ALPHA_LINOLENIC_ACID_ALA_METABOLISM	0,013	down	5/208	10/4186	HSD17B4, FADS1, FADS2, ACSL1, ELOVL5
HC/1x	REACTOME	CHOLESTEROL_BIOSYNTHESIS	0,001	down	8/208	19/4186	FDPS, FDFT1, HMGCS1, MVD, MSMO1, LSS, IDI1, TM7SF2
HC/1x	REACTOME	COMPLEMENT_CASCADE	0,019	down	7/208	25/4186	C9, C4BPA, C5, CFH, C1S, CFB, MASP1
HC/1x	REACTOME	FORMATION_OF_FIBRIN_CLOT_CLOTTING_CASCADE	0,019	down	7/208	25/4186	A2M, TFPI, F10, FGA, F5, PROC, F12

HC/1x	REACTOME	METABOLISM_OF_AMINO_ACIDS_AND_DERIVATIVES	0,019	down	21/208	179/4186	CDO1, ACAT1, CTH, DDC, KMO, INHBA, DIO1, ACADSB, BBOX1, OTC, CPS1, BCKDHB, ASS1, MAT1A, PRODH, MCCC2, AASS, GPT2, GPT, AADAT, SLC25A21
HC/1x	REACTOME	METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	0,000	down	51/208	412/4186	FDPS, HSD17B4, ACADM, FASN, ACAT1, AMACR, A2M, FDFT1, ACLY, FADS1, HMGCS1, LRP2, MVD, MSMO1, GC, STS, CROT, FADS2, LRAT, SLC10A1, SMPD3, PIK3C2G, LIPC, PI4KA, PLD1, ACACA, SLC44A1, ACSL1, HAACL1, ACOX2, GLB1, PCCA, HEXB, LSS, PLBD1, MTMR7, PPM1L, MUT, NPAS
HC/1x	REACTOME	METABOLISM_OF_STEROID_HORMONES_AND_VITAMINS_A_AND_D	0,496	down	5/208	28/4186	LRP2, GC, LRAT, CYP17A1, STARD4
HC/6x	KEGG	GLUTATHIONE_METABOLISM	0,000	up	20/313	42/3825	G6PD, GGT1, GSR, GSTM3, GPX3, GCLM, GSS, GCLC, GSTM5, GSTM2, GSTA5, RRM1, GPX7, MGST2, GPX2, SMS, GSTM4, GSTM1, GSTP1, RRM2
HC/6x	KEGG	CELL_CYCLE	0,000	up	31/313	110/3825	PCNA, YWHAH, CDK1, PTTG1, CDKN2C, YWHAQ, CDC20, PLK1, CCNB1, WEE1, MCM6, CDKN1C, CCNE1, MCM4, MCM2, CCNE2, MCM5, ESPL1, ORC6, MAD2L1, TTK, CCNA2, RBL1, CCND1, MDM2, BUB1B, BUB1, YWHAG, CDKN1A, MCM7, CCNB2
HC/6x	KEGG	METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0,000	up	14/313	34/3825	UGT2A1, GSTM3, CYP1A1, UGT2B7, GSTM5, GSTM2, GSTA5, MGST2, GSTM4, GSTM1, EPHX1, AKR1C3, GSTP1, ALDH3B1
HC/6x	KEGG	P53_SIGNALING_PATHWAY	0,000	up	17/313	53/3825	CCNG1, CDK1, APAF1, BID, CCNB1, PERP, CCNE1, CCNE2, CCND1, MDM2, FAS, ZMAT3, CDKN1A, CASP3, RRM2, CCNB2, SESN3
HC/6x	KEGG	DNA_REPLICATION	0,000	up	13/313	33/3825	PCNA, FEN1, MCM6, RNASEH2A, MCM4, MCM2, MCM5, RPA2, RFC4, MCM7, PRIM2, RFC3, POLE2
HC/6x	KEGG	DRUG_METABOLISM_CYTOCHROME_P450	0,003	up	11/313	36/3825	UGT2A1, GSTM3, UGT2B7, GSTM5, GSTM2, GSTA5, MGST2, GSTM4, GSTM1, GSTP1, ALDH3B1

HC/6x	KEGG	PYRIMIDINE_METABOLISM	0,013	up	16/313	79/3825	TYMS, RRM1, TK1, CDA, DCTD, ENTPD5, POLR3G, CMPK2, DCK, TXNRD1, DUT, PRIM2, RRM2, UMPS, CTPS, POLE2
HC/6x	KEGG	VIRAL_MYOCARDITIS	0,020	up	10/313	39/3825	BID, MYH10, SGCA, RAC2, SGCB, CCND1, MYH14, CXADR, ICAM1, CASP3
HC/6x	KEGG	STEROID_BIOSYNTHESIS	0,000	down	7/167	14/3825	MSMO1, LSS, EBP, HSD17B7, SC5DL, TM7SF2, NSDHL
HC/6x	KEGG	PPAR_SIGNALING_PATHWAY	0,001	down	12/167	60/3825	EHHADH, CYP8B1, FADS2, CYP7A1, FABP1, FABP7, ACSL1, RXRG, CD36, ACSL5, SLC27A5, ANGPTL4
HC/6x	KEGG	PYRUVATE_METABOLISM	0,047	down	7/167	36/3825	PKLR, ALDH7A1, MDH1, ACSS2, PC, ACYP2, ME3
HC/6x	BIOARTA	MCM_PATHWAY	0,001	up	9/101	17/1118	MCM6, CCNE1, MCM4, MCM2, MCM5, ORC6, CDT1, MCM7, KITLG
HC/6x	BIOARTA	G2_PATHWAY	0,028	up	8/101	21/1118	YWHAH, CDK1, YWHAQ, PLK1, CCNB1, WEE1, MDM2, CDKN1A
HC/6x	REACTOME	CELL_CYCLE	0,000	up	75/335	309/4186	PCNA, CDK1, PTTG1, FEN1, CLIP1, LMNA, AURKB, CENPI, BIRC5, TYMS, CDKN2C, CDC20, PLK1, CCNB1, WEE1, MAPRE1, MCM6, SEC13, NHP2, CDCA8, HJURP, CCNE1, MCM4, KIF20A, LMNB1, MCM2, CCNE2, KIF2C, NUP133, AURKA, MCM5, ORC6, CKS1B, MAD2L1, KNTC1, PLK4, CDT1, GMNN,
HC/6x	REACTOME	CELL_CYCLE_MITOTIC	0,000	up	68/335	266/4186	PCNA, CDK1, PTTG1, FEN1, CLIP1, AURKB, CENPI, BIRC5, TYMS, CDKN2C, CDC20, PLK1, CCNB1, WEE1, MAPRE1, MCM6, SEC13, CDCA8, CCNE1, MCM4, KIF20A, MCM2, CCNE2, KIF2C, NUP133, AURKA, MCM5, ORC6, CKS1B, MAD2L1, KNTC1, PLK4, CDT1, GMNN, CCNA2, RBL1, MCM8, CENPK,
HC/6x	REACTOME	DNA_REPLICATION	0,000	up	48/335	165/4186	PCNA, FEN1, CLIP1, AURKB, CENPI, BIRC5, CDC20, PLK1, MAPRE1, MCM6, SEC13, CDCA8, MCM4, KIF20A, MCM2, KIF2C, NUP133, MCM5, ORC6, MAD2L1, KNTC1, CDT1, GMNN, CCNA2, MCM8, CENPK, KIF2A, DSN1,

							BUB1B, NUF2, BUB1, ZWILCH, CDKN1A, RPA2, CKAP5, RFC4, MCM7, PRIM2,
HC/6x	REACTOME	MITOTIC_M_M_G1_PHASES	0,000	up	41/335	146/4186	CLIP1, AURKB, CENPI, BIRC5, CDC20, PLK1, MAPRE1, MCM6, SEC13, CDCA8, MCM4, KIF20A, MCM2, KIF2C, NUP133, MCM5, ORC6, MAD2L1, KNTC1, CDT1, GMNN, MCM8, CENPK, KIF2A, DSN1, BUB1B, NUF2, BUB1, ZWILCH, RPA2, CKAP5, MCM7, PRIM2, SPC25, KIF23, SKA1, KIF18A, CENPQ
HC/6x	REACTOME	MITOTIC_PROMETAPHASE	0,000	up	27/335	74/4186	CLIP1, AURKB, CENPI, BIRC5, CDC20, PLK1, MAPRE1, SEC13, CDCA8, KIF2C, NUP133, MAD2L1, KNTC1, CENPK, KIF2A, DSN1, BUB1B, NUF2, BUB1, ZWILCH, CKAP5, SPC25, SKA1, KIF18A, CENPQ, CENPN, CASC5
HC/6x	REACTOME	KINESINS	0,000	up	11/335	20/4186	KIF22, RACGAP1, KIF20A, KIF15, KIF2C, KIFC1, KIF4A, KIF2A, KIF11, KIF23, KIF18A
HC/6x	REACTOME	DNA_STRAND_ELONGATION	0,000	up	13/335	29/4186	PCNA, FEN1, MCM6, MCM4, MCM2, MCM5, MCM8, RPA2, RFC4, MCM7, PRIM2, GINS4, RFC3
HC/6x	REACTOME	G2_M_CHECKPOINTS	0,000	up	14/335	34/4186	CDK1, CCNB1, WEE1, MCM6, MCM4, MCM2, MCM5, ORC6, MCM8, RPA2, RFC4, MCM7, RFC3, CCNB2
HC/6x	REACTOME	PHASE_II_CONJUGATION	0,000	up	16/335	45/4186	UGDH, GGT1, SULT1E1, UGT2A1, GCLM, GSS, UGT2B7, GCLC, GSTM5, GSTA5, MAT2A, PAPSS1, MGST2, GSTM4, GSTM1, GSTP1
HC/6x	REACTOME	GLUTATHIONE_CONJUGATION	0,000	up	10/335	20/4186	GGT1, GCLM, GSS, GCLC, GSTM5, GSTA5, MGST2, GSTM4, GSTM1, GSTP1
HC/6x	REACTOME	MITOTIC_G1_G1_S_PHASES	0,000	up	26/335	118/4186	PCNA, CDK1, TYMS, CDKN2C, CCNB1, WEE1, MCM6, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CKS1B, CDT1, CCNA2, RBL1, MCM8, CCND1, LIN9, CDKN1A, RPA2, MCM7, PRIM2, RRM2, POLE2

HC/6x	REACTOME	ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	0,000	up	11/335	26/4186	MCM6, MCM4, MCM2, MCM5, ORC6, CDT1, MCM8, RPA2, MCM7, PRIM2, POLE2
HC/6x	REACTOME	UNWINDING_OF_DNA	0,000	up	7/335	10/4186	MCM6, MCM4, MCM2, MCM5, MCM8, MCM7, GINS4
HC/6x	REACTOME	S_PHASE	0,000	up	23/335	100/4186	PCNA, FEN1, WEE1, MCM6, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CKS1B, CDT1, CCNA2, MCM8, CCND1, CDKN1A, RPA2, RFC4, MCM7, PRIM2, GINS4, RFC3, POLE2
HC/6x	REACTOME	CHROMOSOME_MAINTENANCE	0,000	up	18/335	69/4186	PCNA, FEN1, LMNA, CENPI, NHP2, HJURP, LMNB1, CENPK, H2AFZ, RPA2, RFC4, PRIM2, RFC3, CENPQ, CENPN, POLE2, CASC5, MIS18A
HC/6x	REACTOME	METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	0,000	down	47/165	412/4186	FDPS, FASN, AMACR, ACLY, FADS1, MVD, MSMO1, STS, CYP8B1, FADS2, CYP7A1, SLC10A1, ABCB11, IDI1, PIK3C2G, FABP1, PEMT, LIPC, SLCO1B3, PIK3R1, SRD5A1, NR1D1, ACSL1, PPAP2B, HACL1, SREBF1, DGAT2, LSS, PLBD1, PMVK, MTMR7, MED4, CRLS1, MUT, NPAS2, CD36, ACSL5,
HC/6x	REACTOME	CHOLESTEROL_BIOSYNTHESIS	0,000	down	11/165	19/4186	FDPS, MVD, MSMO1, IDI1, LSS, PMVK, EBP, HSD17B7, SC5DL, TM7SF2, NSDHL
HC/6x	REACTOME	METABOLISM_OF_AMINO_ACIDS_AND_DERIVATIVES	0,004	down	20/165	179/4186	OAT, HPD, ASL, BBOX1, TAT, SUOX, GLS2, ALDH7A1, PRODH, MCCC1, AASS, PAH, GPT, CBS, AADAT, HAL, SLC25A21, FTCD, GSTZ1, KYNU
HC/6x	REACTOME	BILE_ACID_AND_BILE_SALT_METABOLISM	0,006	down	7/165	25/4186	AMACR, CYP8B1, CYP7A1, SLC10A1, ABCB11, SLCO1B3, SLC27A5
HC/6x	REACTOME	PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS	0,008	down	8/165	36/4186	CYP2E1, CYP8B1, CYP7A1, PTGIS, ACSS2, FMO1, CYP1A2, CYP26A1
HC/6x	REACTOME	SYNTHESIS_OF_BILE_ACIDS_AND_BILE_SALT_S_VIA_7ALPHA_HYDROXYCHOLESTEROL	0,014	down	5/165	14/4186	AMACR, CYP8B1, CYP7A1, ABCB11, SLC27A5

HC/6x	REACTOME	CYTOCHROME_P450_ARRANGED_BY_SUBSTRATE_TYPE	0,014	down	6/165	22/4186	CYP2E1, CYP8B1, CYP7A1, PTGIS, CYP1A2, CYP26A1
HC/6x	REACTOME	FATTY_ACYL_COA_BIOSYNTHESIS	0,016	down	5/165	15/4186	FASN, ACLY, ACSL1, ACSL5, ELOVL5
HC/6x	REACTOME	FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM	0,019	down	16/165	152/4186	FASN, ACLY, FADS1, CYP7A1, FABP1, NR1D1, ACSL1, SREBF1, DGAT2, MED4, MUT, NPAS2, CD36, ACSL5, ELOVL5, ANGPTL4
HC/6x	REACTOME	RECYCLING_OF_BILEACIDS_AND_SALTS	0,025	down	4/165	10/4186	SLC10A1, ABCB11, SLCO1B3, SLC27A5
HC/6x	REACTOME	ALPHA_LINOLENIC_ACID_ALA_METABOLISM	0,025	down	4/165	10/4186	FADS1, FADS2, ACSL1, ELOVL5
HC/6x	REACTOME	SYNTHESIS_OF_BILEACIDS_AND_BILE_SALTS	0,028	down	5/165	18/4186	AMACR, CYP8B1, CYP7A1, ABCB11, SLC27A5
HC/6x	REACTOME	REGULATION_OF_PYRUVATE_DEHYDROGENASE_PDH_COMPLEX	0,032	down	4/165	11/4186	PDK2, PDK1, PDK4, PDP2
MC/1x	KEGG	ASCORBATE_AND_ALDARATE_METABOLISM	0,005	up	4/92	12/3825	UGDH, UGT2B15, UGT2A1, UGT2B17
MC/1x	KEGG	CELL_CYCLE	0,027	up	9/92	110/3825	CDK1, CCNB1, CCNE1, CCNE2, ORC6, CCNA2, MDM2, CHEK1, CDKN1A
MC/1x	KEGG	P53_SIGNALING_PATHWAY	0,000	up	9/92	53/3825	CDK1, CCNB1, CCNE1, CCNE2, MDM2, CHEK1, CDKN1A, PERP, RRM2
MC/1x	KEGG	PENTOSE_AND_GLUCONATE_INTERCONVERSIONS	0,006	up	4/92	13/3825	UGDH, UGT2B15, UGT2A1, UGT2B17
MC/1x	KEGG	PORPHYRIN_AND_CHLOROPHYLL_METABOLISM	0,036	up	4/92	23/3825	ALAS1, UGT2B15, UGT2A1, UGT2B17
MC/1x	KEGG	PYRIMIDINE_METABOLISM	0,044	up	7/92	79/3825	TYMS, POLD2, CDA, ENTPD5, TXNRD1, RRM2, CTPS
MC/1x	KEGG	RETINOL_METABOLISM	0,008	up	5/92	26/3825	UGT2B15, UGT2A1, DHRS4, ALDH1A1, UGT2B17
MC/1x	KEGG	BETA_ALANINE_METABOLISM	0,001	down	4/21	21/3825	DPYD, EHHADH, GAD1, ALDH1B1
MC/1x	KEGG	BUTANOATE_METABOLISM	0,029	down	3/21	29/3825	EHHADH, GAD1, ALDH1B1

MC/1x	KEGG	LIMONENE_AND_PINENE_DEGRADATION	0,031	down	2/21	8/3825	EHHADH, ALDH1B1
MC/1x	KEGG	LYSINE_DEGRADATION	0,031	down	3/21	37/3825	EHHADH, BBOX1, ALDH1B1
MC/1x	KEGG	RETINOL_METABOLISM	0,029	down	3/21	26/3825	LRAT, CYP26B1, CYP26A1
MC/1x	KEGG	TAURINE_AND_HYPOTHAURINE_METABOLISM	0,031	down	2/21	9/3825	CDO1, GAD1
MC/1x	BIOCARTA	G2_PATHWAY	0,016	up	5/26	21/1118	CDK1, CCNB1, MDM2, CHEK1, CDKN1A
MC/1x	REACTOME	BIOLOGICAL_OXIDATIONS	0,000	up	12/107	80/4186	UGDH, CYP8B1, UGT2A1, GSS, GCLC, GSTA5, MGST2, GSTM4, GSTM1, ALDH1A1, SULT1B1, UGT2B17
MC/1x	REACTOME	CELL_CYCLE	0,000	up	25/107	309/4186	CDK1, AURKB, TYMS, CCNB1, ZWINT, CKS1B, TUBA4A, CCNE1, POLD2, CCNE2, GINS1, ORC6, CDT1, CCNA2, CENPK, MDM2, CHEK1, CDKN1A, RFC4, UBE2C, RRM2, PSMD8, SPC25, SKA1, MIS18A
MC/1x	REACTOME	CELL_CYCLE_CHECKPOINTS	0,002	up	11/107	99/4186	CDK1, CCNB1, CCNE1, CCNE2, ORC6, MDM2, CHEK1, CDKN1A, RFC4, UBE2C, PSMD8
MC/1x	REACTOME	CELL_CYCLE_MITOTIC	0,000	up	22/107	266/4186	CDK1, AURKB, TYMS, CCNB1, ZWINT, CKS1B, TUBA4A, CCNE1, POLD2, CCNE2, GINS1, ORC6, CDT1, CCNA2, CENPK, CDKN1A, RFC4, UBE2C, RRM2, PSMD8, SPC25, SKA1
MC/1x	REACTOME	CHYLOMICRON_MEDIATED_LIPID_TRANSPORT	0,002	up	5/107	15/4186	SDC1, APOA1, APOA2, APOB, MTPP
MC/1x	REACTOME	DNA_REPLICATION	0,011	up	13/107	165/4186	AURKB, ZWINT, POLD2, GINS1, ORC6, CDT1, CCNA2, CENPK, CDKN1A, RFC4, PSMD8, SPC25, SKA1
MC/1x	REACTOME	E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	0,001	up	7/107	30/4186	CDK1, TYMS, CCNB1, CCNE1, ORC6, CDT1, RRM2
MC/1x	REACTOME	G1_S_SPECIFIC_TRANSCRIPTION	0,002	up	5/107	15/4186	CDK1, TYMS, CCNE1, CDT1, RRM2
MC/1x	REACTOME	G1_S_TRANSITION	0,001	up	12/107	97/4186	CDK1, TYMS, CCNB1, CKS1B, CCNE1, CCNE2, ORC6, CDT1, CCNA2, CDKN1A, RRM2, PSMD8

MC/1x	REACTOME	LIPID_DIGESTION_MOBILIZATION_AND_TRANSPORT	0,003	up	7/107	41/4186	SDC1, LCAT, APOA1, ABCG5, APOA2, APOB, MTPP
MC/1x	REACTOME	LIPOPROTEIN_METABOLISM	0,002	up	6/107	25/4186	SDC1, LCAT, APOA1, APOA2, APOB, MTPP
MC/1x	REACTOME	MITOTIC_G1_G1_S_PHASES	0,002	up	12/107	118/4186	CDK1, TYMS, CCNB1, CKS1B, CCNE1, CCNE2, ORC6, CDT1, CCNA2, CDKN1A, RRM2, PSMD8
MC/1x	REACTOME	S_PHASE	0,002	up	11/107	100/4186	CKS1B, CCNE1, POLD2, CCNE2, GINS1, ORC6, CDT1, CCNA2, CDKN1A, RFC4, PSMD8
MC/1x	REACTOME	BIOLOGICAL_OXIDATIONS	0,002	down	6/22	80/4186	PTGIS, SULT1A1, MAT1A, CYP26B1, FMO1, CYP26A1
MC/1x	REACTOME	CYTOCHROME_P450_ARRANGED_BY_SUBSTRATE_TYPE	0,040	down	3/22	22/4186	PTGIS, CYP26B1, CYP26A1
MC/1x	REACTOME	PHASE1_FUNCTIONALIZATION_OF_COMPOUNDS	0,010	down	4/22	36/4186	PTGIS, CYP26B1, FMO1, CYP26A1
MC/6x	KEGG	CELL_CYCLE	0,000	up	28/120	110/3825	CDK1, PTTG1, MYC, CDKN2C, CDC20, PLK1, CCNB1, MCM6, CCNE1, MCM4, MCM2, CCNE2, MCM5, ESPL1, ORC6, MAD2L1, CDC45, TTK, CCNA2, E2F1, BUB1B, MDM2, CDKN2D, BUB1, CDKN1A, MCM7, CCNB2, SKP2
MC/6x	KEGG	DNA_REPLICATION	0,000	up	8/120	33/3825	FEN1, MCM6, MCM4, MCM2, MCM5, MCM7, PRIM2, POLE2
MC/6x	KEGG	P53_SIGNALING_PATHWAY	0,001	up	9/120	53/3825	CDK1, CCNB1, PERP, CCNE1, CCNE2, MDM2, CDKN1A, RRM2, CCNB2
MC/6x	KEGG	OOCYTE_MEIOSIS	0,001	up	12/120	97/3825	CDK1, PTTG1, CDC20, PLK1, CCNB1, CCNE1, CCNE2, AURKA, ESPL1, MAD2L1, BUB1, CCNB2
MC/6x	KEGG	RETINOL_METABOLISM	0,003	up	6/120	26/3825	ADH1C, UGT2B15, CYP1A1, CYP26B1, ALDH1A1, UGT2B17
MC/6x	KEGG	STEROID_HORMONE_BIOSYNTHESIS	0,007	up	6/120	31/3825	UGT2B15, CYP1A1, HSD11B1, UGT2B17, AKR1C3, AKR1D1
MC/6x	KEGG	SMALL_CELL_LUNG_CANCER	0,007	up	9/120	72/3825	MYC, PTGS2, FN1, CKS1B, COL4A1, CCNE1, CCNE2, E2F1, SKP2
MC/6x	KEGG	ECM_RECEPTOR_INTERACTION	0,023	up	8/120	70/3825	SPP1, SDC1, FN1, HMMR, COL5A2, COL4A1, ITGA8, VWF

MC/6x	KEGG	PYRIMIDINE_METABOLISM	0,047	up	8/120	79/3825	TYMS, RRM1, TK1, TXNRD1, PRIM2, RRM2, CTPS, POLE2
MC/6x	BIOARTA	MCM_PATHWAY	0,000	up	8/49	17/1118	MCM6, CCNE1, MCM4, MCM2, MCM5, ORC6, CDT1, MCM7
MC/6x	BIOARTA	CELLCYCLE_PATHWAY	0,002	up	7/49	22/1118	CDK1, CDKN2C, CCNB1, CCNE1, E2F1, CDKN2D, CDKN1A
MC/6x	BIOARTA	G2_PATHWAY	0,012	up	6/49	21/1118	CDK1, PLK1, CCNB1, MDM2, CDKN2D, CDKN1A
MC/6x	REACTOME	CELL_CYCLE	0,000	up	57/157	309/4186	CDK1, PTTG1, FEN1, AURKB, MYC, BIRC5, TYMS, CDKN2C, CDC20, PLK1, CCNB1, MCM6, CKS1B, CDCA8, HJURP, CCNE1, MCM4, KIF20A, LMNB1, MCM2, CCNE2, KIF2C, AURKA, MCM5, GINS1, ORC6, MAD2L1, KNTC1, PLK4, CDT1, GMNN, CDC45, CCNA2, CENPK, E2F1, DSN1, BUB1B, NUF2, MDM
MC/6x	REACTOME	CELL_CYCLE_MITOTIC	0,000	up	52/157	266/4186	CDK1, PTTG1, FEN1, AURKB, MYC, BIRC5, TYMS, CDKN2C, CDC20, PLK1, CCNB1, MCM6, CKS1B, CDCA8, CCNE1, MCM4, KIF20A, MCM2, CCNE2, KIF2C, AURKA, MCM5, GINS1, ORC6, MAD2L1, KNTC1, PLK4, CDT1, GMNN, CDC45, CCNA2, CENPK, E2F1, DSN1, BUB1B, NUF2, CDKN2D, BUB1, ZWI
MC/6x	REACTOME	DNA_REPLICATION	0,000	up	36/157	165/4186	FEN1, AURKB, BIRC5, CDC20, PLK1, MCM6, CDCA8, MCM4, KIF20A, MCM2, KIF2C, MCM5, GINS1, ORC6, MAD2L1, KNTC1, CDT1, GMNN, CDC45, CCNA2, CENPK, E2F1, DSN1, BUB1B, NUF2, BUB1, ZWILCH, CDKN1A, MCM7, PRIM2, SPC25, KIF23, SKA1, CENPN, POLE2, CASC5
MC/6x	REACTOME	MITOTIC_M_M_G1_PHASES	0,000	up	32/157	146/4186	AURKB, BIRC5, CDC20, PLK1, MCM6, CDCA8, MCM4, KIF20A, MCM2, KIF2C, MCM5, ORC6, MAD2L1, KNTC1, CDT1, GMNN, CDC45, CENPK, E2F1, DSN1, BUB1B, NUF2, BUB1, ZWILCH, MCM7, PRIM2, SPC25, KIF23, SKA1, CENPN, POLE2, CASC5

MC/6x	REACTOME	G1_S_TRANSITION	0,000	up	22/157	97/4186	CDK1, MYC, TYMS, CCNB1, MCM6, CKS1B, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CDT1, CDC45, CCNA2, E2F1, CDKN1A, MCM7, PRIM2, RRM2, SKP2, POLE2
MC/6x	REACTOME	MITOTIC_G1_G1_S_PHASES	0,000	up	24/157	118/4186	CDK1, MYC, TYMS, CDKN2C, CCNB1, MCM6, CKS1B, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, CDT1, CDC45, CCNA2, E2F1, CDKN2D, CDKN1A, MCM7, PRIM2, RRM2, SKP2, POLE2
MC/6x	REACTOME	MITOTIC_PROMETAPHASE	0,000	up	18/157	74/4186	AURKB, BIRC5, CDC20, PLK1, CDCA8, KIF2C, MAD2L1, KNTC1, CENPK, DSN1, BUB1B, NUF2, BUB1, ZWILCH, SPC25, SKA1, CENPN, CASC5
MC/6x	REACTOME	S_PHASE	0,000	up	19/157	100/4186	FEN1, MYC, MCM6, CKS1B, CCNE1, MCM4, MCM2, CCNE2, MCM5, GINS1, ORC6, CDT1, CDC45, CCNA2, CDKN1A, MCM7, PRIM2, SKP2, POLE2
MC/6x	REACTOME	UNWINDING_OF_DNA	0,000	up	7/157	10/4186	MCM6, MCM4, MCM2, MCM5, GINS1, CDC45, MCM7
MC/6x	REACTOME	ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	0,000	up	10/157	26/4186	MCM6, MCM4, MCM2, MCM5, ORC6, CDT1, CDC45, MCM7, PRIM2, POLE2
MC/6x	REACTOME	KINESINS	0,000	up	9/157	20/4186	KIF22, RACGAP1, KIF20A, KIF15, KIF2C, KIFC1, KIF4A, KIF11, KIF23
MC/6x	REACTOME	CELL_CYCLE_CHECKPOINTS	0,000	up	18/157	99/4186	CDK1, CDC20, CCNB1, MCM6, CCNE1, MCM4, MCM2, CCNE2, MCM5, ORC6, MAD2L1, CDC45, BUB1B, MDM2, CDKN1A, UBE2C, MCM7, CCNB2
MC/6x	REACTOME	E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	0,000	up	10/157	30/4186	CDK1, TYMS, CCNB1, CCNE1, ORC6, CDT1, CDC45, E2F1, PRIM2, RRM2
MC/6x	REACTOME	BIOLOGICAL_OXIDATIONS	0,000	up	15/157	80/4186	UGDH, ADH1C, PTGS2, GCLM, CYP1A1, GCLC, GSTM5, GSTA5, MGST2, CYP26B1, GSTM1, ALDH1A1, FMO1, SULT1B1, UGT2B17
MC/6x	REACTOME	G2_M_CHECKPOINTS	0,000	up	10/157	34/4186	CDK1, CCNB1, MCM6, MCM4, MCM2, MCM5, ORC6, CDC45, MCM7, CCNB2

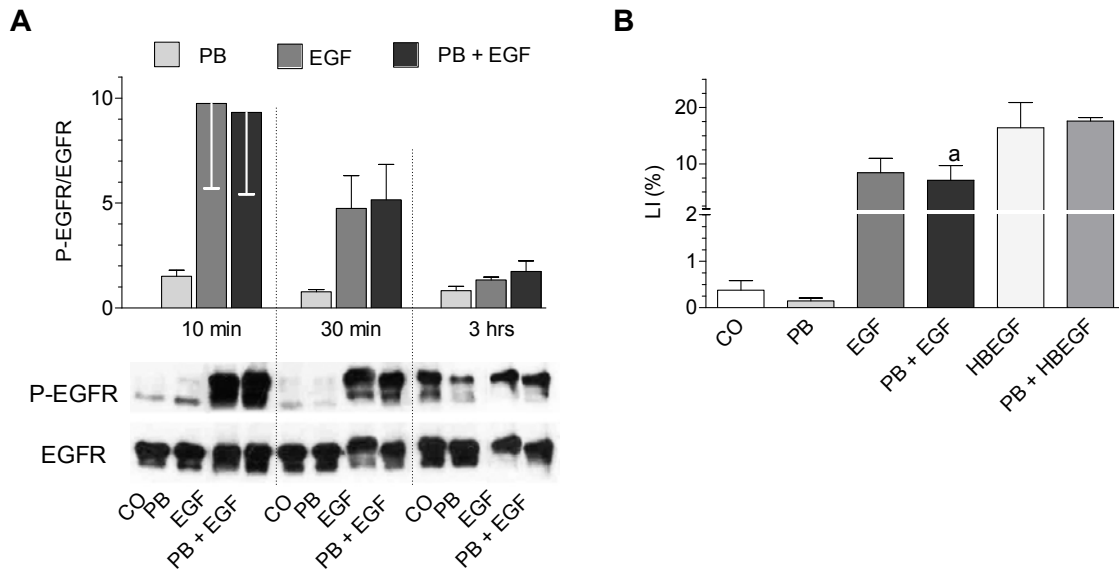


Figure S3. PB treatment does not impair the EGFR phosphorylation status and DNA synthesis induction by EGF or HBEGF in primary rat HC. The livers of untreated male Wistar rats were perfused with collagenase. The cell suspension obtained was used to separate HC from MC by low-speed centrifugation in percoll-gradients. HC were seeded onto collagen coated petri dishes and were allowed to attach in Williams medium E containing 10% fetal calf serum. Two hrs after seeding, cells were switched to serum-free Williams medium E and were treated with 1mM PB, 10ng EGF/ml medium and/or 10ng HBEGF/ml medium. (A), Ten min, 30 min or 3hrs after start of treatment proteins were harvested in RIPA buffer [500 mM NaCl, 50 mM Tris (pH7.4), 0.1% SDS, 1% igepal CA630, 0.5% Na-deoxycholate, 0.5 mM sodium orthovanadate, 1 mM phenylmethylsulfonylfluorid; all obtained from Sigma-Aldrich], homogenized by sonication and centrifugation (12.000g, 5 min), and loaded at equal amounts (10 μ g) onto 10% SDS gels. Separated protein were transferred onto PVDF membranes, incubated with anti-phospho-EGFR antibody (Tyr1173, Cell Signalling) and anti-panEGFR (Cell signalling), and subjected to ECL Plus Western Blotting Detection Kit (GE Healthcare, St Gilles, GB). Bands were evaluated by densitometry (Optimax 2010 X-ray film processor and Quantity One 4.2.1; Bio-Rad, Hercules, CA). Data represent the mean \pm SD of two independent experiments. (B), After 24 hrs in culture, 3 H-thymidine was added for further 24hrs. HC were harvested, fixed and subjected to autoradiography to determine the percentage of nuclei with incorporated 3 H-thymidine (LI %). In each of the experiments at least 2000 HC nuclei were counted. Data are means \pm SD of ≥ 3 independent experiments.

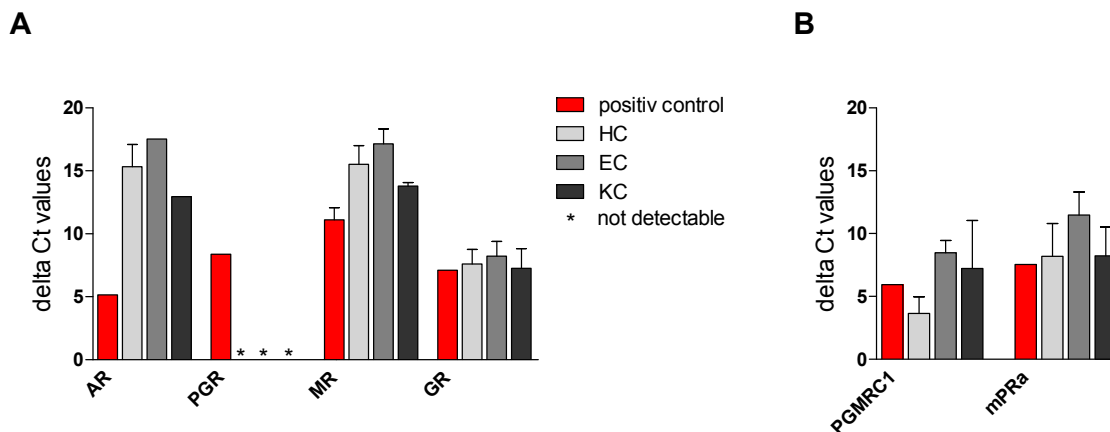


Figure S4. Expression level of nuclear hormone receptors, PGMRC1 (progesterone membrane receptor component 1) and mPR α (membrane progestin receptor α) in cell types of rat liver.. mRNA was obtained from purified rat HC, KC- and EC-enriched fractions, from testis and uterus. Transcript levels of androgen receptor (AR), progesterone receptors (PGR), mineralocorticoid receptors (MR), glucocorticoid receptor (GR), PGMRC1, and mPR α were determined by RT-qPCR and normalized by β 2-microglobulin (deltaCT-values). Primers applied, please see Table S3. Please note that the primers for PGR cover both, PGR α and PGR β . The mRNA of testis served as positive control for AR and mRNA of uterus for PGR, MR, GR, PGMRC1, and mPR α . Data are means \pm SEM derived from ≥ 3 independent cell preparations.

Table S3. Primers were obtained from Eurogentec (Seraing, Belgium) for SYBR green-based RT-qPCR.

Primer		Sequence
Rat NR3C2 (mineralocorticoid receptor; MR)	Forward	5' CAGCGAAACAGATGATCC 3'
	Reverse	5' AGCGAACGATGATAGACAC 3'
Rat NR3C3 (progesteron receptors; PGR)	Forward	5'CACAACGCTTCTATCAAC 3'
	Reverse	5'GCAGCAATAACTTCAGAC 3'
Rat NR3C4 (androgen receptor; AR)	Forward	5' TGGCGGTCCTTCACTAATGTC 3'
	Reverse	5' TCACGCACTGGCTGTACATTC 3'
Rat NR3C1 (glucocorticoid receptor; GR)	Forward	5'GGCAGTGTGAAATTGTATCC 3'
	Reverse	5'CTCTCGTTTGTGTCTTTACC 3'
Rat PGMRC1	Forward	5'CGTGACCAAAGGCCGCAAG 3'
	Reverse	5'TGGGCAGGAGTGAGGTCAG 3'
Rat mPRα	Forward	5'TTCAGTGCCCTGGCTCACCTC 3'
	Reverse	5'CACGGCCACACCCACATAGTC 3'
Rat β2 microgloblin	Forward	5'CGCTCGGTGACCGTGATCTT3'
	Reverse	5'TCCGGTGGATGGCGAGAGTA3'