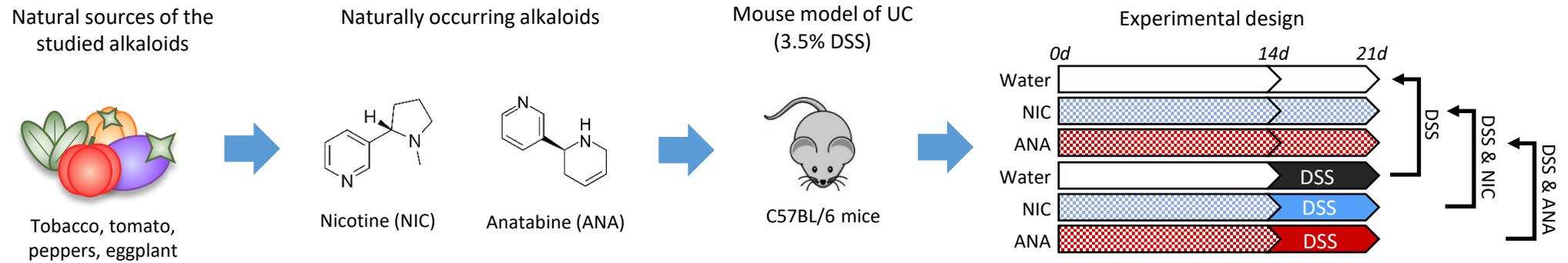
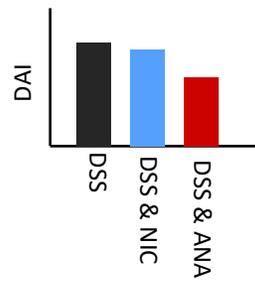


Graphical summary of the study concept and analytical approaches

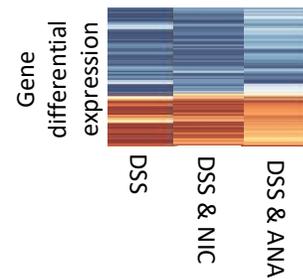


Scientific aim: evaluate the effects of nicotine and anatabine pre-treatments on the DSS mouse model of ulcerative colitis

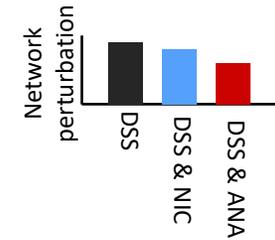
Clinical readouts (Fig. 1)



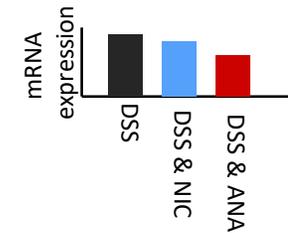
Molecular readouts (Affymetrix): evaluate appropriate statistics for ~20'000 genes (Fig. 2)



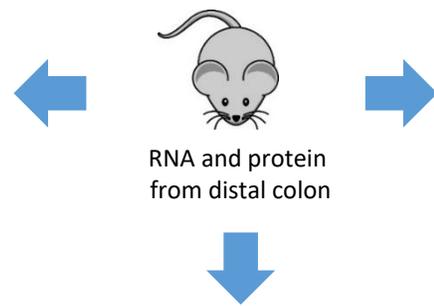
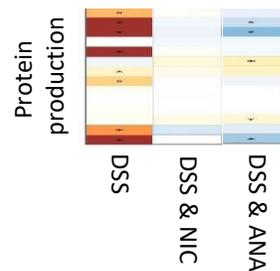
Mechanistic interpretation: use pathways/networks to identify the biology underlying the changes in gene expression (Fig. 3)



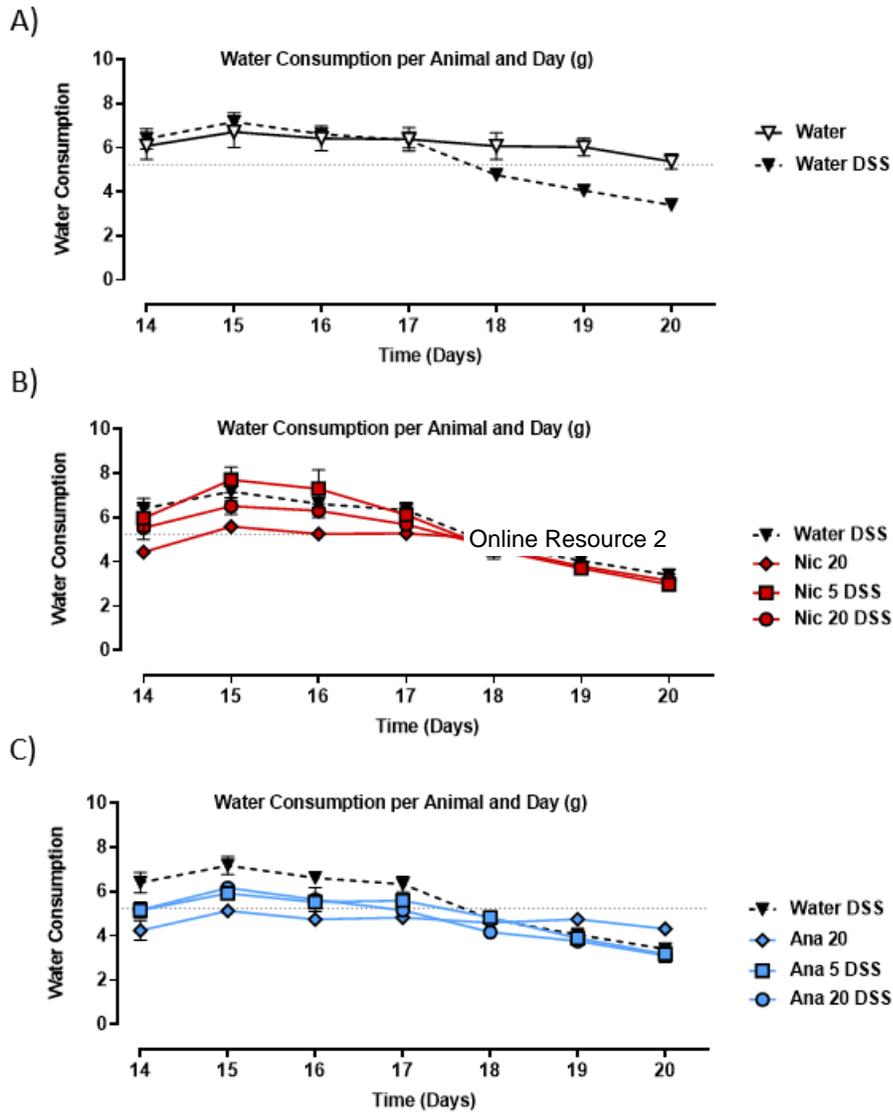
Validation of gene expression regulation using qPCR (Fig. 4)



Molecular readouts: multi analyte profiling (MAP) for 12 pro-inflammatory factors (Fig. 5)

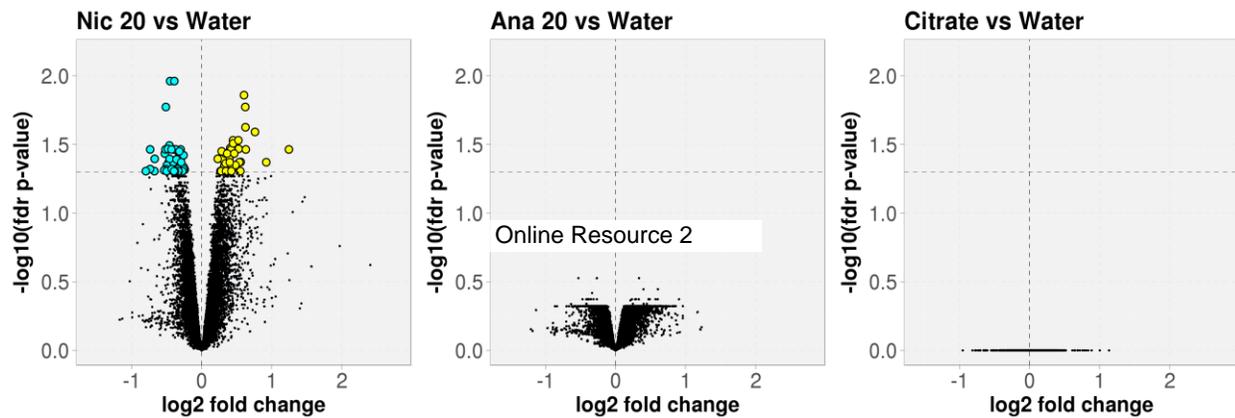


Water consumption monitoring (A) water and DSS, (B) nicotine, and (C) anatabine treatment groups. There was no difference in water consumption across the different treatment groups.



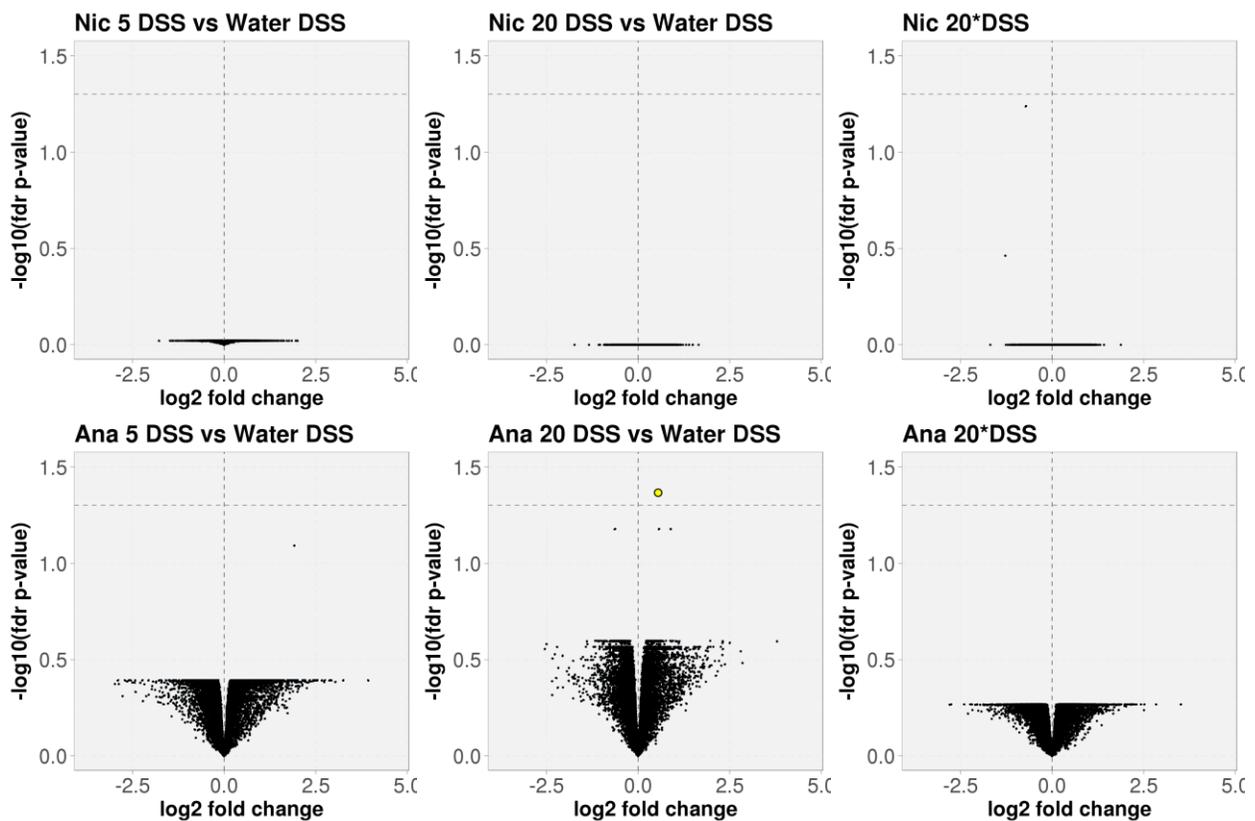
Online Resource 3

Differential gene expression results for pairwise comparisons capturing the pure effects of anatabine/nicotine exposure. The volcano plots (see Fig. 2B) represent the \log_2 fold changes on the horizontal axis and the corresponding statistical significance $-\log_{10}$ FDR on the vertical axis. The threshold for statistical significance indicated by the colored points is $FDR \leq 0.05$. Except for nicotine, the observed signals were rather weak.



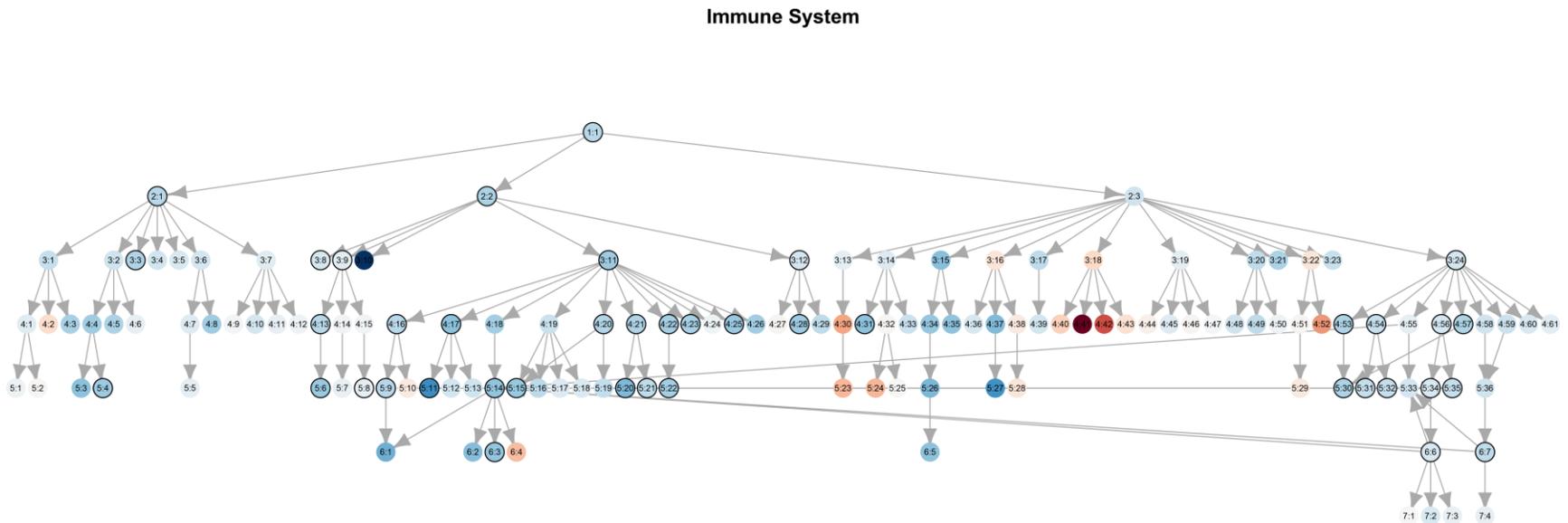
Online Resource 4

Differential gene expression results for various contrasts involving the effects of anatabine/nicotine exposure. Volcano plots for individual gene differential expressions. The volcano plots (see Fig. 2B) represent the log₂ fold changes on the horizontal axis and the corresponding statistical significance $-\log_{10}$ FDR on the vertical axis. Similar to the corresponding pure effects of anatabine/nicotine exposure described in Online Resource 2, the observed signals were weak and apparently unaffected by DSS treatment.



Online Resource 5

Hierarchical representation of the GSA results for all pathways contained in the top Reactome “Immune System” category and for the two-factor “Ana 20*DSS” interaction (larger unannotated version of Fig. 3C). The contents of this plot have been explained in the legends of Fig. 3C and Online Resource 3. Representing all the pathways from the Reactome “Immune System” category enables not only to identify the relevant biological mechanisms, but also to take into account their relationships (i.e. “mechanistic proximity”) at various hierarchical levels, and, complementarily, to examine the parts of the hierarchy that are not involved in the response. The Reactome pathway names corresponding to the node labels are given in the lower part of the figure.



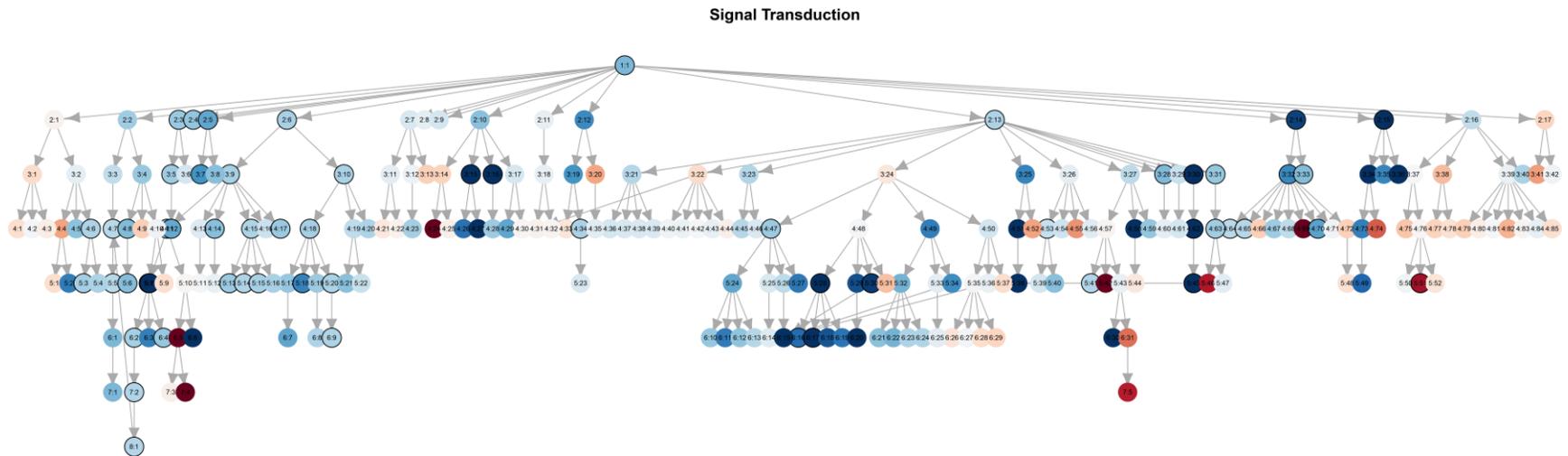
Online Resource 5 continued

For more details please refer to Online Resource 12.

1:1	Immune System	3:4	MHC class II antigen presentation
2:1	Adaptive Immune System	3:5	Rap1 signalling
2:2	Cytokine Signaling in Immune system	3:6	Signaling by the B Cell Receptor (BCR)
2:3	Innate Immune System	3:7	TCR signaling
3:1	Class I MHC mediated antigen processing & presentation	3:8	Growth hormone receptor signaling
3:2	Costimulation by the CD28 family	3:9	Interferon Signaling
3:3	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	3:10	Prolactin receptor signaling
3:11	Signaling by Interleukins	3:18	DDX58/IFIH1-mediated induction of interferon-alpha/beta
3:12	TNFR2 non-canonical NF-kB pathway	3:19	Fc epsilon receptor (FCERI) signaling
3:13	Antimicrobial peptides	3:20	Fcgamma receptor (FCGR) dependent phagocytosis
3:14	C-type lectin receptors (CLRs)	3:21	Neutrophil degranulation
3:15	Complement cascade	3:22	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways
3:16	Cytosolic sensors of pathogen-associated DNA	3:23	ROS and RNS production in phagocytes
3:17	DAP12 interactions	3:24	Toll-like Receptor Cascades

Online Resource 6

Hierarchical representation of the GSA results for all pathways contained in the top Reactome “Signal Transduction” category and for the two-factor “Ana 20*DSS” interaction. The contents of this plot have been explained in the legends of Fig. 3C and Online Resource 3. The Reactome pathway names corresponding to the node labels are given in the lower part of the figure.



Online Resource 6 continued

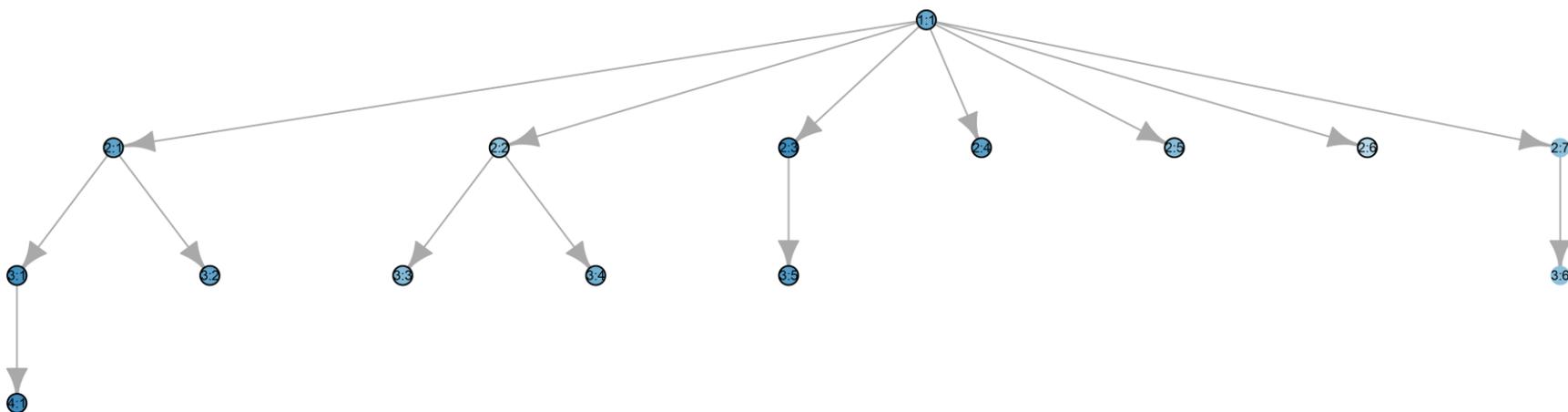
For more details see Online Resource 12.

1:1	Signal Transduction	3:1	TNF signaling
2:1	Death Receptor Signalling	3:2	p75 NTR receptor-mediated signalling
2:2	Intracellular signaling by second messengers	3:3	DAG and IP3 signaling
2:3	MAPK family signaling cascades	3:4	PIP3 activates AKT signaling
2:4	Integrin signaling	3:5	MAPK1/MAPK3 signaling
2:5	Signaling by Erythropoietin	3:6	MAPK6/MAPK4 signaling Erythropoietin activates Phosphoinositide-3-kinase (PI3K)
2:6	Signaling by GPCR	3:7	Erythropoietin activates RAS
2:7	Signaling by Hedgehog	3:8	GPCR downstream signalling
2:8	Signaling by Hippo	3:9	GPCR ligand binding
2:9	Signaling by Leptin	3:10	Hedgehog 'off' state
2:10	Signaling by NOTCH	3:11	Hedgehog 'on' state
2:11	Signaling by Non-Receptor Tyrosine Kinases	3:12	Hedgehog ligand biogenesis
2:12	Signaling by Nuclear Receptors	3:13	Pre-NOTCH Expression and Processing
2:13	Signaling by Receptor Tyrosine Kinases	3:14	Signaling by NOTCH1
2:14	Signaling by Rho GTPases	3:15	Signaling by NOTCH3
2:15	Signaling by TGF-beta family members	3:16	Signaling by NOTCH4
2:16	Signaling by WNT	3:17	Signaling by PTK6
2:17	mTOR signalling	3:18	ESR-mediated signaling

Online Resource 7

Hierarchical representation of the GSA results for all pathways contained in the top Reactome “Extracellular matrix organization” category and for the two-factor “Ana 20*DSS” interaction. The contents of this plot have been explained in the legends of Fig. 3C and Online Resource 3. The Reactome pathway names corresponding to the node labels are given in the lower part of the figure.

Extracellular matrix organization



Online Resource 7 continued

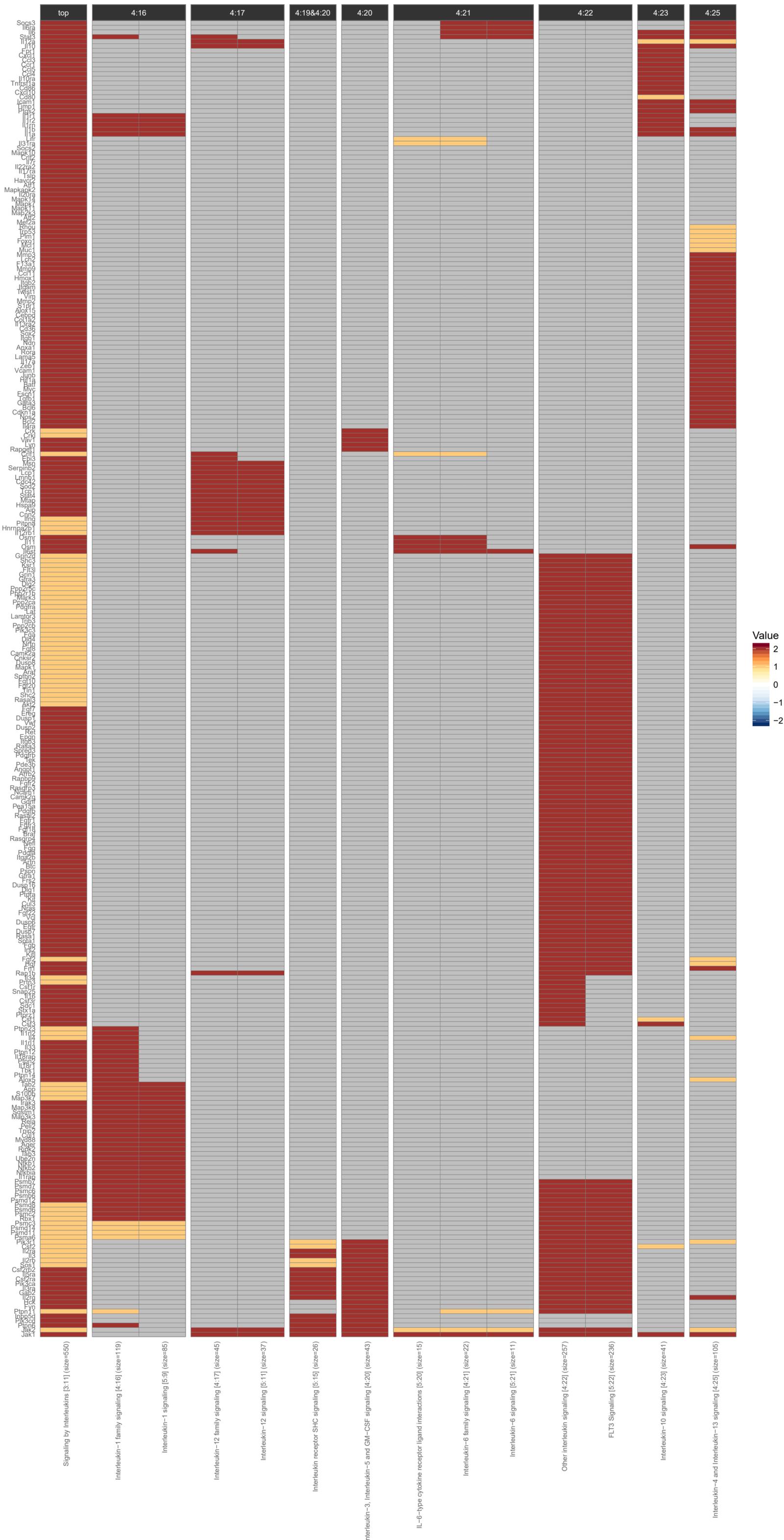
For more details see Online Resource 12.

- 3:1 Collagen biosynthesis and modifying enzymes
- 4:1 Collagen chain trimerization
- 2:1 Collagen formation
- 3:2 Assembly of collagen fibrils and other multimeric structures
- 2:2 Degradation of the extracellular matrix
- 3:3 Activation of Matrix Metalloproteinases
- 3:4 Collagen degradation
- 2:3 Elastic fibre formation
- 3:5 Molecules associated with elastic fibres
- 1:1 Extracellular matrix organization
- 2:4 ECM proteoglycans
- 2:5 Integrin cell surface interactions
- 2:6 Laminin interactions
- 2:7 Non-integrin membrane-ECM interactions
- 3:6 Syndecan interactions

Membership heatmap for all pathways situated downstream of “Signaling by Interleukins” and “Toll-like Receptor Cascades” in the top Reactome “Immune System” category (nodes “3.11” and “3.24” in Fig. 3C and Online Resource 4). For a given pathway p (horizontal axis) and gene g (vertical axis), the values are either 0, 1, or 2. “0” means g does not belong to p; “1” means g belongs to p; and “2” means g is a leading-edge gene of p for the contrast “Ana 20*DSS”. The membership heatmap enables us to explicitly check whether the GSA results (and, in particular, the statistical significance) of pathways situated downstream of a given high-level pathway are driven by the same set of genes and, therefore, do not specifically reflect the hierarchical relationships between the considered pathways. The figure shows that the pathways downstream of “Signaling by Interleukins” are rather independent, whereas the ones downstream of “Toll-like Receptor Cascades” are strongly overlapping and, therefore, reflect the differential expression of the same set of genes.

A

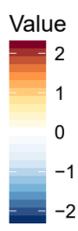
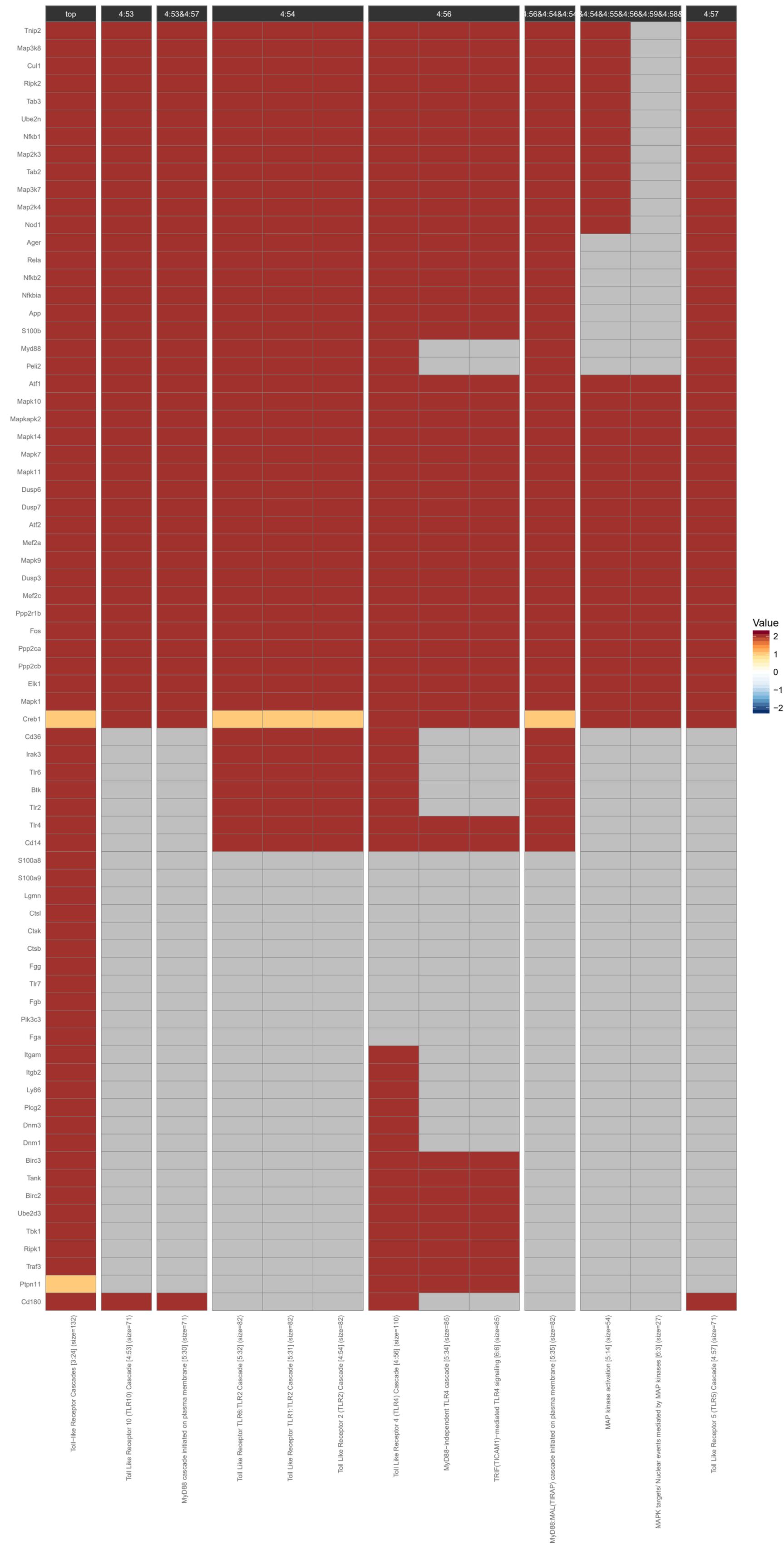
Membership and Leading-Edge gene heatmap Signaling by Interleukins [3:11] (Immune System)



Membership and Leading-Edge gene heatmap

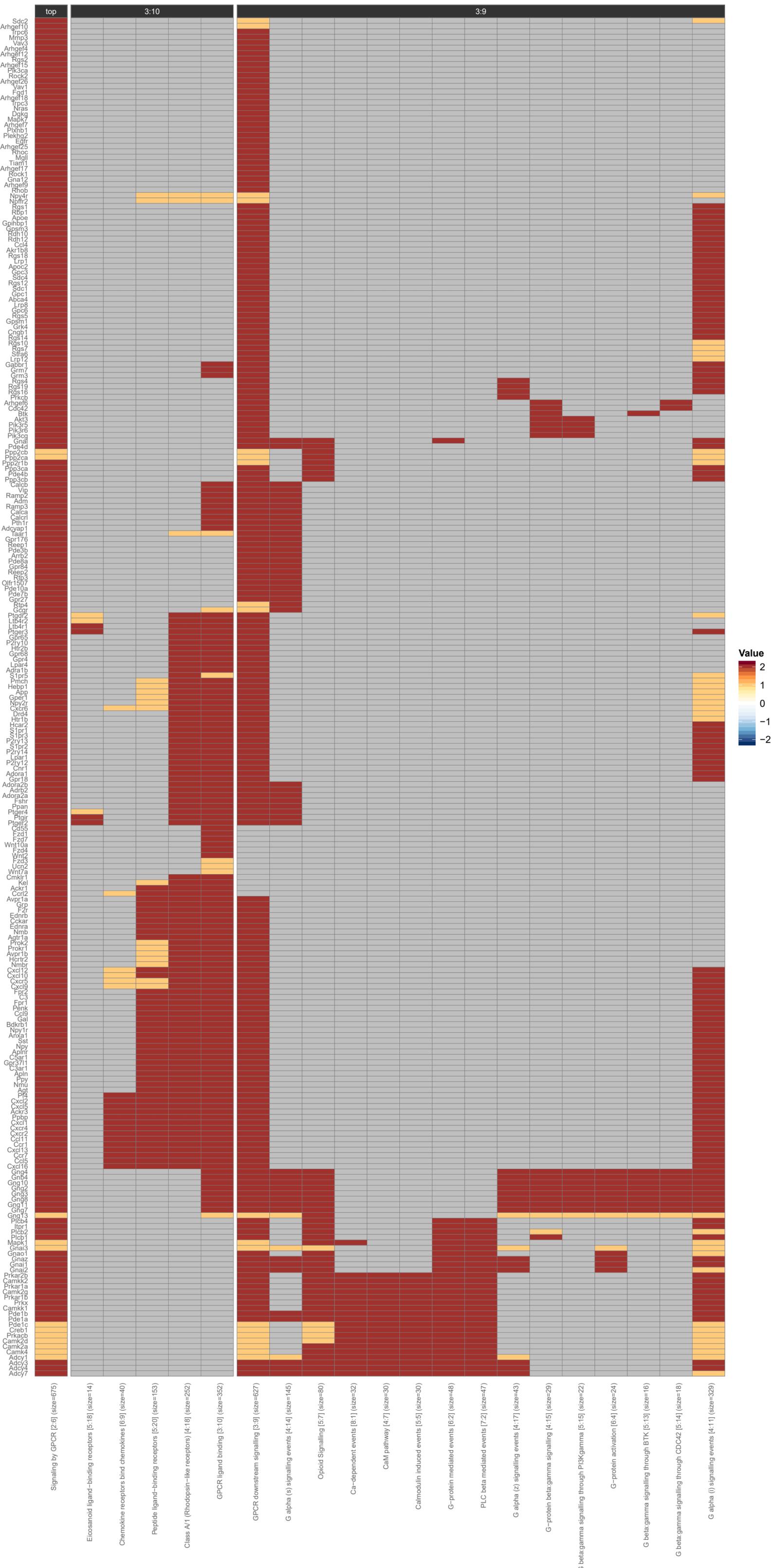
Toll-like Receptor Cascades [3:24] (Immune System)

B



Membership heatmap for all the pathways situated downstream of “Signaling by GPCR” in the top Reactome “Signal Transduction” category (nodes “2.6” in Online Resource 5). The contents and utility of the membership heatmap have been explained in the legend of Figure S7. The figure shows that the pathways downstream of “Signaling by GPCR” are rather independent, although the fraction of specific genes are quite small in a few cases.

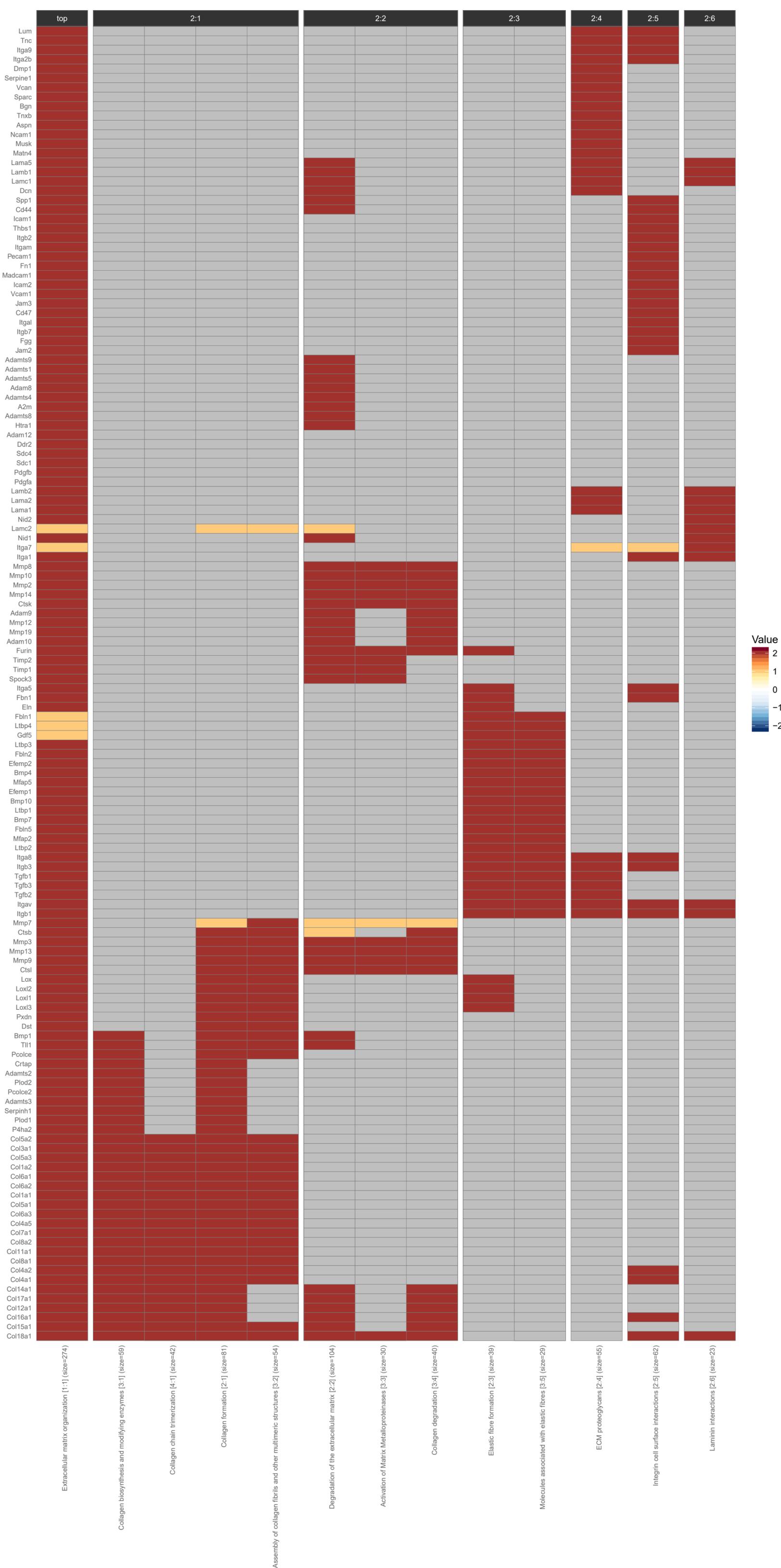
Membership and Leading-Edge gene heatmap
Signaling by GPCR [2:6] (Signal Transduction)



Membership heatmap for all pathways contained in the top “Extracellular matrix organization” category. For a given pathway p (horizontal axis) and gene g (vertical axis), the values are either 0, 1, or 2. “0” means g does not belong to p; “1” means g belongs to p; and “2” means g is a leading-edge gene of p for the contrast “Ana 20*DSS”. The membership heatmap enables us to explicitly check whether the GSA results (and, in particular, the statistical significance) of pathways situated downstream of a given high-level pathway are driven by the same set of genes and, therefore, do not specifically reflect the hierarchical relationships between the considered pathways. The figure shows that the pathways contained in the top “Extracellular matrix organization” category are quite independent.

Membership and Leading-Edge gene heatmap

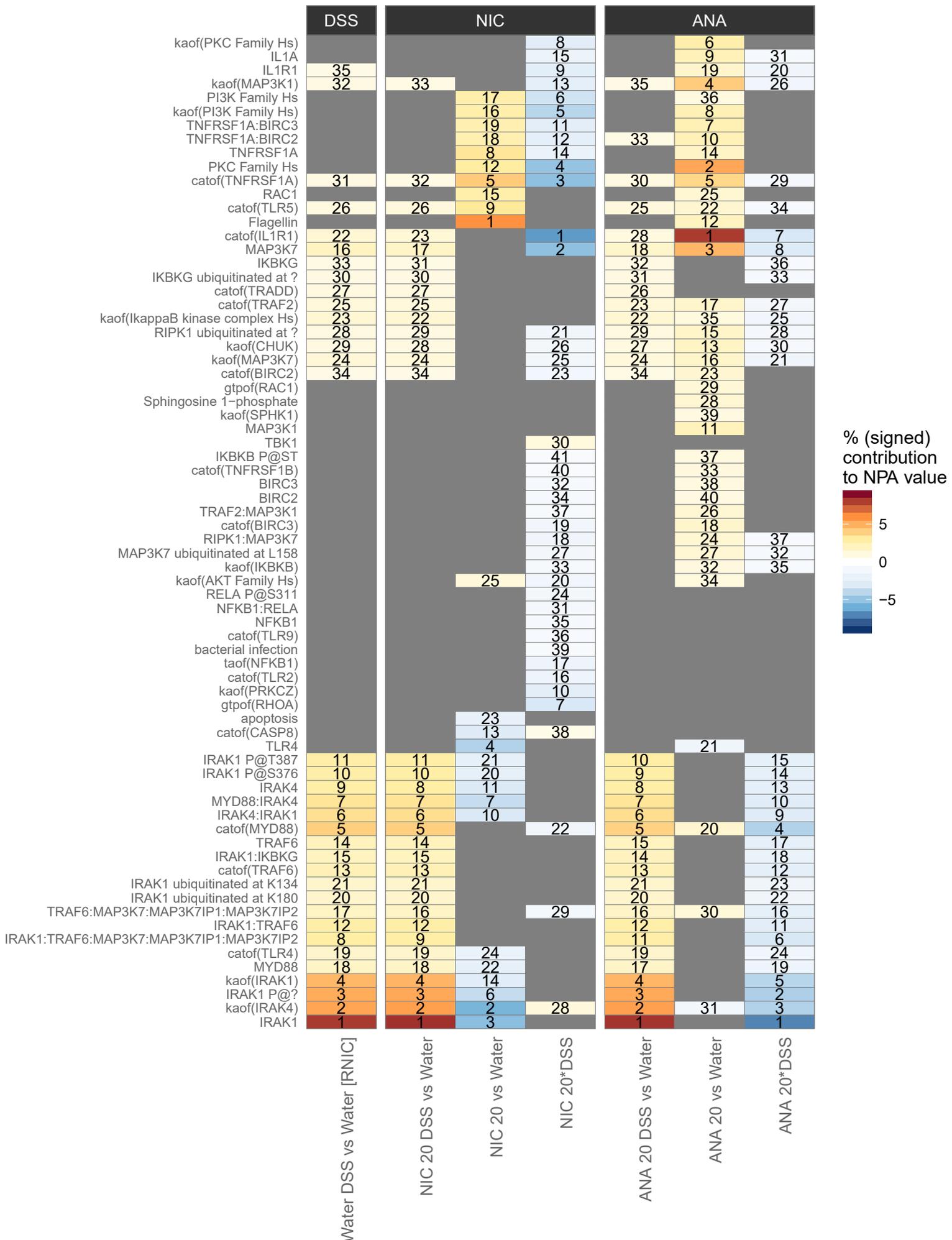
Extracellular matrix organization [1:1] (Extracellular matrix organization)



Heatmap of the leading node perturbations for the TLR–IL1R–TNFR network model. The leading nodes correspond to the network model nodes making the highest contributions to the NPA shown in Fig. 3D. The displayed values correspond to the (positive) percentage NPA contributions (up to a cumulative value of 80%) multiplied by the sign $\in \{-1, 1\}$ of the node-level perturbations. The annotated rank (starting at 1 for the highest contribution) enables us to identify the most relevant nodes.

Leading Nodes for Tnfl1Tlr Network

(Data range truncated in]-10, 10])



Online Resource 12

Reactome labels

Immune System	x
Adaptive Immune System	2:1
Class I MHC mediated antigen processing & presentation	3:1
Costimulation by the CD28 family	3:2
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	3:3
MHC class II antigen presentation	3:4
Rap1 signalling	3:5
Signaling by the B Cell Receptor (BCR)	3:6
TCR signaling	3:7
Antigen processing-Cross presentation	4:1
Cross-presentation of soluble exogenous antigens (endosomes)	5:1
ER-Phagosome pathway	5:2
Antimicrobial peptides	3:13
Defensins	4:30
Antiviral mechanism by IFN-stimulated genes	4:13
ISG15 antiviral mechanism	5:6
C-type lectin receptors (CLRs)	3:14
CD209 (DC-SIGN) signaling	4:31
CLEC7A (Dectin-1) signaling	4:32
Dectin-2 family	4:33
CD28 co-stimulation	4:4
CD28 dependent PI3K/Akt signaling	5:3
CD28 dependent Vav1 pathway	5:4
CLEC7A (Dectin-1) induces NFAT activation	5:24
Dectin-1 mediated noncanonical NF-kB signaling	5:25
Antigen Presentation: Folding, assembly and peptide loading of class I MHC	4:2
Antigen processing: Ubiquitination & Proteasome degradation	4:3
Complement cascade	3:15
Initial triggering of complement	4:34
Regulation of Complement cascade	4:35
CTLA4 inhibitory signaling	4:5
PD-1 signaling	4:6
Creation of C4 and C2 activators	5:26
Classical antibody-mediated complement activation	6:5
Cytokine Signaling in Immune system	2:2
Growth hormone receptor signaling	3:8
Interferon Signaling	3:9
Prolactin receptor signaling	3:10
Signaling by Interleukins	3:11
TNFR2 non-canonical NF-kB pathway	3:12
Cytosolic sensors of pathogen-associated DNA	3:16
Regulation of innate immune responses to cytosolic DNA	4:36
STING mediated induction of host immune responses	4:37
ZBP1(DAI) mediated induction of type I IFNs	4:38
DAP12 interactions	3:17
DAP12 signaling	4:39

DDX58/IFIH1-mediated induction of interferon-alpha/beta	3:18
Negative regulators of DDX58/IFIH1 signaling	4:40
TRAF3-dependent IRF activation pathway	4:41
TRAF6 mediated IRF7 activation	4:42
TRAF6 mediated NF-kB activation	4:43
Beta defensins	5:23
Downstream signaling events of B Cell Receptor (BCR)	4:7
Activation of NF-kappaB in B cells	5:5
Fc epsilon receptor (FCERI) signaling	3:19
FCERI mediated Ca ²⁺ mobilization	4:44
FCERI mediated MAPK activation	4:45
FCERI mediated NF-kB activation	4:46
Role of LAT2/NTAL/LAB on calcium mobilization	4:47
Fc gamma receptor (FCGR) dependent phagocytosis	3:20
FCGR activation	4:48
Regulation of actin dynamics for phagocytic cup formation	4:49
Role of phospholipids in phagocytosis	4:50
Immune System	1:1
Innate Immune System	2:3
Inflammasomes	4:51
The NLRP3 inflammasome	5:29
Neutrophil degranulation	3:21
Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	3:22
ROS and RNS production in phagocytes	3:23
Toll-like Receptor Cascades	3:24
Interferon alpha/beta signaling	4:14
Interferon gamma signaling	4:15
Regulation of IFNA signaling	5:7
Regulation of IFNG signaling	5:8
Interleukin-1 family signaling	4:16
Interleukin-1 signaling	5:9
Interleukin-37 signaling	5:10
MAP3K8 (TPL2)-dependent MAPK1/3 activation	6:1
TAK1 activates NFkB by phosphorylation and activation of IKKs complex	5:33
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Interleukin-27 signaling	5:12
Interleukin-35 Signalling	5:13
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MAP kinase activation	5:14
Interleukin-2 family signaling	4:19
Interleukin receptor SHC signaling	5:15
Interleukin-15 signaling	5:16
Interleukin-2 signaling	5:17
Interleukin-21 signaling	5:18
Interleukin-3, Interleukin-5 and GM-CSF signaling	4:20
Regulation of signaling by CBL	5:19
Interleukin-6 family signaling	4:21
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Interleukin-6 signaling	5:21
JNK (c-Jun kinases) phosphorylation and activation mediated by activated human TAK1	6:2
MAPK targets/ Nuclear events mediated by MAP kinases	6:3
activated TAK1 mediates p38 MAPK activation	6:4
MyD88 cascade initiated on plasma membrane	5:30
MyD88 dependent cascade initiated on endosome	5:36
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	6:7
MyD88-independent TLR4 cascade	5:34
TRIF(TICAM1)-mediated TLR4 signaling	6:6
MyD88:MAL(TIRAP) cascade initiated on plasma membrane	5:35
NOD1/2 Signaling Pathway	4:52
Other interleukin signaling	4:22
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Interleukin-20 family signaling	4:24
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Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	4:8
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Phosphorylation of CD3 and TCR zeta chains	4:11
Translocation of ZAP-70 to Immunological synapse	4:12
NIK-->noncanonical NF-kB signaling	4:27
TNF receptor superfamily (TNFSF) members mediating non-canonical NF-kB pathway	4:28
TNFs bind their physiological receptors	4:29
IRAK2 mediated activation of TAK1 complex upon TLR7/8 or 9 stimulation	7:4
Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	7:1
IKK complex recruitment mediated by RIP1	7:2
TRAF6-mediated induction of TAK1 complex within TLR4 complex	7:3
Toll Like Receptor 10 (TLR10) Cascade	4:53
Toll Like Receptor 2 (TLR2) Cascade	4:54
Toll Like Receptor TLR1:TLR2 Cascade	5:31
Toll Like Receptor TLR6:TLR2 Cascade	5:32
Toll Like Receptor 3 (TLR3) Cascade	4:55
Toll Like Receptor 4 (TLR4) Cascade	4:56
Toll Like Receptor 5 (TLR5) Cascade	4:57
Toll Like Receptor 7/8 (TLR7/8) Cascade	4:58
Toll Like Receptor 9 (TLR9) Cascade	4:59
Regulation of TLR by endogenous ligand	4:60
Trafficking and processing of endosomal TLR	4:61
RIP-mediated NFkB activation via ZBP1	5:28

Extracellular matrix organization	x
Collagen biosynthesis and modifying enzymes	3:1
Collagen chain trimerization	4:1
Collagen formation	2:1
Assembly of collagen fibrils and other multimeric structures	3:2
Degradation of the extracellular matrix	2:2
Activation of Matrix Metalloproteinases	3:3
Collagen degradation	3:4
Elastic fibre formation	2:3
Molecules associated with elastic fibres	3:5
Extracellular matrix organization	1:1
ECM proteoglycans	2:4
Integrin cell surface interactions	2:5
Laminin interactions	2:6
Non-integrin membrane-ECM interactions	2:7
Syndecan interactions	3:6

Signal Transduction	x
Amine ligand-binding receptors	5:17
Serotonin receptors	6:7
Beta-catenin independent WNT signaling	3:37
Ca ²⁺ pathway	4:75
PCP/CE pathway	4:76
Ca-dependent events	8:1
CaM pathway	4:7
Calmodulin induced events	5:5
PKA-mediated phosphorylation of CREB	6:1
Cell death signalling via NRAGE, NRIF and NADE	4:4
NRAGE signals death through JNK	5:1
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Class A/1 (Rhodopsin-like receptors)	4:18
Eicosanoid ligand-binding receptors	5:18
Nucleotide-like (purinergic) receptors	5:19
Peptide ligand-binding receptors	5:20
Class B/2 (Secretin family receptors)	4:19
Calcitonin-like ligand receptors	5:21
Glucagon-type ligand receptors	5:22
DAG and IP3 signaling	3:3
Death Receptor Signalling	2:1
TNF signaling	3:1
p75 NTR receptor-mediated signalling	3:2
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Downstream signaling of activated FGFR1	5:24
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Downstream signaling of activated FGFR2	5:28
FRS-mediated FGFR2 signaling	6:16
PI-3K cascade:FGFR2	6:17
Phospholipase C-mediated cascade; FGFR2	6:18
SHC-mediated cascade:FGFR2	6:19
Downstream signaling of activated FGFR3	5:32
FRS-mediated FGFR3 signaling	6:21
PI-3K cascade:FGFR3	6:22
Phospholipase C-mediated cascade; FGFR3	6:23
SHC-mediated cascade:FGFR3	6:24
Downstream signaling of activated FGFR4	5:35
FRS-mediated FGFR4 signaling	6:26
PI-3K cascade:FGFR4	6:27
Phospholipase C-mediated cascade; FGFR4	6:28
SHC-mediated cascade:FGFR4	6:29
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Estrogen-dependent nuclear events downstream of ESR-membrane signaling	5:23

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FGFR1c ligand binding and activation	6:14
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FGFR2c ligand binding and activation	6:20
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FGFR3c ligand binding and activation	6:25
G alpha (i) signalling events	4:11
Opioid Signalling	5:7
Visual phototransduction	5:10
G alpha (q) signalling events	4:13
Gastrin-CREB signalling pathway via PKC and MAPK	5:11
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Olfactory Signaling Pathway	5:12
G-protein beta:gamma signalling	4:15
G beta:gamma signalling through BTK	5:13
G beta:gamma signalling through CDC42	5:14
G beta:gamma signalling through PI3Kgamma	5:15
G beta:gamma signalling through PLC beta	5:16
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GPCR downstream signalling	3:9
G alpha (12/13) signalling events	4:16
G alpha (z) signalling events	4:17
GPCR ligand binding	3:10
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Hedgehog 'off' state	3:11
Degradation of GLI1 by the proteasome	4:21
GLI3 is processed to GLI3R by the proteasome	4:22
Hedgehog 'on' state	3:12
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IRS-mediated signalling	5:38
Insulin receptor signalling cascade	4:51
Intracellular signaling by second messengers	2:2
PIP3 activates AKT signaling	3:4
MAPK family signaling cascades	2:3
MAPK1/MAPK3 signaling	3:5
MAPK6/MAPK4 signaling	3:6
RAF-independent MAPK1/3 activation	4:12
MET promotes cell motility	4:53
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Signaling by Erythropoietin	2:5
Signaling by GPCR	2:6
Signaling by Hedgehog	2:7
Signaling by Hippo	2:8
Signaling by Leptin	2:9
Signaling by NOTCH	2:10
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