Annotations of the model "MAPK_large_19june2013"

<table>
<tr><th>Nodes</th><th>Logical rules</th><th>Annotations</th></tr>
<tr><td>Apoptosis</td><td>!BCL2 & !ERK & FOXO3 & p53</td><td>http://www.ncbi.nlm.nih.gov/pubmed/20978166
http://www.ncbi.nlm.nih.gov/pubmed/19641508
http://www.ncbi.nlm.nih.gov/pubmed/12792650
http://www.ncbi.nlm.nih.gov/pubmed/12040186
Phenotype

VARIABLE: apoptosis enablement
Modelling hypotheses: apoptosis is supposed to be enabled when at least a pro-apoptotic component is activated (p53, FOXO3) and no anti-apoptotic components are activated (ERK, BCL2).
FOXO3a promotes apoptosis through activation of PUMA.
PMID:20978166
In response to genotoxic stress such as DNA damage, PUMA is transactivated by p53 (leading to apoptosis).
PMID:19641508
Caspase 9 is efficiently phosphorylated on Thr125 by ERK in vitro, suggesting that it is targeted directly by ERK in vivo. This is one of the ways ERK plays its anti-apoptotic role.
PMID:12792650
Akt phosphorylation of the apoptosis-inducing protein Bad creates a binding site for 14-3-3 proteins and prevents Bad from binding to Bcl-2 family members Bcl-2 and Bcl-XL, thus releasing them for a cell survival response.
PMID:12040186

Regulator — Comment
ERK — http://www.ncbi.nlm.nih.gov/pubmed/12792650 Caspase 9 is efficiently phosphorylated on Thr125 by ERK in vitro, suggesting that it is targeted directly by ERK in vivo. This is one of the ways ERK plays its anti-apoptotic role. PMID:12792650
p53 — http://www.ncbi.nlm.nih.gov/pubmed/19641508 In response to genotoxic stress such as DNA damage, PUMA is transactivated by p53 (leading to apoptosis). PMID:19641508
FOXO3 — http://www.ncbi.nlm.nih.gov/pubmed/20978166 FOXO3a promotes apoptosis through activation of PUMA. PMID:20978166
BCL2 — http://www.ncbi.nlm.nih.gov/pubmed/12040186</td></tr>
</table>

		Akt phosphorylation of the apoptosis-inducing protein Bad creates a binding site for 14-3-3 proteins and prevents Bad from binding to Bcl-2 family members Bcl-2 and Bcl-XL, thus releasing them for a cell survival response. PMID:12040186
AKT	PDK1 & !PTEN	http://www.genenames.org/data/hgnc_data.php?hgnc_id=391 http://www.genenames.org/data/hgnc_data.php?hgnc_id=392 http://www.genenames.org/data/hgnc_data.php?hgnc_id=393 http://www.ncbi.nlm.nih.gov/pubmed/15567848 http://www.ncbi.nlm.nih.gov/pubmed/12040186 http://www.ncbi.nlm.nih.gov/pubmed/11882383 http://www.ncbi.nlm.nih.gov/pubmed/10869359 http://www.ncbi.nlm.nih.gov/pubmed/11850850 http://www.ncbi.nlm.nih.gov/pubmed/12217521 AKT1 = v-akt murine thymoma viral oncogene homolog 1 AKT2 = v-akt murine thymoma viral oncogene homolog 2 AKT3 = v-akt murine thymoma viral oncogene homolog 3 VARIABLE: AKT (any isoform) phosphorylation level Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway. EGF stimulates a cell survival pathway mediated by phosphoinositide 3-kinase (PI3K) and the protein kinase Akt by an indirect mechanism in which tyrosine phosphorylation of the docking protein Gab1 or ErbB3 by EGFR leads to recruitment and activation of PI3K. PMID:15567848 Signaling proteins with pleckstrin-homology (PH) domains accumulate at sites of PI3K activation by directly binding to PI(3,4,5)P3. Of particular interest are the protein serine-threonine kinases Akt and phosphoinositide-dependent kinase 1 (PDK1). Association with PI(3,4,5)P3 at the membrane brings these proteins into proximity and facilitates phosphorylation of Akt by PDK1. This phosphorylation stimulates the catalytic activity of Akt, resulting in the phosphorylation of a host of other proteins that affect cell growth, cell cycle entry, and cell survival. Akt phosphorylation of the apoptosis-inducing protein Bad creates a binding site for 14-3-3 proteins and prevents Bad from binding to Bcl-2 family members Bcl-2 and Bcl-XL, thus releasing them for a cell survival response. Glycogen synthase kinase 3 (GSK3) is a target of Akt. This protein kinase is constitutively active in unstimulated cells and phosphorylates many proteins (including glycogen synthase, c-Myc, and cyclin D) to keep them in inactive states or promote their degradation. Phosphorylation of GSK3 (both alpha and beta isoforms) by Akt turns off the catalytic activity of this enzyme, resulting in the activation of pathways that are normally repressed by GSK3. Phosphorylation of FOXO3 by Akt creates a binding site for the 14-3-3 family of proteins. The complex of FOXO3 and 14-3-3 is retained in the cytosol, blocking transcription of genes normally stimulated by FOXO3. PMID:12040186 p21 is a direct substrate of AKT and that this may regulate the subcellular localisation of p21. Phosphorylation of p21

		by AKT correlated with its exit from the nucleus and with increased cell cycle progression. PMID:11882383 Phosphorylation by Akt inhibits EGF-dependent activity of B-Raf and C-Raf. PMID:10869359 Effective recruitment of Akt by appropriate survival signals may lead to activation of Mdm2, inactivation of p53, and eventually inhibition of p53-dependent apoptosis. PMID:11850850 p53 induces transcription of the PTEN gene and elevates cellular levels of the PTEN protein, which in turn inhibits activation of Akt. PMID:12217521 **Regulator** — **Comment** PTEN — http://www.ncbi.nlm.nih.gov/pubmed/12217521 p53 induces transcription of the PTEN gene and elevates cellular levels of the PTEN protein, which in turn inhibits activation of Akt. PMID:12217521 PDK1 — http://www.ncbi.nlm.nih.gov/pubmed/12040186 Signaling proteins with pleckstrin-homology (PH) domains accumulate at sites of PI3K activation by directly binding to PI(3,4,5)P3. Of particular interest are the protein serine-threonine kinases Akt and phosphoinositide-dependent kinase 1 (PDK1). Association with PI(3,4,5)P3 at the membrane brings these proteins into proximity and facilitates phosphorylation of Akt by PDK1. This phosphorylation stimulates the catalytic activity of Akt, resulting in the phosphorylation of a host of other proteins that affect cell growth, cell cycle entry, and cell survival. PMID:12040186
AP1	JUN & (FOS | ATF2)	http://www.ncbi.nlm.nih.gov/pubmed/11274345 http://www.ncbi.nlm.nih.gov/pubmed/18039929 AP-1 VARIABLE: AP-1 formation AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. PMID:11274345 AP-1 mediated gene expression inhibits ERK phosphorylation. PMID:18039929

		Regulator	**Comment**
		JUN	http://www.ncbi.nlm.nih.gov/pubmed/11274345 AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. PMID:11274345
		ATF2	http://www.ncbi.nlm.nih.gov/pubmed/11274345 AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. PMID:11274345
		FOS	http://www.ncbi.nlm.nih.gov/pubmed/11274345 AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. PMID:11274345
ATF2	JNK | p38	http://www.genenames.org/data/hgnc_data.php?hgnc_id=784 http://www.ncbi.nlm.nih.gov/pubmed/11274345 ATF2 = activating transcription factor 2 VARIABLE: ATF2 phosphorylation level AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. JNK and p38 can both phosphorylate ATF2 at Thr69 and Ser71. PMID:11274345	
		Regulator	**Comment**

		JNK	http://www.ncbi.nlm.nih.gov/pubmed/11274345 JNK and p38 can both phosphorylate ATF2 at Thr69 and Ser71. PMID:11274345
		p38	http://www.ncbi.nlm.nih.gov/pubmed/11274345 JNK and p38 can both phosphorylate ATF2 at Thr69 and Ser71. PMID:11274345
ATM	DNA_damage	http://www.genenames.org/data/hgnc_data.php?hgnc_id=795 http://www.ncbi.nlm.nih.gov/pubmed/18235226 http://www.ncbi.nlm.nih.gov/pubmed/18855897 http://www.ncbi.nlm.nih.gov/pubmed/15140942 ATM = ataxia telangiectasia mutated VARIABLE: ATM phosphorylation level ATM autophosphorylates itself at serine 1981 in response to DNA damage and some other cellular stresses. PMID:18235226 Ataxia telangiectasia mutated (ATM) is activated in response to DNA damage and directly phosphorylates TAOK. PMID:18855897 ATM phosphorylates p53 at ser15 and stabilize it. PMID:15140942	
		Regulator DNA_damage	**Comment** http://www.ncbi.nlm.nih.gov/pubmed/18235226 ATM autophosphorylates itself at serine 1981 in response to DNA damage and some other cellular stresses. PMID:18235226
BCL2	CREB & AKT	http://www.genenames.org/data/hgnc_data.php?hgnc_id=990 http://www.ncbi.nlm.nih.gov/pubmed/19815709 http://www.ncbi.nlm.nih.gov/pubmed/12040186 BCL2 = B-cell CLL/lymphoma 2 VARIABLE: BCL2 activation level (implies gene expression) Modelling hypotheses: CREB is needed for BCL2 gene expression, AKT is needed for BCL2 activation. DUSP1, FOS, BCL2 are CREB target genes. PMID:19815709 Akt phosphorylation of the apoptosis-inducing protein Bad creates a binding site for 14-3-3 proteins and prevents Bad from binding to Bcl-2 family members Bcl-2 and Bcl-XL, thus releasing them for a cell survival response. PMID:12040186	
		Regulator CREB	**Comment** http://www.ncbi.nlm.nih.gov/pubmed/19815709

<table>
<tr><td></td><td></td><td>AKT</td><td>DUSP1, FOS and BCL2 are CREB target genes.
PMID:19815709
http://www.ncbi.nlm.nih.gov/pubmed/12040186
Akt phosphorylation of the apoptosis-inducing protein Bad creates a binding site for 14-3-3 proteins and prevents Bad from binding to Bcl-2 family members Bcl-2 and Bcl-XL, thus releasing them for a cell survival response.
PMID:12040186</td></tr>
<tr><td>CREB</td><td>MSK</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=2345
http://www.ncbi.nlm.nih.gov/pubmed/15187187
http://www.ncbi.nlm.nih.gov/pubmed/19815709
CREB1 = cAMP responsive element binding protein 1
VARIABLE: CREB phosphorylation level
MSK1 mediates the mitogen-stimulated phoshphorylation of CREB.
PMID:15187187
DUSP1, FOS and BCL2 are CREB target genes.
PMID:19815709

Regulator | Comment
MSK | http://www.ncbi.nlm.nih.gov/pubmed/15187187
MSK1 mediates the mitogen-stimulated phoshphorylation of CREB.
PMID:15187187</td></tr>
<tr><td>DNA_damage</td><td>input</td><td colspan="2">http://www.ncbi.nlm.nih.gov/pubmed/18235226
Model input
VARIABLE: DNA damaging agents/therapies action
ATM autophosphorylates itself at serine 1981 in response to DNA damage and some other cellular stresses.
PMID:18235226</td></tr>
<tr><td>DUSP1</td><td>CREB</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=3064
http://www.ncbi.nlm.nih.gov/pubmed/19815709
http://www.ncbi.nlm.nih.gov/pubmed/19436832
DUSP1 = dual specificity phosphatase 1
VARIABLE: DUSP1 gene expression level
DUSP1 is a CREB target gene.
PMID:19815709
DUSP1 preferentially inactivates JNK and p38.
PMID:19436832</td></tr>
</table>

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<tr>
<td></td>
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<table>
<tr><th>Regulator</th><th>Comment</th></tr>
<tr><td>CREB</td><td>http://www.ncbi.nlm.nih.gov/pubmed/19815709
DUSP1, FOS and BCL2 are CREB target genes.
PMID:19815709</td></tr>
</table>
</td>
</tr>
<tr>
<td>EGFR</td>
<td>(EGFR_stimulus | SPRY) & !(PKC | GRB2)</td>
<td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=3236
http://www.ncbi.nlm.nih.gov/pubmed/15567848
http://www.ncbi.nlm.nih.gov/pubmed/15173823
http://www.ncbi.nlm.nih.gov/pubmed/6321473
http://www.ncbi.nlm.nih.gov/pubmed/17496910
http://www.ncbi.nlm.nih.gov/pubmed/2472219
EGFR = epidermal growth factor receptor
VARIABLE: EGFR activation level
The ubiquitin ligase Cbl interacts with EGFR directly and indirectly through Grb2, promoting ubiquitination and degradation of EGFR
PMID:15567848
Spry is induced by activated ERK. It positively regulates EGFR signalling by sequestering Cbl (positive feedback in the model, from Spry to EGFR), whereas it negatively regulates FGFR signalling by sequestering Grb2 from FSR2 (negative feedback in the model, from Spry to FSR2).
PMID:15173823
PKC may cause phosphorylation of EGFR, leading to a decrease in its activity.
PMID:6321473
Grb2 is an adaptor protein, normally present in cytosol. It is recruited to the plasma membrane by activated RTKs.
PMID:17496910
Tyrosine phosphorylation of PLC-gamma by EGF receptor leads to its activation.
PMID:2472219
<table>
<tr><th>Regulator</th><th>Comment</th></tr>
<tr><td>GRB2</td><td>http://www.ncbi.nlm.nih.gov/pubmed/15567848
The ubiquitin ligase Cbl interacts with EGFR directly and indirectly through Grb2, promoting ubiquitination and degradation of EGFR
PMID:15567848</td></tr>
<tr><td>SPRY</td><td>http://www.ncbi.nlm.nih.gov/pubmed/15173823
Spry is induced by activated ERK. It positively regulates EGFR signalling by sequestering Cbl (positive feedback in the model, from Spry to EGFR), whereas it negatively regulates FGFR signalling by sequestering Grb2 from FSR2 (negative feedback in the model, from Spry to FSR2).
PMID:15173823</td></tr>
</table>
</td>
</tr>
</table>

		PKC	http://www.ncbi.nlm.nih.gov/pubmed/6321473 PKC may cause phosphorylation of EGFR, leading to a decrease in its activity. PMID:6321473
EGFR_stimulus	input	Model input VARIABLE: any stimulus able to induce EGFR activation	
ELK1	ERK | JNK | p38	http://www.genenames.org/data/hgnc_data.php?hgnc_id=3321 http://www.ncbi.nlm.nih.gov/pubmed/16393692 http://www.ncbi.nlm.nih.gov/pubmed/20506250 http://www.ncbi.nlm.nih.gov/pubmed/11274345 ELK1 = ELK1, member of ETS oncogene family VARIABLE: ELK1 phosphorylation level The rapid and efficient phosphorylation of Elk1 by ERKs is enabled by a direct interaction between the two proteins. PMID:16393692 ELK1 is a nuclear p38 target. PMID:20506250 ELK1 is a nuclear JNK target. ELK1 induces c-fos expression. PMID:11274345	
		Regulator	**Comment**
		JNK	http://www.ncbi.nlm.nih.gov/pubmed/11274345 ELK1 is a nuclear JNK target. PMID:11274345
		p38	http://www.ncbi.nlm.nih.gov/pubmed/20506250 ELK1 is a nuclear p38 target. PMID:20506250
ERK	MEK1_2	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6871 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6877 http://www.ncbi.nlm.nih.gov/pubmed/17496910 http://www.ncbi.nlm.nih.gov/pubmed/18039929 http://www.ncbi.nlm.nih.gov/pubmed/15173823 http://www.ncbi.nlm.nih.gov/pubmed/12792650 http://www.ncbi.nlm.nih.gov/pubmed/15187187 http://www.ncbi.nlm.nih.gov/pubmed/15239952 http://www.ncbi.nlm.nih.gov/pubmed/16393692 http://www.ncbi.nlm.nih.gov/pubmed/11940578 http://www.ncbi.nlm.nih.gov/pubmed/10601235 http://www.ncbi.nlm.nih.gov/pubmed/11431469 MAPK1 = mitogen-activated protein kinase 1	

		MAPK3 = mitogen-activated protein kinase 3 VARIABLE: ERK (any isoform) phosphorylation level Once activated, Raf family members are capable of initiating the phosphorylation cascade, whereby Raf activates MEK, and MEK in turn activates ERK. PMID:17496910 Spry is induced by activated ERK, through phosphorylation on Tyr55. PMID:15173823 Caspase 9 is efficiently phosphorylated on Thr125 by ERK in vitro, suggesting that it is targeted directly by ERK in vivo. This is one of the ways ERK plays its anti-apoptotic role. PMID:12792650 MSK1 and MSK2 are potently activated (by phosphorylation) in vivo by ERK1/2 and p38 but not JNK. RSKs interact with ERK and dissociate upon activation. PMID:15187187 RSK2 is a well known ERK substrate in the cytoplasm and has been shown to undergo autophosphorylation after ERK phosphorylation. PMID:15239952 Phosphorylation by both ERKs and their downstream RSKs can stabilise the c-Fos protein for several hours. The combination of these phosphorylations allows c-Fos sustained activity. The rapid and efficient phosphorylation of Elk1 by ERKs is enabled by a direct interaction between the two proteins. PMID:16393692 p70 activation requires both ERK cascade and PI3K/AKT cascade, at least in some cell types. PMID:11940578, PMID:10601235, PMID:11431469 **Regulator** — **Comment** MEK1_2 — http://www.ncbi.nlm.nih.gov/pubmed/17496910 Once activated, Raf family members are capable of initiating the phosphorylation cascade, whereby Raf activates MEK, and MEK in turn activates ERK. PMID:17496910
FGFR3	FGFR3_stimulus & !(GRB2 | PKC)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=3690 http://www.ncbi.nlm.nih.gov/pubmed/15567848 http://www.ncbi.nlm.nih.gov/pubmed/11447289 http://www.ncbi.nlm.nih.gov/pubmed/1656221 http://www.ncbi.nlm.nih.gov/pubmed/9694798 http://www.ncbi.nlm.nih.gov/pubmed/8622701 http://www.ncbi.nlm.nih.gov/pubmed/14699054 FGFR3 = fibroblast growth factor receptor 3 VARIABLE: FGFR3 activation level Grb2, bound to Cbl, does not interact directly with FGFR but, rather, binds to tyrosine-phosphorylated FRS2, promoting ubiquitination and degradation of FRS2 and FGFR

<table>
<tr><td></td><td></td><td>PMID:15567848
FGF stimulation leads to phosphorylation of Shp2 on a tyrosine residue that forms a complex with an additional molecule of Grb2. Grb2/Sos complexes are thus recruited directly and indirectly via Shp2 upon tyrosine phosphorylation of FRS2a in response to growth factor stimulation.
PMID:11447289
Binding of FGF to FGFR leads to tyrosine phosphorylation of PLCgamma.
PMID:1656221
(Inferred from FGFR1) PKC-mediated phosphorylation can lead to internalization and degradation of FGFR1.
PMID:9694798, PMID:8622701, PMID:14699054

Regulator Comment
GRB2 http://www.ncbi.nlm.nih.gov/pubmed/11997436
FGF-induced tyrosine phosphorylation of FRS2 results in complex formation with the adaptor protein Grb2 bound to Cbl by means of its SH3 domains. FGF-induced ternary complex formation among FRS2, Grb2, and Cbl results in ubiquitination and degradation of FRS2 and FGF receptor (FGFR).
PMID:11997436
PKC http://www.ncbi.nlm.nih.gov/pubmed/9694798
http://www.ncbi.nlm.nih.gov/pubmed/8622701
http://www.ncbi.nlm.nih.gov/pubmed/14699054
(Inferred from FGFR1) PKC-mediated phosphorylation can lead to internalization and degradation of FGFR1.
PMID:9694798, PMID:8622701, PMID:14699054</td></tr>
<tr><td>FGFR3_stimulus</td><td>input</td><td>Model input
VARIABLE: any stimulus able to induce FGFR3 activation</td></tr>
<tr><td>FOS</td><td>ERK & RSK & (ELK1 | CREB)</td><td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=3796
http://www.ncbi.nlm.nih.gov/pubmed/11274345
http://www.ncbi.nlm.nih.gov/pubmed/19815709
http://www.ncbi.nlm.nih.gov/pubmed/16393692
FOS = FBJ murine osteosarcoma viral oncogene homolog
VARIABLE: FOS phosphorylation level
Further observations: ELK1 or CREB are supposed to induce FOS gene expression, ERK or RSK are supposed to activate it
AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers.
ELK1 induces c-fos expression.
PMID:11274345</td></tr>
</table>

<table>
<tr><td></td><td></td><td>FOS is a CREB target gene.
PMID:19815709
Phosphorylation by both ERKs and their downstream RSKs can stabilise the c-Fos protein for several hours. The combination of these phosphorylations allows c-Fos sustained activity.
PMID:16393692

Regulator | Comment
ERK | http://www.ncbi.nlm.nih.gov/pubmed/16393692 Phosphorylation by both ERKs and their downstream RSKs can stabilise the c-Fos protein for several hours. The combination of these phosphorylations allows c-Fos sustained activity. PMID:16393692
RSK | http://www.ncbi.nlm.nih.gov/pubmed/16393692 Phosphorylation by both ERKs and their downstream RSKs can stabilise the c-Fos protein for several hours. The combination of these phosphorylations allows c-Fos sustained activity. PMID:16393692
ELK1 | http://www.ncbi.nlm.nih.gov/pubmed/11274345 ELK1 induces c-fos expression. PMID:11274345
CREB | http://www.ncbi.nlm.nih.gov/pubmed/19815709 DUSP1, FOS and BCL2 are CREB target genes. PMID:19815709</td></tr>
<tr><td>FOXO3</td><td>JNK & !AKT</td><td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=3821
http://www.ncbi.nlm.nih.gov/pubmed/20028971
http://www.ncbi.nlm.nih.gov/pubmed/20978166
http://www.ncbi.nlm.nih.gov/pubmed/12040186
FOXO3 = forkhead box O3
VARIABLE: FOXO3 phosphorylation level
JNK phosphorylates MST1 at serine 82, which leads to the enhancement of MST1 activation. The activation of MST1 phosphorylates FOXO3 at serine 207 and promotes cell death.
PMID:20028971
FOXO3a promotes apoptosis through activation of PUMA.
PMID:20978166
Phosphorylation of FOXO3 by Akt creates a binding site for the 14-3-3 family of proteins. The complex of FOXO3 and 14-3-3 is retained in the cytosol, blocking transcription of genes normally stimulated by FOXO3.
PMID:12040186</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Regulator
JNK

AKT</td><td>Comment
http://www.ncbi.nlm.nih.gov/pubmed/20028971
JNK phosphorylates MST1 at serine 82, which leads to the enhancement of MST1 activation. The activation of MST1 phosphorylates FOXO3 at serine 207 and promotes cell death.
PMID:20028971
http://www.ncbi.nlm.nih.gov/pubmed/12040186
Phosphorylation of FOXO3 by Akt creates a binding site for the 14-3-3 family of proteins. The complex of FOXO3 and 14-3-3 is retained in the cytosol, blocking transcription of genes normally stimulated by FOXO3.
PMID:12040186</td></tr>
<tr><td>FRS2</td><td>FGFR3 & !SPRY & !GRB2</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=16971
http://www.ncbi.nlm.nih.gov/pubmed/11447289
http://www.ncbi.nlm.nih.gov/pubmed/15173823
http://www.ncbi.nlm.nih.gov/pubmed/11997436
FRS2 = fibroblast growth factor receptor substrate 2
VARIABLE: FRS2 phosphorylation level
FGF stimulation leads to phosphorylation of Shp2 on a tyrosine residue that forms a complex with an additional molecule of Grb2. Grb2/Sos complexes are thus recruited directly and indirectly via Shp2 upon tyrosine phosphorylation of FRS2a in response to growth factor stimulation.
PMID:11447289
Spry is induced by activated ERK. It positively regulates EGFR signalling by sequestering Cbl (positive feedback in the model, from Spry to EGFR), whereas it negatively regulates FGFR signalling by sequestering Grb2 from FSR2 (negative feedback in the model, from Spry to FSR2).
PMID:15173823
FGF-induced tyrosine phosphorylation of FRS2 results in complex formation with the adaptor protein Grb2 bound to Cbl by means of its SH3 domains. FGF-induced ternary complex formation among FRS2, Grb2, and Cbl results in ubiquitination and degradation of FRS2 and FGF receptor (FGFR).
PMID:11997436

Regulator | Comment
GRB2 | http://www.ncbi.nlm.nih.gov/pubmed/11997436
FGF-induced tyrosine phosphorylation of FRS2 results in complex formation with the adaptor protein Grb2 bound to Cbl by means of its SH3 domains. FGF-induced ternary complex formation among FRS2, Grb2, and Cbl results in ubiquitination and degradation of FRS2 and FGF receptor (FGFR).</td></tr>
</table>

		SPRY	PMID:11997436 http://www.ncbi.nlm.nih.gov/pubmed/15173823 Spry is induced by activated ERK. It positively regulates EGFR signalling by sequestering Cbl (positive feedback in the model, from Spry to EGFR), whereas it negatively regulates FGFR signalling by sequestering Grb2 from FSR2 (negative feedback in the model, from Spry to FSR2). PMID:15173823
		FGFR3	http://www.ncbi.nlm.nih.gov/pubmed/11447289 FGF stimulation leads to phosphorylation of Shp2 on a tyrosine residue that forms a complex with an additional molecule of Grb2. Grb2/Sos complexes are thus recruited directly and indirectly via Shp2 upon tyrosine phosphorylation of FRS2a in response to growth factor stimulation. PMID:11447289
GAB1	GRB2 | PI3K	http://www.genenames.org/data/hgnc_data.php?hgnc_id=4066 http://www.ncbi.nlm.nih.gov/pubmed/15567848 http://www.ncbi.nlm.nih.gov/pubmed/15199124 GAB1 = GRB2-associated binding protein 1 VARIABLE: GAB1 phosphorylation level Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by EGFR or FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway. PMID:15567848 Recruitment of PI 3-kinase by Gab1 results in a positive-feedback loop mediated by binding of the PH domain of Gab1 to the product of PI3-kinase activation, phosphatidylinositol-3,4,5-triphosphate. PMID:15199124	
		Regulator GRB2	**Comment** http://www.ncbi.nlm.nih.gov/pubmed/15567848 Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway. EGF stimulates a cell survival pathway mediated by phosphoinositide 3-kinase (PI3K) and the protein kinase Akt by an indirect mechanism in which tyrosine phosphorylation of the docking protein Gab1 or ErbB3 by EGFR leads to recruitment and activation of PI3K. PMID:15567848

<table>
<tr><td></td><td></td><td>PI3K</td><td>http://www.ncbi.nlm.nih.gov/pubmed/15199124
Recruitment of PI 3-kinase by Gab1 results in a positive-feedback loop mediated by binding of the PH domain of Gab1 to the product of PI3-kinase activation, phosphatidylinositol-3,4,5-triphosphate.
PMID:15199124</td></tr>
<tr><td>GADD45</td><td>SMAD | p53</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=4095
http://www.genenames.org/data/hgnc_data.php?hgnc_id=4096
http://www.genenames.org/data/hgnc_data.php?hgnc_id=4097
http://www.ncbi.nlm.nih.gov/pubmed/21614932
http://www.ncbi.nlm.nih.gov/pubmed/11274345
GADD45A = growth arrest and DNA-damage-inducible, alpha
GADD45B = growth arrest and DNA-damage-inducible, beta
GADD45G = growth arrest and DNA-damage-inducible, gamma
VARIABLE: GADD45 gene (any isoform) expression level
The GADD45 gene is inducible by various environmental stresses.
Smad-dependent gene expression can provoke p38 activation in response to TGFbeta. GADD45beta was identified as the TGFbeta-inducible gene whose expression activates the p38 pathway.
Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1.
PMID:21614932
Expression of GADD45 is the culmination of a signaling pathway that requires prior expression of the tumor suppressor protein p53 which trans-activates the GADD45 gene.
PMID:11274345

Regulator | Comment
SMAD | http://www.ncbi.nlm.nih.gov/pubmed/21614932
Smad-dependent gene expression can provoke p38 activation in response to TGFbeta. GADD45beta was identified as the TGFbeta-inducible gene whose expression activates the p38 pathway.
PMID:21614932
p53 | http://www.ncbi.nlm.nih.gov/pubmed/11274345
Expression of GADD45 is the culmination of a signaling pathway that requires prior expression of the tumor suppressor protein p53 which trans-activates the GADD45 gene.
PMID:11274345</td></tr>
<tr><td>GRB2</td><td>EGFR | FRS2 | TGFBR</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=4566
http://www.ncbi.nlm.nih.gov/pubmed/17496910</td></tr>
</table>

http://www.ncbi.nlm.nih.gov/pubmed/15567848
http://www.ncbi.nlm.nih.gov/pubmed/11997436
http://www.ncbi.nlm.nih.gov/pubmed/17673906
http://www.ncbi.nlm.nih.gov/pubmed/11447289
GRB2 = growth factor receptor-bound protein 2
VARIABLE: GRB2 recruitment by activated RTKs
Grb2 is an adaptor protein, normally present in cytosol. It is recruited to the plasma membrane by activated RTKs.
Sos is recruited from the cytosol to the plasma membrane as a result of its constitutive interaction with Grb2. It is in an autoinhibited state.
PMID:17496910
The signaling pathways activated by FGFRs substantially overlap with those activated by EGFRs.
Grb2 molecules recruit the nucleotide exchange factor SOS, leading to the activation of the Ras-MAPK signaling cascade.
Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by EGFR or FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway.
The ubiquitin ligase Cbl interacts with EGFR directly and indirectly through Grb2, promoting ubiquitination and degradation of EGFR
Grb2, bound to Cbl, does not interact directly with FGFR but, rather, binds to tyrosine-phosphorylated FRS2, promoting ubiquitination and degradation of FRS2 and FGFR
PMID:15567848
FGF-induced tyrosine phosphorylation of FRS2 results in complex formation with the adaptor protein Grb2 bound to Cbl by means of its SH3 domains. FGF-induced ternary complex formation among FRS2, Grb2, and Cbl results in ubiquitination and degradation of FRS2 and FGF receptor (FGFR).
PMID:11997436
TGF-beta-induced ShcA phosphorylation induces ShcA association with Grb2 and Sos, thereby initiating the well-characterised pathway linking receptor tyrosine kinases with Erk MAP kinases.
PMID:17673906
FGF stimulation leads to phosphorylation of Shp2 on a tyrosine residue that forms a complex with an additional molecule of Grb2. Grb2/Sos complexes are thus recruited directly and indirectly via Shp2 upon tyrosine phosphorylation of FRS2a in response to growth factor stimulation.
PMID:11447289

Regulator	**Comment**
EGFR	http://www.ncbi.nlm.nih.gov/pubmed/17496910 Grb2 is an adaptor protein, normally present in cytosol. It is recruited to the plasma membrane by activated RTKs. PMID:17496910
TGFBR	http://www.ncbi.nlm.nih.gov/pubmed/17673906 TGF-beta-induced ShcA phosphorylation induces ShcA association with Grb2 and Sos, thereby initiating the well-characterised pathway linking receptor tyrosine

		FRS2	kinases with Erk MAP kinases. PMID:17673906 http://www.ncbi.nlm.nih.gov/pubmed/11447289 FGF stimulation leads to phosphorylation of Shp2 on a tyrosine residue that forms a complex with an additional molecule of Grb2. Grb2/Sos complexes are thus recruited directly and indirectly via Shp2 upon tyrosine phosphorylation of FRS2a in response to growth factor stimulation. PMID:11447289
Growth_Arrest	p21	http://www.ncbi.nlm.nih.gov/pubmed/8614832 Phenotype VARIABLE: growth arrest enablement Cell growth arrest is induced through cyclin-dependent kinase inhibitor p21 WAF1/CIP1. PMID:8614832 **Regulator** p21 **Comment** http://www.ncbi.nlm.nih.gov/pubmed/8614832 Cell growth arrest is induced through cyclin-dependent kinase inhibitor p21 WAF1/CIP1. PMID:8614832	
JNK	(TAOK & MAP3K1_3) | (MAP3K1_3 & MTK1) | (TAOK & MTK1) | (TAK1 & MTK1) | (TAK1 & MAP3K1_3) | (TAK1 & TAOK) | ((TAOK | MTK1 | MAP3K1_3 | TAK1) & !DUSP1)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6881 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6886 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6872 http://www.ncbi.nlm.nih.gov/pubmed/21614932 http://www.ncbi.nlm.nih.gov/pubmed/19436832 http://www.ncbi.nlm.nih.gov/pubmed/20028971 http://www.ncbi.nlm.nih.gov/pubmed/11274345 http://www.ncbi.nlm.nih.gov/pubmed/20060931 MAPK8 = mitogen-activated protein kinase 8 MAPK9 = mitogen-activated protein kinase 9 MAPK10 = mitogen-activated protein kinase 10 VARIABLE: JNK (any isoform) phosphorylation level p38 and JNK are activated after expression of GADD45, following stress, through MTK1. Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. TAO kinases are MAP3Ks that function upstream of p38 and JNK. PMID:21614932 DUSP1 preferentially inactivates JNK and p38. PMID:19436832	

JNK phosphorylates MST1 at serine 82, which leads to the enhancement of MST1 activation. The activation of MST1 phosphorylates FOXO3 at serine 207 and promotes cell death.
PMID:20028971
JNK and p38 can both phosphorylate ATF2 at Thr69 and Ser71.
JNK can phosphorylate the c-Juntrans-activating domain at Ser63 and Ser73. JNKs, but not the ERKs or p38s, binds c-Jun quite strongly.
ELK1 is a nuclear JNK target.
MEKK1 can interact with Ras in a GTP-dependent manner. The GTP-dependent coupling of MEKK1 to Ras indicates that MEKK1 may be an effector for those agonists that recruit JNK through Ras-dependent mechanisms.
MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways.
PMID:11274345
Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK.
PMID:20060931

Regulator	**Comment**
TAK1	http://www.ncbi.nlm.nih.gov/pubmed/20060931 Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK. PMID:20060931
MAP3K1_3	http://www.ncbi.nlm.nih.gov/pubmed/11274345 The GTP-dependent coupling of MEKK1 to Ras indicates that MEKK1 may be an effector for those agonists that recruit JNK through Ras-dependent mechanisms. MEKK1 selectively activates the endogenous JNK pathway. MEKK1 can activate MEK4 and MEK7 in vivo. MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345
DUSP1	http://www.ncbi.nlm.nih.gov/pubmed/19436832 DUSP1 preferentially inactivates JNK and p38. PMID:19436832
TAOK	http://www.ncbi.nlm.nih.gov/pubmed/21614932 TAO kinases are MAP3Ks that function upstream of p38 and JNK. PMID:21614932
MTK1	http://www.ncbi.nlm.nih.gov/pubmed/21614932 Expression of GADD45 genes in mammalian cells

		strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. PMID:21614932
JUN	JNK	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6204 http://www.ncbi.nlm.nih.gov/pubmed/11274345 JUN = jun proto-oncogene VARIABLE: JUN phosphorylation level AP-1 is a heterodimer comprised of bZIP transcription factors, typically c-Jun and JunD, along with members of the fos (usually c-Fos) and ATF (usually ATF2) families. All bZIP transcription factors contain leucine zippers that enable homo- and heterodimerisation, and AP-1 components are organised into Jun-Jun, Jun-Fos, or Jun-ATF dimers. JNK can phosphorylate the c-Jun trans-activating domain at Ser63 and Ser73. JNKs, but not the ERKs or p38s, binds c-Jun quite strongly. PMID:11274345 **Regulator** JNK **Comment** http://www.ncbi.nlm.nih.gov/pubmed/11274345 JNK can phosphorylate the c-Jun trans-activating domain at Ser63 and Ser73. JNKs, but not the ERKs or p38s, binds c-Jun quite strongly. PMID:11274345
MAP3K1_3	RAS	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6848 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6854 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6855 http://www.ncbi.nlm.nih.gov/pubmed/11274345 MAP3K1 = mitogen-activated protein kinase kinase kinase 1 MAP3K2 = mitogen-activated protein kinase kinase kinase 2 MAP3K3 = mitogen-activated protein kinase kinase kinase 3 VARIABLE: MAP3K1/2/3 (any isoform) phosphorylation level The GTP-dependent coupling of MEKK1 to Ras indicates that MEKK1 may be an effector for those agonists that recruit JNK through Ras-dependent mechanisms. MEKK1 selectively activates the endogenous JNK pathway. MEKK1 can activate MEK4 and MEK7 in vivo. MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345 **Regulator** RAS **Comment** http://www.ncbi.nlm.nih.gov/pubmed/11274345 The GTP-dependent coupling of MEKK1 to Ras indicates that MEKK1 may be an effector for those agonists that recruit JNK through Ras-dependent

			mechanisms. MEKK1 selectively activates the endogenous JNK pathway. MEKK1 can activate MEK4 and MEK7 in vivo. MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345
MAX	p38	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6913 http://www.ncbi.nlm.nih.gov/pubmed/11274345 MAX = MYC associated factor X VARIABLE: MAX phosphorylation level MAX interacts with the transcription factor c-Myc, enabling c-Myc to trans-activate at least a subset of its target genes. MAX is phosphorylated (and activated) by p38, through complex formation. PMID:11274345 **Regulator** p38	**Comment** http://www.ncbi.nlm.nih.gov/pubmed/11274345 MAX is phosphorylated (and activated) by p38, through complex formation. PMID:11274345
MDM2	(p53 | AKT) & !p14	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6973 http://www.ncbi.nlm.nih.gov/pubmed/17158541 http://www.ncbi.nlm.nih.gov/pubmed/11850850 MDM2 = Mdm2, p53 E3 ubiquitin protein ligase homolog (mouse) VARIABLE: MDM2 gene expression level The Mdm2 protein is involved in an autoregulatory feedback loop with p53, thus controlling its activity. Increased p53 levels transactivate the MDM2 promoter causing its upregulation. The translated protein then binds to p53 and transports it to the proteasome for ubiquitin-mediated degradation. The resultant lowered p53 levels then reduce the levels of Mdm2. The MDM2 gene is, in turn, transcriptionally inhibited by p14, providing another fine level of control for p53 activity. PMID:17158541 Effective recruitment of Akt by appropriate survival signals may lead to activation of Mdm2, inactivation of p53, and eventually inhibition of p53-dependent apoptosis. PMID:11850850 **Regulator** p53	**Comment** http://www.ncbi.nlm.nih.gov/pubmed/17158541 The Mdm2 protein is involved in an autoregulatory feedback loop with p53, thus controlling its activity. Increased p53 levels transactivate the MDM2 promoter

			causing its upregulation. The translated protein then binds to p53 and transports it to the proteasome for ubiquitin-mediated degradation. The resultant lowered p53 levels then reduce the levels of Mdm2. PMID:17158541
		p14	http://www.ncbi.nlm.nih.gov/pubmed/17158541 The MDM2 gene is transcriptionally inhibited by p14. PMID:17158541
		AKT	http://www.ncbi.nlm.nih.gov/pubmed/11882383 Effective recruitment of Akt by appropriate survival signals may lead to activation of Mdm2, inactivation of p53, and eventually inhibition of p53-dependent apoptosis. PMID:11850850
MEK1_2	RAF | MAP3K1_3) & !(PPP2CA | AP1)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6840 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6842 http://www.ncbi.nlm.nih.gov/pubmed/17496910 http://www.ncbi.nlm.nih.gov/pubmed/18039929 MAP2K1 = mitogen-activated protein kinase kinase 1 MAP2K2 = mitogen-activated protein kinase kinase 2 VARIABLE: MEK (any isoform) phosphorylation level Once activated, Raf family members are capable of initiating the phosphorylation cascade, whereby Raf activates MEK, and MEK in turn activates ERK. PMID:17496910 MEK is continuously dephosphorylated by PP2A (PPP2CA), whose activity is stimulated by p38: p38 activity increases the physical association between PP2A and MEK/ERK complex. AP-1 mediated gene expression inhibits ERK phosphorylation. PMID:18039929	
		Regulator	**Comment**
		RAF	http://www.ncbi.nlm.nih.gov/pubmed/17496910 Once activated, Raf family members are capable of initiating the phosphorylation cascade, whereby Raf activates MEK, and MEK in turn activates ERK. PMID:17496910
		MAP3K1_3	http://www.ncbi.nlm.nih.gov/pubmed/11274345 MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345
		AP1	http://www.ncbi.nlm.nih.gov/pubmed/18039929

		PPP2CA	AP-1 mediated gene expression inhibits ERK phosphorylation. PMID:18039929 http://www.ncbi.nlm.nih.gov/pubmed/18039929 MEK is continuously dephosphorylated by PP2A (PPP2CA), whose activity is stimulated by p38: p38 activity increases the physical association between PP2A and MEK/ERK complex. PMID:18039929
MSK	ERK | p38	http://www.genenames.org/data/hgnc_data.php?hgnc_id=10433 http://www.genenames.org/data/hgnc_data.php?hgnc_id=10434 http://www.ncbi.nlm.nih.gov/pubmed/15187187 http://www.ncbi.nlm.nih.gov/pubmed/17158541 RPS6KA4 = ribosomal protein S6 kinase, 90kDa, polypeptide 4 RPS6KA5 = ribosomal protein S6 kinase, 90kDa, polypeptide 5 VARIABLE: MSK (any isoform) phosphorylation level MSK1 and MSK2 are potently activated (by phosphorylation) in vivo by ERK1/2 and p38 but not JNK. MSK1 mediates the mitogen-stimulated phoshphorylation of CREB. PMID:15187187 Translocation of ERK into the nucleus activates the mitogen activated and stress-activated protein kinase 1 (MSK1), a histone H3 kinase that can relax chromatin, thus making it more transcriptionally accessible. This alteration in the chromatin state induces MYC, a gene that encodes the c-Myc protein, a transcription factor that controls the cell cycle. PMID:17158541	
		Regulator	**Comment**
		ERK	http://www.ncbi.nlm.nih.gov/pubmed/15187187 MSK1 and MSK2 are potently activated (by phosphorylation) in vivo by ERK1/2 and p38 but not JNK. PMID:15187187
		p38	http://www.ncbi.nlm.nih.gov/pubmed/15187187 MSK1 and MSK2 are potently activated (by phosphorylation) in vivo by ERK1/2 and p38 but not JNK. PMID:15187187
MTK1	GADD45	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6856 http://www.ncbi.nlm.nih.gov/pubmed/21614932 MAP3K4 = mitogen-activated protein kinase kinase kinase 4 VARIABLE: MTK1 phosphorylation level	

		The delayed activation of p38 by TGFbeta is mediated mainly by Smad-dependent GADD45beta expression and by its subsequent activation of MTK1. Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. PMID:21614932 **Regulator** / **Comment** GADD45 / http://www.ncbi.nlm.nih.gov/pubmed/21614932 Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. PMID:21614932
MYC	(MSK & MAX) | (MSK & AKT)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=7553 http://www.ncbi.nlm.nih.gov/pubmed/17158541 http://www.ncbi.nlm.nih.gov/pubmed/11274345 http://www.ncbi.nlm.nih.gov/pubmed/12040186 http://www.ncbi.nlm.nih.gov/pubmed/11805123 MYC = v-myc myelocytomatosis viral oncogene homolog (avian) VARIABLE: MYC activation level (implies gene expression) Modelling hypotheses: MSK determines MYC gene expression, so it is always needed for MYC activation; MAX activates MYC protein; AKT inhibits GSK3B, which in turn inactivates MYC protein Translocation of ERK into the nucleus activates the mitogen activated and stress-activated protein kinase 1 (MSK1), a histone H3 kinase that can relax chromatin, thus making it more transcriptionally accessible. This alteration in the chromatin state induces MYC, a gene that encodes the c-Myc protein, a transcription factor that controls the cell cycle. c-Myc signals downstream to promote expression of cyclins that complex with CDKs. MYC inhibits p16, whereas it activates p14. PMID:17158541 MAX interacts with the transcription factor c-Myc (this interaction is modelled here by complex formation) enabling c-Myc to trans-activate at least a subset of its target genes. PMID:11274345 Glycogen synthase kinase 3 (GSK3) is a target of Akt. This protein kinase is constitutively active in unstimulated cells and phosphorylates many proteins (including glycogen synthase, c-Myc, and cyclin D) to keep them in inactive states or promote their degradation. Phosphorylation of GSK3 (both alpha and beta isoforms) by Akt turns off the catalytic activity of this enzyme, resulting in the activation of pathways that are normally repressed by GSK3. PMID:12040186 MYC contributes to E2F-induced cell cycle progression. PMID:11805123 **Regulator** / **Comment** MSK / http://www.ncbi.nlm.nih.gov/pubmed/17158541

			Translocation of ERK into the nucleus activates the mitogen activated and stress-activated protein kinase 1 (MSK1), a histone H3 kinase that can relax chromatin, thus making it more transcriptionally accessible. This alteration in the chromatin state induces MYC, a gene that encodes the c-Myc protein, a transcription factor that controls the cell cycle. PMID:17158541
		MAX	http://www.ncbi.nlm.nih.gov/pubmed/11274345 MAX interacts with the transcription factor c-Myc, enabling c-Myc to trans-activate at least a subset of its target genes. PMID:11274345
		AKT	http://www.ncbi.nlm.nih.gov/pubmed/12040186 Glycogen synthase kinase 3 (GSK3) is a target of Akt. This protein kinase is constitutively active in unstimulated cells and phosphorylates many proteins (including glycogen synthase, c-Myc, and cyclin D) to keep them in inactive states or promote their degradation. Phosphorylation of GSK3 (both alpha and beta isoforms) by Akt turns off the catalytic activity of this enzyme, resulting in the activation of pathways that are normally repressed by GSK3. PMID:12040186
PDK1	PI3K	http://www.genenames.org/data/hgnc_data.php?hgnc_id=8809 http://www.ncbi.nlm.nih.gov/pubmed/12040186 PDK1 = pyruvate dehydrogenase kinase, isozyme 1 VARIABLE: PDK1 activation level PDK1 is a PI3K target, leading to activation of p70 and subsequent cell growth. Signaling proteins with pleckstrin-homology (PH) domains accumulate at sites of PI3K activation by directly binding to PI(3,4,5)P3. Of particular interest are the protein serine-threonine kinases Akt and phosphoinositide-dependent kinase 1 (PDK1). Association with PI(3,4,5)P3 at the membrane brings these proteins into proximity and facilitates phosphorylation of Akt by PDK1. This phosphorylation stimulates the catalytic activity of Akt, resulting in the phosphorylation of a host of other proteins that affect cell growth, cell cycle entry, and cell survival. PMID:12040186	
		Regulator	**Comment**
		PI3K	http://www.ncbi.nlm.nih.gov/pubmed/15199124 Phosphatidylinositol-3,4,5-triphosphate (PIP3), the reaction product of PI 3-kinase, is responsible for

<table>
<tr><td></td><td></td><td>activation of phosphoinositide-dependent kinase (PDK) and the antiapoptotic protein kinase Akt.
PMID:15199124</td></tr>
<tr><td>PI3K</td><td>GAB1 | (RAS & SOS)</td><td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=8975
http://www.ncbi.nlm.nih.gov/pubmed/15567848
http://www.ncbi.nlm.nih.gov/pubmed/15199124
http://www.ncbi.nlm.nih.gov/pubmed/21779497
PIK3CA = phosphoinositide-3-kinase, catalytic, alpha polypeptide
VARIABLE: PI3K activation level
Grb2 recruits the docking protein Gab1, which is tyrosine phosphorylated by FGFR, leading to recruitment and activation of the PI3K-Akt cell survival pathway.
EGF stimulates a cell survival pathway mediated by phosphoinositide 3-kinase (PI3K) and the protein kinase Akt by an indirect mechanism in which tyrosine phosphorylation of the docking protein Gab1 or ErbB3 by EGFR leads to recruitment and activation of PI3K.
PMID:15567848
Recruitment and activation of PI 3-kinase by Gab1 results in a positive-feedback loop mediated by binding of the PH domain of Gab1 to the product of PI3-kinase activation, phosphatidylinositol-3,4,5-triphosphate.
Phosphatidylinositol-3,4,5-triphosphate (PIP3), the reaction product of PI 3-kinase, is responsible for activation of phosphoinositide-dependent kinase (PDK) and the antiapoptotic protein kinase Akt.
PMID:15199124
PI3K is a well characterised effector of RAS, through GRB2/SOS pathway.
PMID:21779497

Regulator — Comment
RAS — http://www.ncbi.nlm.nih.gov/pubmed/21779497
PI3K is a well characterised effector of RAS, through GRB2/SOS pathway.
PMID:21779497
SOS — http://www.ncbi.nlm.nih.gov/pubmed/21779497
PI3K is a well characterised effector of RAS, through GRB2/SOS pathway.
PMID:21779497
GAB1 — http://www.ncbi.nlm.nih.gov/pubmed/15199124
Recruitment of PI 3-kinase by Gab1 results in a positive-feedback loop mediated by binding of the PH domain of Gab1 to the product of PI3-kinase activation, phosphatidylinositol-3,4,5-triphosphate.
PMID:15199124</td></tr>
<tr><td>PKC</td><td>PLCG</td><td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=9393
http://www.genenames.org/data/hgnc_data.php?hgnc_id=9395</td></tr>
</table>

		http://www.genenames.org/data/hgnc_data.php?hgnc_id=9402 http://www.ncbi.nlm.nih.gov/pubmed/15567848 http://www.ncbi.nlm.nih.gov/pubmed/6321473 http://www.ncbi.nlm.nih.gov/pubmed/8321321 http://www.ncbi.nlm.nih.gov/pubmed/9694798 http://www.ncbi.nlm.nih.gov/pubmed/8622701 http://www.ncbi.nlm.nih.gov/pubmed/14699054 PRKCA = protein kinase C, alpha PRKCB = protein kinase C, beta PRKCG = protein kinase C, gamma VARIABLE: PKC (any isoform) enzymatic activity Recruitment to the membrane and tyrosine phosphorylation enhance the enzymatic activity of PLC-g, leading to the formation of two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 releases Ca2+ from internal stores, which in turn acts in concert with DAG to translocate protein kinase C (PKC) to the cell membrane and stimulate its enzymatic activity. PMID:15567848 PKC may cause phosphorylation of EGFR, leading to a decrease in its activity. PMID:6321473 PKCalpha can directly phosphorylate and activates Raf-1. PMID:8321321 (Inferred from FGFR1) PKC-mediated phosphorylation can lead to internalization and degradation of FGFR1. PMID:9694798, PMID:8622701, PMID:14699054 **Regulator** PLCG **Comment** http://www.ncbi.nlm.nih.gov/pubmed/15567848 Recruitment to the membrane and tyrosine phosphorylation enhance the enzymatic activity of PLC-g, leading to the formation of two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 releases Ca2+ from internal stores, which in turn acts in concert with DAG to translocate protein kinase C (PKC) to the cell membrane and stimulate its enzymatic activity. PMID:15567848
PLCG	EGFR | FGFR3	http://www.genenames.org/data/hgnc_data.php?hgnc_id=9065 http://www.genenames.org/data/hgnc_data.php?hgnc_id=9066 http://www.ncbi.nlm.nih.gov/pubmed/1656221 http://www.ncbi.nlm.nih.gov/pubmed/2472219 http://www.ncbi.nlm.nih.gov/pubmed/15567848 http://www.ncbi.nlm.nih.gov/pubmed/17496910

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<td>http://www.ncbi.nlm.nih.gov/pubmed/16488589
PLCG1 = phospholipase C, gamma 1
PLCG2 = phospholipase C, gamma 2 (phosphatidylinositol-specific)
VARIABLE: PLCG (any isoform) phosphorylation level
Binding of FGF to FGFR leads to tyrosine phosphorylation of PLCgamma.
PMID:1656221
Tyrosine phosphorylation of PLC-gamma by EGF receptor leads to its activation.
PMID:2472219
Recruitment to the membrane and tyrosine phosphorylation enhance the enzymatic activity of PLC-g, leading to the formation of two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 releases Ca2+ from internal stores, which in turn acts in concert with DAG to translocate protein kinase C (PKC) to the cell membrane and stimulate its enzymatic activity.
PMID:15567848
RasGRP1 is a C1-domain containing protein that is activated by DAG and Ca2+, in a manner analogous to members of the PKC family.
PMID:17496910
Calcium liberated from internal stores by IP3 acts on the calcium- and DAG-sensitive RasGRP1 and causes it to translocate to the Golgi. RasGRP1 activates Golgi-associated Ras on this compartment.
PMID:16488589

Regulator — Comment
EGFR — http://www.ncbi.nlm.nih.gov/pubmed/2472219 Tyrosine phosphorylation of PLC-gamma by EGF receptor leads to its activation. PMID:2472219
FGFR3 — http://www.ncbi.nlm.nih.gov/pubmed/1656221 Binding of FGF to FGFR leads to tyrosine phosphorylation of PLCgamma. PMID:1656221</td>
</tr>
<tr>
<td>PPP2CA</td>
<td>p38</td>
<td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=9299
http://www.ncbi.nlm.nih.gov/pubmed/18039929
PPP2CA = protein phosphatase 2, catalytic subunit, alpha isozyme
VARIABLE: PPP2CA activation level
MEK is continuously dephosphorylated by PP2A (PPP2CA), whose activity is stimulated by p38: p38 activity increases the physical association between PP2A and MEK/ERK complex.
PMID:18039929

Regulator — Comment
p38 — http://www.ncbi.nlm.nih.gov/pubmed/18039929 MEK is continuously dephosphorylated by PP2A</td>
</tr>
</table>

		(PPP2CA), whose activity is stimulated by p38: p38 activity increases the physical association between PP2A and MEK/ERK complex. PMID:18039929
Proliferation	p70 & MYC & !p21	http://www.ncbi.nlm.nih.gov/pubmed/12040186 http://www.ncbi.nlm.nih.gov/pubmed/11805123 http://www.ncbi.nlm.nih.gov/pubmed/8614832 Proliferation VARIABLE: proliferation enablement Proliferation is an output variable of the model. Modelling hypotheses: proliferation is supposed to be enabled when both MYC and p70 are activated, and p21 (CDK inhibitor) is inactive PDK1 is a PI3K target, leading to activation of p70 and subsequent cell growth. PMID:12040186 MYC contributes to E2F-induced cell cycle progression. PMID:11805123 Cell growth arrest is induced through cyclin-dependent kinase inhibitor p21 WAF1/CIP1. PMID:8614832 **Regulator** — **Comment** p70 — http://www.ncbi.nlm.nih.gov/pubmed/12040186 PDK1 is a PI3K target, leading to activation of p70 and subsequent cell growth. PMID:12040186 MYC — http://www.ncbi.nlm.nih.gov/pubmed/11805123 MYC contributes to E2F-induced cell cycle progression. PMID:11805123 p21 — http://www.ncbi.nlm.nih.gov/pubmed/8614832 Cell growth arrest is induced through cyclin-dependent kinase inhibitor p21 WAF1/CIP1. PMID:8614832
PTEN	p53	http://www.genenames.org/data/hgnc_data.php?hgnc_id=9588 http://www.ncbi.nlm.nih.gov/pubmed/12217521 PTEN = phosphatase and tensin homolog VARIABLE: PTEN protein expression level p53 induces transcription of the PTEN gene and elevates cellular levels of the PTEN protein, which in turn inhibits activation of Akt. PMID:12217521 **Regulator** — **Comment**

		p53	http://www.ncbi.nlm.nih.gov/pubmed/12217521 p53 induces transcription of the PTEN gene and elevates cellular levels of the PTEN protein, which in turn inhibits activation of Akt. PMID:12217521
p14	MYC	http://www.genenames.org/data/hgnc_data.php?hgnc_id=1787 http://www.ncbi.nlm.nih.gov/pubmed/17158541 CDKN2A = cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) VARIABLE: p14 activation level MYC inhibits p16, whereas it activates p14. The MDM2 gene is transcriptionally inhibited by p14. PMID:17158541 **Regulator** / **Comment** MYC / http://www.ncbi.nlm.nih.gov/pubmed/17158541 MYC inhibits p16, whereas it activates p14. PMID:17158541	
p21	!AKT & p53	http://www.genenames.org/data/hgnc_data.php?hgnc_id=1784 http://www.ncbi.nlm.nih.gov/pubmed/11882383 http://www.ncbi.nlm.nih.gov/pubmed/17158541 http://www.ncbi.nlm.nih.gov/pubmed/8614832 CDKN1A = cyclin-dependent kinase inhibitor 1A (p21, Cip1) VARIABLE: p21 activation level p21 is a direct substrate of AKT and this may regulate the subcellular localisation of p21. Phosphorylation of p21 by AKT correlated with its exit from the nucleus and with increased cell cycle progression. PMID:11882383 p21 is transcriptionally induced by the p53 protein. p21 is a CDK inhibitor. PMID:17158541 Cell growth arrest is induced through cyclin-dependent kinase inhibitor p21 WAF1/CIP1. PMID:8614832 **Regulator** / **Comment** p53 / http://www.ncbi.nlm.nih.gov/pubmed/17158541 p21 is transcriptionally induced by the p53 protein. PMID:17158541 AKT / http://www.ncbi.nlm.nih.gov/pubmed/11882383 p21 is a direct substrate of AKT and this may regulate the subcellular localisation of p21. Phosphorylation of p21	

		by AKT correlated with its exit from the nucleus and with increased cell cycle progression. PMID:11882383
p38	(TAOK & MAP3K1_3) | (MAP3K1_3 & MTK1) | (TAOK & MTK1) | (TAK1 & MTK1) | (TAK1 & MAP3K1_3) | (TAK1 & TAOK) | ((TAOK | MTK1 | MAP3K1_3 | TAK1) & !DUSP1)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6873 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6874 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6875 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6876 http://www.ncbi.nlm.nih.gov/pubmed/21614932 http://www.ncbi.nlm.nih.gov/pubmed/19436832 http://www.ncbi.nlm.nih.gov/pubmed/11274345 http://www.ncbi.nlm.nih.gov/pubmed/15187187 http://www.ncbi.nlm.nih.gov/pubmed/20506250 http://www.ncbi.nlm.nih.gov/pubmed/18039929 http://www.ncbi.nlm.nih.gov/pubmed/20060931 MAPK11 = mitogen-activated protein kinase 11 MAPK12 = mitogen-activated protein kinase 12 MAPK13 = mitogen-activated protein kinase 13 MAPK14 = mitogen-activated protein kinase 14 VARIABLE: p38 (any isoform) phosphorylation level p38 and JNK are activated after expression of GADD45, following stress, through MTK1. Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. TAO kinases are MAP3Ks that function upstream of p38 and JNK. Activated p38 phosphorylates p53 at several residues, including Ser33, and thereby increases the transcriptional activity of p53. Activated p53 then induces apoptosis in cells that have suffered extensive DNA damage. When the intensity of the damage is moderate, however, the cell can repair the damage and escape apoptotic cell death by down-regulating p38-p53 signaling. Under these conditions, p53-induced Wip1 phosphatase interacts with activated p38 and selectively dephosphorylates p38 at the phospho-Thr180 residue, thereby reducing its kinase activity towards p53. PMID:21614932 DUSP1 preferentially inactivates JNK and p38. PMID:19436832 JNK and p38 can both phosphorylate ATF2 at Thr69 and Ser71. MAX is phosphorylated (and activated) by p38, through complex formation. MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345 MSK1 and MSK2 are potently activated (by phosphorylation) in vivo by ERK1/2 and p38 but not JNK. PMID:15187187 ELK1 is a nuclear p38 target. PMID:20506250

		MEK is continuously dephosphorylated by PP2A (PPP2CA), whose activity is stimulated by p38: p38 activity increases the physical association between PP2A and MEK/ERK complex. PMID:18039929 Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK. PMID:20060931 **Regulator** — **Comment** TAK1 — http://www.ncbi.nlm.nih.gov/pubmed/20060931 Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK. PMID:20060931 MAP3K1_3 — http://www.ncbi.nlm.nih.gov/pubmed/11274345 MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways. PMID:11274345 DUSP1 — http://www.ncbi.nlm.nih.gov/pubmed/19436832 DUSP1 preferentially inactivates JNK and p38. PMID:19436832 TAOK — http://www.ncbi.nlm.nih.gov/pubmed/21614932 TAO kinases are MAP3Ks that function upstream of p38 and JNK. PMID:21614932 MTK1 — http://www.ncbi.nlm.nih.gov/pubmed/21614932 Expression of GADD45 genes in mammalian cells strongly activates co-expressed MTK1, as well as p38 and JNK, the MAPKs downstream of MTK1. PMID:21614932
p53	(ATM & p38) | ((ATM | p38) & ! MDM2)	http://www.genenames.org/data/hgnc_data.php?hgnc_id=11998 http://www.ncbi.nlm.nih.gov/pubmed/15140942 http://www.ncbi.nlm.nih.gov/pubmed/21614932 http://www.ncbi.nlm.nih.gov/pubmed/17158541 http://www.ncbi.nlm.nih.gov/pubmed/11274345 http://www.ncbi.nlm.nih.gov/pubmed/19641508 http://www.ncbi.nlm.nih.gov/pubmed/12217521 TP53 = tumor protein p53 VARIABLE: p53 phosphorylation level ATM phosphorylates p53 at ser15 and stabilize it.

PMID:15140942
Activated p38 phosphorylates p53 at several residues, including Ser33, and thereby increases the transcriptional activity of p53. Activated p53 then induces apoptosis in cells that have suffered extensive DNA damage. When the intensity of the damage is moderate, however, the cell can repair the damage and escape apoptotic cell death by down-regulating p38-p53 signaling. Under these conditions, p53-induced Wip1 phosphatase interacts with activated p38 and selectively dephosphorylates p38 at the phospho-Thr180 residue, thereby reducing its kinase activity towards p53.
PMID:21614932
The Mdm2 protein is involved in an autoregulatory feedback loop with p53, thus controlling its activity. Increased p53 levels transactivate the MDM2 promoter causing its upregulation. The translated protein then binds to p53 and transports it to the proteasome for ubiquitin-mediated degradation. The resultant lowered p53 levels then reduce the levels of Mdm2. p21 is transcriptionally regulated by the p53 protein.
PMID:17158541
Expression of GADD45 is the culmination of a signaling pathway that requires prior expression of the tumor suppressor protein p53 which trans-activates the GADD45 gene.
PMID:11274345
In response to genotoxic stress such as DNA damage, PUMA is transactivated by p53 (leading to apoptosis).
PMID:19641508
p53 induces transcription of the PTEN gene and elevates cellular levels of the PTEN protein.
PMID:12217521

Regulator	**Comment**
ATM	http://www.ncbi.nlm.nih.gov/pubmed/15140942 ATM phosphorylates p53 at ser15 and stabilize it. PMID:15140942
p38	http://www.ncbi.nlm.nih.gov/pubmed/21614932 Activated p38 phosphorylates p53 at several residues, including Ser33, and thereby increases the transcriptional activity of p53. Activated p53 then induces apoptosis in cells that have suffered extensive DNA damage. When the intensity of the damage is moderate, however, the cell can repair the damage and escape apoptotic cell death by down-regulating p38-p53 signaling. Under these conditions, p53-induced Wip1 phosphatase interacts with activated p38 and selectively dephosphorylates p38 at the phospho-Thr180 residue, thereby reducing its kinase activity towards p53. PMID:21614932
MDM2	http://www.ncbi.nlm.nih.gov/pubmed/17158541 The Mdm2 protein is involved in an autoregulatory feedback loop with p53, thus controlling its activity.

<table>
<tr><td></td><td></td><td></td><td>Increased p53 levels transactivate the MDM2 promoter causing its upregulation. The translated protein then binds to p53 and transports it to the proteasome for ubiquitin-mediated degradation. The resultant lowered p53 levels then reduce the levels of Mdm2.
PMID:17158541</td></tr>
<tr><td>p70</td><td>PDK1 & ERK</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=10436
http://www.genenames.org/data/hgnc_data.php?hgnc_id=10437
http://www.ncbi.nlm.nih.gov/pubmed/12040186
http://www.ncbi.nlm.nih.gov/pubmed/11940578
http://www.ncbi.nlm.nih.gov/pubmed/10601235
http://www.ncbi.nlm.nih.gov/pubmed/11431469
RPS6KB1 = ribosomal protein S6 kinase, 70kDa, polypeptide 1
RPS6KB2 = ribosomal protein S6 kinase, 70kDa, polypeptide 2
VARIABLE: p70 (any isoform) phosphorylation level
PDK1 is a PI3K target, leading to activation of p70 (through phosphorylation) and subsequent cell growth.
PMID:12040186
p70 activation requires both ERK cascade and PI3K/AKT cascade, at least in some cell types.
PMID:11940578, PMID:10601235, PMID:11431469

Regulator | Comment
ERK | http://www.ncbi.nlm.nih.gov/pubmed/11940578
http://www.ncbi.nlm.nih.gov/pubmed/10601235
http://www.ncbi.nlm.nih.gov/pubmed/11431469
p70 activation requires both ERK cascade and PI3K/AKT cascade, at least in some cell types.
PMID:11940578, PMID:10601235, PMID:11431469
PDK1 | http://www.ncbi.nlm.nih.gov/pubmed/12040186
PDK1 is a PI3K target, leading to activation of p70 and subsequent cell growth.
PMID:12040186</td></tr>
<tr><td>RAF</td><td>(RAS | PKC) & !(ERK | AKT)</td><td colspan="2">http://www.genenames.org/data/hgnc_data.php?hgnc_id=9829
http://www.genenames.org/data/hgnc_data.php?hgnc_id=1097
http://www.genenames.org/data/hgnc_data.php?hgnc_id=646
http://www.ncbi.nlm.nih.gov/pubmed/17496910
http://www.ncbi.nlm.nih.gov/pubmed/8321321
http://www.ncbi.nlm.nih.gov/pubmed/18039929
http://www.ncbi.nlm.nih.gov/pubmed/19933846
RAF1 = v-raf-1 murine leukemia viral oncogene homolog 1
BRAF = v-raf murine sarcoma viral oncogene homolog B1</td></tr>
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<td>ARAF = v-raf murine sarcoma 3611 viral oncogene homolog
VARIABLE: RAF (any isoform) phosphorylation
Once activated, Raf family members are capable of initiating the phosphorylation cascade, whereby Raf activates MEK, and MEK in turn activates ERK.
PMID:17496910
PKCalpha directly phosphorylates and activates Raf-1.
PMID:8321321
Activated Ras recruits cytoplasmic Raf (MAPKKK) for activation. There are three mammalian serine/threonine Raf kinases: A-Raf, B-Raf, and Raf-1 (also known as C-Raf). All three Raf proteins share the same downstream MAPKK substrate mitogen activated protein kinase kinases 1,2 (MEK1,2).
PMID:18039929
Phosphorylation by Akt inhibits EGF-dependent activity of B-Raf and C-Raf.
PMID:10869359
B-Raf phosphorylated by activated ERK and find that feedback phosphorylation of B-Raf inhibits binding to activated Ras.
PMID:19933846

Regulator | Comment
ERK | http://www.ncbi.nlm.nih.gov/pubmed/19933846 B-Raf phosphorylated by activated ERK and find that feedback phosphorylation of B-Raf inhibits binding to activated Ras. PMID:19933846
RAS | http://www.ncbi.nlm.nih.gov/pubmed/18039929 Activated Ras recruits cytoplasmic Raf (MAPKKK) for activation (through phosphorylation). There are three mammalian serine/threonine Raf kinases: A-Raf, B-Raf, and Raf-1 (also known as C-Raf). All three Raf proteins share the same downstream MAPKK substrate mitogen activated protein kinase kinases 1,2 (MEK1,2). PMID:18039929
AKT | http://www.ncbi.nlm.nih.gov/pubmed/10869359 Phosphorylation by Akt inhibits EGF-dependent activity of B-Raf and C-Raf. PMID:10869359
PKC | http://www.ncbi.nlm.nih.gov/pubmed/8321321 PKCalpha can directly phosphorylate and activates Raf-1. PMID:8321321</td>
</tr>
<tr>
<td>RAS</td>
<td>SOS | PLCG</td>
<td>http://www.genenames.org/data/hgnc_data.php?hgnc_id=5173
http://www.genenames.org/data/hgnc_data.php?hgnc_id=6407</td>
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</table>

http://www.genenames.org/data/hgnc_data.php?hgnc_id=7989
http://www.ncbi.nlm.nih.gov/pubmed/18039929
http://www.ncbi.nlm.nih.gov/pubmed/11274345
http://www.ncbi.nlm.nih.gov/pubmed/21779497
http://www.ncbi.nlm.nih.gov/pubmed/16488589
HRAS = v-Ha-ras Harvey rat sarcoma viral oncogene homolog
KRAS = v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
NRAS = neuroblastoma RAS viral (v-ras) oncogene homolog
VARIABLE: RAS (any isoform) phosphorylation level
Grb2 molecules recruit the nucleotide exchange factor SOS, leading to the activation of the Ras-MAPK signaling cascade.
Most of the signals activating the ERK pathway are initiated through receptor-mediated activation of the small G-protein, Ras. Ras is a membrane-bound protein activated through the exchange of bound GDP to GTP. The process of activating Ras thereby requires the recruitment of proteins responsible for initiating GDP/GTP exchange to the membrane, such as SOS (son of sevenless).
Activated Ras recruits cytoplasmic Raf (MAPKKK) for activation (through phosphorylation). There are three mammalian serine/threonine Raf kinases: A-Raf, B-Raf, and Raf-1 (also known as C-Raf). All three Raf proteins share the same downstream MAPKK substrate mitogen activated protein kinase kinases 1,2 (MEK1,2).
PMID:18039929
The GTP-dependent coupling of MEKK1 to Ras indicates that MEKK1 may be an effector for those agonists that recruit JNK through Ras-dependent mechanisms. MEKK1 selectively activates the endogenous JNK pathway.
MEKK1 can activate MEK4 and MEK7 in vivo.
MEKK2 and MEKK3 can activate JNK, p38 and ERK pathways.
PMID:11274345
PI3K is a well characterised effector of RAS, through GRB2/SOS pathway.
PMID:21779497
Calcium liberated from internal stores by IP3 acts on the calcium- and DAG-sensitive RasGRP1 and causes it to translocate to the Golgi. RasGRP1 activates Golgi-associated Ras on this compartment.
PMID:16488589

Regulator	**Comment**
SOS	http://www.ncbi.nlm.nih.gov/pubmed/18039929 The process of activating Ras requires the recruitment of proteins responsible for initiating GDP/GTP exchange to the membrane, such as SOS (son of sevenless). PMID:18039929
PLCG	http://www.ncbi.nlm.nih.gov/pubmed/17496910 http://www.ncbi.nlm.nih.gov/pubmed/16488589 RasGRP1 is a C1-domain containing protein that is activated by DAG and Ca2+, in a manner analogous to members of the PKC family.

		PMID:17496910 Calcium liberated from internal stores by IP3 acts on the calcium- and DAG-sensitive RasGRP1 and causes it to translocate to the Golgi. RasGRP1 activates Golgi-associated Ras on this compartment. PMID:16488589
RSK	ERK	http://www.genenames.org/data/hgnc_data.php?hgnc_id=10430 http://www.genenames.org/data/hgnc_data.php?hgnc_id=10431 http://www.genenames.org/data/hgnc_data.php?hgnc_id=10432 http://www.genenames.org/data/hgnc_data.php?hgnc_id=10435 http://www.ncbi.nlm.nih.gov/pubmed/15239952 http://www.ncbi.nlm.nih.gov/pubmed/16393692 http://www.ncbi.nlm.nih.gov/pubmed/9242373 RPS6KA1 = ribosomal protein S6 kinase, 90kDa, polypeptide 1 RPS6KA2 = ribosomal protein S6 kinase, 90kDa, polypeptide 2 RPS6KA3 = ribosomal protein S6 kinase, 90kDa, polypeptide 3 RPS6KA6 = ribosomal protein S6 kinase, 90kDa, polypeptide 6 VARIABLE: RSK (any isoform) phosphorylation level RSK2 is a well known ERK substrate in the cytoplasm and has been shown to undergo autophosphorylation after ERK phosphorylation. PMID:15239952 Phosphorylation by both ERKs and their downstream RSKs can stabilise the c-Fos protein for several hours. The combination of these phosphorylations allows c-Fos sustained activity. PMID:16393692 p90 Rsk-2 is involved in SOS phosphorylation and may be important in down-regulation of the growth factor response. PMID:9242373 **Regulator** ERK **Comment** http://www.ncbi.nlm.nih.gov/pubmed/15239952 RSK2 is a well known ERK substrate in the cytoplasm and has been shown to undergo autophosphorylation after ERK phosphorylation. PMID:15239952
SMAD	TGFBR	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6768 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6769 http://www.genenames.org/data/hgnc_data.php?hgnc_id=6770 http://www.ncbi.nlm.nih.gov/pubmed/21614932 SMAD2 = SMAD family member 2 SMAD3 = SMAD family member 3

		SMAD4 = SMAD family member 4 VARIABLE: SMAD gene (any isoform) expression level Smad-dependent gene expression can provoke p38 activation in response to TGFbeta. GADD45beta was identified as the TGFbeta-inducible gene whose expression activates the p38 pathway. PMID:21614932 **Regulator** TGFBR **Comment** http://www.ncbi.nlm.nih.gov/pubmed/21614932 Smad-dependent gene expression can provoke p38 activation in response to TGFbeta. GADD45beta was identified as the TGFbeta-inducible gene whose expression activates the p38 pathway. PMID:21614932
SOS	GRB2 & !RSK	http://www.genenames.org/data/hgnc_data.php?hgnc_id=11187 http://www.genenames.org/data/hgnc_data.php?hgnc_id=11188 http://www.ncbi.nlm.nih.gov/pubmed/17496910 http://www.ncbi.nlm.nih.gov/pubmed/18039929 http://www.ncbi.nlm.nih.gov/pubmed/21779497 http://www.ncbi.nlm.nih.gov/pubmed/9242373 SOS1 = son of sevenless homolog 1 (Drosophila) SOS2 = son of sevenless homolog 2 (Drosophila) VARIABLE: SOS (any isoform) recruitment by GRB2 Sos is recruited from the cytosol to the plasma membrane as a result of its constitutive interaction with Grb2. It is in an autoinhibited state. PMID:17496910 The signaling pathways activated by FGFRs substantially overlap with those activated by EGFRs. Grb2 molecules bound to FRS2 recruit the nucleotide exchange factor SOS, leading to the activation of the Ras-MAPK signaling cascade. The process of activating Ras requires the recruitment of proteins responsible for initiating GDP/GTP exchange to the membrane, such as SOS (son of sevenless). PMID:18039929 PI3K is a well characterised effector of RAS, through GRB2/SOS pathway. PMID:21779497 p90 Rsk-2 is involved in SOS phosphorylation and may be important in down-regulation of the growth factor response. PMID:9242373 **Regulator** GRB2 **Comment** http://www.ncbi.nlm.nih.gov/pubmed/17496910 Sos is recruited from the cytosol to the plasma membrane

		RSK	as a result of its constitutive interaction with Grb2. It is in an autoinhibited state. PMID:17496910 http://www.ncbi.nlm.nih.gov/pubmed/9242373 p90 Rsk-2 is involved in SOS phosphorylation and may be important in down-regulation of the growth factor response. PMID:9242373
SPRY	ERK	http://www.genenames.org/data/hgnc_data.php?hgnc_id=11270 http://www.ncbi.nlm.nih.gov/pubmed/15173823 SPRY2 = sprouty homolog 2 (Drosophila) VARIABLE: SPRY2 phosphorylation level Spry is induced by activated ERK, through phosphorylation on Tyr55. It positively regulates EGFR signalling by sequestering Cbl, whereas it negatively regulates FGFR signalling by sequestering Grb2 from FSR2. PMID:15173823 **Regulator** ERK **Comment** http://www.ncbi.nlm.nih.gov/pubmed/15173823 Spry is induced by activated ERK, through phosphorylation on Tyr55. PMID:15173823	
TAK1	TGFBR	http://www.genenames.org/data/hgnc_data.php?hgnc_id=6885 http://www.ncbi.nlm.nih.gov/pubmed/20060931 MAP3K7 = mitogen-activated protein kinase kinase kinase 7 VARIABLE: TAK1 phosphorylation level Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK. PMID:20060931 **Regulator** TGFBR **Comment** http://www.ncbi.nlm.nih.gov/pubmed/20060931 Activated TGFBR1/TGFBR2 complex attracts the TAB2/TAB3 proteins which promote activation of TAK1 (by phosphorylation), leading to activation of p38 and JNK. PMID:20060931	
TAOK	ATM	http://www.genenames.org/data/hgnc_data.php?hgnc_id=29259 http://www.genenames.org/data/hgnc_data.php?hgnc_id=16835	

		http://www.genenames.org/data/hgnc_data.php?hgnc_id=18133 http://www.ncbi.nlm.nih.gov/pubmed/18855897 http://www.ncbi.nlm.nih.gov/pubmed/21614932 TAOK1 = TAO kinase 1 TAOK2 = TAO kinase 2 TAOK3 = TAO kinase 3 VARIABLE: TAOK (any isoform) phosphorylation level Ataxia telangiectasia mutated (ATM) is activated in response to DNA damage and directly phosphorylates TAOK. PMID:18855897 TAO kinases are MAP3Ks that function upstream of p38 and JNK. PMID:21614932 **Regulator** — **Comment** ATM — http://www.ncbi.nlm.nih.gov/pubmed/18855897 Ataxia telangiectasia mutated (ATM) is activated in response to DNA damage and directly phosphorylates TAOK. PMID:18855897
TGFBR	TGFBR_stimulus	http://www.genenames.org/data/hgnc_data.php?hgnc_id=11772 http://www.genenames.org/data/hgnc_data.php?hgnc_id=11773 http://www.genenames.org/data/hgnc_data.php?hgnc_id=11774 http://www.ncbi.nlm.nih.gov/pubmed/21614932 http://www.ncbi.nlm.nih.gov/pubmed/17673906 TGFBR1 = transforming growth factor, beta receptor 1 TGFBR2 = transforming growth factor, beta receptor II (70/80kDa) TGFBR3 = transforming growth factor, beta receptor III VARIABLE: TGFBR activation level Smad-dependent gene expression can provoke p38 activation in response to TGFbeta. PMID:21614932 TGF-beta-induced ShcA phosphorylation induces ShcA association with Grb2 and Sos, thereby initiating the well-characterised pathway linking receptor tyrosine kinases with Erk MAP kinases. PMID:17673906
TGFBR_stimulus	input	Model input VARIABLE: any stimulus able to induce TGFBR activation