Supplements

I. Network topology: Feedback loops in IL-1 and IL-6 signalling

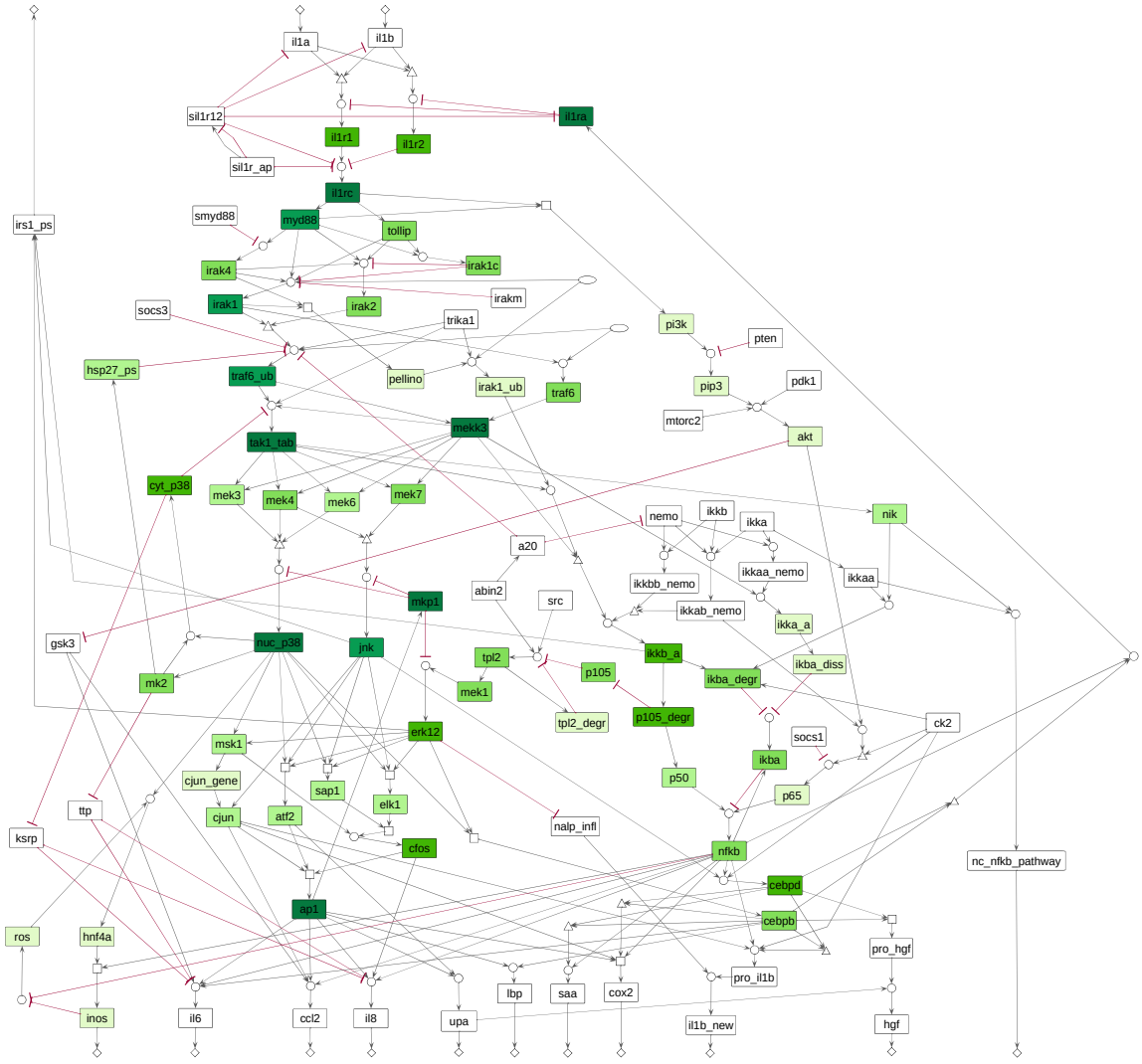

Fig. S1. Feedback loop participation of IL-1-associated species in the interaction graph IG1 underlying the logical model M1 (primary and secondary events included).The more intensely a species is coloured, the more feedback loops it contributes to. Hence, white effectors do not participate in any feedback loop. IL-1 receptor antagonists (IL-1Ra) show the highest participation level, being involved in 99% of all FLs. Black arrows (red blunt-ended lines) indicate activations (inhibitions).

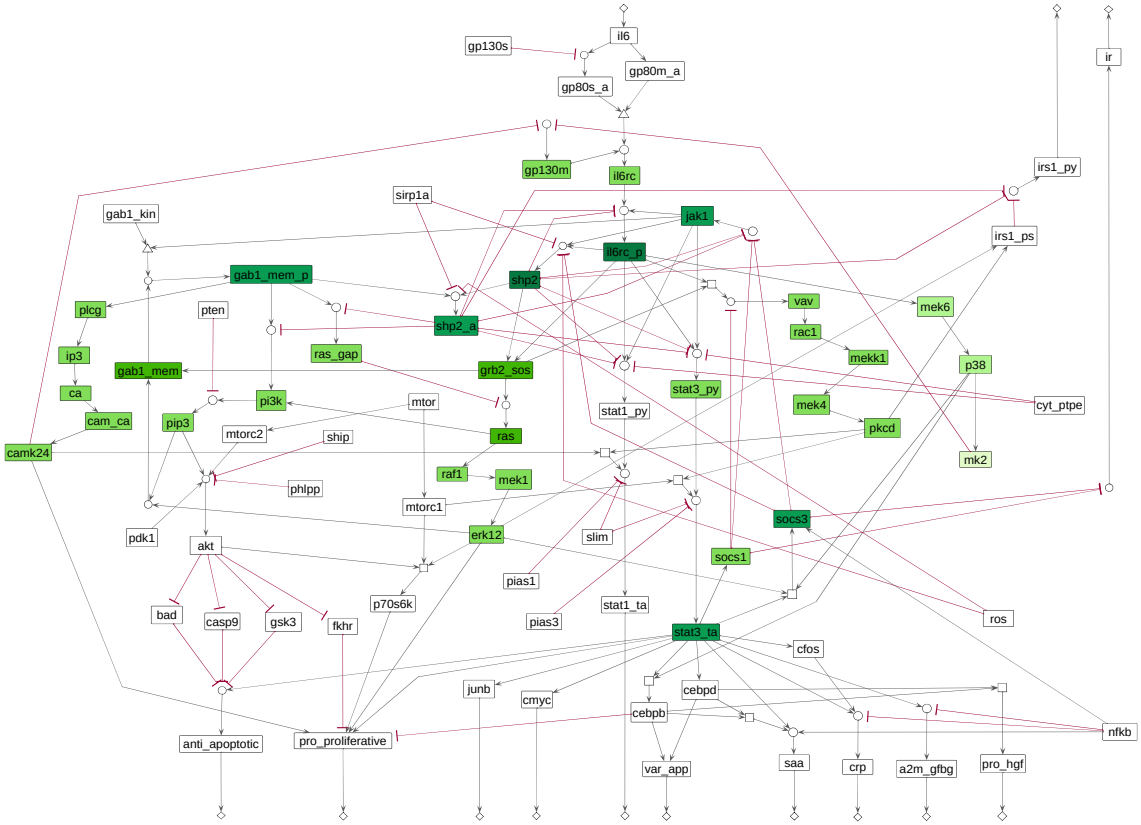

Fig. S2. Feedback loop participation of IL-6-associated species in the interaction graph IG2 underlying the logical model M2 (primary and secondary events included). SHP2 shows the highest participation level, being involved in 84% of all FLs. See Fig. S1 for further explanations.

II. Species dependencies (dependency matrices)

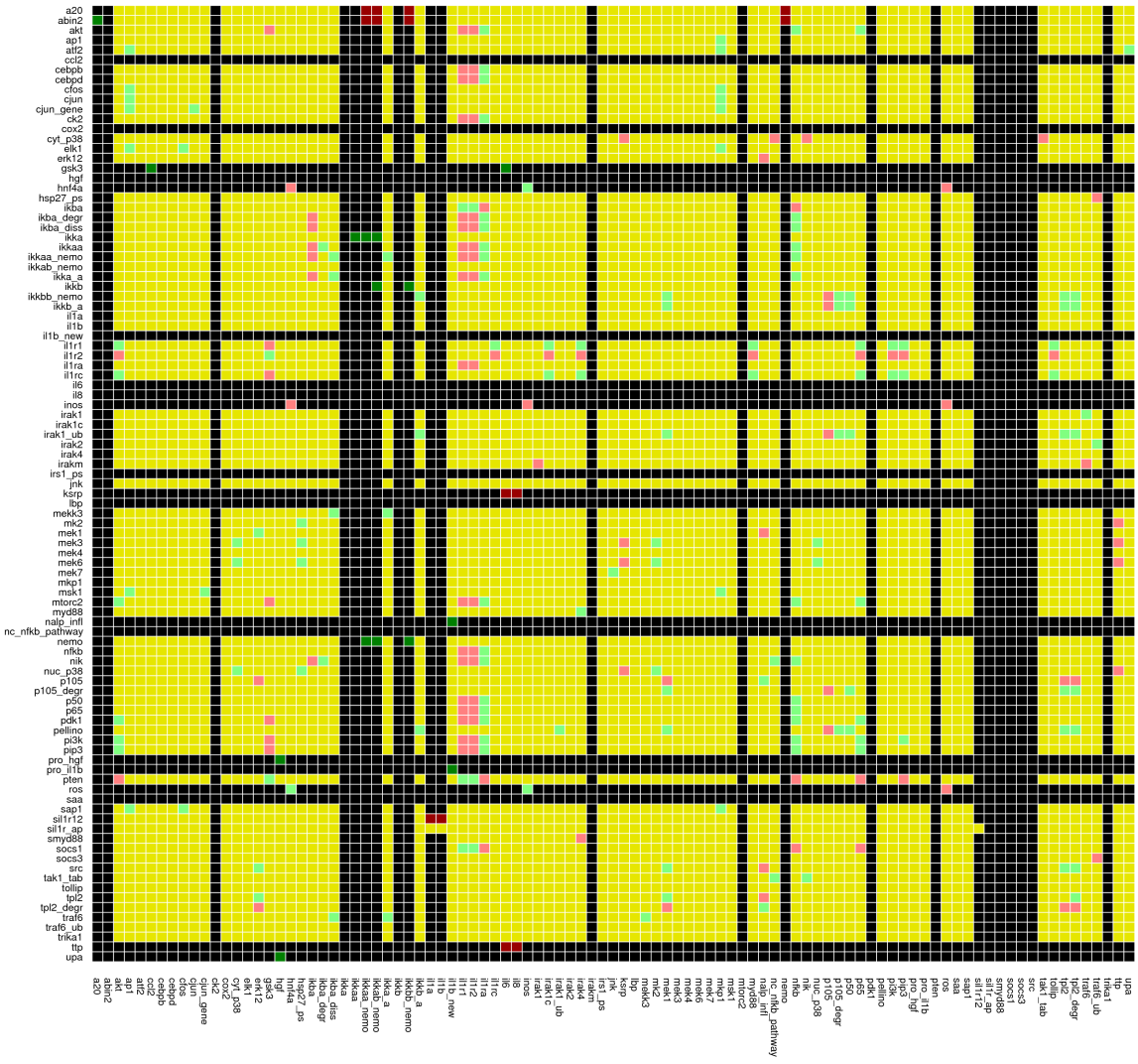

Fig. S3. Dependency matrix $D^{IL\text{-}1}$ derived from IG1 (primary and secondary events included). Colour coding of matrix element D_{ij} characterises the influence of effector *i* with respect to species *j*: dark green: activator (only positive paths connecting *i* with *j* exist); dark red: inhibitor (only negative paths connecting *i* with *j* exist); light green/red: *i* is a weak activator/inhibitor of *j*, meaning that only positive/negative paths connecting *i* with *j* exist and at least one of them includes a species that is involved in a negative feedback loop; yellow: ambivalent factor (positive *and* negative paths connecting *i* with *j* exist); black: *i* has no effect on *j* (no path connects *i* with *j*). See also *Klamt et al.*[3, 5]

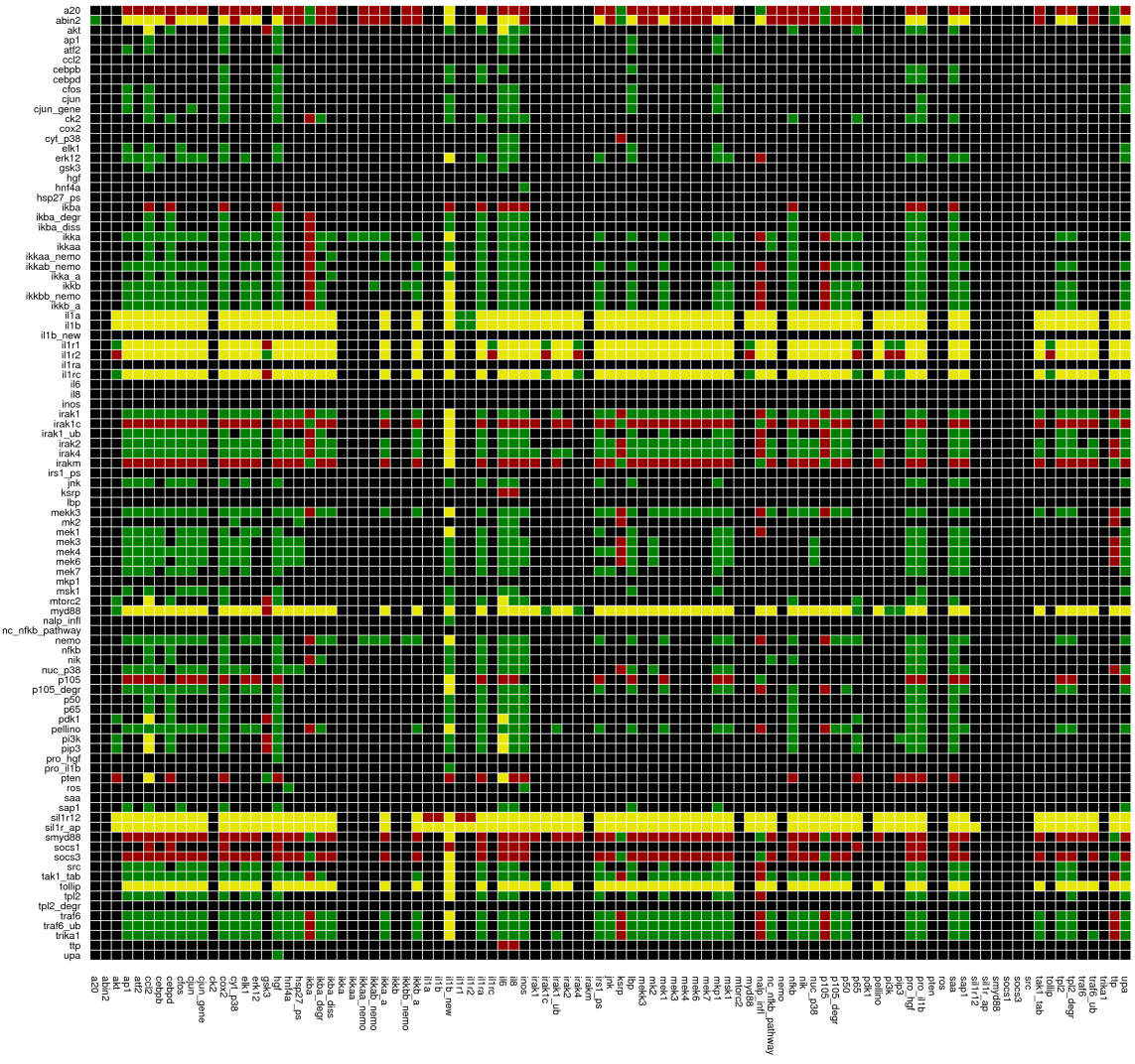

Fig. S4. Dependency matrix $D^{IL\text{-}1}$ derived from *acyclic* IG1. Interactions *closing* feedback loops (see "Methods" and dashed lines in Fig. 1) were ignored. See Fig. S3 for further information on colour scheme.

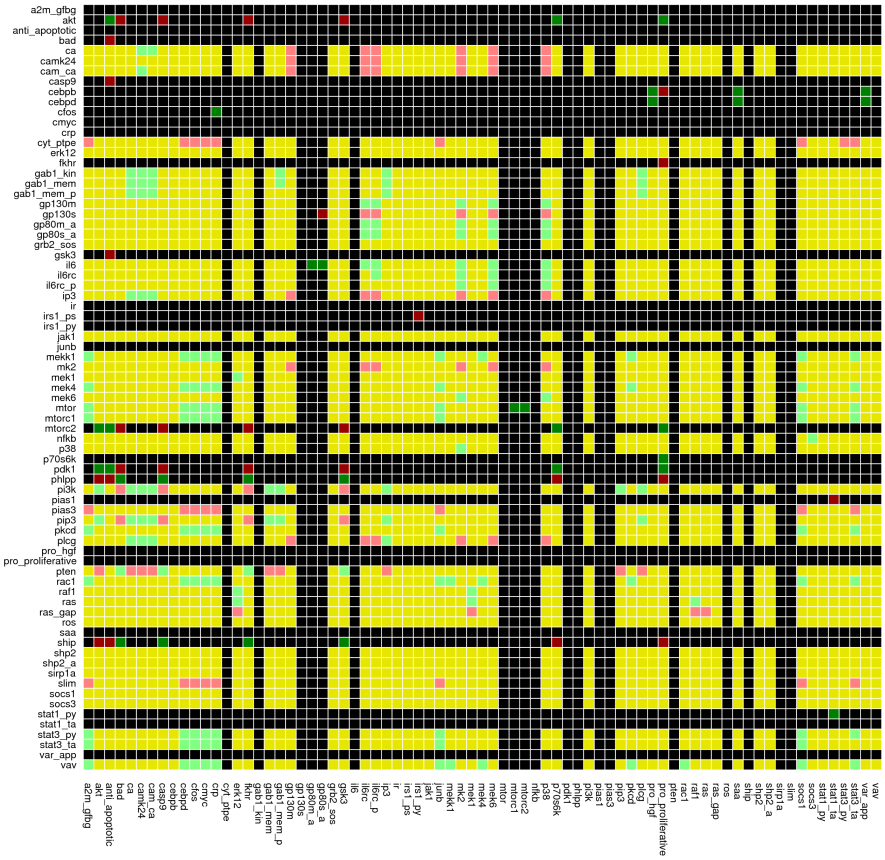

Fig. S5. Dependency matrix $D^{IL\text{-}6}$ derived from IG2 (primary and secondary events included). See Fig. S3 for further explanations.

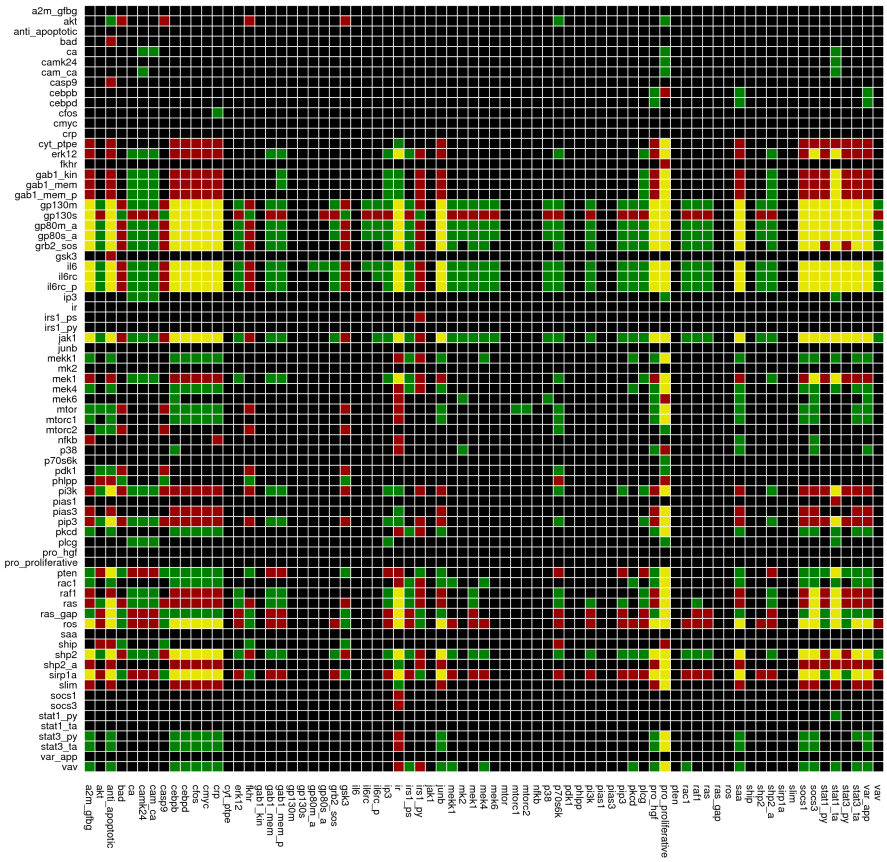

Fig. S6. Dependency matrix $D^{IL\text{-}6}$ derived from *acyclic* IG2. Interactions *closing* feedback loops (see “Methods” and dashed lines in Fig. 2) were ignored. See Fig. S3 for further information on colour scheme.

III. Prediction of qualitative I/O behaviour

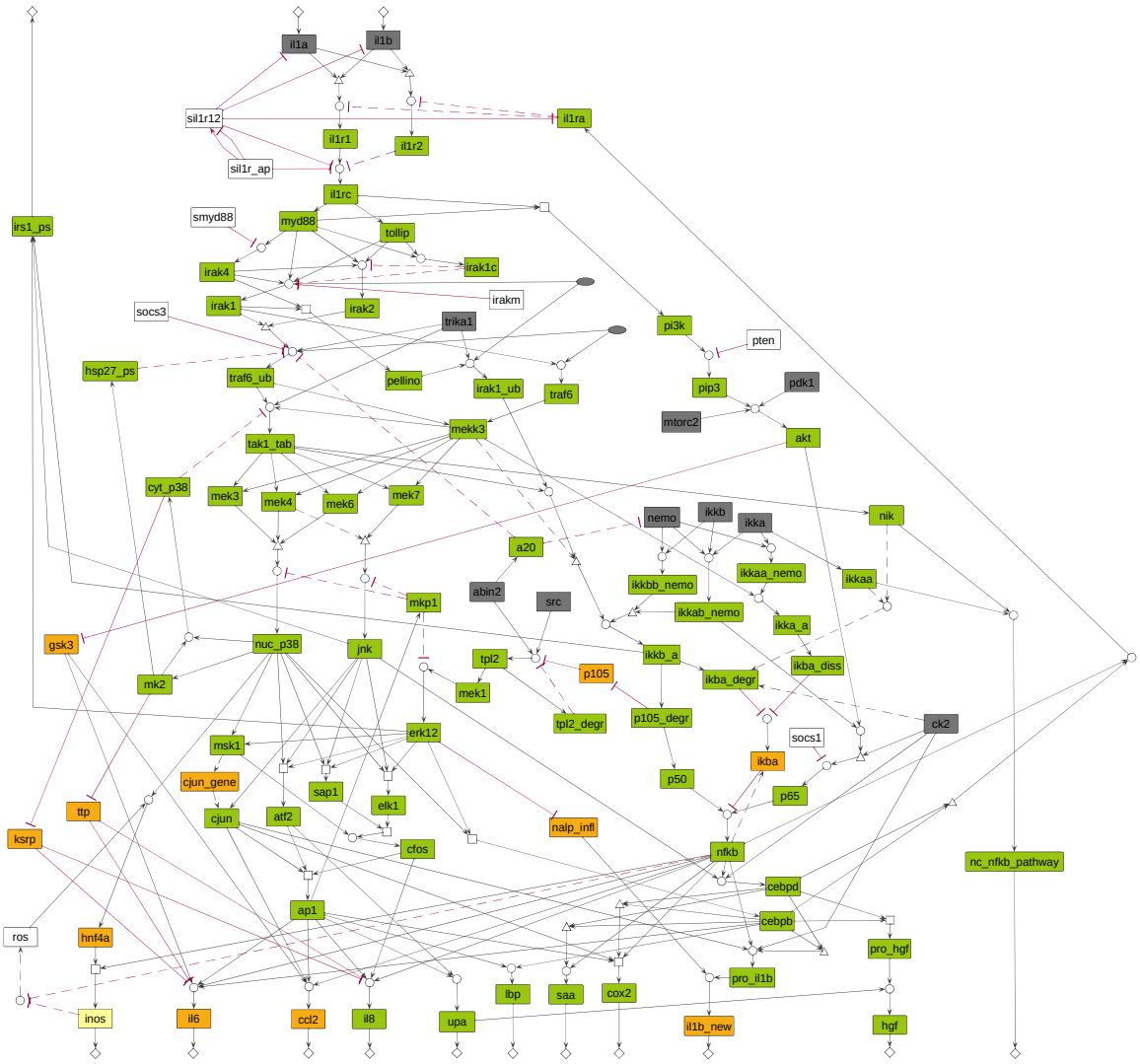

Fig. S7. Initial I/O behaviour in response to IL-1 as predicted using the logical model M1. Simulations were performed in M1 with focus on primary effects ("$\tau = 2$" interactions omitted). See "Methods" and Fig. 1 for further explanations. Confidence levels are not displayed for reasons of clarity. Species colours indicate the predicted initial response upon IL-1 stimulation: green: 1/active; orange: 0/inactive; yellow: indefinite. Model inputs (ligands and "side effectors"), preassigned *1/on* or *0/off* by default value (see "Methods" and model documentation) are coloured grey or white, respectively.

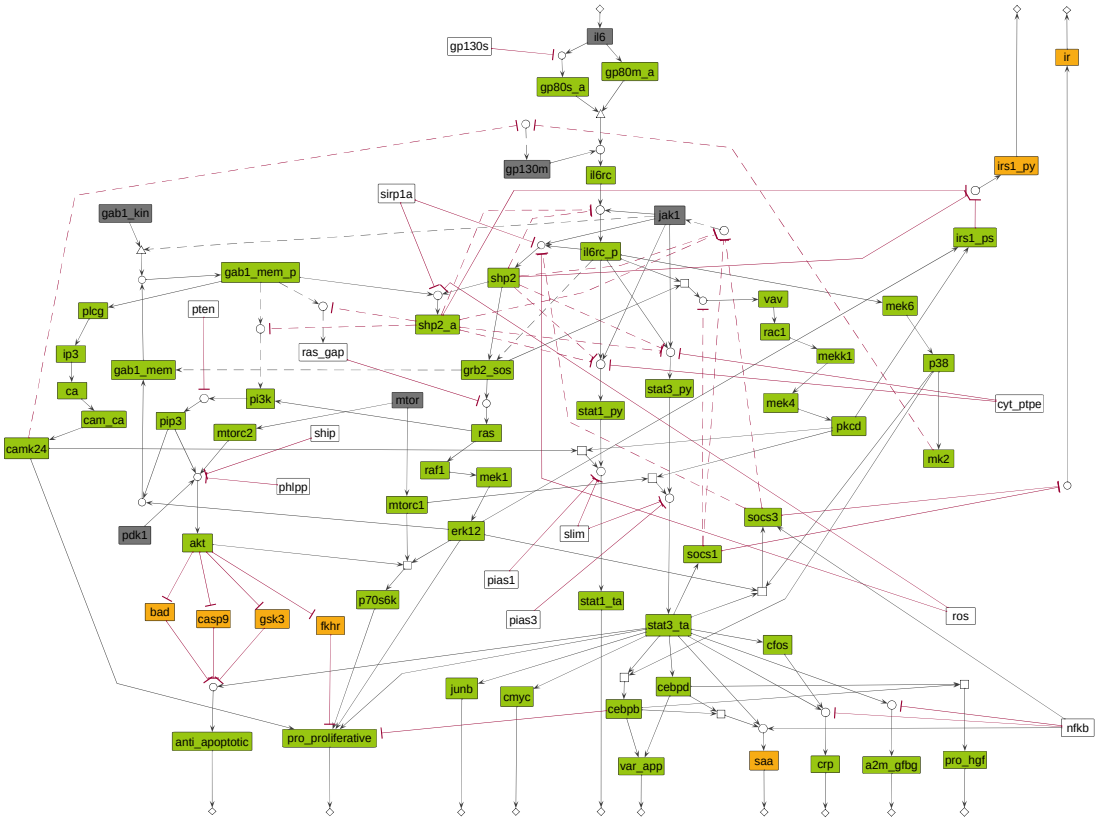

Fig. S8. Initial I/O behaviour in response to IL-6 as predicted using logical model M2. Simulations were performed in M2 with focus on primary effects ("$\tau = 2$" interactions omitted; *cf.* Fig. 2). See Fig. S7 for further explanations.

Electronic Supplementary Material (ESI) for Molecular BioSystems

IV. Data sets

The data sets used herein were taken from *Alexopoulos et al.*[2]

Tab. S1. Intracellular proteins assayed by phosphoproteomic readouts (using multiplexed xMAP technology (Luminex Corp., Austin/TX) performed with reagents from Bio-Rad, Hercules/CA; for further information see *Alexopoulos et al.*[2]) and their mapping to species integrated in represented models.

Signal	Phophosite(s)	Corresponding network species
Akt	S473	akt
ERK1/2	T202/Y204 and T185/Y187	erk12
GSK3α/β	S21/S9	gsk3
IκBα	S32/S36	ikba
JNK	T183/Y185	jnk
p38	T180/Y182	nuc_p38*, p38
p70S6K	T421/S424	p70s6k
STAT3	Y705	stat3_py
HSP27	S78	hsp27_ps
IRS1	S636/S639	irs1_ps
MEK1	S217/S221	mek1

Tab. S2. Applied ligands and small molecule kinase inhibitors linked to corresponding network species.

Ligand/ kinase inhibitor	Drug	Supplier	Concentration	Corresponding/ affected network species
IL-1α	-	R&D Systems, Minneapolis/MN	100 ng/ml	il1a
IL-6	-	Sigma-Aldrich, St. Louis/MO	100 ng/ml	il6
GSK3βi	inhibitor XI	Calbiochem, Gibbstown/NJ	0.5 µM	gsk3
IKKβi	BMS-345541	Calbiochem, Gibbstown/NJ	10 µM	ikkb
JNKi	SP600125	Calbiochem, Gibbstown/NJ	15 µM	jnk
MEK1/2i	PD325901	Pfizer Pharmaceuticals, New York/NY	5 nM	mek1
mTORi	Rapamycin	Calbiochem, Gibbstown/NJ	100 nM	mtorc1
p38i	PHA818637	Pfizer Pharmaceuticals, New York/NY	10 nM	nuc_p38*, p38
PI3Ki	ZSTK474	Calbiochem, Gibbstown/NJ	2 µM	pi3k

* corresponding network species within M2 (representing IL-1 signalling), stressing *nuclear* p38 MAPK localisation

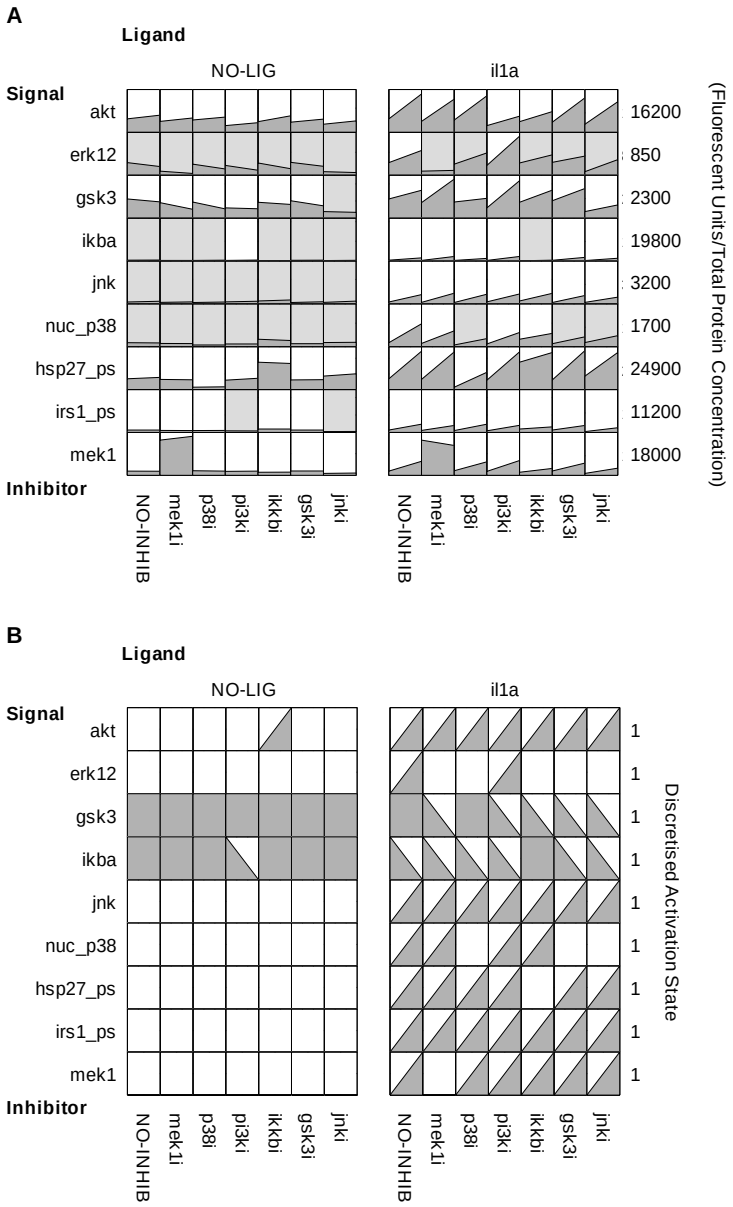

Fig. S9. A: IL-1α signalling raw data set measured in primary human hepatocytes. *Rows* display the phosphoproteomic profiles of 9 intracellular proteins involved in modelled IL-1 signalling pathways (mentioned on the left hand side) assayed at *t = 0* and *30 min* (relative to ligand (IL-1α) addition) and induced by applied ligand/inhibitor cues depicted in the *columns*. Grey face colour marks signals completely ranging below technical detection limit. Signal, inhibitor, and ligand labelling conforms to model notation (see also Tabs. S1 and S2).
B: Corresponding discretised data (*cf.* "Methods"; used parameters: $p_1 = 1.5$; $p_2 = 0.15$; $p_3 = 500$; negative states: gsk3, ikba). Data management and visualisation was performed with *DataRail*[1, 4]. Abbreviations: NO-LIG: no ligand/negative control; NO-INHIB: no inhibitor.

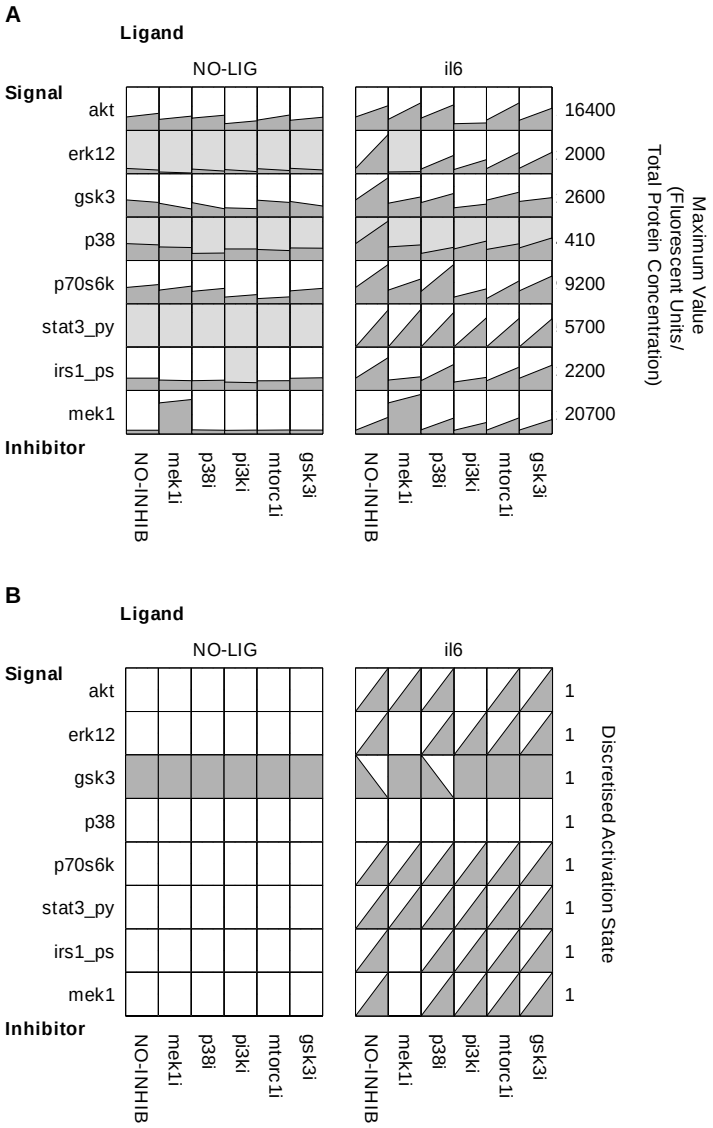

Fig. S10. A: IL-6 signalling data set measured in primary human hepatocytes. B: Corresponding discretised data. See Fig. S9 for further descriptions (negative state: gsk3).

V. Results of model optimisation for hepatocytes: IL-1

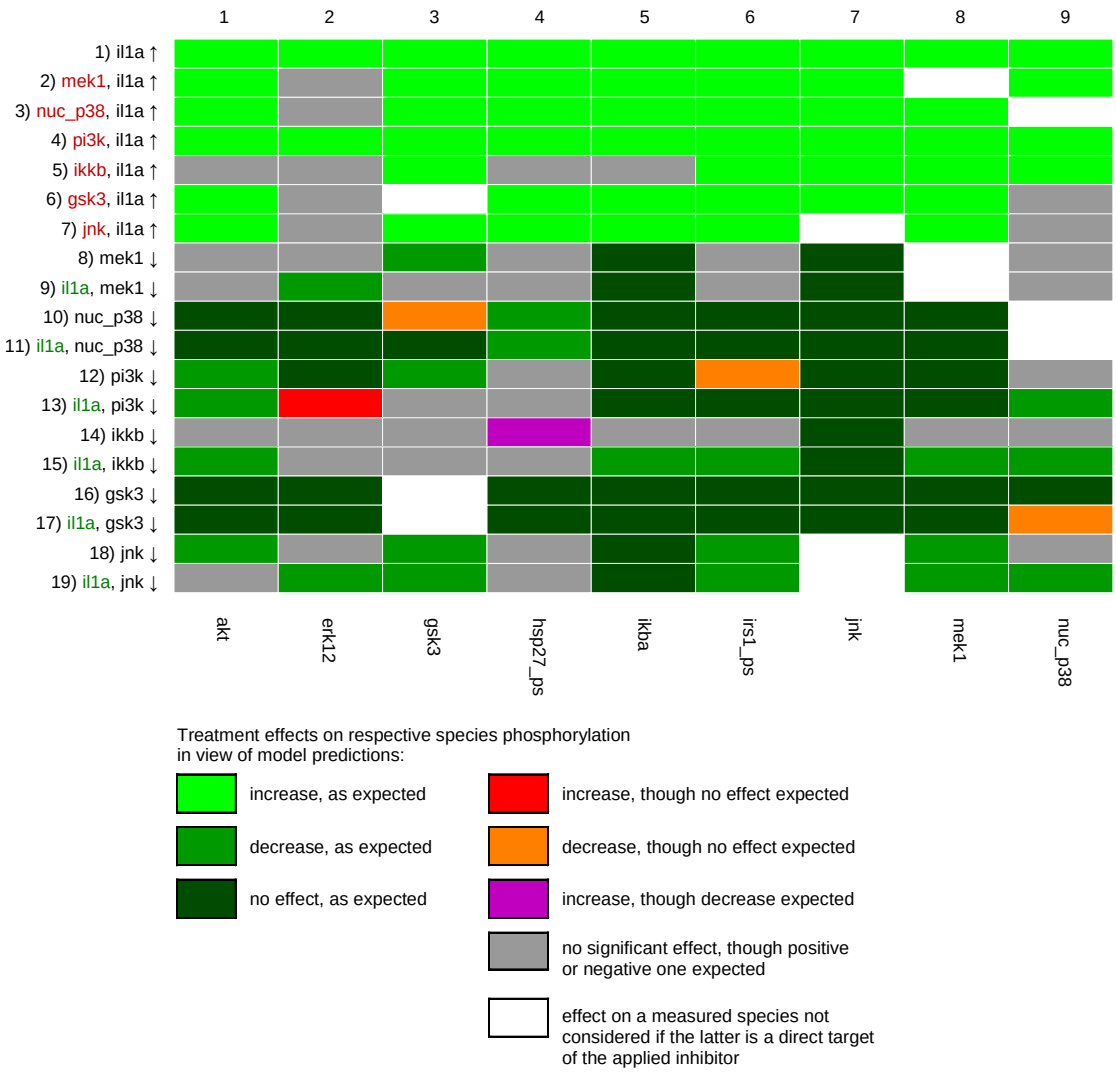

Fig. S11. Interaction graph-based verification of *optimised* IL-1 network topology. See Fig. 4 for further explanations. The underlying IG1 was modified according to Fig. 8. Negative states: gsk3, ikba.

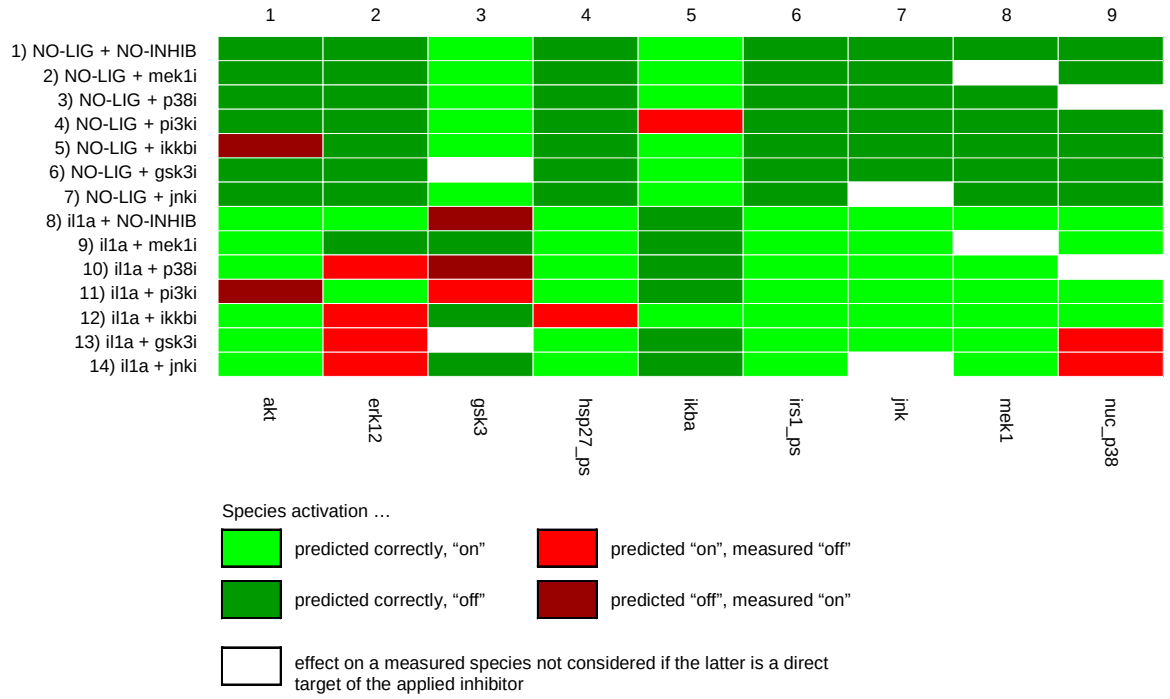

Fig. S12. Verification of the *optimised* logical network representing initial IL-1 receptor signalling. See Fig. 6 for further explanations. Associated logical modifications are visualised in Fig. 8. Negative states: gsk3, ikba; NO-LIG: no ligand/negative control; NO-INHIB: no inhibitor.

VI. Results of model optimisation for hepatocytes: IL-6

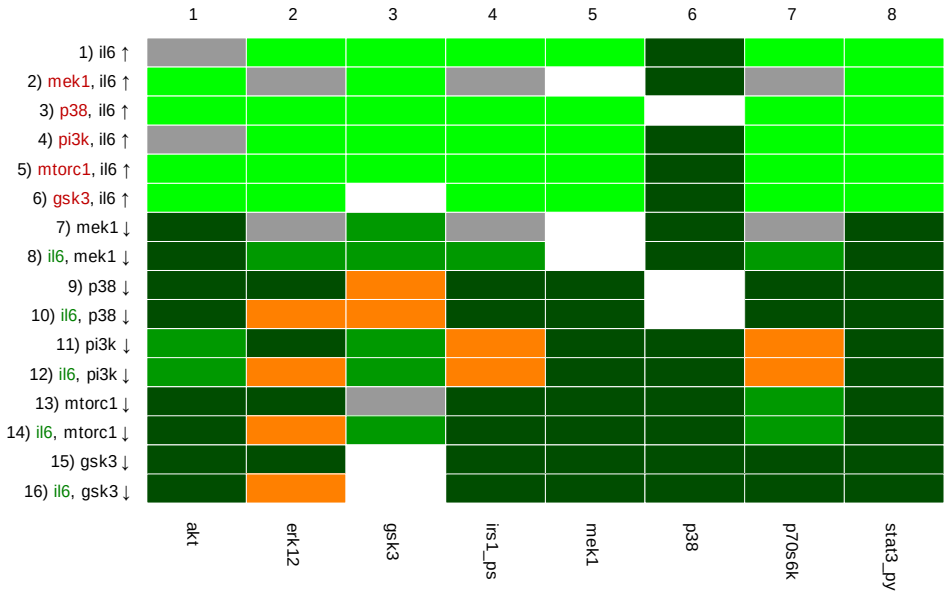

Fig. S13. Interaction graph-based verification of *optimised* IL-6 network topology. See Fig. 5 for further explanations. The underlying IG2 was modified according to Fig. 9. Negative state: gsk3.

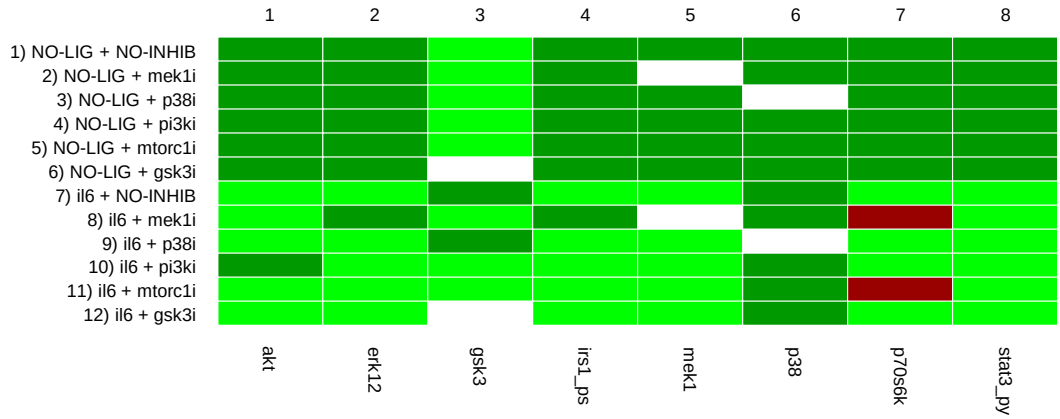

Fig. S14. Verification of the *optimised* logical network representing initial IL-6 receptor signalling. See Fig. 7 for further explanations. Associated logical modifications are visualised in Fig. 9. Negative state: gsk3; NO-LIG: no ligand/negative control; NO-INHIB: no inhibitor.

VII. Coverage analysis

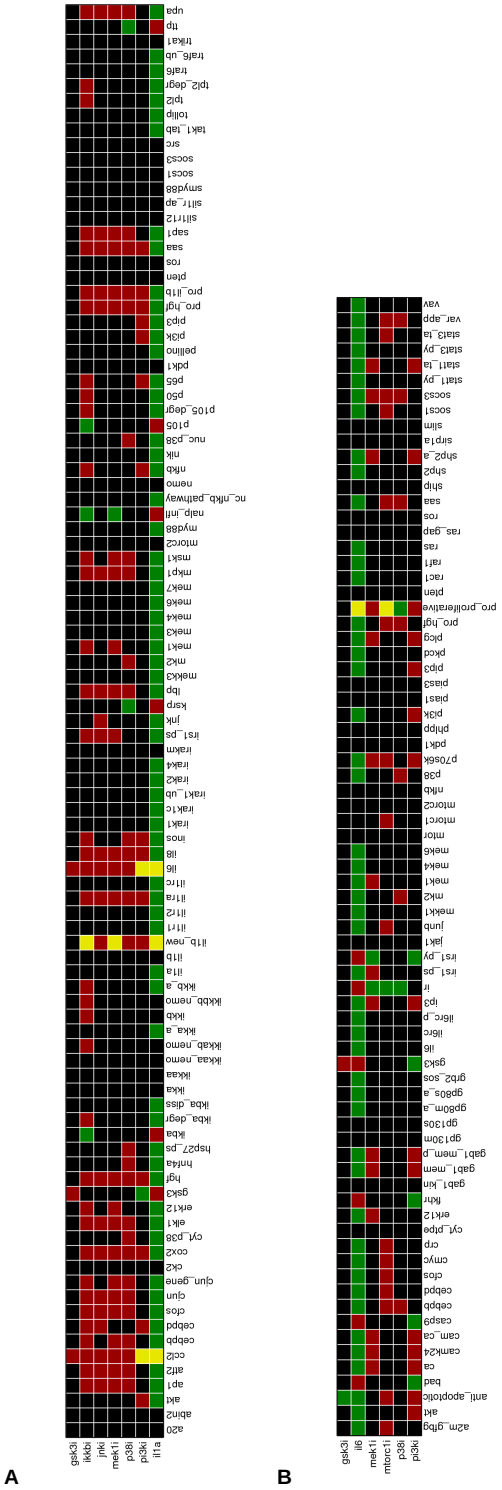

Fig. S15. Dependency matrix segments displaying perturbation effects on IL-1 (A) and IL-6 (B) signalling species (secondary events omitted). Applied cytokines/inhibitors (*cf.* Tab. S2 and Figs. S9.A/S10.A) are depicted in the rows. See Fig. S3 for further information on colour scheme.

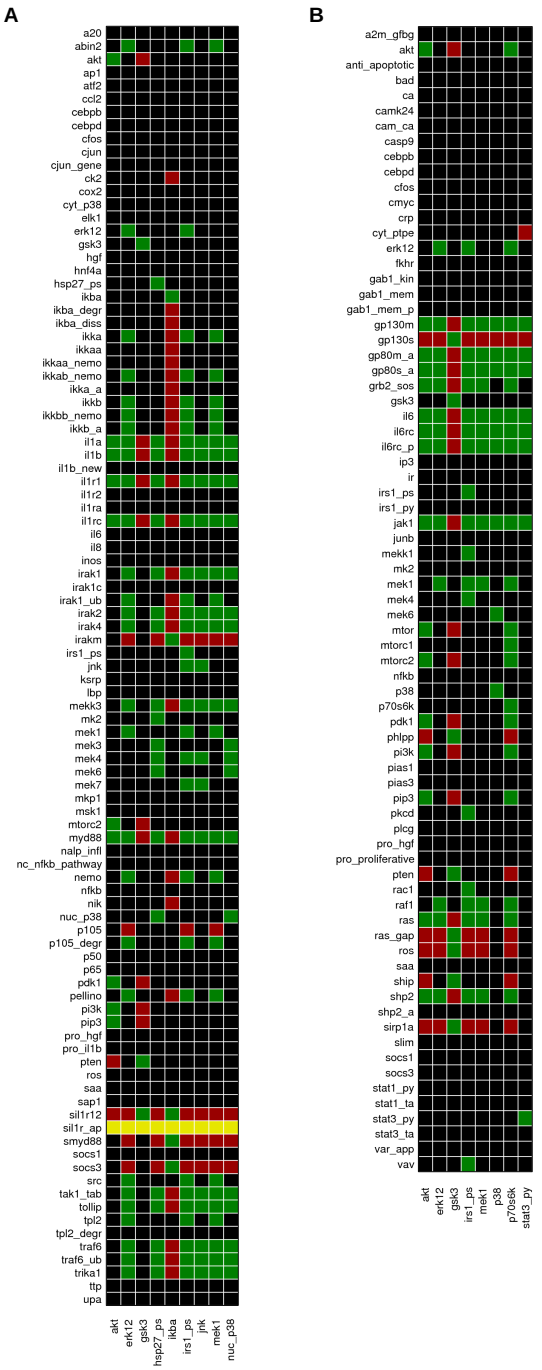

Fig. S16. Dependency matrix segments displaying the effects of signalling species on phosphoproteomic readouts in the IL-1 (A) and IL-6 (B) network (secondary events omitted). Readouts (*cf.* Tab. S1 and Figs. S9.A/S10.A) are depicted in the columns. See Fig. S3 for further information on colour scheme.

References

1 *DataRail*: http://code.google.com/p/sbpipeline/wiki/DataRail. Version 1.2.

2 **Alexopoulos LG, Saez-Rodriguez J, Cosgrove BD, Lauffenburger DA*, et al.*:** Networks inferred from biochemical data reveal profound differences in toll-like receptor and inflammatory signaling between normal and transformed hepatocytes. *Mol Cell Proteomics* **2010** (Sep), 9: 1849-65.

3 **Klamt S, Saez-Rodriguez J, Lindquist JA, Simeoni L*, et al.*:** A methodology for the structural and functional analysis of signaling and regulatory networks. *BMC Bioinformatics* **2006**, 7: 56.

4 **Saez-Rodriguez J, Goldsipe A, Muhlich J, Alexopoulos LG*, et al.*:** Flexible informatics for linking experimental data to mathematical models via DataRail. *Bioinformatics* **2008** (Mar 15), 24: 840-7.

5 **Samaga R, Saez-Rodriguez J, Alexopoulos LG, Sorger PK*, et al.*:** The logic of EGFR/ErbB signaling: theoretical properties and analysis of high-throughput data. *PLoS Comput Biol* **2009** (Aug), 5: e1000438.

VIII. Model documentations

Notation:

d: default value of a species' logical state (on: 1; off: 0); *e.g.* reference to basal (in)activity

τ: relevance level

1.. primary event;
active/available interaction during the initial cellular response

2.. secondary event;
interactions closing feedback loops, initiating negative-regulatory events that require the prior onset of species to be inhibited, delineating influences of catalytically aberrant enzyme isoforms, or seeming of minor initial relevance with respect to associated species regulation

"Timescale dummy species" were introduced to decouple "*τ = 2*" events from preceding (*τ = 1*) AND gates. Related (primarily inhibitory) terms integrating species that function via interposed timescale dummies are *italicised* in corresponding SOP representation:
A · *!B* = C (*τ = 1*) equals A · !tdum_B_C = C (*τ = 1*), whereas B = tdum_B_C (*τ = 2*).

c: confidence level

Cell line: / Ligand:	Primary human hepatocytes, human hepatoma cell lines	Other
IL-1/IL-6	1.0	0.8
Other	0.6	0.4

Complex AND nodes were subjectively estimated with regard to the individual confidence levels of reactions involved, respectively.

Interactions:

→ A	species A functions as a model input
A →	species A functions as a model output
A = B	species A activates/positively regulates species B
A » B	A influences B in some way
A * B = C	A AND/OR B effect C in some way, whereas the precise mechanism is still unknown
A · B = C	species A AND B *cooperatively* activate/positively regulate species C (both species A and B are essential to cause activation)
A + B = C	species A OR B *redundantly/alternatively* activate/positively regulate species C (either species A or B is essential to cause activation)
A · !B = C	species C gets activated/positively regulated, if species A AND NOT species B (*e.g.* an inhibitor) function *cooperatively*
(A + B) · C = D ⇒ dum_A_or_B · C = D	species A OR B *redundantly/alternatively* cooperate with species C to activate/positively regulate species D (context-dependently, the OR term (A+B) is expressed employing a so-called dummy species ensuring SOP representation: dum_A_or_B · C = D)

VIII.A IL-1 signalling

Tab. S3.1. IL-1 signalling species.

№	**Model name**	Full name	d	**Documentation**
1	a20	A20		zinc finger protein and dual-function ubiquitin-editing enzyme with distinct peptidase and ligase domains[82a, 185a]
2	abin2	ABIN2	1	A20-binding inhibitor of NF-κB 2
3	akt*	Akt		also: PKB (protein kinase B); oncogenic AGC kinase, serine/threonine-specific; transduces survival signals[94a]
4	ap1	AP-1		activator protein 1; basic leucine-zipper protein (bZIP); homo- or heterodimeric transcription factor complex
5	atf2	ATF2		activating transcription factor 2; ubiquitously expressed member of the ATF/cyclic AMP-response element (CRE)-binding protein family of basic region-leucine zipper (bZIP) transcription factors; intrinsic histone acetyltransferase (HAT) activity (for review see [21a])
6	ccl2	CCL2		chemokine (C-C-motif) ligand 2, also: MCP-1 (monocyte chemoattractant protein 1); IL-1 induces CCL2 expression in human primary and MRC5 fibroblasts[192a]
7	cebpb	C/EBPβ		CCAAT/enhancer binding protein β, also: LAP (liver activator protein), CRP2, NF-IL6); key transcription factor concerning the activation of APP gene transcription; member of the C/EBP subfamily of the basic region leucine zipper (bZIP) protein family; constitutive basal expression in hepatocytes and HepG2 cells[141a] is up-regulated in response to IL-1 and IL-6[3a, 61a, 195a]
8	cebpd	C/EBPδ		CCAAT/enhancer binding protein δ, also: NF-IL6β; key transcription factor concerning the activation of APP gene transcription; member of the C/EBP subfamily of the basic region leucine zipper (bZIP) protein family

* *Dark grey* marking points to species (model outputs) that also act during or effect (are directly regulated in) IL-6 signalling.

9	cfos	c-Fos		v-Fos Finkel-Biskis-Jinkins osteosarcoma virus oncogene homolog; member of the bZIP family of transcription factors; early immediate (IE) gene product/cellular oncoprotein; leucine zipper mediates DNA binding
10	cjun	c-Jun		v-Jun avian sarcoma virus 17 oncogene homolog; member of the bZIP family of transcription factors; highly inducible early immediate (IE) gene product/cellular oncoprotein; leucine zipper mediates DNA binding; IL-1 up-regulates c-Jun- and c-Fos-mRNA levels/gene transcription in HepG2 cells within 15 min[42a, 124a]
11	cjun_gene			immediate early (IE) c-Jun gene expression
12	ck2	CK2	1	casein kinase 2; dual specificity IκB kinase
13	cox2	COX2		cyclooxygenase 2, also: PGHS2 (prostaglandin G/H synthase 2); oxidoreductase/peroxidase, mediator of inflammation; anti-proliferative, pro-apoptotic
14	cyt_p38			active, cytosolic p38 MAPK (for description see “nuc_p38“)
15	dum_cebp_cox2			dummy species
16	dum_cebp_il1ra			
17	dum_cebp_pro_il1b			
18	dum_cebp_saa			
19	dum_ikkab_nemo_akt_or_ck2_p65			
20	dum_ikkab_or_ikkbb_nemo_ikkb_a			
21	dum_il1_r1			
22	dum_il1_r2			
23	dum_irak1_or_2_traf6_ub			
24	dum_mek3_or_4_or_6_p38			
25	dum_mek4_or_7_jnk			
26	dum_sap1_or_elk_cfos			
27	dum_tak1_tab_or_mekk3_ikkb_a			

28	elk1	Elk-1		ETS-domain protein 1; ternary complex transcription factor (TCF); ETS domain mediates DNA binding
29	erk12	ERK1/2		extracellular signal-regulated kinase 1/2, also: p42/44; cytosolic, serine/threonine specific and proline direct (phosphorylate serine or threonine residues in the motif P/LXT/SP)
30	gsk3	GSK3		glycogen synthase kinase 3 α/β (species refers to both currently known isoforms); serine/threonine specific; basally active (for review see [110a]); GSK3β was shown to support the promoter-specific recruitment of NF-κB to the *il6*- and *ccl2*-locus (as shown in MEFs (murine embryonic fibroblasts) in response to TNFα[168a])
31	hgf	HGF		hepatocyte growth factor, also: SF (scatter factor); pro-proliferative and -angiogenic growth factor, that furthermore stimulates cell motility and supports tissue regeneration (→ liver; for review see [22a])
32	hnf4a	HNF4α		hepatocyte nuclear factor 4 α, also: TCF14 (transcription factor 14); constitutively active, nuclear transcription factor (homodimer), regulating liver-specific genes
33	hsp27_ps	HSP27$^{(pS)}$		heat shock protein 27; serine-phosphorylated oligomeric phosphoprotein
34	ikba	IκBα		NF-κB inhibitor α; rapidly degraded and resynthetised by NF-κB (for review see [133a])
35	ikba_degr			proteasomal IκBα degradation
36	ikba_diss			incomplete IκBα phosphorylation and subsequent inhibitor dissociation (no degradation!)
37	ikka	IKKα	1	IκB kinase α, also: IKK1; catalytic subunit of the IKK complex
38	ikka_a			activated (canonical) IKK complex; attributable to catalytic IKKα activity
39	ikkb	IKKβ	1	IκB kinase β, also: IKK2; catalytic subunit of the IKK complex; predominant kinase in regulating NF-κB activity (10 to 20-fold higher level of kinase activity for IκBα than IKKα[103a]); IKKβ preferentially phosphorylates the carboxyl terminus of NEMO (IKKγ)[143a]
40	ikkb_a			activated (canonical) IKK complex; primarily attributable to catalytic IKKβ activity

41	ikkaa	IKKα:IKKα	noncanonical homodimeric IKKα complex (for review see [133a])
42	ikkaa_nemo	IKKα:IKKα:NEMO	canonical heterotrimeric NEMO-containing IκB kinase (IKK) complexes; IKKα:IKKβ:NEMO seems to be the predominant form (for review see [133a, 155a])
43	ikkab_nemo	IKKα:IKKβ:NEMO	
44	ikkbb_nemo	IKKβ:IKKβ:NEMO	
45	il1a	IL-1α	interleukin 1α; pro-inflammatory cytokine (17 kDa, 159 amino acids, pI = 5.0); predominant form in mice
46	il1b	IL-1β	interleukin 1β; pro-inflammatory cytokine (17 kDa, 153 amino acids, pI = 7.0); predominant form in humans[55a]
47	il1b_new		re- (“newly”) synthesised IL-1β
48	il1r1	IL-1RI	transmembrane interleukin 1 receptor, type I, also: CD121a; 80 kDa, predominantly expressed on T cells and fibroblasts[58a, 159a]; IL-6 up-regulates IL-1RI mRNA levels in murine hepatocytes[81a]
49	il1r2	IL-1RII	transmembrane interleukin 1 receptor, type II, also: CD121b; decoy receptor (60 kDa)/ functions as a ligand sink (for review see [115a]); predominantly expressed on B cells, macrophages/monocytes, neutrophils, and HepG2 cells[58a, 63a, 118a]; short (29 amino acids) cytoplasmic region, no TIR domain → no signal transduction; may serve as a precursor for a shed, soluble receptor, acting similarly to the soluble type I IL-1R in antagonizing or otherwise regulating IL-1 action[160a]
50	il1ra	IL-1Ra	IL-1 receptor antagonist
51	il1rc	IL-1 receptor complex	heterotrimeric (IL-1:IL-1RI:IL-1RAcP) IL-1R signalling complex with cytoplasmic TIR domains
52	il6	IL-6	interleukin 6, also: BSF-2, IFNβ-2; pleiotropic cytokine
53	il8	IL-8	interleukin 8; chemokine

54	inos	iNOS		inducible nitric oxide synthase, also: HEP-NOS (hepatocyte NOS); oxido-reductase/nitric-oxide synthase; functions anti-oxidantly
55	irak1	IRAK1		IL-1R-associated kinase 1; serine/threonine specific, dimerized; IRAK1:IL-1R association detectable within 30 s after IL-1 treatment followed by subsequent phosphorylation of IRAK1[33a] (MyD88 does not bind the hyperphosphorylated/kinase active form of IRAK1[186a])
56	irak1c	IRAK1c		alternative splice variant of IRAK1; predominant form of IRAK1 expressed in the brain; inducible in monocytes and dendritic cells; kinase-dead, dominant-negative protein; cannot be phosphorylated by IRAK4 due to a lack of IRAK4 phosphorylation sites → no hyperphosphorylation/dissociation from the receptor complex[145a]
57	irak1_ub			ubiquitinated IRAK1
58	irak2	IRAK2		IL-1R-associated kinase 2; serine/threonine-specific, dimerised
59	irak4	IRAK4		IL-1R-associated kinase 4; serine/threonine-specific, dimerised; IRAK1/IRAK2 kinase[92a, 111a]
60	irakm	IRAK-M	0	kinase-inactive → inducible negative regulator, restricted to monocytes/ macrophages[188a]
61	irs1_ps	IRS1$^{(pS)}$		serine-phosphorylated insulin receptor substrat 1
62	jnk	JNK		c-Jun N-terminal kinase, also: stress-activated protein kinase (SAPK); serine/threonine specific; 3 established isoforms: JNK1/SAPKγ, JNK2/SAPKα (both ubiquitously expressed); JNK3/SAPKβ (largely restricted to brain, heart, and testis; for review see [46a])
63	ksrp	KSRP		KH-type splicing regulatory protein, also: FUBP2 (far upstream sequence binding protein 2); ARE binding protein and decay-promoting factor
64	lbp	LBP		LPS binding protein; hepatic acute-phase protein (APP)

65	mekk3	MEKK3		mitogen-activated protein kinase (MAPK)/ERK kinase kinase 3; MAP3K, serine/threonine-specific
66	mk2	MK2		MAP kinase-activated protein kinase 2, also: MAPKAP-K2; serine/threonine-specific
67	mek1	MEK1		mitogen-activated ERK kinase 1, also: MKK1 (mitogen-activated protein kinase (MAPK) kinase 1); MAP2K with dual substrate specificity
68	mek3	MEK3		mitogen-activated ERK kinase 3, also: MKK3 (mitogen-activated protein kinase kinase 3); MAP2K with dual substrate specificity
69	mek4	MEK4		mitogen-activated ERK kinase 4, also: MKK4 (mitogen-activated protein kinase kinase 4), SEK1, JNKK1; MAP2K with dual substrate specificity
70	mek6	MEK6		mitogen-activated ERK kinase 6, also: MKK6 (mitogen-activated protein kinase kinase 6); MAP2K with dual substrate specificity
71	mek7	MEK7		mitogen-activated ERK kinase 7, also: MKK7 (mitogen-activated protein kinase kinase 7), SEK2, JNKK2; MAP2K with dual substrate specificity
72	mkp1	MKP1		MAPK phosphatase 1, also: DUSP1 (dual-specificity phosphatase 1), CL100
73	msk1	MSK1		nuclear mitogen- and stress-activated protein kinase 1, also: p90S6K5 (ribosomal protein S6 kinase, 90 kDa, polypeptide 5); serine/threonine-specific nucleosomal kinase
74	mtorc2	mTORC2	1	mTOR complex 2: mTOR + mLST8 (mammalian LST8/G-protein β-subunit like protein) + PROTOR (protein observed with Rictor) + mSIN1 (stress-activated protein kinase interacting protein 1) + Rictor (rapamycin-insensitive companion of mTOR) + DEPTOR (DEP domains and specific inter-action with mTOR, negative regulator); insensitive to FKBP12-rapamycin
75	myd88	MyD88		myeloid differentiation primary response gene 88; member of the IL-1 receptor family and bipartite adaptor (N-terminal death domain (DD) and C-terminal Toll/IL-1 receptor (TIR) domain), linking the TIR domains of the IL-1RI complex with the death domains of IRAK; MyD88 forms homodimers through DD:DD and Toll:Toll interactions *in vivo*[28a]

76	nalp_infl	NALP-inflamma-some		Casp1 (caspase 1) + Casp5 (caspase 5) + PYCARD (PYD and CARD domain containing protein, also: ASC (apoptosis-associated speck-like protein containing a CARD)) + NALP1/3 (NACHT, LRR and PYD domains-containing protein 1/3); caspase-activating complex[116a]
77	nc_nfkb_pathway			noncanonical NF-κB pathway → p52-RelB activation via NIK and IKKα homodimers
78	nemo	NEMO	1	NF-κB essential modulator, also: IKKγ, IKKAP1, FIP-3; noncatalytic/regulatory subunit of the IKK complex; scaffold protein
79	nfkb	NF-κB		nuclear factor κB; pleiotropic, heterodimeric transcription factor (refering to p65(RelA):p50 heterodimers in this context)
80	nik	NIK		NF-κB-inducing kinase, also: MAP3K14; serine/threonine-specific
81	nuc_p38	p38 MAPK		nuclear p38-mitogen activated protein kinase (MAPK), also: p38α, SAPK2 (stress-activated protein kinase 2); serine/threonine-specific
82	p105	p105		p50 precursor and IκB with C-terminal ankyrin repeats (for review see [129a])
83	p105_degr			complete and/or limited proteasomal degradation of p105
84	p50	p50		also: NF-κB1; Rel protein, subunit of the dimeric NF-κB transcription complex; no C-terminal transactivation domain (TAD); N-terminal Rel homology domain (RHD) mediates its dimerisation, nuclear translocation, DNA binding and IκB interaction (for review see [129a, 133a])
85	p65	p65		also: RelA; Rel protein, subunit of the dimeric NF-κB transcription complex; C-terminal transactivation domain (TAD); N-terminal Rel homology domain (RHD) mediates dimeri-zation, nuclear translocation, DNA binding, and IκB interaction (for review see [129a, 133a]
86	pellino	Pellino		Pelle (Drosophila orthologue of IRAK1)-associated protein; 3 established mammalian homologues: Pellino 1, 2, 3; RING-like-domain-containing protein with intrinsic ubiquitin E3 ligase activity (for review see [123a])

87	pdk1	PDK1	1	phosphoinositide-dependent kinase 1; serine/threonine-specific
88	pi3k	PI3K		phosphatidylinositol 3'-kinase; p85 adaptor subunit associates with phospotyrosines via SH2 domain, whereas p110 encompasses the catalytic activity
89	pip3	PIP_3		phosphatidylinositol(3,4,5)-triphosphate
90	pro_hgf	pro-HGF		matrix-associated, inactive HGF precursor
91	pro_il1b	pro-IL-1β		also: p35; inactive cytoplasmic IL-1β precursor
92	pten	PTEN	0	phosphatase and tensin homolog, also: MMAC1 (mutated in multiple advanced cancers 1); lipid tyrosine-phosphatase and tumor suppressor
93	ros	ROS		reactive oxygen species
94	saa	SAA		serum amyloid A; hepatic acute-phase protein (APP)
95	sap1	SAP-1		SRF (serum response factor) accessory protein 1, also: Elk-4 (ETS-domain protein 4); ternary complex transcription factor (TCF); ETS domain mediates DNA binding
96	sil1r12	sIL-1RI/II	0	soluble IL-1RI/II (IL-1R, type I/II); shedded soluble IL-1RII binds IL-1α/β and IL-1RAcP, preventing formation of an active IL-1R signalling complex
97	sil1r_ap	sIL-1RAcP	0	soluble IL-1R accessory protein; truncated intracellular domain/alternative splicing product → antagonistic co-receptor; IL-1RAcP/ sIL-1RAcP ratio of 2:1 in untreated human HepG2 cells changes upon treatment with inflammatory mediators[87a]
98	smyd88	sMyD88	0	short MyD88 protein (no intermediary domain (ID), amino acids 110 - 157); binds IL-1R and IRAK1 without inducing IRAK1 phosphorylation, acting as a dominant-negative inhibitor of IL-1- and LPS-, but not TNF-induced NF-κB activation[85a]
99	socs1	SOCS1	0	suppressor of cytokine signalling 1/3, also: CIS1/3 (cytokine-inducible SH2 protein 1/3), SSI-1/3 (STAT-induced STAT inhibitor 1/3)
100	socs3	SOCS3	0	

101	src	Src	1	yet unknown Src kinase
102	tak1_tab	TAK1:TAB		preassociated TAK1:TAB1:TAB2/3 complex [**TAK1**: TGFβ-activated kinase 1, also: MAP3K7, MEKK7; MAP3K, serine/threonine-specific; **TAB1**: TGFβ-activated kinase (TAK)-binding protein 1; inactive pseudophosphatase and specific activator of TAK1, interacting with its N-terminal kinase domain; TAB1 becomes phosphorylated on the membrane upon IL-1 treatment (therefore IRAK1 acts as an adaptor and not as a kinase[89a, 144a]); **TAB2/3**: TGFβ-activated kinase (TAK)-binding protein 2/3; both were shown to act redundantly in IL-1- and TNFα-treated HEK293 cells[80a]; IL-1 stimulation mediates their release from the membrane and cytosolic translocation, where they facilitate TRAF6:TAK1 interactions[171a]]
103	tdum_a20_traf6_ub			timescale dummy species
104	tdum_cyt_p38_tak1_tab			
105	tdum_hsp27_ps_traf6_ub			
106	tdum_il1r2_il1rc			
107	tdum_il1ra_il1r12			
108	tdum_irak1c_irak12			
109	tdum_mkp1_p38_jnk_erk12			
110	tdum_tpl2_degr_tpl2			
111	tollip	Tollip		Toll-interacting protein
112	tpl2	TPL2		proto-oncogene serine/threonine protein kinase encoded by the tumor progression locus 2 (*tpl2*), also: cancer osaka thyroid (COT), MAP3K8; MEK kinase; two established isoforms: M1-TPL2, M30-TPL2[8a]
113	tpl2_degr			TPL2 proteolysis/degradation
114	traf6	TRAF6		TNF receptor-associated factor 6; K63-specific RING finger E3 ubiquitin ligase[34a, 53a]; TRAF6 seems to act as a pure scaffolder/adaptor related to the MEKK3-dependent/TAK1-independent ("Zinc") NF-κB activation pathway[196a, 200a]

115	traf6_ub	TRAF6^{ub}		ubiquitinated TNF receptor-associated factor 6; K63-specific RING finger E3 ubiquitin ligase[34a, 53a]
116	trika1	TRIKA1	1	TRAF6-regulated IKK activator 1; dimeric E2 enzyme, subunits: Ubc13 (Ub-conjugating E2 enzyme), Uev1A (Ub-conjugating E2 enzyme variant (UEV), no catalytic cysteine residue)[53a]
117	ttp	TTP		tristetraprolin, also: zinc finger protein 36 (ZFP36), C3H type, homolog (mouse); ARE (adenosine/uridine-rich elements)-binding and mRNA-destabilising tandem zinc finger protein; represses translation when dephosphorylated
118	upa	uPA		urokinase-type plasminogen activator; secreted serine protease; catalyses the proteolytic cleavage of plasminogen to plasmin, promoting extracellular matrix remodelling during the early stages of liver regeneration (→ liver acute-phase response) and functions as an essential pro-HGF convertase[127a]

Tab. S3.2. IL-1 signalling interactions.

№	Interaction	τ	c	Documentation
Ligand binding/assembly of the IL-1 receptor complex				
1	→ il1a	1	1.0	model inputs
2	→ il1b	1	1.0	
3	sil1r12 = il1a	1	0.8	soluble IL-1RI binds IL-1Ra with a greater affinity than IL-1α or -β, predominantly withdrawing the receptor antagonist (as shown for synovial fluid samples[9a]); relevance for hepatic IL-1 signalling has to be checked! soluble IL-1RII more avidly binds IL-1β than IL-1α or IL-1Ra, neutralising the receptor agonist (as shown for synovial fluid samples[9a]);
4	sil1r12 = il1b	1	0.8	
5	sil1r12 = il1ra	1	0.8	
6	sil1r_ap » sil1r12	1	0.8	soluble IL-1RAcP interacts with sIL-1RII, increasing its binding affinity for IL-1α and -β without changing its low IL-1Ra binding affinity, therefore supporting the neutralization of IL-1α/β activities but also reducing the amount of antagonizing soluble IL-1RII → no influence on IL-1Ra as a second antagonist (as shown for IL-1-treated A375 and COS-7 cells[165a]); sIL-1RI:sIL-1RAcP association would decrease the serum concentration of IL-1Ra by trapping the receptor antagonist, but: interaction not verified yet!
7	il1ra = tdum_il1ra_il1r12	2	0.8	timescale dummy activation
8a	il1a = dum_il1_r1	1	0.8	dummy activation
8b	il1b = dum_il1_r1	1	0.8	
8	*!il1ra* · dum_il1_r1 = il1r1	1	0.8	IL-1α and -β identically bind IL-1R, type I with similiar affinities[57a, 95a, 104a]; IL-1Ra competes with IL-1α/β for receptor binding, eliciting no biological response (as shown for 70Z/3 cells (murine pre-B cell line)[71a]) → occupancy of the receptor by IL-1Ra prevents recruitment of the IL-1RAcP co-receptor and heterodimer formation (for review see [56a])
9a	il1a = dum_il1_r2	1	0.8	dummy activation
9b	il1b = dum_il1_r2	1	0.8	

9	*!il1ra* · dum_il1_r2 = il1r2	1	0.8	IL-1α and -β bind IL-1R, type II[57a] (as shown for CB23 cells (B lymphoblastoid line)[118a]); IL-1Ra competes with IL-1α/β for receptor binding, eliciting no biological response[118a] (as shown for 70Z/3 cells (murine pre-B cell line)[71a]) → occupancy of the receptor by IL-1Ra prevents recruitment of the IL-1RAcP co-receptor and heterodimer formation (for review see [56a]); HepG2 cells were shown to predominantly express IL-1RII[63a]
10a	il1r2 = tdum_il1r2_il1rc	2	0.8	timescale dummy activation
10	il1r1 · *!il1r2* · !sil1r12 · !sil1r_ap = il1rc	1	0.8	IL-1 binding to IL-1R leads to interaction of transmembrane IL-1R and IL-1RAcP (→ transmembrane IL-1R accessory protein; IL-1 co-receptor[64a]) due to conformational changes possibly increasing their mutual affinity (IL-1RAcP itself does not bind IL-1)[64a, 87a, 187a]; transmembrane IL-1RII and soluble IL-1RI/II recruit IL-1RAcP into an ineffectual trimeric complex upon IL-1 binding, sequestrating it from signal transducing IL-1RI co-receptor competition[106a] (for review see [56a]); but: relevance for hepatic IL-1 signalling has to be checked!; soluble IL-1RAcP antagonisticly associates with IL-1RI and inhibits IL-1 signal transduction in HepG2 cells by rendering the IL-1RI:IL-1β complex non-functional (IL-1RAcP/sIL-1RAcP ratio of 2:1 in untreated human HepG2 cells changes upon treatment with inflammatory mediators)[87a]
11	il1rc = myd88	1	0.8	the sequence-homologous C-terminal region of MyD88 (TIR (Toll-IL-1R) homology domain) transiently binds to the cytoplasmic IL-1RAcP-TIR domain (homophilic interaction, no direct IL-1RI:MyD88 association upon IL-1 stimulation; as shown by co-transfection studies in HEK293T cells[125a]); MyD88:IL-1R complex association (independent of IRAK:receptor interaction) detectable within 30 s (up to 10 min) upon IL-1 treatment (as shown for HEK293[186a] and EL-4.6.10 cells[29a])

12	il1rc = tollip	1	0.8	the activated IL-1R complex rapidly recruits pre-existing Tollip:IRAK complexes (detectable within 2 min after IL-1β stimulation, subsequent IRAK:Tollip dissociation within 2 – 5 min; as shown for EL-4.6.10 (murine lymphoma) cells[29a])
IRAK and TRAF6 recruitment				
13	myd88 · !smyd88 = irak4	1	0.6	MyD88 interacts with IRAK4 ID (intermediary domain)- and DD (death domain)-dependently[30a, 111a], thus both proteins remain associated with the receptor complex for at least 1 h (as shown for IL-1-stimulated EL4 6.1 murine thymoma cells[25a]); IRAK4 might become hyperphosphorylated on serines and threonines/catalytically active due to autophosphorylation (as shown for IL-1-treated EL4 6.1 cells[25a]) upon MyD88 interaction and stays MyD88-associated[30a]; sMyD88:IRAK4 interaction (impaired IRAK4 recruitment to the IL-1RI due to the loss of the intermediary domain (ID)) may prevent the initial IRAK1 phosphorylation/ activation[85a], but: relevance for hepatic IL-1 signalling has to be checked!
14	myd88 · tollip = irak1c	1	0.8	negative regulatory IRAK1c associates with IL-1RI, MyD88, and Tollip, suggesting its recruitment to the activated receptor complex (as shown for IL-1-treated G292 (human osteosarcoma) cells[145a])
15	irak1c = tdum_irak1c_irak12	2	0.8	timescale dummy activation
16	irak4 · myd88 · tollip · *!irak1c* · !irakm = irak1	1	0.8	IL-1 was shown to induce IRAK1 activation in murine hepatocytes[81a]; Tollip preassociates with dimerised IRAK1 in the cytosol, blocking its (spontaneous) activation and recruiting it to the IL-1R complex MyD88-independently[145a] (as shown by co-expression studies in HEK293T cells[29a]); IRAK1 hyperphosphorylation (especially (p)T66) may abolish the IRAK1:Tollip interaction leading to IRAK1 release (as supposed by co-transfection studies and for IL-1-treated COS-1 cells[150a]); MyD88 merely binds kinase-inactive IRAK1, also releasing it upon hyperphosphorylation (as shown for IL-1-treated HEK293 cells[186a]); IRAK4 transiently links to IRAK1 and TRAF6 within 2 min (up to 30 min) upon IL-1

				treatment (as shown for HEK293 cells[111a]); close proximity of IRAK4 and IRAK1 (due to their MyD88 (homo-dimerised[28a]) association) causes IRAK4-triggered phosphorylation of critical residue(s) within the kinase activation loop of IRAK1 (as shown *in vitro*[30a, 111a]); sequential IRAK1 (dimerised) phosphorylation leads to its activation and release (as shown *in vitro* and supposed for IL-1-treated HEK293 cells[100a]): initial IRAK1-T209 phosphorylation by IRAK4 causes a conformational change of the IRAK1-kinase domain (KD) and weak kinase activity permitting T387 phosphorylation within the activation loop → resulting full kinase activity catalyses hyperphosphorylation of the Pro-ST region/UD domain, which impairs the death domain interactions, finally leading to IRAK1 dissociation from the IL-1R complex and possibly promoting the IRAK1 K63-linked polyubiquitination (K134, K180; as shown for IL-1-treated MEFs[44a]) as a prerequisite for TAK1 recruitment[196a]; the nature of IRAK1 modification in response to IL-1 strictly regulates the two co-existing (TAK1-dependent ”RING” pathway *vs.* MEKK3-dependent ”Zinc” pathway) signalling pathways leading to NF-κB activation[196a, 200a]; IRAK-M inhibits the dissociation of IRAK1 and IRAK4 from MyD88 and formation of activated IRAK:TRAF6 complexes (as shown for IL-1-treated HEK293T cells[99a]); kinase-dead IRAK1c dimerizes with IRAK1, impairing its autophosphorylation and/or receptor release upon ligand treatment → shutdown of signalling through selective depletion of functional IRAK1 (as shown for IL-1-treated G292 cells[145a]; alternatively: non-effective IRAK1c homodimers may compete with catalytically active IRAK1 dimers for receptor interaction)
17	irak4 · myd88 · tollip · *!irak1c* = irak2	1	0.4	assuming that IRAK1 and -2 function redundantly, Tollip was shown to preassociate with dimerized IRAK in the cytosol, blocking its (spontaneous) activation and recruiting it to the IL-1R complex MyD88-independently (IRAK1 hyperphosphorylation (esspecially (p)T66) may abolish the IRAK1:Tollip interaction,

				causing IRAK1 release[29a, 145a, 150a]); MyD88 links IRAK2 via N-terminal DDs (death domains; as shown by co-expression studies in HEK293T cells[125a]); later but sustained (up to 8 h → IRAK1: 1 h) IRAK4:IRAK2 interaction upon TLR stimulation supposes that IRAK2 seems essential for late-phase TLR response; IRAK4 phosphorylates IRAK2, thereby inducing its autophosphorylation activity (as shown for MALP-2-treated murine peritoneal macrophages[92a]); kinase-dead IRAK1c dimerizes with IRAK2, impairing its autophosphorylation and/or receptor release upon ligand treatment → shutdown of signalling through selective depletion of functional IRAK2 (as shown by overexpression studies in HEK293 cells[145a]; alternatively: noneffective IRAK1c homodimers may compete with catalytically active IRAK2 dimers for receptor interaction); but: the general relevance of IRAK2 for hepatic IL-1 signalling has to be checked!
18a	a20 = tdum_a20_traf6_ub	2	0.8	timescale dummy activation
18b	hsp27_ps = tdum_hsp27_ps_traf6_ub	2	0.8	
18c	irak1 = dum_irak1_or_2_traf6_ub	1	0.8	dummy activation
18d	irak2 = dum_irak1_or_2_traf6_ub	1	0.4	
18	dum_irak1_or_2_traf6_ub · trika1· *!hsp27_ps* · !socs3* · *!a20* = traf6_ub	1	0.8	IL-1R complex-associated IRAK1 (or IRAK2, as shown by co-expression studies in HEK293T cells[125a]) interacts with TRAF6 in response to IL-1 (as shown for HEK293 cells[34a, 89a]), ensuring the TRAF6:IL-1R complex interaction; IRAK4 transiently associates with IRAK1 and TRAF6[89a] within 2 min (up to 30 min) after IL-1 treatment (as shown for HEK293 cells[111a]); subsequent IRAK1 hyperphosphorylation may cause the dissociation of the IRAK1:TRAF6- from the IL-1R complex[145a] followed by TRAF6 oligomerisation[13a], which might stabilise or enhance the affinity of N-terminal TRAF domains towards effectors[90a]; TRIKA1 (Ubc13:Uev1A) seems to mediate the synthesis of nondegradative K63-linked

* Species affecting IL-1 signalling while being regulated by IL-6 (→ crosstalk effects) are highlighted in *grey*.

				polyUb chains[53a] on TRAF6 (as shown for IL-1-treated HeLa cells[183a]) as a basis for the "RING" pathway[196a]; IL-1-induced, K63-linked TRAF6 autoubiquitination (K124) was shown as well[105a], but: autoubiquitination and the TRAF6 RING finger domain appear dispensable for recruitment of the TAB1:TAB2:TAK1 complex (as shown for IL-1-treated MEFs[182a]); HSP27 associates with TRAF6 in response to IL-1, likely supporting/enhancing its polyubiquitination and facilitating TAK1-, p38-, JNK-, and IKK activation (as shown for HEK293[194a] and HeLa cells[5a]; HSP27 phosphorylation at S78 and S82 by activated MK2 promotes TRAF6:HSP27 dissociation, which in turn depresses IKK activation → negative feedback loop (as shown for IL-1-treated HeLa cells[194a]); A20 inhibits IL-1-induced NF-κB activation quite likely through interaction with TRAF6[73a, 179a], removing K63-linked polyUb chains via its N-terminal OUT (ovarian tumour) domain followed by a K48-linked substrate (possibly TRAF6 or IRAK1) polyubiquitination through its ubiquitin ligase domain within the ZnF region, leading to proteasomal degradation (as shown within the context of TNFR1/RIP signalling[185a] ⇒ **link to IL-6**: SOCS3 inhibits TRAF6 ubiquitination, preventing TRAF6:TAK1 interaction and TAK1 activation (as shown for IL-1-treated INS-1 cells (insulinoma β-cells)[60a])
19	irak1 * irak4 = pellino	1	0.4	IRAK1 and/or IRAK4 catalyse the phosphorylation of Pellino isoforms *in vitro*, activating/enhancing their E3 ligase function (as shown by co-transfection studies in HEK293 cells[135a], for review see [123a]); but: relevance for hepatic IL-1 signalling has to be checked!
20	pellino · trika1 = irak1_ub	1	0.8	activated Pellino isoforms mediate the IL-1-induced, TRIKA1-supported formation of K63-pUb IRAK1 (detectable within 5 -10 min upon IL-1 stimulation of HEK293 cells[135a], for review see [123a])

21	irak1 = traf6	1	0.8	IRAK1 also interacts with TRAF6 independently of hyperphosphorylation within its Pro-ST/UD domain or IRAK1-K134 polyubiquitination, but therefore fails to complex TAK1 → MEKK3-dependent/ TAK1-independent ("Zinc") NF-κB activation pathway[196a] (as shown for IL-1-treated HEK293 cells[200a])
MAPK signalling				
22a	cyt_p38 = tdum_cyt_p38_tab_tak1	2	0.8	timescale dummy activation
22	traf6_ub · trika1 · mekk3 · *!cyt_p38* = tak1_tab	1	0.6	TAB1, TAB2/3 (as regulatory subunits), and TAK1 (as the catalytic subunit, constitutively TAB1-associated[152a]) preassociate on the membrane before stimulation and remain assembled in response to IL-1, whereas the major pool of TAK1:TAB1 complexes resides in the cytosol (as shown for IL-1-treated HEK293[89a] and human epithelial KB cells[39a]); IRAK1:TRAF6 leaves the IL-1R complex (*complex I*) in response to IL-1 and interacts with preassociated TAK1:TAB1:TAB2/3 (= TRIKA2[183a]) on the membrane (*complex II*), leading to phosphorylation of TAB2/3 (dependent on IRAK1 as an adaptor but independent of its kinase activity; as shown in IL-1-treated HEK293 cells[89a, 144a]) and TAK1 (prerequisite for TAK1 activation!); [IL-1 transiently induces the formation of TAB2:IRAK1:TRAF6 complexes within 2 – 5 min after stimulation (persisting for 20 min); therefore IRAK1 acts as a scaffolding protein, regulating the redistribution of TAB2 (or TAB3; both were shown to act redundantly in IL-1- and TNFα-treated HEK293 cells[80a] or within co-expression studies in HEK293 cells[20a]) and enabling the association of TRAF6 and TAB2 (no direct IRAK1:TAB2 interaction; as shown for IL-1-treated HEK293 cells[172a]); TAB2/3 possibly bind to IL-1-induced K63-linked polyUb chains of TRAF6 (as shown for HeLa cells[183a]) through a highly conserved, C-terminal zinc finger (ZnF) domain, leading to their own polyubiquitination by TRAF6[90a] (as shown in IL-1-treated HEK293 cells[80a])]; finally TRAF6:TAK1:TAB1:TAB2/3 dissociates from IRAK1 and translocates to the cytosol

				(*complex III*), where TAK1 becomes catalytically active (as shown for IL-1-treated HEK293 cells[89a]); IL-1-induced IRAK1 degradation (→ hyperphosphorylation and K48-linked polyubiquitination of IRAK1 in response to IL-1 may target it to proteasomal degradation[200a] (as shown for IL-1-treated MRC-5 cells[197a])) might be necessary for the release of the TAK1:TRAF6:TAB1:TAB2/3 complex from membrane-associated, modified IRAK1, causing cytosolic TAK1 activity[200a]; TAB1 promotes the TAK1 activation/ autophosphorylation at T178, T184, T187, and S192 within the kinase activation loop upon IL-1 teatment[201a]; IL-1 furthermore induces the TRAF6/TRIKA1-mediated K63-linked poly-ubiquitination of TAK1 at K209 (essential for TRAF6:TAK1 interaction and complex formation with MEKK3 within 5 min (up to 30 min) after IL-1 stimulation of MEFs[196a]); MEKK3 seems to act as an upstream activator of TAK1, therefore phosphorylating it within the activation loop (see above) upon conformational changes caused by TAK1 K209-polyubiquitination (as shown for IL-1-treated MEFs and HEK293T cells[196a]); but: undetectable interaction between endogenous TAK1 and MEKK3 upon IL-1 treatment suggests two distinct complexes (IRAK1:TRAF6:TAK1 *vs.* IRAK1:TRAF6:MEKK3)[200a]; p38α was shown to interact with and phosphorylate TAB1 at S423, T431, and S438 within 20 min after IL-1 treatment, down-regulating or suppressing TAK1 activity as a feedback control (as shown for human epithelial KB cells[38a]) and might furthermore phosphorylate TAB2 at S582 and TAB3 at S60/T404 (depending on previous p38α recruitment by TAB1), also supporting the down-regulation of TAK1 (as shown for IL-1-treated MEFs[39a, 119a])
23	tak1 = mek3	1	0.4	activated TAK1 functions as a direct activator of MEK3[121a], but: relevance for hepatic IL-1 signalling has to be checked!
24	tak1 = mek4	1	0.4	TAK1 induces MEK4 phosphorylation/ activation (as shown by overexpression studies in COS-7 cells[158a])

25	tak1 = mek6	1	0.4	ubiquitinated and activated TAK1 phosphorylates MEK6 at S207 and T211 within the activation loop *in vitro*[121a, 183a]; but: relevance for hepatic IL-1 signalling has to be checked!
26	tak1 = mek7	1	0.6	IL-1-induced MEK7 activity (as shown for IL-1-treated MEFs[178a]) might result from TAK1-mediatd MEK7 phosphorylation (as shown by overexpression studies in HEK293 cells[126a])
27	traf6_ub = mekk3	1	0.8	TRAF6 associates with MEKK3 (within a complex with polyubiquitinated TAK1), binding it via its ZnF- and TRAF-C-domain and facilitating its oligomerization (as shown for IL-1-treated MEFs[196a]); MEKK3 activation (S526 trans-/ autophosphorylation owing to dimerisation[37a]; dimerisation motif within its catalytic domain; as shown for LPS-treated MEFs[202a]) involves the TRAF6-RING- and ZnF-domains (as shown by overexpression studies in HEK293T cells[196a]) → MEKK3- and TAK1-dependent (”RING”) NF-κB activation pathway (as shown for IL-1-treated MEFs[196a]); but: relevance for hepatic IL-1 signalling has to be checked!
28	traf6 = mekk3	1	0.8	the IRAK1:TRAF6 complex recruits MEKK3 independently of hyperphosphorylation within the IRAK1-Pro-ST/UD domain or IRAK1 K134-polyubiquitination as well (as shown for IL-1-treated HEK293 cells and MEFs[200a]), probably via the TRAF6-ZnF domain → MEKK3-dependent/TAK1-independent (”Zinc”) NF-κB activation pathway (as shown for IL-1-treated MEFs[196a]); but: relevance for hepatic IL-1 signalling has to be checked!
29	mekk3 = mek3	1	0.4	MEKK3 directly phosphorylates and/or promotes the MEK3 autophosphorylation at S189 and T193, leading to MEK3 activity (as shown by overexpression studies in COS-7 cells[47a])
30	mekk3 = mek4	1	0.4	MEKK3 directly phosphorylates and/or promotes the MEK4 autophosphorylation at S221 and T225, leading to MEK4 activity (as shown by overexpression studies in COS-7 cells[47a]); MEK7-, but no detectable MEK4-activation in MEFs upon IL-1 stimulation[178a]!

31	mekk3 = mek6	1	0.4	MEKK3 directly phosphorylates/activates MEK6/7 or at least enhances their autophosphorylation (as shown by overexpression studies in COS-7 cells[48a]); but: relevance for hepatic IL-1 signalling has to be checked!
32	mekk3 = mek7	1	0.4	
33	mkp1 = tdum_mkp1_p38_jnk_erk12	2	0.4	timescale dummy activation
34a	mek3 = dum_mek3_or_4_or_6_nuc_p38	1	0.4	dummy activation
34b	mek4 = dum_mek3_or_4_or_6_nuc_p38	1	0.4	
34c	mek6 = dum_mek3_or_4_or_6_nuc_p38	1	0.4	
34	dum_mek3_or_4_or_6_nuc_p38 · *!mkp1* = nuc_p38	1	0.4	although not proved for hepatic IL-1 signalling yet, MEK4 generally acts as a MAP2K for JNK and p38, preferentially phosphorylating nuclear p38 at T180 and/or Y182 within its tripeptide dual phosphorylation motif, leading to p38 activation and nuclear export/cytosolic accumulation (IL-1-induced p38-T180/Y182 phosphorylation detectable within 5 min as shown for HepG2 cells[78a]); MEK3 and MEK6 are regarded as sheer p38 activators[18a, 54a]; MKP1 selectively interacts with and dephosphorylates (inactivates) ERK2, JNK1, and p38α within their kinase actvation loops[164a], gaining its catalytic activity through association with the C-terminal domains of the above-mentioned kinases (as shown for p38[79a]); but: individual relevance of MEK3/4 or -6 and MKP1 for hepatic IL-1 signalling has to be checked!
35	nuc_p38 = mk2	1	0.8	p38 interacts with and activates nuclear MK2 (as shown for IL-1-treated primary monocytes and U-937 cells[2a]) possibly by phosphorylating T222, S272, and T334 in response to IL-1, causing its nuclear export[18a, 189a]
36	mk2 = hsp27_ps	1	0.8	IL-1 induces HSP27 phosphorylation at S78 and S82 by activated MK2, promoting the TRAF6:HSP27 dissociation, which in turn depresses IKK activation → negative feedback loop (as shown in IL-1-treated HeLa cells[194a])

37	mk2 · nuc_p38 = cyt_p38	1	0.4	stimulus-induced activation of nuclear p38 leads to MK2 phosphorylation/activation by p38, probably causing conformational changes, masking the nuclear localisation signal (NLS) and eventually exposing a nuclear export signal (NES) of MK2, which entails the cytoplasmic relocalisation/ nuclear export of the p38:MK2 complex (as shown for sodium arsenite-treated HEK293T cells[18a])
38	!cyt_p38 = ksrp	1	0.8	p38-catalysed KSRP phosphorylation (presumeably T692) reduces its affinity to AREs and counteracts its destabilising effect on mRNAs (as shown or IL-1-treated HeLa cells[191a] (and references cited therein)), but: relevance for hepatic IL-1 signalling has to be checked!
39	!mk2 = ttp	1	0.4	MK2-catalysed TTP phosphorylation (S52, S178) reduces its affinity to AREs and counteracts its destabilising effect on mRNAs (as shown for anisomycin-treated NIH 3T3 cells[41a] and by overexpression studies in HEK293 cells[74a]), but: relevance for hepatic IL-1 signalling has to be checked!
40a	mek4 = dum_mek4_or_7_jnk	2	0.4	dummy activation
40b	mek7 = dum_mek4_or_7_jnk	1	0.8	
40	dum_mek4_or_7_jnk · *!mkp1* = jnk	1	0.6	IL-1 induces JNK phosphorylation (T183/ Y185)/activation within 5 min (up to 45 min) in HepB3[6a] or HepG2 cells[78a]; MEK4 binds JNK via its conserved, N-terminal MAPK docking site (”D-site”, residues 38 - 48) and mediates its activation (as shown *in vitro*[54a, 75a]); MEK7 was shown (by co-transfection assays in COS cells) to act as a specific and more potent activator of JNK[177a]; MEK4 and MEK7 preferentially phosphorylate JNK on Y182 (MEK4) and T180 (MEK7) within its tripeptide dual phosphorylation motif, leading to optimal JNK activity and nuclear translocation, but: T180-phosphorylation by MEK7 alone seems sufficient for partial JNK activation in response to IL-1 (as shown in IL-1-treated MEFs[178a]); *hence, the impact of MEK4 on JNK activity will initially be regarded as secondary!*; MKP1 selectively interacts with and dephosphorylates/ inactivates ERK2, JNK1, and p38α within

				their kinase actvation loops (as shown for serum- and anisomycin-treated COS-1 cells[164a]), but: individual relevance for hepatic IL-1 signalling has to be checked!
41a	tpl2_degr = tdum_tpl2_degr_tpl2	2	0.8	timescale dummy activation
41	src · abin2 · !p105 · *!tpl2_degr* = tpl2	1	0.6	the majority of the cellular pool of TPL2 is complexed with p105 (as shown in HeLa cells[17a]), whereby p105 inhibits the MEK kinase activity of TLP2 through p105-DD:TLP2-KD interaction (a further association of the TLP2 C-terminus and a region N-terminal to the p105 ankyrin repeats ensures metabolic stability of TPL2 in the absence of stimuli, maintaining its steady-state expression[15a, 184a]); an additional TPL2 phosphorylation at T290 (leading to S62 autophosphorylation) within the activation loop by a yet unidentified kinase (distinct from IKKβ, potentially a Src kinase) seems essential for catalytic TLP2 activity in response to IL-1 (as shown for IL-1-treated HEK293[167a] and HeLa cells[149a]); ABIN2 specifically forms a ternary complex with TPL2 and p105, contributing to metabolic TPL2 stability; although TLP2 activation correlates with its release from ABIN2, the latter does not seem to function as an inhibitor of TPL2 MEK kinase activity (as shown for LPS-treated BMDMs (bone marrow-derived macrophages)[108a, 137a])
42	tpl2 = tpl2_degr	1	0.8	the pool of free, catalytically active TPL2 decreases 30 – 45 min after IL-1 stimulation due to proteolysis, outlining a negative feedback mechanism (as shown for IL-1-treated HeLa[149a] and LPS-treated RAW264.7 cells[16a])
43	tpl2 = mek1	1	0.6	TPL2 functions as a direct activator on MEK1 by phosphorylating MEK1-S217 and/or S221 (as shown *in vitro*[153a] and for LPS-treated RAW264.7 cells[16a]) and is the only currently known MAP3K that triggers ERK1/2 activation in response to IL-1[149a]
44	mek1 · *!mkp1* = erk12	1	0.6	MEK1 acts as a direct activator on ERK1/2 (for review see [148a]; maximal, IL-1-induced ERK1/2 phosphorylation (ERK1: T202/Y204)/activation detectable within 15 - 30 min in HeLa cells[149a]); ERK1/2 activation might lead to their subsequent

				nuclear translocation (as shown for serum-stimulated HeLa cells[36a]); MKP1 selectively interacts with and inactivates ERK2, JNK1, and p38α by dephosphorylation within their kinase activation loops (as shown by co-expression studies in COS-1 cells[164a])
PI3K/Akt signalling				
45	il1rc * myd88 = pi3k	1	0.8	IL-1 transiently stimulates PI3K activity within 0.5 – 3 min (decline after 3 min; as shown for HepG2 cells[147a, 162a]) and induces IL-1RI(p)Y496:p85[147a] and/or IL-1RAcP:p85 interaction[162a]; owing to the detectable association of Rac1 (PI3K regulator/Rho family GTPase) and MyD88 (interacting with the IL-1R complex; as shown for IL-1-treated EL4.NOB-1 cells[86a]), the latter might contribute to PI3K activation
46	pi3k · !pten = pip3	1	1.0	as established, PI3K catalyses the phosphorylation of PIP_2 (phosphatidyl-inositol(4,5)-bisphosphate) to generate PIP_3; for review see [180a]; direct correlation between PI3K activity and PIP_3 concentration demonstrated for IL-1-treated HepG2 cells[162a]); endogenous PTEN reverses the reaction[114a] and was shown to inhibit IL-1-induced NF-κB-dependent transcriptional activity due to its lipid phospatase function (as shown for MEFs[163a])
47	pip3 · pdk1 · mtorc2 = akt	1	0.6	IL-1 stimulates Akt phosphorylation (S473[175a]) within 15 min PI3K-dependently (as shown for primary rat hepatocytes[175a] and MEFs[163a]) possibly involving mTORC2 (as shown for IL-6-treated HepG2 cells[40a]); PDK1, (when bound to PIP_3 at the plasma membrane as Akt) might contribute to the initial T308 phosphorylation within the activation loop of Akt (as shown for IL-6-treated HepG2 cells[40a]); but: individual relevances of PDK1 and mTORC2 for hepatic IL-1 signalling have to be checked!
48	!akt = gsk3b	1	1.0	IL-1 induces inhibitory S21 phosphorylation of GSK3α (→ established downstream target of PI3K/Akt signalling) within 15 min in a PI3K-dependent manner (as shown for HepG2 cells[162a]); but: relevance for yet demonstrated GSK3β-mediated co-regulation of transcriptional NF-κB activity

				(as shown for TNFα-treated MEFs[168a]) or a possible IL-1-stimulated GSK3β-S9 phosphorylation has to be checked!
NF-κB activation				
49	ikkb · nemo = ikkbb_nemo	1	0.4	NEMO (itself forming multimers) interacts with the C-terminal SCD (serine cluster domain) of IKKα and -β via its N-terminal half, leading to oligomerisation of the catalytic subunits (homo- *vs.* heterodimerization; for review see [133a]), which in turn may trigger the autophosphorylation of their T loops *in trans*, resulting in full kinase activity[142a] (overexpression of IKKα/β or direct phosphorylation bypasses the NEMO-induced oligomerisation) → association seems critical for the assembly of high molecular weight canonical IKK complexes, facilitating the recruitment of IκB proteins and the onset of IKK kinase activity[156a] (for review see [155a]); although IL-1 has been shown to increase IKKβ activity[143a] and to alternatively signal via NEMO:IKKα:IKKα complexes[196a, 200a], the individual relevance for hepatic IL-1 signalling has to be checked!
50	ikkb · ikka · nemo = ikkab_nemo	1	0.8	
51	ikka · nemo = ikkaa_nemo	1	0.8	
52	ikka = ikkaa	1	0.8	IKKα was also shown to homodimerise, generating noncanonical IKK complexes in a NEMO-independent manner but requiring NIK for catalytic activity (for review see [155a]); relevance confirmed for IL-1-treated HEK293 cells[112a]
53	abin2 = a20	1	0.4	ABIN2 (constitutively expressed in different cell types[179a]) may directly interact with the C-terminal ZnF domain of A20 via its AHD1 domain and binds polyubiquitinated NEMO possibly via its UBAN and 4th CC domain (as shown for TNF-treated HEK293T cells[181a]), which inhibits NF-κB activation (as shown for IL-1-treated HEK293T cells[179a]) likely through competition with upstream effectors for NEMO interaction (as shown by co-expression studies in HEK293T cells[113a]) and/or linking A20 to NEMO, leading to subsequent proteasomal NEMO degradation[185a]
54	!a20 = nemo	2	0.8	
55a	tak1_tab · irak1_ub = dum_tak1_tab_or_mekk3_ikkb_a	1	0.8	dummy activation

55b	mekk3 = dum_tak1_tab_or_mekk3_ikkb_a	2	0.4	
55c	ikkbb_nemo = dum_ikkab_or_ikkbb_nemo_ikkb_a	1	0.4	
55d	ikkab_nemo = dum_ikkab_or_ikkbb_nemo_ikkb_a	1	0.8	
55	dum_tak1_tab_or_mekk3_ikkb_a · dum_ikkab_or_ikkbb_nemo_ikkb_a = ikkb_a	1	0.6	IL-1 induces a rapid (within 10 min), but transient NEMO (IKKγ) phosphorylation that correlates with an increase in IKKβ activity[143a]; IRAK1 K63-linked poly-ubiquitination (K134, K208) in response to IL-1 stimulation provides docking sites for NEMO (via its UBD[193a]; no interaction of NEMO and ubiqutinated TRAF6, as shown for IL-1-treated HEK293 cells[44a]) and may enable TRAF6-associated TAK1 to mediate the phosphorylation/activation of the IKK complex[135a] (as shown for IL-1-treated HEK293 cells[200a]); NEMO phosphorylation in response to IL-1 might also occur TAK1-independently but MEKK3-dependently (therefore, IRAK1 polyubiquitination seems dispensable; as shown for IL-1-treated human synoviocytes[200a]) → transient formation of a MEKK3:IκBα:NF-κB:IKK complex in response to IL-1 (as shown for IL-1-treated MEFs[156a]); activated TAK1 (ubiquitinated by TRIKA1 and TRAF6) causes a specific IKKβ-S177/181 phosphorylation, acting as a ubiquitin-dependent IKK kinase (as shown *in vitro*[183a]); active MEKK3 might directly phosphorylate IKKβ at S177 and S181 within its activation loop in response to IL-1 (as shown for TNFα-treated MEFs[156a]; T-loop phosphorylation of IKKβ, but not IKKα, followed by its progressive autophospho-rylation at multiple C-terminal serines seems sufficient for IKK activation[52a]) and seems to contribute to rapid and transient NF-κB activation via IκBα degradation (as shown for IL-1-treated MEFs[156a]; but: no detectable IκBα degradation in IL-1-treated TAK1-deficient MEFs[200a], *thus the impact of MEKK3 is so far regarded as secondary!*); but: the individual relevance of TAK1, MEKK3 and IKK subunit constellation for hepatic, IL-1-induced IKK activation has to be checked!

56	mekk3 · ikkaa_nemo = ikka_a	1	0.8	MEKK3 seems to specifically activate NEMO:IKKα:IKKα complexes → the TAK1-independent/MEKK3-dependent ("Zinc") pathway may be mainly involved in the late phase (30 – 60 min after stimulation) of NF-κB activation and/or in the presence of low IL-1 concentrations (0.1 ng/ml)[196a, 200a]; but: relevance for hepatic IL-1 signalling has to be checked!
57	tak1_tab = nik	1	0.8	TAK1 phosphorylates/activates NIK in response to IL-1 (as shown for HEK293 cells[131a])
58	nik · ikkaa = nc_nfkb_pathway	1	0.8	NIK and IKKα homodimers (NEMO-independently[50a]) act upstream of p100/p52:RelB heterodimers (→ alternative/noncanonical NF-κB activation pathway)[51a]; NIK functions as a direct IKKα kinase, phosphorylating IKKα-S176 within the kinase activation loop in response to IL-1 (as shown for HEK293 cells[112a]), which might be a prerequisite for p100 processing within the noncanonical NF-κB activation pathway (for review see [51a]); but: relevance for hepatic IL-1 signalling not yet demonstrated!
59	nc_nfkb_pathway →	1	0.8	model output
60	ikkb_a = p105_degr	1	0.8	IKKα and IKKβ constitutively (hardly increased by TNFα stimulation) associate with NF-κB1 p105 via its death domain (DD), facilitating the IKK-mediated phosphorylation and subsequent proteolysis of p105, leading to TPL2 release from its inhibitor, which triggers the catalytic kinase activity (as shown in response to TNFα or LPS[14a, 16a] and IL-1[149a]); signal-induced, IKK-mediated phosphorylation of p105 within the PEST region (S927, S932) may target it for βTrCP-catalysed polyubiquitination causing proteasomal degradation (as shown upon TNFα[107a] and IL-1 treatment[154a]); but: whether IKKα presence is dispensable has to be checked!
61	!p105_degr = p105	1	0.8	IL-1-induced proteasomal p105 degradation reduces the amount of inhibitory p105 (as shown for HeLa cells and human primary synoviocytes[149a])
62	p105_degr = p50	1	0.4	p50 is generated through limited proteolysis (post- *vs.* co-translational) due

				to a glycine-rich region (GRR) within the C-terminal half of the p50 moiety of p105, which seems to act as a physical barrier to 26S proteasome entry (as shown *in vitro*[136a]; for review see [129a]); but: relevance for hepatic IL-1 signalling has to be checked!
63a	ikkab_nemo · akt = dum_ikkab_nemo_akt_or_ck2_p65	1	0.8	IL-1 mediates the regulatory S536-phosphorylation within the C-terminal transactivation domain 1 (TAD1) of p65 IKKβ-dependently (and via additional kinases, which may act redundantly), increasing its transcriptional activity (as shown in in HeLa[31a] and HepG2 cells[4a]) → evidences for a PI3K-initiated NF-κB activation pathway distinct from IκB degradation, nuclear translocation and DNA binding stressed by a PI3K-mediated p65 phosphorylation within its TAD upon IL-1 stimulation (as shown for HepG2 cells[162a]); whereas IKKβ seems essential for IκBα degradation, IKKα is required for PI3K/Akt-dependent p65 phosphorylation (TAD) and transactivation but dispensable for NF-κB liberation (no efficient p65-TAD phosphorylation, but functional IκBα degradation in IL-1-treated IKKα-deficient MEFs; PI3K/Akt pathway does not participate in NF-κB liberation[163a]); nevertheless, both IKKα and -β (most likely complexed to NEMO) contribute to PI3K/Akt-mediated NF-κB activation[163a] → IKKβ was shown to phosphorylate p65-S468 within TAD2 (corresponding to TAD1-S536) while the latter is bound to IκB, suggesting multiple IKK sites with additive or redundant functions (as shown for IL-1-treated Hep3B cells and primary HSCs (primary human hepatic stellate cells)[157a]); IL-1 was also shown to induce the positive regulatory p65 phosphorylation at serine residues by CK2 in HepG2 cells[23a] (cytoplasmic CK2:NF-κB interaction detectable within 2 – 5 min after IL-1 treatment), but whether CK2 functions synergistically or redundantly has to be worked out! (p)S276 critical for p65-dependent IL-6 production in response to IL-1[134a]); necessity of explicit IKK activation *e.g.* via TAK1 or MEKK3 not yet demonstrated!
63b	ck2 = dum_ikkab_nemo_akt_or_ck2_p65	1	1.0	
63	dum_ikkab_nemo_akt_or_ck2_p65 · !socs1 = p65	1	0.8	

				⇒ **link to IL-6**: SOCS1 inhibits NF-κB activation in response to IL-1 or LPS possibly by acting as an ubiquitin ligase on p65, supporting its degradation (as shown for MEFs[151a])
64	ikkb_a = ikba_degr	1	1.0	IL-1 induces IKKα/β phosphorylation[183a] via the TAK1-dependent "RING" pathway, leading to kinase-active IKKβ and phosphorylation of IκBα at S32 and S36, which targets it for proteasomal degradation (detectable within 2 – 5 min upon IL-1 treatment of HepG2 cells[4a]; no detectable IκBα degradation in IL-1-treated TAK1-deficient MEFs[200a]!) → the TAK1-dependent "RING" pathway might be mainly involved in the early phase (0 – 30 min after stimulation) of NF-κB activation and/or in the presence of high IL-1 concentrations (10 ng/ml)[196a, 200a]; generally, IKKβ seems essential, whereas IKKα might be dispensable for IκBα degradation and subsequent NF-κB liberation (substantially deficient IκBα degradation in IKKβ-null MEFs upon IL-1 stimulation[163a]); nevertheless, mere IκBα degradation insufficient for IL-1-induced NF-κB-dependent gene transcription[19a]
65	ck2 = ikba_degr	2	0.4	CK2 was found to phosphorylate IκBα, triggering its degradation (for review see [161a]); but: relevance for hepatic IL-1 signalling has to be checked, *thus regarded as initially secondary pending further notice!*
66	ikkaa · nik = ikba_degr	2	0.4	IKKα-S176 phosphorylation/activation by NIK significantly increases IκBα phosphorylation and transcriptional NF-κB activity (as shown by overexpression studies in HeLa and HEK293 cells[112a]) suggesting their impact on IκBα degradation; confirmed by detectable IκBα degradation (within 20 min) upon IL-1 treatment of HeLa cells in the presence of IKKβ inhibitor SC-514[149a]; but: relevance for hepatic IL-1 signalling has to be checked, *thus regarded as initially secondary pending further notice!*
67	ikka_a = ikba_diss	1	0.8	IL-1 also effects the phosphorylation of NEMO and IKKα activation in IKKβ-deficient MEFs probably via the TAK1-independent/MEKK3-dependent ("Zinc")

				pathway, resulting in NF-κB activation through different/incomplete IκBα phosphorylation ((p)S36 only) and subsequent inhibitor dissociation (→ no degra-dation!)[200a]; the latter might be due to impaired βTrcP E3 ligase binding; but: effect predominantly present in primary intestine/colon epithelial cells[200a], therefore relevance for hepatic IL-1 signalling has to be checked!
68	!ikba_degr · !ikba_diss = ikba	1	1.0	IκBα degradation (detectable within 2 – 5 min upon IL-1 stimulation of HepG2 cells[4a]) and/or time-delayed dissociation (as shown for IL-1-treated MEFs[200a]) counteract its inhibitory effect on NF-κB
69	p50 · p65 · !ikba = nfkb	1	1.0	as generally accepted, IκBα interacts with the NF-κB p50:p65 (= RelA) heterodimer and blocks its nuclear translocation as well as transcriptional activity; the inhibitory effect is removed upon IκBα proteolysis (for review see [129a]); IL-1 was shown to induce the nuclear translocation of p50 and p65 in HepG2 cells[23a, 192a]
70	nfkb = ikba	2	0.8	p50:p65 heterodimers bind to the *ikbα* promoter and induce IκBα gene expression (detectable within 1 h in IL-1-treated 1321N1 cells (human astrocytoma cell line)[65a]) → potential autoregulatory negative feedback loop[169a]
71	nfkb · jnk · ck2 = cebpd	1	1.0	IL-1 induces C/EBPδ gene expression in Hep3B cells (peaks at 3 h) in a p50:p65-, JNK-, and CK2-dependent manner[6a]
72	nuc_p38 * erk12 = cebpb	1	0.6	C/EBPβ is constitutively expressed (as shown for HepG2 cells[61a]), though intrinsically repressed in adult hepatocytes (the C/EBPβ mRNA pool is rapidly increased by IL-1 in a liver-specific manner; for review see [26a]) and appears to be activated mainly by posttranslational modifications[141a]; therefore p38 seems essential (as shown for IL-1β expression by RAW264.7 cells (murine macrophages) in response to LPS[12a]); ERK1/2 were shown to phosphorylate C/EBPβ-T235 in IL-1-treated A549 lung carcinoma cells[10a]; but: no current link to hepatic IL-1 signalling!

73	!erk12 = nalp_infl	1	0.6	ERK1/2 were shown to mediate C/EBPβ-T266 phosphorylation (possibly via p90RSK activation), causing an increased C/EBPβ:pro-Casp association, that impedes subsequent caspase activation (as shown for CCl_4-treated primary human HSCs (hepatic stellate cells) relating to Casp8[27a]); though not proved yet, this negative regulatory mechanism might inhibit signal amplification by preventing the accumulation of pro-inflammatory IL-1[26a]
74a	cebpb = dum_cebp_pro_il1b	1	0.4	dummy activation
74b	cebpd = dum_cebp_pro_il1b	1	0.4	
74	dum_cebp_pro_il1b · nfkb · ck2 · cjun = pro_il1b	1	0.4	PU.1 (ETS transcription factor) and C/EBPβ (or C/EBPδ[12a]; bound to the *il1β* locus) recruit c-Jun homodimers as co-activators, supporting polymerase II interaction and transactivation of the *il1β* promoter in response to TPA (as shown for RAW cells (murine macrophages)[66a]); CK2 triggers NF-κB and IRF (interferon regulatory factor) association with the *il1β* promoter/enhancer upon LPS stimulation of MM6 monocytes (detectable within 30 min) by modulating PU.1-S148 phosphorylation, which in turn regulates IRF-4 recruitment and facilitates polymerase II binding[203a] → transcriptional IL-1β regulation may involve the inducible and/or constitutive binding of IRF4, IRF8, NF-κB p65, c-Jun homodimers, C/EBPβ, and PU.1 (SPI-1) to the *il1* locus[203a]; but: the respective relevance for hepatic IL-1 signalling has to be checked!
75	pro_il1b · nalp_infl = il1b_new	1	0.4	pro-IL-1β is cleaved at D116 by Casp1 (caspase 1, NALP-inflammasome-associated!) to generate the mature, active IL-1β peptide p17 (as shown for LPS-treated THP-1 cells, human keratinocytes, and murine macrophages[93a, 116a], for review see [117a]); whether IL-1 stimulation of hepatocytes triggers an autocrine positive feedback loop by newly synthesised IL-1 peptids controlled by the inflammasome has to be checked!
76	il1b_new →	1	0.4	model output

77a	cebpb = dum_cebp_il1ra	1	1.0	dummy activation
77b	cebpd = dum_cebp_il1ra	1	1.0	
77	dum_cebp_il1ra · nfkb = il1ra	1	1.0	IL-1β is a potent inducer of IL-1Ra expression by human primary hepatocytes and HepG2 cells (combination of IL-1β and IL-6 exhibits a strong synergistic effect; detectable within 4 h/increase through 72 h); therefore NF-κB p65 and C/EBPδ (or to a lesser extend C/EBPβ) trigger IL-1Ra gene expression (as shown for IL-1- and/or IL-6-treated HepG2 cells[61a]) → negative feedback loop
78a	cebpb = dum_cebp_saa	1	1.0	dummy activation
78b	cebpd = dum_cebp_saa	1	1.0	
78	dum_cebp_saa · nfkb = saa	1	1.0	IL-1 induces SAA2 (serum amyloid A2; acute-phase protein) expression via NF-κB p50:p65 and C/EBPβ and/or -δ in HepG2 and murine embryonic liver cells, respectively[146a, 195a] (posttranslational phosphorylation of C/EBPδ was shown to enhance its transactivation potential[146a])
79	saa →	1	1.0	model output
80	cebpb · ap1 = lbp	1	1.0	IL-1 induces and/or augments LBP (LPS binding protein; acute-phase protein) expression via AP-1 and C/EBPβ in human hepatoma or murine embryonic liver cells, respectively[97a, 146a, 195a]
81	lbp →	1	1.0	model output
82a	cebpb = dum_cebp_cox2	1	0.8	dummy activation
82b	cebpd = dum_cebp_cox2	1	0.8	
82	dum_cebp_cox2 * nfkb * cjun * ap1 = cox2	1	0.6	IL-1 induces and might prolong COX2 gene expression possibly by temporarily altering transcription factor sets including NF-κB p50:p65 hetero- and/or p50 homodimers, members of the AP-1 transcription factor family (predominantly phosphorylated c-Jun homodimers), and C/EBP transcription factors (as partly shown for IL-1-treated primary human ASM or HeLa[5a, 130a] and LPS-treated RAW264.7 cells[91a]); but: relevance for hepatic IL-1 signalling has to be checked!
83	cox2 →	1	0.6	model output

HNF and AP-1 activation				
84	nuc_p38 · ros = hnf4a	1	1.0	IL-1β and ROS induce a specific HNF4α-serine phosphorylation pattern (S133/S134 [basal]; S158, S181, S304, T450), that increases constitutive HNF4α binding to the *inos* promoter; therefore p38-catalysed (p)S158 seems critcial for IRX (inflammatory redox)-dependent up-regulation of HNF4α-mediated *inos* promoter activity, facilitating HNF4α:PC4 (transcriptional co-activator) association (as shown for IL-1 + H_2O_2-treated HepG2 cells[68a, 69a])
85	hnf4a * nfkb = inos	1	0.8	HNF4α up-regulates iNOS gene expression and mRNA levels (as shown for IL-1 + H_2O_2-treated HepG2 cells[68a, 69a]); IL-1β was also shown to induce iNOS expression via NF-κB activation in different cell types[132a] (for review see [98a]), but: relevance for hepatic IL-1 signalling has to be checked!
86	inos →	1	1.0	model output
87	!inos · !nfkb = ros	2	0.6	antioxidant iNOS is up-regulated by the hepatocellular redox state (IRX-dependently) and counteracts ROS (reactive oxygen species) by generating NO as an ubiquitous, multifunctional free radical, eradicating infection and limiting tissue injury[69a] (and references cited therein); additionally, NF-κB functions in an antioxidant manner in part through up-regulation of FHC (ferritin heavy chain)- and superoxide dismutase 2 gene expression (as shown within 1 h for TNFα-treated MEFs[140a]), preventing ROS accumulation[72a] (and references cited therein); but: relevance for hepatic IL-1 signalling has to be cecked!
88	nuc_p38 = msk1	1	0.6	IL-1 induces MSK1-S376 phosphorylation/ activation in HepG2 cells[78a]; ERK1/2 or p38 seem capable of activating MSK1 (as shown for EGF- or TPA-treated HEK293 and TNF-treated HeLa cells[49a]); but: a similar function in the context of hepatic IL-1 signalling has to be verified!
89	erk12 = msk1	1	0.6	

90	msk1 = cjun_gene	2	0.4	IL-1 up-regulates c-Jun- and c-Fos mRNA levels/gene transcription in HepG2 cells within 15 min[42a, 124a]; therefore MSK1 might indirectly contribute to increased immediate early (IE) gene expression by histone H3-S10 phosphorylation (as shown for TPA- and anisomycin-treated MEFs[166a]), altering induction efficiency; but: *the mechanism of hepatic c-Jun enhancement by IL-1 has yet to be resolved, hence not being initially considered!*
91	cjun_gene = cjun	2	0.4	
92	jnk = cjun	1	0.8	JNK interacts with and phosphorylates c-Jun at least at S63 and/or S73 within its N-terminal transactivation domain (TAD), increasing its transcriptional activity (as shown for IL-1-treated human MRC5 fibroblasts and MEFs[192a])
93	nuc_p38 * jnk * erk12 = atf2	1	0.6	JNK (and p38, thus alternatively or redundantly) bind(s) to and phosphorylate(s) ATF2 at T69 and T71 within its activation domain upon IL-1 stimulation, causing increased transcriptional activity (as shown for IL-1-treated CHO cells[70a] and EGF- and TNFα-treated MEFs[122a]); but: the individual relevance for hepatic IL-1 signalling has to be checked! (IL-1 induces ATF2/c-Jun phosphorylation within 15 – 30 min upon stimulation of HepG2 cells[42a]); ERK1/2 seem only able to phosphorylate ATF2-T71 and might thus partially replace JNK and/or p38 function (as shown for TNFα-treated MEFs[122a])
94	nuc_p38 * jnk * erk12 = sap1	1	0.6	p38 phosphorylates SAP-1 (probably S381 and S287) in response to IL-1 in a strictly cell-type specific manner, leading to increased ternary complex formation, DNA binding activity, transcriptional activation and SRE (small response element)-dependent gene expression[84a] (as shown for IL-1-treated CHO and NIH 3T3 cells[190a]); SAP-1 was shown to serve as a convergence point for all three major MAPK classes (p38, ERK, JNK)[84a]; but: no detectable IL-1-induced, JNK-mediated transcriptional activity of SAP-1 in CHO cells[190a]; the individual relevance for hepatic IL-1 signalling has to be checked!

95	nuc_p38 * jnk * erk12 = elk1	1	0.8	p38 and/or JNK phosphorylate Elk-1 (probably at S383, S389) in response to IL-1 strictly cell-type specifically, leading to increased ternary complex formation, DNA binding activity, transcriptional activation and SRE (small response element)-dependent gene expression, whereas p38 might be an inferior Elk-1 activator[84a] (as shown for IL-1-treated CHO and NIH 3T3 cells[190a]); ERK1/2 target Elk-1 via the Elk-1 D domain to promote its transcriptional activation (as shown for IL-1-treated CHO and NIH 3T3 cells[199a]) likely by phosphorylation (as proposed by [[35a]]); but: the individual relevance for hepatic IL-1 signalling has to be checked!
96a	sap1 * elk1 = dum_sap1_or_elk1_cfos	1	0.8	dummy activation
96	dum_sap1_or_elk1_cfos · msk1 = cfos	1	0.6	active SAP-1 and/or Elk-1 interact with SRF (small response factor), forming a ternary complex that may bind to the SRE (small response element) within the *cfos* promoter, mediating increased c-Fos gene expression upon IL-1 stimulation[43a, 45a] (as shown for IL-1-treated CHO and NIH 3T3 cells[190a]); IL-1 up-regulates c-Jun and c-Fos mRNA levels/gene transcription in HepG2 cells[124a], therefore MSK1-catalysed CREB (cAMP-response element binding protein) S133 phosphorylation (as shown for TNF-treated HeLa cells[49a]) and subsequent CREB:CRE (cAMP response element) association within the *c-fos* promoter may be essential for c-Fos expression[49a, 166a] (not yet checked within the hepatic IL-1 signalling context!); additionally, MSK1 might indirectly contribute to increased immediate early (IE) gene expression by histone H3-S10 phosphorylation (as shown for TPA- and anisomycin-treated MEFs[166a]), altering induction efficiency
97	atf2 * cjun * cfos = ap1	1	1.0	AP-1 proteins (*e.g.* c-Jun, c-Fos, ATF2) form homo- and/or heterodimers via their leucine-zipper domains, whereas the combination determines the subsequent gene regulation by AP-1 (for review see [59a]); activity of heterodimeric AP-1 detectable within 15 min upon IL-1 treatment of HepG2 cells[124a]

98	ap1 = mkp1	1	0.4	IL-1 rapidly up-regulates the transient MKP1 expression[109a] (maximal at 1 h post stimulation, as shown for human fibroblast-like synoviocytes (FLS) related to rheumatoid arthritis[176a]); AP-1, beside other transcription factors, might contribute to MKP1 gene expression (for review see [102a]); but: relevance for hepatic IL-1 signalling has to be checked!
99	!ksrp · !ttp · ap1 · nfkb · cebpb · gsk3 = il6	1	0.6	TTP binds adenine/uridine-rich elements (AREs) within the 3'-untranslated region (UTR) of cytokine mRNA, targeting mRNA transcripts for degradation possibly by deadenylation to maintain low levels of inflammatory cytokines[24a, 74a] → probably TTP-mediated posttranscriptional regulation of IL-1-induced IL-6 mRNA transcripts (as shown for IL-1-treated MC3T3-E1 cells[138a] and LPS-treated RAW264.7 macrophages[139a]); KSRP interacts with IL-6 mRNA AREs, promoting the deadenylation and degradation of IL-1-induced IL-6 transcripts (as shown for IL-1-treated HeLa cells[191a]); p50:p65 heterodimers, C/EBPβ, CBF-1 (C-promoter binding factor 1), and AP-1 contribute to IL-1-induced IL-6 gene expression[3a, 101a] (as shown for IL-1-treated human primary FLSs (rheumatoid fibroblast-like synoviocytes)[120a]); ⇒ **link to IL-6**: GSK3β controls promoter-specific NF-κB recruitment in a gene-specific manner, therefore being essential for efficient IL-6 and CCL2 expression (as shown in TNFα-treated MEFs[168a])
100	il6 →	1	0.6	model output
101	!ksrp · !ttp · nfkb · cfos · ap1 = il8	1	0.8	TTP binds adenine/uridine-rich elements (AREs) within the 3'-untranslated region (UTR) of cytokine mRNA, targeting mRNA transcripts for degradation possibly by deadenylation to maintain low levels of inflammatory cytokines[11a, 24a, 74a] → TTP-mediated posttranscriptional regulation of IL-1-induced IL-8 mRNA transcripts (as shown for IL-1-treated HeLa[191a] and pulmonary A549 cells[96a]); KSRP interacts with IL-8 mRNA AREs, promoting the deadeny-lation and degradation of IL-1-induced IL-8 transcripts (as shown for HeLa[191a] and malignant

				HS578t/MDA-MB-231 breast cancer cells[170a]); c-Fos synergises with NF-κB p65 in transactivating IL-8 gene expression (p65: *il8* promoter interaction and subsequent RNA polymerase II recruitment detectable within 30 min upon IL-1 stimulation of KB cells[77a]; for review see [76a])
102	il8 →	1	0.8	model output
103	ap1 · cjun · nfkb · gsk3 = ccl2	1	0.6	IL-1 induces CCL2 gene expression via c-Jun homo- and/or c-Jun:ATF2 heterodimers (c-Fos less important), that recruit RNA polymerase II: JNK-catalysed c-Jun phosphorylation (S63/S73) promotes HDAC (histone deacetylase) dissociation, resulting in a modest increase in histone-acetylation accross the *ccl2* locus → rearranged chromatin structure may facilitate the essential p50:p65 recruitment, leading to CCL2 gene expression (as shown for IL-1-treated MEFs[192a]); ⇒ **link to IL-6**: GSK3β controls promoter-specific NF-κB recruitment in a gene-specific manner, therefore being essential for efficient IL-6- and CCL2-expression (as shown for TNFα-treated MEFs[168a]); but: relevance for hepatic IL-1 signalling has to be checked!
104	ccl2 →	1	0.6	model output
105	ap1 · atf2 = upa	1	1.0	IL-1 induces the JNK-dependent uPA gene expression within 2 – 4 h in HepG2 cells via c-Jun:ATF2 hetero- and/or ATF2 homodimers, whereas ERK1/2 seem dispensable[42a]
106	upa →	1	1.0	model output
Effects on insulin signalling				
107	erk12 = irs1_ps	1	0.4	JNK associates with IRS1 and promotes its S307 (as shown for TNFα-treated CHO cells[1a]) and S312 phosphorylation (as shown for IL-6-treated HUVECs[7a]) near the PTB domain, probably inhibiting its insulin-stimulated Y phosphorylation as a prerequisite for downstream effectors (as shown in murine liver and for HepG2 cells[198a]) and supporting its proteasomal degradation (for review see [174a]); ERK1/2 may exert their negative effect on IRS1 by phosphorylating S307 (for review
108	jnk = irs1_ps	1	0.4	
109	ikkb_a = irs1_ps	1	0.6	

				see [67a, 174a]), impairing IR-mediated IRS1-Y phosphorylation by inhibitory IRS1-S616 phosphorylation (as shown for IL-6-treated HUVECs (human umbilical vein endothelial cells)[7a]) and/or down-regulation of IRS1 expression through reduction of IRS1 mRNA (as shown in IL-1-treated 3T3-L1 adipocytes[83a]); IKKβ negatively regulates IRS1 possibly by direct (or indirect) serine phosphorylation (as shown for TNFα-treated HepG2 cells[62a]) and/or up-regulation of tyrosine phosphatases or IL-6 (as shown in murine liver[32a]) via NF-κB (for review see [174a]); respective correlations with hepatic IL-1 signalling have to be verified!
110	irs1_ps →	1	0.6	model output
Effects on HGF signalling				
111	cebpb * cebpd = pro_hgf	1	0.6	IL-1 was shown to induce HGF gene expression and secretion of immunoreactive HGF in MRC-5 cells (human embryonic lung fibroblasts)[173a]; therefore, although just proved in response to IL-6 or TNFα stimulation, C/EBPβ and/or -δ might elicit *hgf* promoter activation and function as initiators of transcription (as shown for murine NIH 3T3 fibroblasts[88a]); but: relevance for hepatic IL-1 signalling has to be checked!
112	upa · pro_hgf = hgf	1	0.4	uPA functions as a limiting, potent pro-HGF/SF convertase, proteolytically cleaving the biologically inactive, matrix-associated HGF precursor thereby generating the active mature HGF heterodimer and ensuring its bio-availability[128a] (as shown for serum-treated MRC-5 human embryonic lung fibroblasts[127a]); but: relevance for hepatic IL-1 signalling has to be checked!
113	hgf →	1	0.8	model output

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VIII.B IL-6 signalling

Tab. S4.1. IL-6 signalling species.

№	**Model name**	Full name	d	**Documentation**
1	a2m_gfbg	α_2M/γFBG		α_2-macroglobulin and γ-fibirinogen; hepatic acute-phase proteins (APPs)
2	akt*	Akt		also: PKB (protein kinase B); oncogenic AGC kinase, serine/threonine-specific; transduces survival signals[67b]
3	anti_apoptotic			viability counteracts apoptosis; the latter (induced by TGFβ/blocked by insulin or IRS in hepatocytes) ensures the maintenance of liver size/tissue homeostasis[24b]
4	bad	BAD		Bcl-2/Bcl-xL antagonist, causing cell death; member of the Bcl-2 family
5	ca	Ca^{2+}		calcium; secondary messenger
6	camk24	CaMK II/IV		Ca^{2+}/calmodulin (CaM)-dependent protein kinase II/IV; multifunctional, serine/threonine-specific
7	cam_ca			calmodulin (CaM):Ca^{2+} complex
8	casp9	Casp9		caspase 9; intracellular protease
9	cebpb	C/EBPβ		CCAAT/enhancer binding protein β, also: LAP (liver activator protein), CRP2, NF-IL6; key transcription factor concerning the activation of APP gene transcription; member of the C/EBP subfamily of the basic region leucine zipper (bZIP) protein family; constitutive basal expression in hepatocytes and HepG2 cells[109b] is upregulated in response to IL-1 and IL-6[6b, 39b, 150b]
10	cebpd	C/EBPδ		CCAAT/enhancer binding protein δ, also: NF-IL6β; key transcription factor concerning the activation of APP gene transcription; member of the C/EBP subfamily of the basic region leucine zipper (bZIP) protein family
11	cfos	c-Fos		v-Fos Finkel-Biskis-Jinkins osteosarcoma virus oncogene homolog; member of the bZIP family of transcription factors; early immediate (IE) gene product/cellular oncoprotein; leucine zipper mediates DNA binding

* *Dark grey* marking points to species (model outputs) that also act during or effect (are directly regulated in) IL-1 signalling.

12	cmyc	c-Myc		product of the *c-myc* gene; helix-loop-helix/ leucin-zipper (HLH-LZ) transcription factor; critical regulator of cell growth (especially G1/S phase transition)[73b] (and references cited therein)
13	crp	CRP		C-reactive protein; hepatic acute-phase protein (APP)
14	cyt_ptpe	PTPεC	0	protein tyrosine phosphatase ε/cytosolic isoform, also: cyt-PTPε
15	dum_cebp_saa			dummy species
16	dum_gab1_kin_or_jak1_ gab1_mem_p			
17	dum_gp80_a_il6rc			
18	dum_il6rc_p_or_grb2_vav			
19	dum_mtorc1_or_pkcd_ stat3_ta			
20	dum_pkcd_camk24_ stat1_ta			
21	erk12	ERK1/2		extracellular signal-regulated kinase 1/2, also: p42/44; cytosolic, serine/threonine-specific and proline direct (phosphorylate serine or threonine residues in the motif P/LXT/SP)
22	fkhr	FKHR		forkhead family of transcription factors
23	gab1_kin		1	yet unknown alternative Gab1 tyrosine protein kinase, located at the plasma membrane
24	gab1_mem	$Gab1^{m}$		membrane-bound Gab1 (Grb2-associated binder-1); constitutively Grb2-associated[84b] scaffolding adaptor/multisite docking protein → Gab1-PH:PIP_3 interaction[91b]
25	gab1_mem_p	$(p)Gab1^{m}$		Y-phosphorylated Gab1 (membrane-bound); (p)Y627 and (p)Y659 (= BTAM/bisphosphoryl tyrosine-based activation motif) are required for SHP2 binding (as shown in response to EGF stimulation[29b])
26	gp130m	$gp130^{m}$	1	transmembrane glycoprotein 130, also: CD130; non-ligand-binding → universal signal-transducing receptor subunit[56b, 136b]; ubiquitously expressed type I cytokine family recetor; constitutive JAK-association[130b]; disulfide-linked homodimerisation after IL-6:gp80 complex binding[99b]

27	gp130s	$gp130^{s}$	0	soluble glycoprotein 130; acts as a gp80s antagonist[98b] (soluble gp130 as well as soluble gp80 are both present in human serum[53b])
28	gp80m_a	$gp80^{m,a}$		ligand-occupied gp80m (transmembrane glycoprotein 80, also: IL-6Rα (IL-6 receptor α-subunit), CD126)[152b]; non-signalling but specifically ligand (IL-6)-binding; associates with gp130[56b, 136b]
29	gp80s_a	$gp80^{s,a}$		ligand-occupied gp80s (naturally occuring soluble IL-6Rα (IL-6 receptor α-subunit), also: CD126)[152b] (for review see [118b]); non-signalling but specifically ligand (IL-6)-binding; associates with gp130[56b, 136b] and acts agonistically[86b]
30	grb2_sos	Grb2:SOS		Grb2:SOS complex: SOS (Son of Sevenless → GDP/GTP exchanger for Ras) constitutively associates with Grb2 (growth-factor-receptor-binding protein 2)[38b]; Grb2 binds SOS via its SH3 domain[58b]; IL-6 stimulation induces complex translocation to the cell membrane
31	gsk3	GSK3		glycogen synthase kinase 3 α/β (species refers to both currently known isoforms); serine/threonine specific; basally active (for review see [79b]); GSK3β was shown to support the promoter-specific recruitment of NF-κB to the *il6*- and *ccl2*-locus (as shown in MEFs in response to TNFα[134b])
32	il6	IL-6	1	interleukin 6, also: BSF-2, IFNβ-2; pleiotropic cytokine (21.5 – 28 kDa); influences antigen-specific immune responses and inflammatory pathways; sources: stimulated monocytes, fibroblasts, endothelial cells, smooth muscle cells, macrophages, T cells, B lymphocytes, granulocytes, *etc.*; physiological stimuli: IL-1, TNF, PDGF, bacterial endotoxins, oncostatin M, *etc.* (for review see [65b]); LPS and endotoxin induce IL-6 expression by human Kupffer cells (HKC → liver macrophages)[19b]
33	il6rc	IL-6 receptor complex		functional IL-6 receptor complex
34	il6rc_p			phosphorylated (→ gp130) IL-6 receptor complex: (p)YXXQ motifs: Y767, Y814, Y905, Y915 → STAT3 (APFR) recruitment/Y905, Y915 → STAT1 recruitment[40b, 131b]; (p)Y759 → SHP2 recruitment[38b, 117b, 131b]

35	ip3	IP_3		inositol 1,4,5-trisphosphate; secondary messenger/minor phospholipid
36	ir	IR		insulin receptor
37	irs1_ps	$IRS1^{(pS)}$		S/T-phosphorylated insulin receptor substrat 1
38	irs1_py	$IRS1^{(pY)}$		Y-phosphorylated insulin receptor substrat 1
39	jak1	JAK1	1	Janus kinase 1; constitutively receptor-associated (→ gp130, for review see [129b]) tyrosine kinase; essential for IL-6 signal transduction[47b]; receptor association via membrane-proximal, proline-rich box1 and box2 motifs[139b]; JAK1:gp130 interaction via FERM1 domain[48b]; involvement of JAK2 and Tyk2 seems cell-type specific[130b]; auto- and/or crossphosphorylation (*in trans*) causes JAK activation on receptor dimerisation in response to ligand binding[130b]
40	junb	junB		product of the *junB* gene; member of the bZIP/AP-1 family of transcription factors; early immediate gene (IEG) product/cellular oncoprotein; leucine zipper mediates DNA binding
41	mekk1	MEKK1		MAP kinase/ERK kinase (MEK) kinase 1; serine/threonine-specific
42	mk2	MK2		MAP kinase-activated protein kinase 2, also: MAPKAP-K2; serine/threonine-specific
43	mek1	MEK1		mitogen-activated ERK kinase 1, also: MKK1 (mitogen-activated protein kinase (MAPK) kinase 1); MAP2K with dual substrate specificity
44	mek4	MEK4		mitogen-activated ERK kinase 4, also: MKK4 (mitogen-activated protein kinase kinase 4), SEK1, JNKK1; MAP2K with dual substrate specificity
45	mek6	MEK6		mitogen-activated ERK kinase 6, also: MKK6 (mitogen-activated protein kinase kinase 6); MAP2K with dual substrate specificity

46	mtor	mTOR	1	mammalian target of rapamycin, also: RAFT1 (rapamycin and FKBP12 target 1), FRAP1 (FKBP12-rapamycin complex-associated protein 1); member of the PIKK (phosphatidyl-inositol kinase-like kinase) family, serine/ threonine-specific; IL-6 induces mTOR-S2481 autophosphorylation/catalytic activity in HepG2 cells within 30 min[72b]
47	mtorc1	mTORC1		mTOR complex 1: mTOR + mLST8 (mammalian LST8/G-protein β-subunit like protein) + Raptor (regulatory associated protein of mTOR) and DEPTOR (DEP domains and specific interaction with mTOR) + PRAS40 (proline-rich Akt substrate, 40 kDa) as negative regulators; sensitive to FKBP12-rapamycin
48	mtorc2	mTORC2		mTOR complex 2: mTOR + mLST8 (mammalian LST8/G-protein β-subunit like protein) + PROTOR (protein observed with Rictor) + mSIN1 (stress-activated protein kinase interacting protein 1) + Rictor (rapamycin-insensitive companion of mTOR) + DEPTOR (DEP domains and specific interaction with mTOR, negative regulator); insensitive to FKBP12-rapamycin
49	nfkb	NF-κB	0	nuclear factor κB; pleiotropic, heterodimeric transcription factor
50	p38	p38 MAPK		p38-mitogen activated protein kinase (MAPK), also: p38α, SAPK2 (stress-activated protein kinase 2); serine/threonine-specific; functions via activation of transcription factors and *de novo* gene transcription, stabilisation of mRNA, induction of translation and posttranslational modification of numerous proteins
51	p70s6k	p70S6K		ribosomal protein S6 kinase, 70 kDa, polypeptide 1, also: S6K1; serine/threonine-specific
52	pdk1	PDK1	1	phosphoinositide-dependent kinase 1; serine/ threonine-specific
53	phlpp	PHLPP	0	PH domain and leucine rich repeat protein phosphatase; S473 phosphatase
54	pi3k	PI3K		phosphatidylinositol 3'-kinase; p85 adaptor subunit associates with phosphorylated Gab1 via SH2 domain[137b], p110 encompasses the catalytic activity

55	pias1	PIAS1	0	PIAS1/3 (protein inhibitor of activated STAT1/3); E3-type SUMO protein ligases[74b]
56	pias3	PIAS3	0	
57	pip3	PIP_3		phosphatidylinositol(3,4,5)-triphosphate
58	pkcd	PKCδ		protein kinase C δ; serine/threonine-specific
59	plcg	PLCγ		phospholipase C γ
60	pro_hgf	pro-HGF		matrix-associated, inactive HGF precursor[103b] [HGF: hepatocyte growth factor, also: SF (scatter factor); pro-proliferative and pro-angiogenic growth factor, that furthermore stimulates cell motility and supports tissue regeneration (→ liver; for review see [13b])]
61	pro_proliferative			IL-6-induced proliferation facilitates liver regeneration[24b] (and references cited therein)
62	pten	PTEN	0	phosphatase and tensin homolog, also: MMAC1 (mutated in multiple advanced cancers 1); lipid tyrosine phosphatase and tumor suppressor
63	rac1	Rac1		Ras-related C3 botulinum toxin substrate 1; member of the RAS superfamily and Rho family; small GTP-binding protein
64	raf1	Raf1		v-raf-1 murine leukemia viral oncogene homolog 1; MAP3K, serine/threonine-specific
65	ras	Ras		active Ras (v-Ha-ras Harvey rat sarcoma viral oncogene homolog, also: transforming protein p21); small GTP-binding protein with intrinsic GTPase activity (active if GTP-bound!); crucial signalling relay of receptor tyrosine kinases
66	ras_gap	RasGAP	0	Ras GTPase activating protein, also: RASA1 (RAS p21 protein activator 1); translocates to the plasma membrane upon stimulation[1b], inactivating Ras by turning on its intrinsic GTPase activity[44b, 95b]
67	ros	ROS	0	reactive oxygen species
68	saa	SAA		serum amyloid A; hepatic acute-phase protein
69	ship	SHIP	0	SH2 domain-containing inositol phosphatase

70	shp2	SHP2		SH2 domain-containing protein tyrosine phosphatase (PTP) 2, also: PTP1D, SHPTP2, Syp, PTP2C; catalytic cysteine[51b] (and references cited therein); constitutive association with JAK1, JAK2 or Tyk2 (as shown in fibrosarcoma cells[117b]), whereas SH2 domains seem to be irrelevant for JAK interaction (furthermore JAK1 appears to be a bad SHP2 substrate)[157b]; SHP2:gp130 association via gp130-(p)Y759[38b, 117b, 131b]
71	shp2_a	SHP2[a]		fully activated SHP2 (released from the IL-6R complex) functions as a phosphatase
72	sirp1a	SIRP1α	0	phosphorylated signal regulatory protein 1α, also: SHPS-1 (SHP substrate 1); transmembrane glycoprotein; recruits key protein tyrosine phosphatases (PTPs) to the membrane via phosphotyrosines within its immunoreceptor tyrosine-based inhibitory motif (ITIM), whereas its proline-rich region may serve as a binding site for SH3 domains[68b] (for review see [20b]); prior Y phosphorylation of cytoplasmic SIRP1α by so far unknown kinases is required for SHP2 interaction (for review see [20b])
73	slim	SLIM	0	STAT-interacting LIM protein; nuclear ubiquitin E3 ligase
74	socs1	SOCS1		suppressor of cytokine signalling 1/3, also: CIS-1/3 (cytokine-inducible SH2 protein 1/3), SSI-1/3 (STAT-induced STAT inhibitor 1/3); SOCS1 and SOCS3 (not SOCS2 or CIS) potently inhibit acute-phase protein gene induction upon IL-6 treatment in HepG2 cells[119b]; direct JAK1:SOCS3 interaction just shown for OSMR signalling in HepG2 cells yet (different JAK phosphorylation status might be crucial)[104b, 135b]
75	socs3	SOCS3		
76	stat1_py	STAT1$^{(pY)}$		Y-phosphorylated and homodimerised STAT1 (signal transducer and activator of transcription 1)
77	stat3_py	STAT3$^{(pY)}$		Y-phosphorylated and homodimerised STAT3 (signal transducer and activator of transcription 3; also APRF (acute-phase response factor))
78	stat1_ta	STAT1$^{(ta)}$		transactivated (ta) STAT1/3 (S/Y-phosphorylated)
79	stat3_ta	STAT3$^{(ta)}$		

80	tdum_shp2_il6rc_p		timescale dummy species
81	tdum_shp2_stat1_py		
82	tdum_shp2_stat3_py		
83	tdum_socs1_vav		
84	tdum_socs3_shp2		
85	var_app		various hepatic acute-phase plasma protein (APP) gene promoters (*e.g.* Hp (haptoglobin), complement C3, hemopexin; as shown for human hepatoma cells upon IL-6 stimulation[21b, 158b])
86	vav	Vav	'Vav' stands for the sixth letter of the Hebrew alphabet; 95 kDa protooncogene product and GDP/GTP exchanger (member of the Dbl family of guanine nucleotide exchange factors (GEFs) for the Rho family of GTP binding proteins), exclusively expressed in hematopoietic cells and trophoblasts[78b]

Tab. S4.2. IL-6 signalling interactions.

№	Interaction	T	C	Documentation
Ligand binding/assembly of the IL-6 receptor complex				
1	→ il6*	1	1.0	model input; ⇒ **link to IL-1:** IL-1 was shown to induce IL-6 expression in human primary FLSs (rheumatoid fibroblast-like synoviocytes)[94b]
2	il6 = gp80m_a	1	1.0	ligand binding and preformation of the transmembrane IL-6:gp80^{m} α-receptor complex (for review see [53b])
3	!gp130s · il6 = gp80s_a	1	1.0	ligand binding and preformation of the soluble IL-6:gp80^{s} α-receptor complex (facilitating responses to circulating IL-6, soluble gp80 functions in an agonistical manner by potentiating biological IL-6 activity → transsignalling; as reviewed by [53b]); by contrast, soluble gp130 competes with transmembrane gp130 for IL-6:gp80^{s} complex binding, acting as an antagonist (as shown for IL-6-treated HepG2 cells[98b], for review see [118b])
4	!mk2 · !camk24 = gp130	2	0.8	⇒ **link to IL-1:** IL-1-induced MK2 was shown to phosphorylate gp130 at S782 within its cytoplasmic part, triggering IL-6R turnover (internalisation + degradation)[110b]; these findings link to previous reports, delineating that p38 rapidly inhibits IL-6 signalling independently of *de novo* gene expression (*e.g.* SOCS), possibly by phosphorylating an IL-6 pathway component (most likely target: cytoplasmic domain of gp130, but no Y759 involvement; furthermore JAK1 seems to be no direct target), which results in impaired, IL-6-induced STAT3-Y phosphorylation (initial STAT3 activation phase) and ERK activation → inhibition correlates with the receptor and targets the IL-6R (gp130) and/or IL-6R-associated molecules (as shown for IL-6-treated HEK293T and HepG2 cells[4b, 5b]); CaMII/IV may also phosphorylate gp130-S782 (adjacent to a dileucine motif) MAPK-dependently, supporting receptor internalisation (as shown for LIF-treated 3T3-L1 cells[41b])

* Species affecting IL-6 signalling while being regulated by IL-1 (→ crosstalk effects) are highlighted in *grey*.

5a	gp80m_a = dum_gp80_a_il6rc	1	1.0	dummy activation
5b	gp80s_a = dum_gp80_a_il6rc	1	1.0	
5	dum_gp80_a_ il6rc · gp130m = il6rc	1	1.0	recruitment of the signalling receptor subunits (gp130^{m}) by the ligand-occupied α-receptor subunit (gp80$^{s/m,a}$) leads to their homodimerisation and results in formation of the functional IL-6 receptor complex (as shown for IL-6-treated Hep3B cells[99b])
6a	shp2 = tdum_shp2_il6rc_p	2	0.4	timescale dummy activation
6b	shp2_a = tdum_shp2_il6rc_p	2	0.4	
6	*!shp2* · *!shp2_a* · il6rc · jak1 = il6rc_p	1	0.8	the IL-6 receptor complex gets Y-phosphorylated by activated JAK1 (gp130-associated, as shown for IL-6-treated COS[130b] and HepG2 cells[87b]) → generated (p)Y759 (binding site for SHP2 and SOCS3) functions as a hub for balanced signalling (JAK-STAT1/3 *vs.* Ras/ERK & Akt, for review see [34b]); although expression of dominant-negative SHP2 mutants enhances IL-6R phosphorylation[81b], it has to be checked, whether the gp130 subunits function as direct SHP2 substrats!
7a	socs3 = tdum_socs3_shp2	2	0.8	timescale dummy activation
7	il6rc_p · jak1 · !ros · !sirp1a · *!socs3* = shp2	1	0.8	SHP2 binds to (p)Y759 of the gp130 subunit (activated IL-6 receptor complex) via its SH2 domain (as shown for IL-6-treated HepG2 cells[38b, 117b]) and becomes Y-phosphorylated JAK1-dependently[117b] (Y304, Y327, Y542, Y580; as shown for COS-1 cells overexpressing JAK1 and SHP2[85b, 157b]); additionally, the N-terminal SH2 domain of SHP2 interacts intramolecularly with (p)Y542 to overcome autoinhibition[81b, 85b]; Y-phosphorylated SHP2 leaves the IL-6R complex → receptor de-repression (as shown for IL-6-treated rat hepatoma H-35 cells[71b]; no Shc phosphorylation/participation in response to IL-6 → Shc acts OSM-specifically[55b]); up-regulated SOCS3 (not SOCS1!) competitively interacts with gp130-(p)Y759 and SHP2-(p)Y542, blocking the SHP2 receptor binding and/or coupling of Grb2:SOS, which might modulate the IL-6 induced MAPK activity[81b] → receptor desensitisation (SOCS1 and SOCS3 (not SOCS2 or CIS) potently inhibit

				acute-phase protein gene induction upon IL-6 treatment in HepG2 cells[119b]); SHP2:SIRP1α interaction in response to IL-6 (30 min post stimulation of MEFs) limits SHP2 phosphorylation/activation[127b]; ⇒ **link to IL-1:** ROS facilitate oxidative inhibition of SHP2 (→ protein tyrosine phosphatase), given that its catalytic cysteine is extremely susceptible to oxidation (enhanced, ROS-mediated STAT3 activity due to SHP2 inactivation in the absence of regulatory NF-κB activity within hepatic liver tumourigenesis[51b, 93b] (and references cited therein))
8	il6rc_p = grb2_sos	2	0.4	proposes for a SHP2-independent[71b] Ras activation by Grb2:SOS due to direct receptor-(p)Y association; but: just (p)EGFR:Grb2 interaction (as shown for Vero cells and MEFs[95b]) proved so far; *thus, the interaction is regarded as secondary pending further notice!*
9	shp2 = grb2_sos	1	0.4	Grb2 binds to Y304- and/or Y546-phosphorylated SHP2 (as shown for COS-1 cells overexpressing JAKs[157b]) through its SH2 domain and constitutively links effector SOS via its SH3 domains[38b]
STAT1/3 activation				
10a	shp2 = tdum_shp2_stat1_py	2	0.4	timescale dummy activation
10b	shp2_a = tdum_shp2_stat1_py	2	0.4	
10	!cyt_ptpe · *!shp2* · *!shp2_a* · il6rc_p · jak1 = stat1_py	1	0.6	STAT1 binds to (p)Y905 or (p)Y915 of the IL-6 receptor complex subunit gp130 via its SH2 domains[40b, 54b] (concerning the context of IL-6 signalling, STAT1 seems only prominent in the absence of STAT3[82b, 83b]), followed by subsequent STAT1-Y701 phosphorylation (as shown for IL-6-treated HepG2 cells[142b]) by JAK1, dissociation from the receptor, STAT1-homodimerisation/activation, and nuclear import[66b] (for review see [34b]); weak STAT1 induction upon IL-6 treatment of HepG2 cells strengthens the STAT3 predominance[83b]; cyt-PTPε negatively regulates the onset of STAT1-Y phosphorylation (as shown for IL6-treated murine M1 myeloid cells[141b]); SHP2 may act as a dual-specificity protein phosphatase on STAT1, accumulating in

				the nucleus and dephosphorylating (p)Y701 and (p)S727 (→ negative regulation; as shown for A431 cells upon EGF or IFN stimulation[149b]); whether Gab1:SHP2 interaction (explicit activation) is indispensable, has to be worked out!
11a	shp2 = tdum_shp2_stat3_py	2	0.4	timescale dummy activation
11b	shp2_a = tdum_shp2_stat3_py	2	0.4	
11	!cyt_ptpe · *!shp2* · *!shp2_a* · il6rc_p · jak1 = stat3_py	1	0.6	STAT3 binds to (p)Y767, (p)Y814, (p)Y905 or (p)Y915 of the IL-6 receptor complex subunit gp130 via its SH2 domains[40b, 54b], followed by subsequent STAT3-Y705 phosphorylation (2 min after IL-6 stimulation of HepG2 cells; prerequisite for S727 phosphorylation by PKCδ[123b, 142b]) by JAK1, dissociation from the receptor, STAT3 homodimerisation via SH2 domains/activation, nuclear import, and DNA binding[66b] (for review see [34b]); cyt-PTPε negatively regulates the onset of STAT3-Y phosphorylation (as shown for IL6-treated murine M1 myeloid cells[141b]); SHP2 may dephosphorylate/inactivate STAT3 → down-regulation of acute-phase proteins[117b] (dual-specifity phosphatase activity just proved for the SHP2:STAT1 interaction in IFN-treated HEK293T and EGF-treated A431 cells so far[149b]); whether Gab1:SHP2 interaction (explicit/strong activation) is indispensable, has to be worked out!
12a	pkcd * camk24 = dum_pkcd_camk24_stat1_ta	1	0.4	dummy activation
12	dum_pkcd_camk24_stat1_ta · stat1_py · !pias1 · !slim = stat1_ta	1	0.6	additional, PKCδ-induced STAT1-S727 phosphorylation (as shown for IFNα-treated Molt-4 and U-266 cells[143b]) seems essential for maximal transactivation (relevant for assembly of active transcription complexes[147b, 146b]), but: no detectable PKCδ:STAT1 interaction upon IL-6 treatment of HepG2, PC12 or A431 cells[63b]; alternatively: CaMKII was shown to phosphorylate STAT1-S727 upon IFN stimulation of NIH 3T3 cells[101b]; ligand-dependent, specific PIAS1:STAT1(p)Y701 association upon IL-6 treatment (detectable within 15 min) of HepG2 cells inhibits DNA binding activity of STAT1[83b], possilbly by preventing its dimerisation, causing

				repression of STAT1 signalling (for review see [34b]); PIAS-mediated sumorylation[113b] may lead to sequestration of STATs to subnuclear structures (as shown for Wnt-induced LEF1 (lymphoid enhancer factor 1) and PIASy[115b]); nuclear SLIM promotes the ubiquitination/proteasome-dependent degradation of STAT1/4 and impairs the Y phosphorylation of STAT4 (as shown for IFNα-treated HEK293T cells[138b], for review see [118b]); general relevance of SLIM for hepatic IL-6 signalling has to be checked!
13	stat1_ta →	1	0.6	model output
14a	mtorc1 * pkcd = dum_mtorc1_or_pkcd_stat3_ta	1	1.0	dummy activation
14	dum_mtorc1_or_pkcd_stat3_ta · !pias3 · stat3_py · !slim = stat3_ta	1	1.0	additional nuclear (!), PKCδ-[63b] (maximal between 10 – 30 min in HepG2 cells[123b]) and/or mTOR-induced (rapamycin-sensitive, as shown for IL-6-treated HepG2 cells[72b]) STAT3-S727 phosphorylation leads to maximal transactivation (relevant for assembly of active transcription complexes[147b, 146b]); ligand-dependent, specific PIAS3:STAT3 interaction upon IL-6 treatment of HepG2 (and M1 or MCF7) cells (detectable within 10 min) inhibits DNA binding activity of STAT3, possilbly by preventing its dimerisation[26b] (no PIAS3:STAT1 interaction, for review see [34b]); PIAS-mediated sumorylation[113b] may lead to sequestration of STATs to subnuclear structures (as shown for Wnt-induced LEF1 (lymphoid enhancer factor 1) and PIASy[115b]); nuclear SLIM promotes the ubiquitination/proteasome-dependent degradation of STAT1/4 and impairs the Y phosphorylation of STAT4 (as shown in IFNα-treated HEK293T cells[138b], for review see [118b]; presumably, not shown for STAT3 yet!); general relevance of SLIM for hepatic IL-6 signalling has to be checked!
15	stat3_ta = socs1	1	1.0	STAT3 targets SOCS genes upon IL-6 stimulation → transient SOCS1 expression (as shown for IL-6-treated M1 cells[102b]) detectable within 20 min upon IL-6 treatment/decline to basal level within 4 h in murine liver or M1 cells[133b]
16	stat3_ta * p38 * erk12 = socs3	1	1.0	STAT3 targets SOCS genes upon IL-6 stimulation (as shown for SOCS3 in IL-6-

				treated HepG2 cells[72b]) → transient SOCS3 induction upon IL-6 stimulation detectable within 20 min upon IL-6 treatment of HepG2 cells[81b, 125b]/decline to basal level within 8 h in murine liver[133b]; p38 essentially conduces to SOCS3 mRNA expression upon IL-6 treatment of HepG2 cells[15b], possibly by mRNA stabilisation and/or regulation of transcriptional co-factors[32b]; ERK1/2 inhibit STAT3 activity by contributing to SOCS3 gene expression in HepG2 cells upon IL-6 treatment possibly also by regulation of transcriptional co-factors like Elk-1 and/or TCF[124b, 142b]; whether ERK1/2 act synergistically with or alternatively to p38 and need STAT3 involvement has yet to be concerned!
17	nfkb = socs3	1	1.0	⇒ **link to IL-1:** although not causing SOCS3 gene expression, IL-1 stabilises IL-6-induced SOCS3 mRNA NF-κB-dependently, possibly via secondary effector proteins (as shown for IL-(1+6)-treated HepG2 cells[155b])
18	!socs1 · !socs3 · !shp2 · !shp2_a = jak1	2	0.6	SOCS1 and SOCS3 (not SOCS2 or CIS) potently inhibit acute-phase protein gene induction upon IL-6 treatment in HepG2 cells[120b]; SOCS1 (or SOCS3 with markedly lower affinity/prefers gp130 association!) interacts with JAK1-(p)Y via its SH2 domain, leading to close proximity of its KIR (kinase inhibitory region) domain with the substrate binding site of the JAK1 KD (kinase domain), which in turn decreases catalytic JAK1 activity (as shown for HEK293T cells overexpressing SOCS1 and JAK1[104b]; SOCS1:JAK2-(p)Y1007 interaction was demonstrated by [[33b, 156b]], for review see [77b]); no SOCS1:gp130-(p)Y759 interaction (as shown for Epo-treated HepG2 cells[120b]); SHP2 may directly act as a phosphatase on JAK1, exerting its inhibitory function on IL-6 signalling independently from receptor-bound SOCS3, supporting early signal modulation (as shown for IL-6- treated rat hepatoma H-35 cells[70b] and IL-5-treated COS-7 cells[81b], for review see [34b, 53b]); but: phosphorylated JAK1 seems to be no good SHP2 substrate (as shown by overexpression studies in COS-1 cells[157b])

19	stat3_ta = cfos	1	1.0	IL-6 induces c-Fos- (as shown for murine hepatocytes and HepG2 cells[82b, 154b]) and junB- (as shown for HepG2 cells and murine hepatocytes[27b, 82b]) gene expression via STAT3
20	stat3_ta = junb	1	1.0	
21	junb →	1	1.0	model output
22	stat3_ta = cmyc	1	1.0	STAT3 rapidly interacts with the *c-myc* gene promoter in response to IL-6 and up-regulates c-Myc gene expression in HepG2 cells[73b]
23	cmyc →	1	1.0	model output
24	stat3_ta * p38 = cebpb	1	0.8	C/EBPβ is constitutively expressed in adult hepatocytes and appears to be activated mainly by posttranslational modifications in response to IL-6 (for review see [109b]); therefore p38 seems essential (as shown for C/EBPβ-triggered IL-1β expression by RAW264.7 cells (murine macrophages) in response to LPS[9b]); STAT3 (not STAT1!) contributes to the up-regulation of C/EBPβ expression by murine hepatocytes and human HepG2 cells within 30 min (peaks at 6 h) in response to IL-6; this gene expression is supported by a yet unknown protein complex (acting CREB-independently) at the CRE-like elements of the *c/ebpβ* promoter[105b] (for review see [121b])
25	stat3_ta = cebpd	1	1.0	STAT3 (not STAT1!) also triggers the IL-6-induced transcriptional activation of the *c/ebpδ* gene in human hepatoma cells (detectable within 30 min) by interacting with the APR element (APRE) of the promoter region (therefore, SP1 and STAT3 function cooperatively)[21b, 151b]
26	!cebpb = pro_proliferative	1	0.6	C/EBPβ homodimers are assumed to act anti-proliferative (whereas C/EBPγ may neutralise this growth-inhibitory effect by heterodimerisation)[80b], which might be confirmed by a blocked G1/S phase transition in HepG2 cells overexpressing C/EBPβ[16b]

27	cebpb = var_app	1	1.0	C/EBPδ is the predominant IL-6-induced protein interacting with C/EBP sites in the promoters for complement C3, hemopexin, and haptoglobin in hepatocytes[21b] (transcriptional regulation/induction of acute-phase protein genes by STAT3 as an up-stream effector was proven[52b] (as shown for HepG2 cells[145b]))
28	cebpd = var_app	1	1.0	
29	var_app →	1	1.0	model output
30a	cebpb * cebpd = dum_cebp_saa	1	1.0	dummy activation
30	dum_cebp_saa · stat3_ta · nfkb = saa	1	1.0	IL-6 induces SAA2 (serum amyloid A2, APP) gene expression via C/EBPβ and/or -δ in HepG2 cells[150b]; STAT3 heterodimerises with NF-κB p65 in response to IL-(1+6) stimulation of HepG2 cells, supporting the additional recruitment of co-activator p300 and coordinated interaction with C/EBPβ at the *saa* gene promoter[50b]; ⇒ **link to IL-1**: IL-1 may act as a ”gate keeper”, stressing a certain set of APPs, though simultaneously supressing another one[7b]
31	saa →	1	1.0	model output
32	cfos · stat3_ta · !nfkb = crp	1	1.0	⇒ **link to IL-1:** the transcriptional complex formation of c-Fos:STAT3:HNF-1α (hepatocyte nuclear factor 1α) synergistically induces CRP gene expression in response to IL-(1+6) stimulation, whereas NF-κB seems to block the early induction phase (as shown in Hep3B cells[106b]); contradictorily, IL-1-induced NF-κB (p50:p65) was shown to act synergistically with both C/EBPβ and STAT3 to mediate CRP gene expression in Hep3B cells and therefore enhances the effects of IL-6 on CRP production[2b]
33	crp →	1	1.0	model output
34	stat3_ta · !nfkb = a2m_gfbg	1	1.0	⇒ **link to IL-1:** IL-1 may act as a ”gate keeper”, stressing a certain set of APPs, though simultaneously supressing another one[7b]: NF-κB (p50:p65) competes with STAT3 for *α2m* promoter binding by counteracting DNA binding of STAT3 at overlapping STAT3/NF-κB binding sites, inhibiting α2M gene expression in response to IL-(1+6) stimulation of HepG2

				cells[14b]; STAT3 associates with CDK9 (cyclin-dependent kinase 9) and triggers γFBG expression in response to IL-6 (as shown for HepG2 cells[62b]); IL-1-induced NF-κB activation suppresses γFBG expression by HepG2 cells and human primary hepatocytes possibly by inhibiting late phase STAT3 activation[7b]
35	a2m_gfbg →	1	1.0	model output
Gab1 recruitment/SHP2 activation				
36	erk12 · pip3 = gab1_mem	1	0.8	Gab1 translocation to the plasma membrane: Gab1-S551 phosphorylation by activated ERK1/2 relieves the block of the Gab1 PH (pleckstrin homology) domain and targets it to membrane-bound PIP_3[91b, 111b] (as shown for IL-6- treated HEK293T cells[35b]); Gab1:(p)ERK2 interaction probably via MBD (Met-binding domain; as shown for HGF-treated murine IMCD3 cells[114b])
37	grb2_sos = gab1_mem	2	0.4	Gab1 constitutively associates with Grb2 via two special Grb2 binding sites and SH3 domains of Grb2 (as shown for HEK293T cells overexpressing EGFR[84b], for review see [44b]), likely facilitating its receptor recruitment; *so far regarded as secondary due to outstanding relevance for Gab1 membrane translocation!*
38a	gab1_kin = dum_gab1_kin_or_jak1_ gab1_mem_p	1	1.0	dummy activation
38b	jak1 = dum_gab1_kin_or_jak1_ gab1_mem_p	2	0.4	
38	dum_gab1_kin_or_jak1_ gab1_mem_p · gab1_mem = gab1_mem_p	1	0.6	Gab1 (membrane-bound) gets Y-phosphorylated within 5 min upon IL-6 stimulation (as shown for HepG2 cells[137b]); involvement of receptor-associated JAK1 or yet unknown alternative intermediate tyrosine protein kinases[44b] has to be checked; *hence, the relating influence of JAK1 is assumed to be secondary until further notice!*
39	gab1_mem_p · !ros · shp2 · !sirp1a = shp2_a	1	0.6	SHP2:Gab1 interaction targets SHP2 to the membrane and relieves its basal inhibition, leading to strong activation[85b, 108b] (as shown by overexpression studies in COS-7 cells[30b], for review see [44b]); Gab1-(p)Y627 and (p)Y659 (= BTAM/

				bisphosphoryl tyrosine-based activation motif) required for SHP2 binding (as shown for EGF-treated COS-7 cells[29b]); SHP2:SIRP1α association in response to IL-6 (30 min post stimulation of MEFs) limits SHP2 phosphorylation/activation[127b]; ⇒ **link to IL-1:** ROS facilitate oxidative inhibition of SHP2 (protein tyrosine phosphatase), given that its catalytic cysteine is extremely susceptible to oxidation (enhanced, ROS-mediated STAT3 activity due to SHP2 inactivation in the absence of regulatory NF-κB activity within hepatic liver tumourigenesis[51b, 93b] (and references cited therein))
40	gab1_mem_p · !shp2_a = ras_gap	2	0.4	RasGAP:(p)Gab1 (membrane-bound) interaction via Gab1-(p)Y317; activated SHP2 dephosphorylates RasGAP binding sites to disengage it from Ras-activating Gab1 complexes (as shown for EGF-treated Vero cells (monkey kidney cell line) and MEFs[95b])
41	gab1_mem _p = plcg	1	0.4	Y-phosphorylated Gab1 (Y307, Y373, Y407) binds and activates PLCγ (as shown for HGF-treated HEK293 cells[45b]); but: relevance for hepatic IL-6 signalling has to be checked!
MAPK signalling				
42	grb2_sos · !ras_gap = ras	1	0.4	SOS (Grb2-associated) activates Ras via GDP/GTP exchange (for review see [69b]), whereas RasGAP inhibits Ras activity by turning on its intrinsic GTPase activity (as shown for EGF-treated Vero cells[95b], for review see [44b])
43	ras = raf1	1	0.8	GTP-Ras activates Raf1 (as shown in HeLa cells in response to IFNβ and OSM (oncostatin M)[132b] or IL-6-treated AF-10 cells (human B-cell line)[76b]); conformational changes of Raf1 upon GTP-Ras binding may serve to expose its kinase domain (for review see [97b])
44	raf1 = mek1	1	0.8	Raf1 phosphorylates/activates MEK1 in response to IL-6 stimulation (as shown for AF-10 cells[76b])
45	mek1 = erk12	1	0.4	Ras-dependent MEK1/ERK2 activation via the membrane-tagged Gab1:SHP2 complex (as shown for COS-7 cells overexpressing Gab1 and MEK1[30b]); IL-6

				induces ERK1/2 phosphorylation (ERK1: T202/Y204; ERK2: T185/Y187)/activation (as shown for HepG2 cells within 15 min[55b]) in a Gab1- and SHP2-dependent manner[137b]; but: relevance of MEK1 as an upstream kinase of ERK1/2 for hepatic IL-6 signalling has to be checked!
46a	socs1 = tdum_socs1_vav	2	0.4	timescale dummy activation
46b	il6rc _p * grb2_sos = dum_il6rc_p_or_grb2_vav	1	0.8	dummy activation
46	dum_il6rc_p_or_grb2_vav · *!socs1* = vav	1	0.6	gp130:Vav interaction via the membrane-distal region of gp130 and/or Vav:Grb2 association regardless of IL-6 stimulation (as shown for the human myeloma B-cell line U266 upon IL-6 treatment[78b]); transient Vav-Y phosphorylation (maximal after 10 min in HepG2 cells) in response to IL-6[78b, 122b]; SOCS1 binds and may target Vav to ubiquitin-mediated protein degradation (as shown for COS-7 cells overexpressing Vav and SOCS1[31b])
47	vav = rac1	1	1.0	transient Vav:Rac1 association (detectable within 5 min upon IL-6 stimulation of HepG2 cells) leads to Vav-catalysed GDP/GTP exchange on Rac1 and subsequent release of active GTP-Rac1[122b]; pre-existing Vav-Y phosphorylation seems essential for Rac1 activation/GTP-Rac1 release (complete after 20 min in HepG2 cells) rather than for Vav:Rac1 interaction[28b, 122b]
48	rac1 = mekk1	1	1.0	MEKK1 associates with GTP-Rac1[36b] and becomes activated upon IL-6 stimulation of HepG2 cells[122b]
49	mekk1 = mek4	1	1.0	IL-6 induces MEK4-T223 phosphorylation/ activation by MEKK1 within 5 min (maximal after 10 min) in HepG2 cells[123b, 122b]

50	mek4 = pkcd	1	1.0	MEK4 phosphorylates PKCδ at T505 (only detectable in nuclear fractions; maximal between 5 – 30 min in HepG2 cells) IL-6-dependently, leading to its release from the MEK4 complex (after 15 min) and activation (neither detectable JNK1 activation nor JNK1:MEK4 association in IL-6-treated HepG2 cells)[123b]; but: IL-6 was shown to increase JNK-T183/Y185 phosphorylation within 30 min up to 4 h in HUVECs (human umbilical vein endothelial cells)[8b]
51	il6rc_p = mek6	1	1.0	IL-6 induces p38 activation via MEK6[122b, 158b] (as shown for HepG2 cells, detectable after 1 min[15b]); no detectable JNK activation upon IL-6 treatment of HepG2 cells[15b, 123b]!
52	mek6 = p38	1	1.0	MEK6 activates p38 upon IL-6 treatment of HepG2 cells[15b] (IL-6-induced p38-T180/Y182 phosphorylation detectable within 5 min as shown for human KMCH (combined hepatocellular and cholangio-carcinoma) cells[92b])
53	p38 = mk2	1	1.0	p38 interacts with and activates nuclear MK2 by phosphorylating T222, S272, and T334 in response to IL-6 (and IL-1), causing its nuclear export[3b, 10b, 11b, 148b] (as shown for IL-6-treated HepG2 cells[158b])
Ca^{2+} signalling				
54	plcg = ip3	1	0.4	PLCγ hydrolyses PIP_2, generating IP_3 and DAG (diacylglycerol)[89b]; but: relevance for hepatic IL-6 signalling has to be checked!
55	ip3 = ca	1	0.4	IP_3 induces Ca^{2+} release from the endoplasmatic reticulum (ER) via IP_3 receptors (for review see [60b]), resulting in an intracellular Ca^{2+} increase (soluble gp80 was shown to induce a Ca^{2+} flux in human dermal foreskin fibroblasts[128b]); but: relevance for hepatic IL-6 signalling has to be checked!
56	ca = cam_ca	1	0.4	CaM:Ca^{2+} interaction leads to local conformational changes and activation of CaM (for review see [60b]); but: relevance for hepatic IL-6 signalling has to be checked!

57	cam_ca = camk24	1	0.4	Ca^{2+}:CaM complex association relieves the intramolecular autoinhibition of CaMK (for review see [60b]); but: relevance for hepatic IL-6 signalling has to be checked!
PI3K/Akt signalling				
58	ras = pi3k	1	0.4	GTP-Ras:PI3K interaction through the catalytic (PI3K) subunit p110 may lead to PI3K activation (as shown for EGF- and NGF-treated PC-12 cells (rat phaeochromocytoma cell line) or by overexpression studies in COS cells[112b]); relevance for hepatic IL-6 signalling has to be checked!
59	gab1_mem_p · !shp2_a = pi3k	2	0.8	basal PI3K activity ensures the initial membrane recruitment of Gab1 in response to IL-6 (as shown for HEK293T cells[35b]); IL-6 induces (p)Gab1:PI3K complex formation (likely via PI3K subunit p85) in HepG2 cells, whereas (p)Gab1:SHP2:PI3K and SHP2:gp130 complexes are distinct[137b] (three potential p85 binding sites on Gab1: (p)Y447, Y472, Y589; as shown for NGF-treated PC-12 cells[59b]); (p)Gab1:PI3K association amplifies local PIP_3 accumulation, increasing Gab1 recruitment to the plasma membrane and its tyrosyl phosphorylation, which in turn promotes further PI3K activity (→ positive feedback loop, as shown for IL-6-treated HEK293T cells[35b]); catalytically active SHP2 dephosphorylates PI3K binding sites on Gab1, down-regulating the Gab1:p85 interaction (as shown for EGF-treated NIH 3T3 and HEK293 cells[159b])
60	pi3k · !pten = pip3	1	1.0	as established, PI3K catalyses the phosphorylation of PIP_2 (phosphatidyl-inositol(4,5)-bisphosphate) to generate PIP_3 (for review see [144b]); PTEN (PIP_3 phosphatase) reverses the reaction[88b]
61	mtor = mtorc1	1	1.0	mTOR acts within two functionally distinct protein complexes: mTORC1 *vs.* mTORC2 (for review see [116b])
62	mtor = mtorc2	1	1.0	
63	mtorc2 · pdk1 · pip3 · !phlpp · !ship = akt	1	0.8	Akt and PDK1 bind to PIP_3 at the plasma membrane, leading to PDK1-mediated T308 phosphorylation within the activation loop of Akt; complete Akt activation upon S473 phosphorylation by mTORC2 (as shown for IL-6-treated HepG2 cells[25b]); PI3K/Akt activation in response to IL-6

				stimulation seems strictly cell-type specific; PHLPP inactivates Akt through dephosphorylation of (p)S473 (for review see [90b]); SHIP inhibits Akt membrane translocation[23b]; but: relevance of PHLPP and SHIP for hepatic IL-6 signalling has to be checked!
64	!akt = bad	1	0.8	activated Akt phosphorylates/inactivates BAD upon IL-6 stimulation, leading to Bcl-xL- and Bcl-2- (suppressors of apoptosis) release and activation[24b] (as shown for human multiple myeloma cells (MM.1S)[57b])
65	!akt = casp9	1	0.8	activated Akt blocks caspase 9 cleavage/ protease activity through phosphorylation[22b] upon IL-6 stimulation (as shown for human multiple myeloma cells (MM.1S)[57b])
66	!akt = gsk3	1	0.8	activated Akt phosphorylates (possibly at regulatory S9[79b])/inactivates GSK3β[107b] upon IL-6 stimulation (as shown for human multiple myeloma (MM.1S) cells[57b])
67	!akt = fkhr	1	0.8	activated Akt phosphorylates/negatively regulates FKHR upon IL-6 stimulation (as shown for human multiple myeloma (MM.1S) cells[57b]), possibly promoting its nuclear export[12b]
68	akt * erk12 * mtorc1 = p70s6k	1	0.8	mTOR mediates p70S6K-T389 (as shown for AF-10 MM (detectable within 15 min up to 1 h)[126b] and HepG2 cells (within 15 min up to 2.5 h)[72b]), S411, and T421/S424 phosphorylation (as shown for AF-10 MM cells within 15 min[126b]) and its catalytic activation in response to IL-6 in a rapamycin-sensitive manner; Akt and ERK1/2 may additively or synergistically contribute to sequential p70S6K phosphorylation/activation (as shown for IL-6-treated AF-10 MM cells[126b]: ERK1/2 → p70S6K-T421/S424; ERK1/2 and/or Akt → S411; Akt → T389)
Anti-apoptotic and pro-proliferative effects				
69	!bad · !casp9 · !gsk3 · stat3_ta = anti_apoptotic	1	1.0	inhibition of BAD, Casp9, and GSK3β strengthens the hepatoprotective nature of IL-6: BAD generally promotes cell death through heterodimerisation with the survival proteins Bcl-2 and Bcl-xL, leading to their inactivation[153b]; Casp9 acts as an

				initiator and effector of apoptosis[22b]; GSK3β may negatively regulate the activity of transcription factors, finally leading to apoptosis (for review see [37b]); IL-6 establishes and maintains an adequate, anti-apoptotic level of FLIP, Bcl-2 and Bcl-xL (suppressors of apoptosis) in murine primary hepatocytes and Hep3B cells, therefore PI3K/Akt and STAT3 pathways seem to act cooperatively[24b, 38b, 49b, 75b]; STAT3 acts as a key regulator of human liver tumourigenesis (HCC/hepatocellular carcinoma) by suppressing apoptosis and stressing proliferation during early tumour development[25b, 51b] (and references cited therein); but: relevances of BAD, Casp9, and GSK3β for anti-apoptotic effects concerning hepatic IL-6 signalling have to be checked!
70	anti_apoptotic →	1	1.0	model output
71	camk24 = pro_proliferative	1	0.4	regulatory phosphorylation events mediated by specific kinases (CAM kinase II and/or the Ras-Raf-MEK-ERK-p90RSK cascade; for review see [18b]) seem to counteract C/EBPβ-mediated growth arrest (as shown for TGFα-treated HepG2 cells[17b]); but: relevance for hepatic IL-6 signalling has to be checked!
72	erk12 = pro_proliferative	1	0.6	
73	!fkhr = pro_proliferative	1	0.8	FKHR block G1/S phase transition/proliferation through p27KIP1 up-regulation (down-regulation of p27KIP1 leads to G1/S phase transition, supporting cell cycle progresssion and proliferation (as shown for IL-6-treated human multiple myeloma (MM.1S) cells[57b])
74	p70s6k = pro_proliferative	1	0.8	p70S6K promotes cell cycle progression/ proliferation *inter alia* by inhibitory phosphorylation of the 4E-BP1 translational represssor, subsequent eIF-4E initiation factor release, and assembly of a translation initiation complex (as shown for IL- 6-treated AF-10 MM cells[126b])
75	stat3_ta = pro_proliferative	1	1.0	STAT3 promotes IL-6 induced cell cycle progression and cell proliferation during liver regeneration (as shown in murine liver[82b]) and seems to act as a key regulator of human liver tumourigenesis (HCC/hepatocellular carcinoma) by suppressing apoptosis and stressing

				proliferation during early tumour development[25b, 51b] (and references cited therein)
76	pro_proliferative →	1	1.0	model output
Effects on insulin signalling				
77	pkcd = irs1_ps	1	0.4	PKCδ was shown to mediate IRS1-S24 phosphorylation (within the IRS1 PH domain), interfering with PIP_2 binding (as shown for PMA-treated H4IIE rat hepatoma cells[42b]) and seems to contribute to inhibitory IRS1-S312, S636/639, and S616 phosphorylation possibly by activating downstream S/T kinases (as shown for TNFα-treated H4IIE rat hepatoma cells[43b]); but: relevance for hepatic IL-6 signalling has to be checked!
78	erk12 = irs1_ps	1	0.8	ERK1/2 may exert their negative effect on IRS1 by phosphorylating S307 (for review see [46b, 140b]) or impairing IR-mediated IRS1-Y phosphorylation by inhibitory IRS1-S616 phosphorylation (as shown for IL-6-treated HUVECs (human umbilical vein endothelial cells)[8b])
79	!irs1_ps · !shp2 · !shp2_a = irs1_py	1	1.0	as generally accepted, IRS1-S/T phosphorylation interferes with subsequent insulin-stimulated and IR-mediated Y phosphorylation of IRS1[61b]; SHP2 (phosphorylation/activation state has yet to be analysed!) likely down-regulates insulin signalling by dephosphorylating tyrosine residues on IRS1 (IRS1:SHP2 interaction via IRS1-(p)Y1172 and (p)Y1222, as shown for insulin-treated CHO cells[100b]); but: relevance for hepatic IL-6 signalling has to be checked!
80	irs1_py →	1	1.0	model output
81	!socs1 · !socs3 = ir	1	1.0	IL-6-induced SOCS3 negatively regulates the hepatic insulin receptor (IR) in HepG2 cells and murine liver, possibly by antagonising receptor autophosphorylation (high SOCS3 concentration, → KIR domain) or competing with IRS (insulin receptor substrat) for receptor association (lower SOCS3 concentration[72b, 125b]) (and references cited therein); SOCS1 requires insulin for maximal IR affinity and does not affect receptor autophosphorylation (as shown for insulin-treated HepG2 cells[96b])

82	ir →	1	1.0	model output
Effects on HGF signalling				
83	cebpb * cebpd = pro_hgf	1	0.8	C/EBPβ and/or -δ seem to elicit *hgf* promoter activation and function as initiators of transcription, up-regulating HGF gene expression (as shown for IL-6- or TNFα-treated murine NIH 3T3 fibroblasts[64b]); but: relevance for hepatic IL-6 signalling has to be checked!
84	pro_hgf →	1	0.8	model output

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