1   *Article*
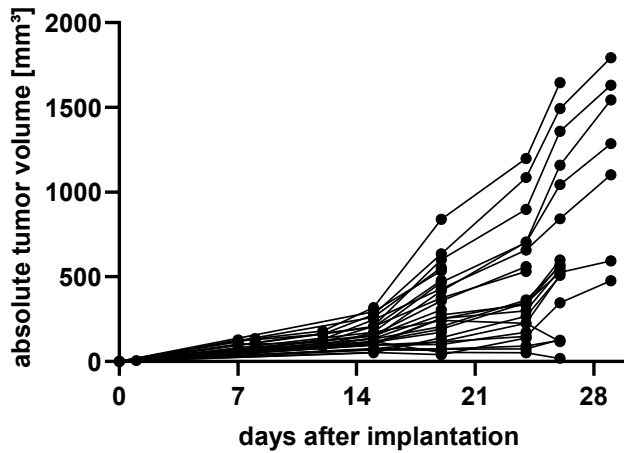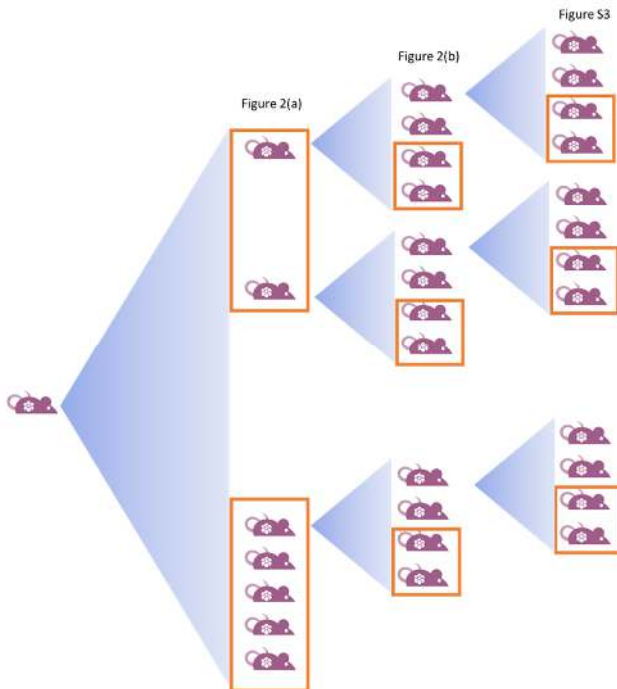
2   **Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1,

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5   Supplemental Figure S1. Tumor growth behavior of subcutaneously implanted LXFA 677 in vivo. LXFA 677 was
6   implanted subcutaneously into NMRI nude mice. Tumor volume was measured twice weekly from the day of
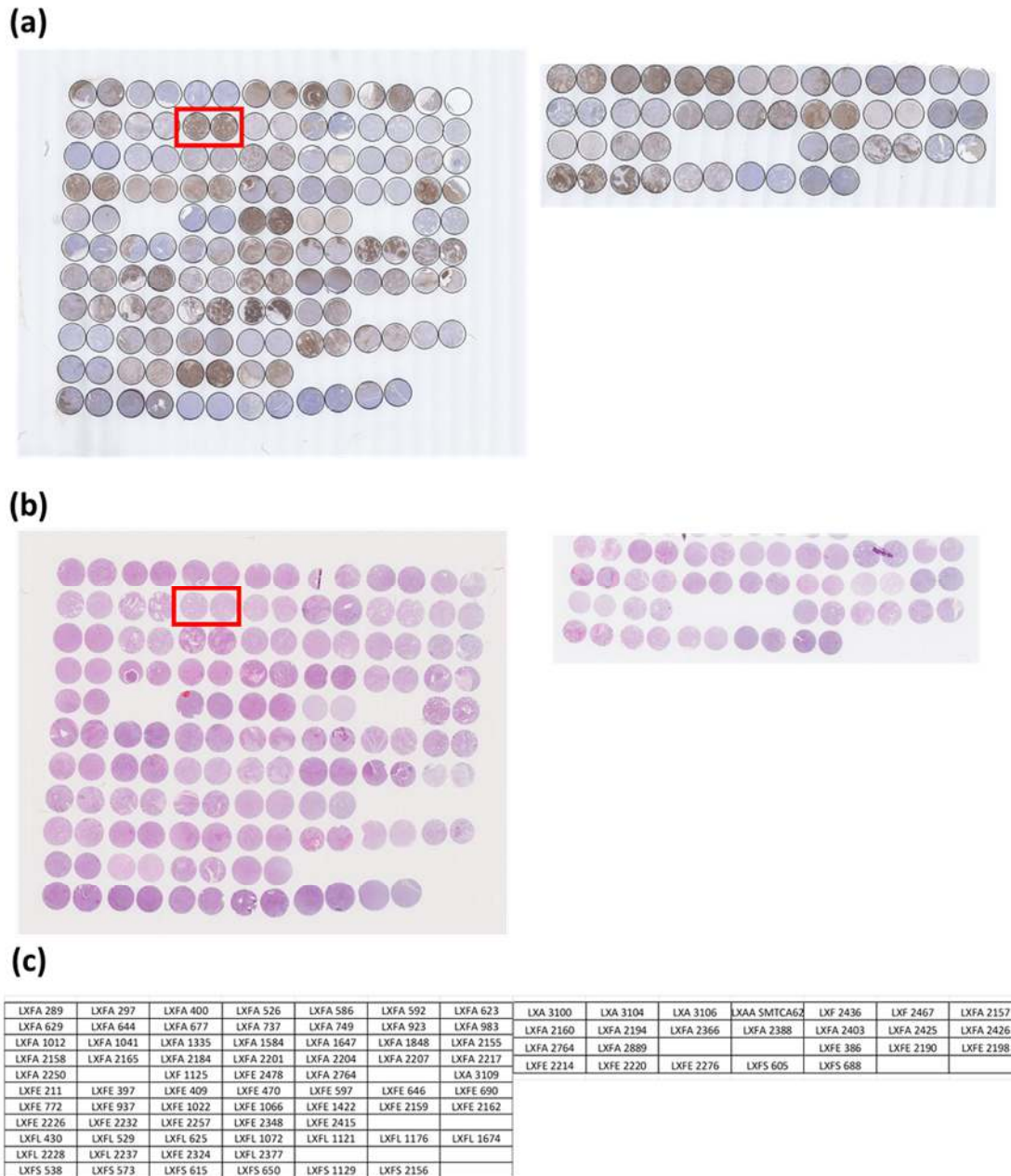7   implantation for four weeks.

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9

10   Supplemental Figure S2: Induction of resistance in NSCLC PDX LXFA 677 in vivo. Flowchart of the
11   transplantation and treatment process of LXFA 677 and the three resistant sublines. Untreated LXFA 677 PDX
12   material was transplanted subcutaneously into six NMRI nude mice and Gefitinib treatment was performed as
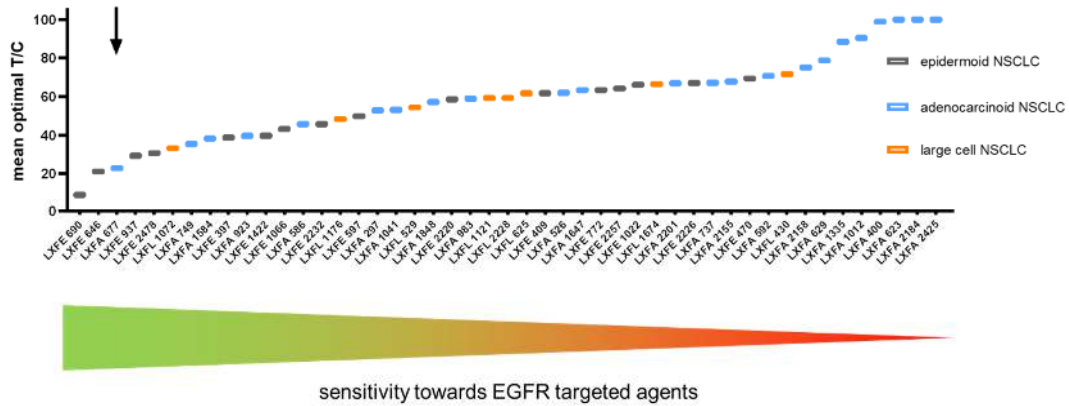
13 described in Figure 2 (a). Three tumor sublines, called LXFA 677res1, -res2 and -res3, showed progressive growth
14 under constant treatment with Gefitinib and were re-transplanted into four NMRI nude mice, respectively. The
15 four mice were stratified into a control group receiving the vehicle or the treatment group receiving Gefitinib as
16 described in Figure 2 (b). One untreated control tumor of each subline served as donor material for a subsequent
17 implantation into four NMRI nude mice. Again animals were stratified into control and treatment arm and
18 Gefitinib was dosed as described in supplemental Figure S5. The orange box is indicating Gefitinib treatment

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(a)

(b)

(c)

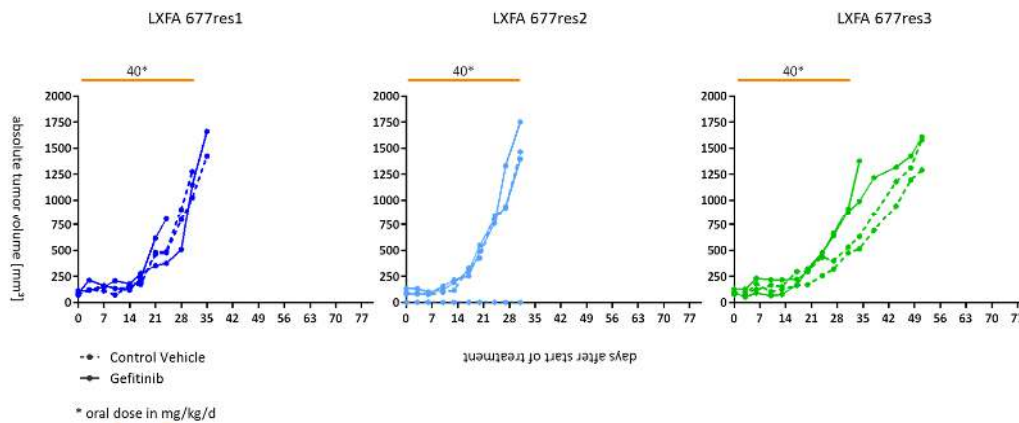| LXFA 289	LXFA 297	LXFA 400	LXFA 526	LXFA 586	LXFA 592	LXFA 623	LXA 3100	LXA 3104	LXA 3106	LXAA SMTCA6Z	LXF 2436	LXF 2467	LXFA 2157
LXFA 629	LXFA 644	LXFA 677	LXFA 737	LXFA 749	LXFA 923	LXFA 983	LXFA 2160	LXFA 2194	LXFA 2366	LXFA 2388	LXFA 2403	LXFA 2425	LXFA 2426
LXFA 1012	LXFA 1041	LXFA 1335	LXFA 1584	LXFA 1647	LXFA 1848	LXFA 2155	LXFA 2764	LXFA 2889			LXFE 386	LXFE 2190	LXFE 2198
LXFA 2158	LXFA 2165	LXFA 2184	LXFA 2201	LXFA 2204	LXFA 2207	LXFA 2217	LXFE 2214	LXFE 2220	LXFE 2276	LXFS 605	LXFS 688		
LXFA 2250		LXF 1125	LXFE 2478	LXFA 2764		LXA 3109							
LXFE 211	LXFE 397	LXFE 409	LXFE 470	LXFE 597	LXFE 646	LXFE 690							
LXFE 772	LXFE 937	LXFE 1022	LXFE 1066	LXFE 1422	LXFE 2159	LXFE 2162							
LXFE 2226	LXFE 2232	LXFE 2257	LXFE 2348	LXFE 2415									
LXFL 430	LXFL 529	LXFL 625	LXFL 1072	LXFL 1121	LXFL 1176	LXFL 1674							
LXFL 2228	LXFL 2237	LXFE 2324	LXFL 2377										
LXFS 538	LXFS 573	LXFS 615	LXFS 650	LXFS 1129	LXFS 2156								

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21 Figure S3: TMA of the NSCLC PDX panel comprising 85 NSCLC PDX models in duplicates. The red box is
22 indicating tumor model LXFA 677. (a): IHC with anti-human EGFR Antibody followed by DAB staining and
23 hematoxylin counterstaining (b): Hematoxylin& Eosin staining (c): Mapping of the individual tumor models on
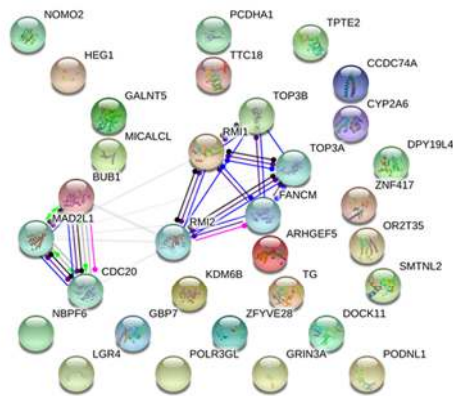24 the TMA. The red box is indicating LXFA 677 model.

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Supplemental Figure S4: Sensitivity towards EGFR targeting agents of 47 NSCLC PDX *in vivo*. Depicted are the mean optimal T/C values of one – five EGFR targeting agents per model. In total nine different compounds were tested: Osimertinib, Afatinib, Cetuximab, Erlotinib, Gefitinib, Necitumumab, Lapatinib, Sorafenib and Sunitinib. Dosing and schedule are depicted in Table 2. The respective tumor model was implanted subcutaneously in NMRI nude mice and treatment started when a group median tumor volume of 250 mm³ was reached. The group size was n = 5 -10 animals/group.
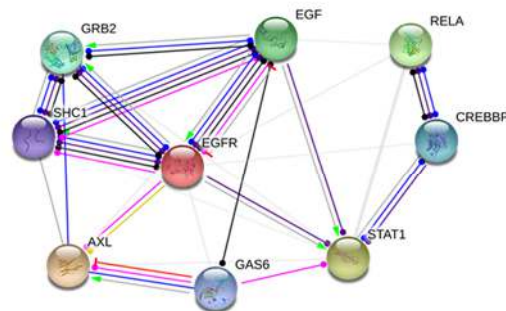

Figure S5. The orange box is indicating the mice receiving Gefitinib treatment: Tumor growth curves for individual tumors after re-implantation of tumors from the untreated control groups of the resistant lines LXFA 677res1, -res2 and res3. The orange line is indicating the duration of the treatment. The respective dose per day is shown above the line.
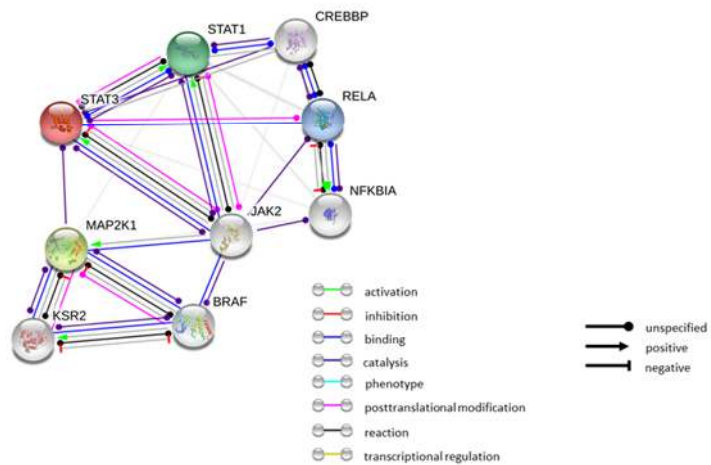
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Figure S6: Functional protein association networks of (a): Genes found to be mutated in all three Gefitinib-resistant LXFA 677 subclones (b): Functional protein association networks of proteins with an upregulated logFC > 0.5 in the resistant lines (c): Functional protein association networks of proteins with an upregulated logFC > 0.5 in the phosphorylated vs total protein ratio. The STRING (https://string-db.org/) program was used to assign mutated genes and the upregulated proteins to a protein network. As a minimum required interaction score the medium confidence level was applied (p= 0.400) allowing a maximal number of five interactors. Analysis of the involvement of the mutated genes/upregulated proteins in biological processes and functions is based on GO-term and KEGG pathways.

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51   Table S1. Number of common and unique mutations in the different sublines of NSCLC PDX LXFA 677

	LXFA 677	LXFA 677res1	LXFA 677res2	LXFA 677res3
common	504	504	504	504
in 2/3 sublines	26	30	42	38
unique	46	53	28	26
total	576	587	574	568

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53 Table S2. Annotation of mutations shared among all three resistant lines based on SIFT and PolyPhen. nd = dot determined

SYMBOL	Transcript	HGVSg Nomenclature	Consequence (ENSEMBL)	Amino_acid_change	SIFT prediction	PolyPhen prediciton	Mutation existent in LXFE_2478
GBP7	ENST00000294671	1:g.89133401G>C	missense_variant	Q507E	tolerated	benign	No
NBPF6	ENST00000495380	1:g.108459067G>A	missense_variant	S329N	tolerated	benign	No
OR2T35	ENST00000641268	1:g.248639168C>T	missense_variant	V31I	tolerated	benign	Yes
CCDC74A	ENST00000295171	2:g.131532868G>A	missense_variant	R294Q	tolerated	benign	No
HEG1	ENST00000311127	3:g.125013588_125013605dup	inframe_insertion	S668SSSSSSS	nd	nd	Yes
ARHGEF5	ENST00000056217	7:g.144374813C>A	missense_variant	L1408I	deleterious	benign	No
MICALCL	ENST00000256186	11:g.12294836_12294841dup	inframe_insertion	A456APP	nd	nd	Yes
TPTE2	ENST00000400230	13:g.19492854T>C	missense_variant	K39E	tolerated - low confidence	benign	Yes
TPTE2	ENST00000400230	13:g.19492871A>C	missense_variant	L33R	tolerated - low confidence	benign	Yes
NOMO2	ENST00000621364	16:g.18531526C>T	missense_variant	V493M	deleterious	possibly damaging	No
SMTNL2	ENST00000389313	17:g.4592373G>A	missense_variant	D138N	deleterious	benign	No
KDM6B	ENST00000254846	17:g.7846893_7846898dup	inframe_insertion	L251LPP	nd	nd	Yes
ZNF417	ENST00000312026	19:g.57909712G>T	missense_variant	A189E	tolerated	benign	No
DOCK11	ENST00000276202	X:g.118598098A>C	missense_variant	E818D	nd	nd	Yes

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56 Table S3. Most significant biological processes and functions (based on GO, KEGG and reactome pathway) in which the mutated genes in at least 2/3 of the resistant lines are

57 involved.

Pathway	#term ID	term description	observed gene count	background gene count	false discovery rate	matching proteins in our network
GO	GO:0003917	DNA topoisomerase type I activity	2	4	0.0069	TOP3A,TOP3B
KEGG	hsa03460	Fanconi anemia pathway	5	51	9.34e-07	FANCM,RMI1,RMI2,TOP3A,TOP3B
	hsa04110	Cell cycle	3	123	0.0148	BUB1,CDC20,MAD2L1
	hsa04114	Oocyte meiosis	3	116	0.0148	BUB1,CDC20,MAD2L1
	hsa03440	Homologous recombination	2	40	0.0165	TOP3A,TOP3B
Reactome	HSA-69620	Cell Cycle Checkpoints	6	265	0.00049	BUB1,CDC20,MAD2L1,RMI1,RMI2,TOP3A
	HSA-73894	DNA Repair	4	290	0.0065	FANCM,RMI1,RMI2,TOP3A

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60   Table S4. Most significant biological processes and functions in which the upregulated proteins are involved based on GO-term

#term ID	term description	observed gene count	background gene count	false discovery rate	matching proteins in our network (labels)
GO:0016032	viral process	8	571	6.59e-09	AXL, CREBBP, EGFR, GAS6, GRB2, RELA, SHC1, STAT1
GO:0038128	ERBB2 signaling pathway	4	31	3.60e-07	EGF, EGFR, GRB2, SHC1
GO:0007166	cell surface receptor signaling pathway	9	2198	7.80e-07	AXL, CREBBP, EGF, EGFR, GAS6, GRB2, RELA, SHC1, STAT1
GO:0051897	positive regulation of protein kinase B signaling	5	157	1.00e-06	AXL, EGF, EGFR, GAS6, GRB2
GO:0007173	epidermal growth factor receptor signaling pathway	4	52	1.44e-06	EGF, EGFR, GRB2, SHC1

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64 Table S5. Most significant biological processes and functions in which the upregulated proteins are involved based on KEGG pathway.

#term ID	term description	observed gene count	background gene count	false discovery rate	matching proteins in your network (labels)
hsa01521	EGFR tyrosine kinase inhibitor resistance	6	78	4.80e-11	AXL, EGF, EGFR, GAS6, GRB2, SHC1
hsa05215	Prostate cancer	5	97	2.39e-08	CREBBP, EGF, EGFR, GRB2, RELA
hsa05160	Hepatitis C	5	131	5.75e-08	EGF, EGFR, GRB2, RELA, STAT1
hsa05165	Human papillomavirus infection	6	317	5.75e-08	CREBBP, EGF, EGFR, GRB2, RELA, STAT1
hsa04630	Jak-STAT signaling pathway	5	160	1.09e-07	CREBBP, EGF, EGFR, GRB2, STAT1
hsa04014	Ras signaling pathway	5	228	3.87e-07	EGF, EGFR, GRB2, RELA, SHC1
hsa04917	Prolactin signaling pathway	4	69	3.87e-07	GRB2, RELA, SHC1, STAT1
hsa05200	Pathways in cancer	6	515	3.87e-07	CREBBP, EGF, EGFR, GRB2, RELA, STAT1
hsa05212	Pancreatic cancer	4	74	3.87e-07	EGF, EGFR, RELA, STAT1
hsa05214	Glioma	4	68	3.87e-07	EGF, EGFR, GRB2, SHC1
hsa04012	ErbB signaling pathway	4	83	4.55e-07	EGF, EGFR, GRB2, SHC1
hsa04066	HIF-1 signaling pathway	4	98	7.94e-07	CREBBP, EGF, EGFR, RELA

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66 Table S6. Most significant biological processes and functions in which the upregulated activated proteins are involved based on GO-term.

#term ID	term description	observed gene count	background gene count	false discovery rate	matching proteins in your network (labels)
GO:0035556	intracellular signal transduction	8	1528	3.96e-06	BRAF, JAK2, KSR2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
GO:0042981	regulation of apoptotic process	8	1501	3.96e-06	BRAF, CREBBP, JAK2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
GO:0070106	interleukin-27-mediated signaling pathway	3	11	4.03e-06	JAK2, STAT1, STAT3
GO:0070757	interleukin-35-mediated signaling pathway	3	11	4.03e-06	JAK2, STAT1, STAT3
GO:0009966	regulation of signal transduction	9	3033	4.73e-06	BRAF, CREBBP, JAK2, KSR2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
GO:0071354	cellular response to interleukin-6	4	30	1.10e-06	JAK2, RELA, STAT1, STAT3
GO:0035556	intracellular signal transduction	8	1528	3.96e-06	BRAF, JAK2, KSR2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
GO:0042981	regulation of apoptotic process	8	1501	3.96e-06	BRAF, CREBBP, JAK2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
GO:0070106	interleukin-27-mediated signaling pathway	3	11	4.03e-06	JAK2, STAT1, STAT3

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71　Table S7. Most significant biological processes and functions in which the upregulated activated proteins are involved based on KEGG pathway.

#term ID	term description	observed gene count	background gene count	false discovery rate	matching proteins in your network (labels)
hsa04062	Chemokine signaling pathway	7	181	2.84e-11	BRAF, JAK2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
hsa05167	Kaposi's sarcoma-associated herpesvirus infection	7	183	2.84e-11	CREBBP, JAK2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
hsa05200	Pathways in cancer	8	515	8.59e-11	BRAF, CREBBP, JAK2, MAP2K1, NFKBIA, RELA, STAT1, STAT3
hsa05161	Hepatitis B	6	142	4.14e-10	CREBBP, MAP2K1, NFKBIA, RELA, STAT1, STAT3
hsa05164	Influenza A	6	168	8.85e-10	CREBBP, JAK2, MAP2K1, NFKBIA, RELA, STAT1
hsa04917	Prolactin signaling pathway	5	69	1.66e-09	JAK2, MAP2K1, RELA, STAT1, STAT3
hsa05212	Pancreatic cancer	5	74	1.99e-09	BRAF, MAP2K1, RELA, STAT1, STAT3
hsa05215	Prostate cancer	5	97	6.41e-09	BRAF, CREBBP, MAP2K1, NFKBIA, RELA
hsa04659	Th17 cell differentiation	5	102	7.27e-09	JAK2, NFKBIA, RELA, STAT1, STAT3
hsa05145	Toxoplasmosis	5	109	9.03e-09	JAK2, NFKBIA, RELA, STAT1, STAT3
hsa05160	Hepatitis C	5	131	2.00e-08	BRAF, NFKBIA, RELA, STAT1, STAT3
hsa05162	Measles	5	133	2.00e-08	JAK2, NFKBIA, RELA, STAT1, STAT3
hsa05168	Herpes simplex infection	5	181	8.21e-08	CREBBP, JAK2, NFKBIA, RELA, STAT1
hsa04024	cAMP signaling pathway	5	195	1.10e-07	BRAF, CREBBP, MAP2K1, NFKBIA, RELA
hsa05221	Acute myeloid leukemia	4	66	1.48e-07	BRAF, MAP2K1, RELA, STAT3
hsa04920	Adipocytokine signaling pathway	4	69	1.64e-07	JAK2, NFKBIA, RELA, STAT3
hsa05140	Leishmaniasis	4	70	1.64e-07	JAK2, NFKBIA, RELA, STAT1
hsa05220	Chronic myeloid leukemia	4	76	2.12e-07	BRAF, MAP2K1, NFKBIA, RELA
hsa01521	EGFR tyrosine kinase inhibitor resistance	4	78	2.22e-07	BRAF, JAK2, MAP2K1, STAT3
hsa04658	Th1 and Th2 cell differentiation	4	88	3.36e-07	JAK2, NFKBIA, RELA, STAT1

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