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Supplementary Methods

Building the KEGG regulatory network

In this study, we used the information of the regulatory pathways of the KEGG database to build a human regulatory network as input for our algorithm. We imported the KEGG regulatory network via the Biochemical Network Database (BNDB) [1] that integrates various external network databases. The BNDB is part of the biological information system BN++ [2], which provides importers for different databases, e.g., for the regulatory network databases as KEGG [3–5] or Transpath [6] and for the protein-protein interaction databases as DIP [7], HPRD [8], MINT [9], and IntAct [10]. The usage of the BNDB has the advantage that we have access to the data of different databases using the same interface. In the BNDB, a pathway is modeled as series of events (e.g. reaction, interaction), in which different participants (e.g. genes/proteins) can take part and play different roles (e.g. product, educt). When building the regulatory network, we retrieve all participants and events in the BNDB that are part of a KEGG regulatory pathway and construct a so called compound graph. The compound graph models the participants as nodes and the events as edges between these nodes. Since KEGG pathways also contain protein families, we transform the original KEGG pathways by splitting the nodes of protein families into their components. Given a protein family, we replace the family node by a set of nodes where each node represents a family member. Each new node is connected to all neighbors of the original family node, i.e., it has the same set of incoming and outcoming edges as the original family node, and receives the score of its corresponding gene. Here, we assume that all family members interact in the same manner with the neighboring nodes of the original family node. Furthermore, we apply a splitting of protein complexes that contain protein families, such that we create a new protein complex for each member of the contained protein family. The score of a protein complex is computed by taking the minimum score of its components, because we assume that the component with lowest amount is the limitating factor for building the complex. For the mapping of the genes and their scores to the nodes of this network, we used the NCBI Gene identifier.

Supplementary Figures

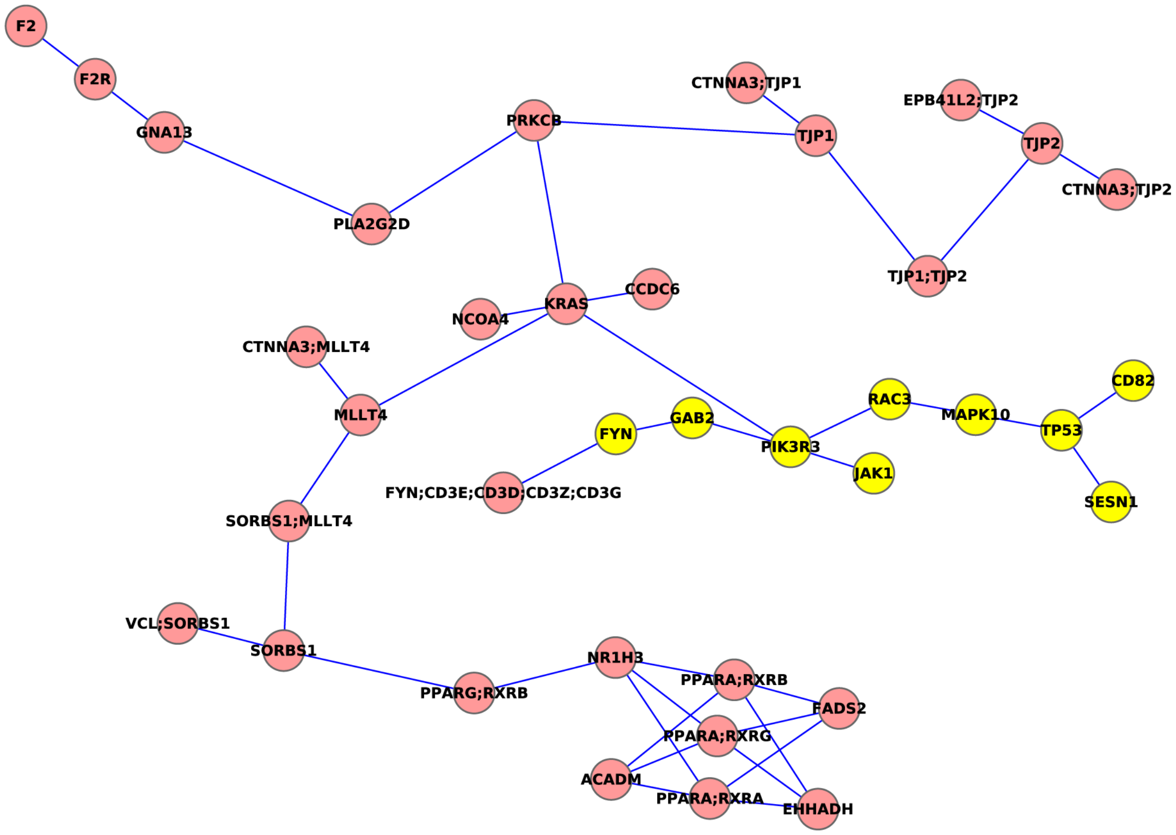
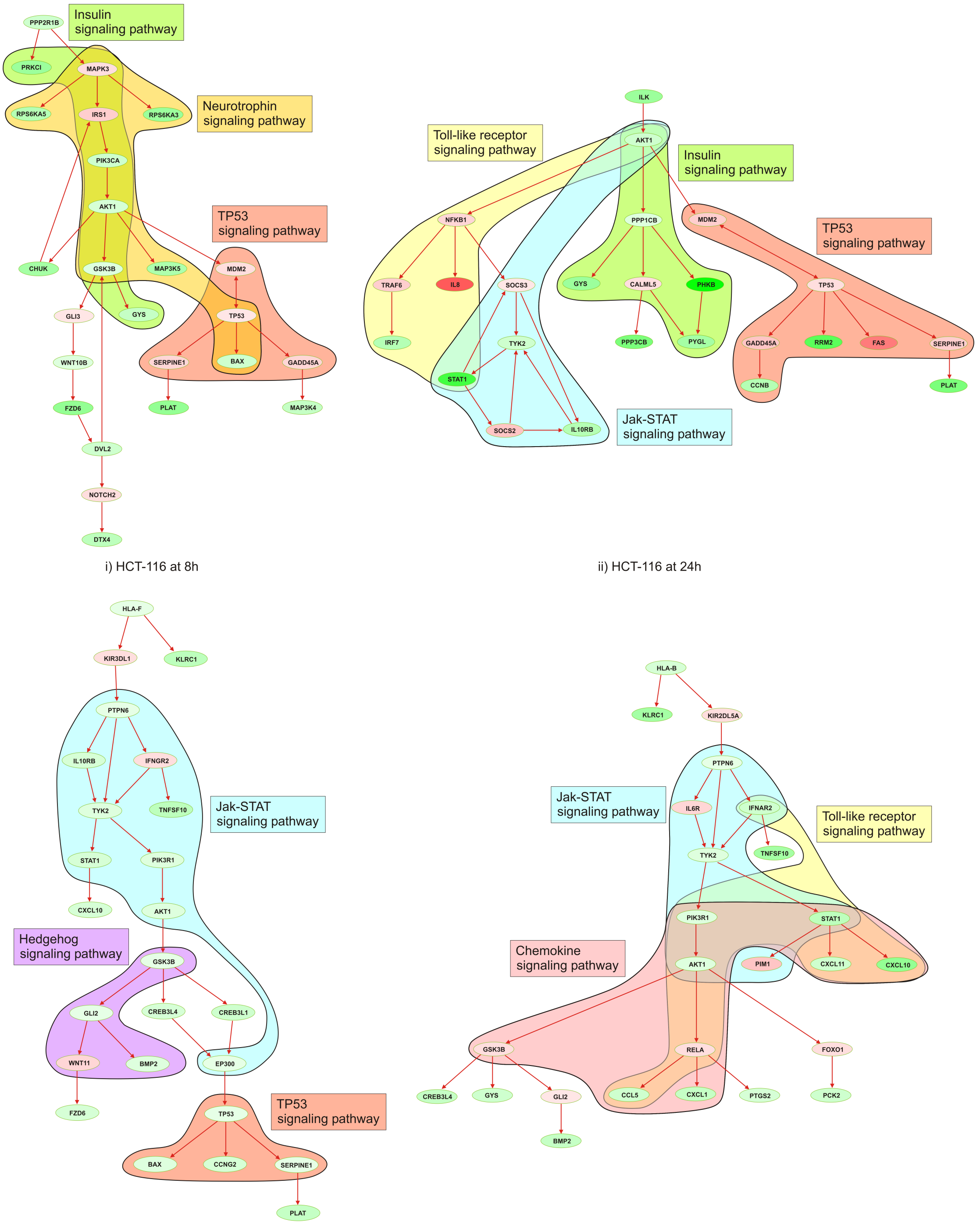


Figure 1: Deregulated network for the glioma data set computed with BioNet. The yellow nodes are also part of the deregulated (directed) network computed with our ILP approach.



i) HCT-116 at 8h

ii) HCT-116 at 24h

iii) HT-29 at 8h

iv) HT-29 at 24h

Figure 2: Significantly enriched regulatory pathways found in the computed subnetworks of size 25 for the different colorectal adenocarcinoma cell lines.

Supplementary Tables

Table 1: Overview of network-based tools and algorithms

Tool/Algorithm	**advantages**	**disadvantages**	**availability**
our ILP	takes network direction into account computes the optimal result according to the scoring method fast run-time for subnetwork sizes 10-25 visualization of the results in BiNA [2] or Cytoscape [11]	runtime can be exponential	`http://genetrail.bioinf.uni-sb.de/ilp/`
BioNet [12]	computes the optimal result according to the scoring method subnetwork size is controlled by the FDR (false discovery rate) integration of multivariate p-values	runtime can be exponential direction in network is not taken into account	`http://bionet.bioapps.biozentrum.uni-wuerzburg.de/`
jActiveModules [13]	integrated in Cytoscape integration of multivariate p-values	heuristic often results are very large modules that are difficult to interpret	plugin in Cytoscape
derivatives of jActiveModules have been developed and expanded in later works [14–17]		heuristics	
ILP of Zhao *et al.* [18]	computes the optimal result according to the scoring method	runtime can be exponential direction in network is not taken into account	
OptDis [19]	computes the optimal result according to the scoring method	runtime only fast for very small subnetworks (sizes << 10)	`http://www.cs.sfu.ca/~pdao/personal/OptDis.html`
HotNet [20]	identifies significantly mutated subnetworks	approximation algorithm direction in network is not taken into account	`http://cs.brown.edu/people/braphael/software.html`
FiDePa [21]	uses a dynamic programming approach (cubic running time) takes network direction into account	computes only simple deregulated paths	
DEGAS [22, 23]	integrated into the MATISSE software	heuristic direction in network is not taken into account	`http://acgt.cs.tau.ac.il/matisse`

RegMOD [24]	employs a regression model	direction in network is not taken into account	
Su *et al.* [25]	dynamic programming	computes simple discriminative paths and combines them greedily into subnetworks direction in network is not taken into account	
Fortney *et al.* [26]	incorporates topological modularity into the subnetwork score	heuristic direction in network is not taken into account	`http://www.cs.utoronto.ca/~juris/data/GB10/`
Wu *et al.* [27]	prediction of a drug effect on network activities	direction in network is not taken into account optimal solution not guaranteed (LP relaxation of the problem)	
NetCover [28]	computes coordinately dysregulated subnetworks	approximation algorithm direction in network is not taken into account	

Table 2: Significantly enriched pathways which are covered by the genes of the deregulated subgraph of size 25 for BRCA1 mutation carriers versus non-mutation carriers. The p-values were computed by using the hypergeometric distribution test (ORA) with the genes of the subgraph as test set and the genes of the regulatory graph as reference set. The p-values are FDR adjusted.

Pathway Source	**Pathway Name**	**p-value**	**number of genes in subgraph**
KEGG	Pathways in cancer	0.000442969	12
KEGG	MAPK signaling pathway	0.000442969	11
KEGG	Focal adhesion	0.000442969	10
KEGG	VEGF signaling pathway	3.22812e-07	10
KEGG	Neurotrophin signaling pathway	4.64128e-05	9
KEGG	Renal cell carcinoma	5.15226e-07	9
KEGG	T cell receptor signaling pathway	0.000288768	8
KEGG	Toll-like receptor signaling pathway	0.000442969	7
KEGG	ErbB signaling pathway	0.000442969	7
KEGG	GnRH signaling pathway	0.000482278	7
KEGG	Insulin signaling pathway	0.00272689	7
KEGG	Chemokine signaling pathway	0.00333032	7
MSigDB	BOQUEST CD31PLUS VS CD31MINUS UP	0.017504	7
KEGG	Glioma	0.000452846	6
KEGG	Pancreatic cancer	0.000587537	6
KEGG	Fc epsilon RI signaling pathway	0.000879813	6
KEGG	Colorectal cancer	0.00118209	6
KEGG	B cell receptor signaling pathway	0.00333032	5
MSigDB	HYPOXIA REVIEW	0.00484667	5
KEGG	Chronic myeloid leukemia	0.00486093	5
KEGG	Bladder cancer	0.00235075	4
KEGG	mTOR signaling pathway	0.00507319	4
KEGG	Epithelial cell signaling in Helicobacter pylori infection	0.00507319	4
KEGG	Non-small cell lung cancer	0.00670911	4
KEGG	Endometrial cancer	0.00803437	4
MSigDB	SHEPARD CRASH AND BURN MUT VS WT UP	0.00860306	4
MSigDB	CHEN HOXA5 TARGETS UP	0.00922605	4
MSigDB	HYPOXIA NORMAL UP	0.0130697	4
MSigDB	METPATHWAY	0.014913	4
MSigDB	KERATINOCYTEPATHWAY	0.0205406	4
KEGG	Melanoma	0.0206123	4
KEGG	p53 signaling pathway	0.0210982	4
KEGG	Fc gamma R-mediated phagocytosis	0.0210982	4
MSigDB	SIG PIP3 SIGNALING IN CARDIAC MYOCTES	0.0267726	4
KEGG	Prostate cancer	0.0273038	4
KEGG	Small cell lung cancer	0.0288885	4
KEGG	Vascular smooth muscle contraction	0.0304471	4
MSigDB	ST INTEGRIN SIGNALING PATHWAY	0.046262	4
MSigDB	RAS ONCOGENIC SIGNATURE	0.0471463	4
MSigDB	INSULIN SIGNALING	0.0488835	4

Table 3: List of genes found in the 16 computed deregulated subgraphs of sizes 10-25 and number of occurrences for HCT116 at 8h.

Gene ID	**Gene Symbol**	**Gene Description**	**Number of occurrences in the 16 deregulated subgraphs**
9252	RPS6KA5	ribosomal protein S6 kinase, 90kDa, polypeptide 5	16
6197	RPS6KA3	ribosomal protein S6 kinase, 90kDa, polypeptide 3	16
5595	MAPK3	mitogen-activated protein kinase 3	16
5584	PRKCI	protein kinase C, iota	16
5519	PPP2R1B	protein phosphatase 2 (formerly 2A), regulatory subunit A, beta isoform	16
5290	PIK3CA	phosphoinositide-3-kinase, catalytic, alpha polypeptide	16
4217	MAP3K5	mitogen-activated protein kinase kinase kinase 5	16
3667	IRS1	insulin receptor substrate 1	16
207	AKT1	v-akt murine thymoma viral oncogene homolog 1	16
1147	CHUK	conserved helix-loop-helix ubiquitous kinase	16
7157	TP53	tumor protein p53	12
5327	PLAT	plasminogen activator, tissue	12
5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	12
4193	MDM2	Mdm2 p53 binding protein homolog (mouse)	12
8323	FZD6	frizzled homolog 6 (Drosophila)	8
7480	WNT10B	wingless-type MMTV integration site family, member 10B	8
2997	GYS1	glycogen synthase 1 (muscle)	8
2932	GSK3B	glycogen synthase kinase 3 beta	8
2737	GLI3	GLI family zinc finger 3	8
581	BAX	BCL2-associated X protein	6
1856	DVL2	dishevelled, dsh homolog 2 (Drosophila)	5
4853	NOTCH2	Notch homolog 2 (Drosophila)	4
4216	MAP3K4	mitogen-activated protein kinase kinase kinase 4	4
23220	DTX4	deltex homolog 4 (Drosophila)	4
1647	GADD45A	growth arrest and DNA-damage-inducible, alpha	4
818	CAMK2G	calcium/calmodulin-dependent protein kinase II gamma	1
7409	VAV1	vav 1 guanine nucleotide exchange factor	1
7294	TXK	TXK tyrosine kinase	1
6195	RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	1
5500	PPP1CB	protein phosphatase 1, catalytic subunit, beta isoform	1

Table 4: Significantly enriched pathways which are covered by the genes of the deregulated subgraph of size 25 for HCT116 at 8h. The p-values were computed by using the hypergeometric distribution test (ORA) with the genes of the subgraph as test set and the genes of the regulatory graph as reference set. The p-values are FDR adjusted.

Pathway Source	**Pathway Name**	**number of genes in subgraph**	**p-value (fdr)**
KEGG	Neurotrophin signaling pathway	10	1.05932e-05
KEGG	Colorectal cancer	8	6.44745e-05
KEGG	Basal cell carcinoma	6	0.000378943
KEGG	Prostate cancer	7	0.000378943
KEGG	Pathways in cancer	12	0.000703051
KEGG	Chronic myeloid leukemia	6	0.00164048
KEGG	Endometrial cancer	5	0.00246245
KEGG	Bladder cancer	4	0.00409835
KEGG	Glioma	5	0.0043246
KEGG	Insulin signaling pathway	7	0.0043246
KEGG	B cell receptor signaling pathway	5	0.00475801
KEGG	Melanoma	5	0.00475801
KEGG	Pancreatic cancer	5	0.00475801
KEGG	p53 signaling pathway	5	0.00505457
KEGG	MAPK signaling pathway	9	0.00546865
KEGG	mTOR signaling pathway	4	0.00619129
KEGG	Non-small cell lung cancer	4	0.00807308
KEGG	Apoptosis	5	0.00901418
KEGG	Acute myeloid leukemia	4	0.0135836
KEGG	Wnt signaling pathway	6	0.013908
KEGG	Melanogenesis	5	0.0186358
KEGG	Notch signaling pathway	3	0.0186358
KEGG	T cell receptor signaling pathway	5	0.0186358
KEGG	Type II diabetes mellitus	3	0.0193725
KEGG	Dorso-ventral axis formation	2	0.0229816
KEGG	Small cell lung cancer	4	0.0340931
KEGG	ErbB signaling pathway	4	0.0356502
KEGG	Amyotrophic lateral sclerosis (ALS)	3	0.0424121
KEGG	Toll-like receptor signaling pathway	4	0.0424121
KEGG	Chemokine signaling pathway	5	0.0424222
KEGG	Hedgehog signaling pathway	3	0.0424222
KEGG	Prion diseases	2	0.0454634

Table 5: List of genes found in the 16 computed deregulated subgraphs of sizes 10-25 and number of occurrences for HCT116 at 24h.

Gene ID	**Gene Symbol**	**Gene Description**	**Number of occurrences in the 16 deregulated subgraphs**
5500	PPP1CB	protein phosphatase 1, catalytic subunit, beta isoform	16
5257	PHKB	phosphorylase kinase, beta	16
4790	NFKB1	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	16
3576	IL8	interleukin 8	16
207	AKT1	v-akt murine thymoma viral oncogene homolog 1	16
7297	TYK2	tyrosine kinase 2	15
7157	TP53	tumor protein p53	15
6772	STAT1	signal transducer and activator of transcription 1, 91kDa	15
6241	RRM2	ribonucleotide reductase M2	15
4193	MDM2	Mdm2 p53 binding protein homolog (mouse)	15
355	FAS	Fas (TNF receptor superfamily, member 6)	15
2997	GYS1	glycogen synthase 1 (muscle)	15
5836	PYGL	phosphorylase, glycogen, liver	12
5327	PLAT	plasminogen activator, tissue	11
5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	11
3611	ILK	integrin-linked kinase	9
9021	SOCS3	suppressor of cytokine signaling 3	8
5532	PPP3CB	protein phosphatase 3 (formerly 2B), catalytic subunit, beta isoform	8
51806	CALML5	calmodulin-like 5	8
5290	PIK3CA	phosphoinositide-3-kinase, catalytic, alpha polypeptide	7
3588	IL10RB	interleukin 10 receptor, beta	6
891	CCNB1	cyclin B1	4
1647	GADD45A	growth arrest and DNA-damage-inducible, alpha	4
8835	SOCS2	suppressor of cytokine signaling 2	3
7189	TRAF6	TNF receptor-associated factor 6	2
3665	IRF7	interferon regulatory factor 7	2

Table 6: Significantly enriched pathways which are covered by the genes of the deregulated subgraph of size 25 for HCT116 at 24h. The p-values were computed by using the hypergeometric distribution test (ORA) with the genes of the subgraph as test set and the genes of the regulatory graph as reference set. The p-values are FDR adjusted.

Pathway Source	**Pathway Name**	**number of genes in subgraph**	**p-value (fdr)**
KEGG	p53 signaling pathway	7	0.000541376
KEGG	Insulin signaling pathway	8	0.00234585
KEGG	Toll-like receptor signaling pathway	6	0.00838484
KEGG	RIG-I-like receptor signaling pathway	4	0.0213575
KEGG	Apoptosis	5	0.0214299
KEGG	Starch and sucrose metabolism	2	0.0214299
KEGG	Jak-STAT signaling pathway	6	0.0231925
KEGG	Bladder cancer	3	0.0335209
KEGG	Glioma	4	0.0335209
KEGG	Neurotrophin signaling pathway	5	0.0335209
KEGG	Pancreatic cancer	4	0.0335209
KEGG	Chronic myeloid leukemia	4	0.0390747
KEGG	Prostate cancer	4	0.0434768
KEGG	Small cell lung cancer	4	0.049026
KEGG	Ubiquitin mediated proteolysis	3	0.049026

Table 7: List of genes found in the 16 computed deregulated subgraphs of sizes 10-25 and number of occurrences for HT29 at 8h.

Gene ID	**Gene Symbol**	**Gene Description**	**Number of occurrences in the 16 deregulated subgraphs**
8743	TNFSF10	tumor necrosis factor (ligand) superfamily, member 10	16
3460	IFNGR2	interferon gamma receptor 2 (interferon gamma transducer 1)	16
7297	TYK2	tyrosine kinase 2	14
6772	STAT1	signal transducer and activator of transcription 1, 91kDa	14
3627	CXCL10	chemokine (C-X-C motif) ligand 10	14
7157	TP53	tumor protein p53	12
5327	PLAT	plasminogen activator, tissue	12
5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	12
901	CCNG2	cyclin G2	11
3588	IL10RB	interleukin 10 receptor, beta	10
90993	CREB3L1	cAMP responsive element binding protein 3-like 1	8
6300	MAPK12	mitogen-activated protein kinase 12	8
5777	PTPN6	protein tyrosine phosphatase, non-receptor type 6	8
5594	MAPK1	mitogen-activated protein kinase 1	8
5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	8
3821	KLRC1	killer cell lectin-like receptor subfamily C, member 1	8
3802	KIR2DL1	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 1	8
3458	IFNG	interferon, gamma	8
3134	HLA-F	major histocompatibility complex, class I, F	8
2932	GSK3B	glycogen synthase kinase 3 beta	8
2353	FOS	FBJ murine osteosarcoma viral oncogene homolog	8
207	AKT1	v-akt murine thymoma viral oncogene homolog 1	8
1847	DUSP5	dual specificity phosphatase 5	8
148327	CREB3L4	cAMP responsive element binding protein 3-like 4	8
8323	FZD6	frizzled homolog 6 (Drosophila)	7
7481	WNT11	wingless-type MMTV integration site family, member 11	7
2736	GLI2	GLI family zinc finger 2	7
581	BAX	BCL2-associated X protein	5
650	BMP2	bone morphogenetic protein 2	4
2033	EP300	E1A binding protein p300	4
9655	SOCS5	suppressor of cytokine signaling 5	2
2535	FZD2	frizzled homolog 2 (Drosophila)	1

Table 8: Significantly enriched pathways which are covered by the genes of the deregulated subgraph of size 25 for HT29 at 8h. The p-values were computed by using the hypergeometric distribution test (ORA) with the genes of the subgraph as test set and the genes of the regulatory graph as reference set. The p-values are FDR adjusted.

Pathway Source	**Pathway Name**	**number of genes in subgraph**	**p-value (fdr)**
KEGG	Basal cell carcinoma	6	0.000600589
KEGG	Prostate cancer	7	0.000600589
KEGG	Jak-STAT signaling pathway	8	0.00132186
KEGG	Colorectal cancer	6	0.00247764
KEGG	Huntington's disease	5	0.00247764
KEGG	Pathways in cancer	11	0.00247764
KEGG	Melanogenesis	6	0.00746352
KEGG	Apoptosis	5	0.0123783
KEGG	Endometrial cancer	4	0.0123783
KEGG	Graft-versus-host disease	3	0.0123783
KEGG	Hedgehog signaling pathway	4	0.0123783
KEGG	Natural killer cell mediated cytotoxicity	6	0.0164234
KEGG	B cell receptor signaling pathway	4	0.024582
KEGG	Neurotrophin signaling pathway	5	0.024582
KEGG	Pancreatic cancer	4	0.024582
KEGG	p53 signaling pathway	4	0.0252623
KEGG	Antigen processing and presentation	3	0.0491967
KEGG	Non-small cell lung cancer	3	0.0491967
KEGG	Toll-like receptor signaling pathway	4	0.0491967
KEGG	Wnt signaling pathway	5	0.0491967
KEGG	Chemokine signaling pathway	5	0.049626

Table 9: List of genes found in the 16 computed deregulated subgraphs of sizes 10-25 and number of occurrences for HT29 at 24h.

Gene ID	**Gene Symbol**	**Gene Description**	**Number of occurrences in the 16 deregulated subgraphs**
8743	TNFSF10	tumor necrosis factor (ligand) superfamily, member 10	16
7297	TYK2	tyrosine kinase 2	16
6772	STAT1	signal transducer and activator of transcription 1, 91kDa	16
6373	CXCL11	chemokine (C-X-C motif) ligand 11	16
5292	PIM1	pim-1 oncogene	16
3627	CXCL10	chemokine (C-X-C motif) ligand 10	16
3455	IFNAR2	interferon (alpha, beta and omega) receptor 2	16
2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	11
5777	PTPN6	protein tyrosine phosphatase, non-receptor type 6	10
57292	KIR2DL5A	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5A	10
3821	KLRC1	killer cell lectin-like receptor subfamily C, member 1	10
3106	HLA-B	major histocompatibility complex, class I, B	10
5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	7
2997	GYS1	glycogen synthase 1 (muscle)	7
2932	GSK3B	glycogen synthase kinase 3 beta	7
207	AKT1	v-akt murine thymoma viral oncogene homolog 1	7
148327	CREB3L4	cAMP responsive element binding protein 3-like 4	7
650	BMP2	bone morphogenetic protein 2	6
6352	CCL5	chemokine (C-C motif) ligand 5	6
5970	RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	6
5595	MAPK3	mitogen-activated protein kinase 3	6
3570	IL6R	interleukin 6 receptor	6
3458	IFNG	interferon, gamma	6
2736	GLI2	GLI family zinc finger 2	6
1847	DUSP5	dual specificity phosphatase 5	6
9540	TP53I3	tumor protein p53 inducible protein 3	5
7157	TP53	tumor protein p53	5
5743	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	5
5603	MAPK13	mitogen-activated protein kinase 13	5
1643	DDB2	damage-specific DNA binding protein 2, 48kDa	4
581	BAX	BCL2-associated X protein	3
3588	IL10RB	interleukin 10 receptor, beta	2
27244	SESN1	sestrin 1	2
9252	RPS6KA5	ribosomal protein S6 kinase, 90kDa, polypeptide 5	1
5106	PCK2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	1
2308	FOXO1	forkhead box O1	1

Table 10: Significantly enriched pathways which are covered by the genes of the deregulated subgraph of size 25 for HT29 at 24h. The p-values were computed by using the hypergeometric distribution test (ORA) with the genes of the subgraph as test set and the genes of the regulatory graph as reference set. The p-values are FDR adjusted.

Pathway Source	**Pathway Name**	**number of genes in subgraph**	**p-value (fdr)**
KEGG	Toll-like receptor signaling pathway	8	0.000248717
KEGG	Chemokine signaling pathway	9	0.000389392
KEGG	Jak-STAT signaling pathway	8	0.00116449
KEGG	Prostate cancer	6	0.00232453
KEGG	Cytokine-cytokine receptor interaction	8	0.00526996
KEGG	Natural killer cell mediated cytotoxicity	7	0.00526996
KEGG	B cell receptor signaling pathway	5	0.00536653
KEGG	Graft-versus-host disease	3	0.0137449
KEGG	Insulin signaling pathway	6	0.0178715
KEGG	Acute myeloid leukemia	4	0.0180175
KEGG	Pathways in cancer	9	0.0213658
KEGG	T cell receptor signaling pathway	5	0.0239912
KEGG	Pancreatic cancer	4	0.0247014
KEGG	Epithelial cell signaling in Helicobacter pylori infection	3	0.0412548
KEGG	Small cell lung cancer	4	0.0412548
KEGG	Apoptosis	4	0.0419982
KEGG	Antigen processing and presentation	3	0.047616
KEGG	Basal cell carcinoma	3	0.047616
KEGG	Endometrial cancer	3	0.047616
KEGG	Hedgehog signaling pathway	3	0.047616

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