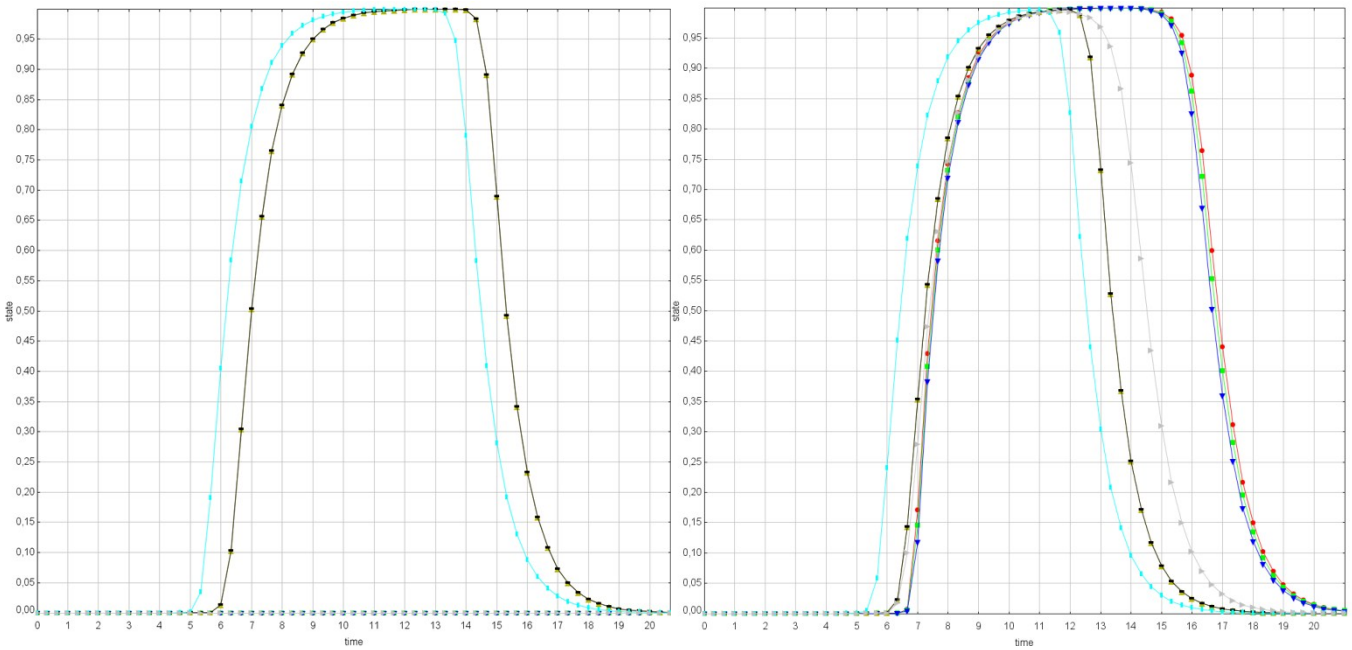
# Supplementary material

## Supplementary file 1: Network assembly

Note that ∧ indicates the logical connection AND
→ indicates activation and
-I indicates inhibition.

| node | node connection and type | | reference | Weight in SQUAD simulation |
|---|---|---|---|---|
| angiotensin II | → | $G_q$-coupled $AT_1$receptor | [1] | 5,00 |
| carbachol | → | $G_i$-coupled $M_2$ receptor | [1] | 10,00 |
| Epac | → | PKC | [2] | 10,00 |
| ERK 1/2 dim 2P | → | p90RSK | [1] | 0,01 |
| ERK 1/2 dim 2P | → | p70S6K | [1] | 0,01 |
| ERK 1/2 dim 2P ∧ $G_{\beta\gamma}$ | → | ERK 1/2 dim 3P | [1] | ERK 1/2 dim 2P –I AND: 100,00<br>AND –I ERK 1/2 dim 3P: 1,00<br>$G_{\beta\gamma}$ → ERK 1/2 dim 3P: 100,00 |
| ERK 1/2 dim 3P | → | Elk1 | [1] | 8,00 |
| ERK 1/2 dim 3P | → | MSK1 | [1] | 7,00 |
| ERK 1/2 dim 3P | → | c-Myc | [1] | 6,00 |
| $G_i$-coupled $M_2$ receptor | → | Ras (GTP bound) | [1] | 10,00 |
| $G_i$-coupled $M_2$ receptor | → | PKC | [3] | 10,00 |
| $G_q$-coupled $AT_1$receptor | → | $G_{\beta\gamma}$ | [1] | 10,00 |
| $G_q$-coupled $AT_1$receptor | → | Ras (GTP bound) | [1] | 1,00 |
| $G_q$-coupled $AT_1$receptor | → | PKC | [4] | 10,00 |
| GRK2 | -I | $G_s$-coupled $\beta_1$-adrenergic receptor | [5] | 0,10 |
| $G_s$-coupled $\beta_1$-adrenergic receptor | → | Ras (GTP bound) | [6] | 1,00 |
| $G_s$-coupled $\beta_1$-adrenergic receptor | → | $G_{\beta\gamma}$ | [6] | 10,00 |
| $G_s$-coupled $\beta_1$-adrenergic receptor | → | Epac | [2] | 10,00 |
| hypertrophic stimulus | → | angiotensin II | [1] | 1,00 |
| hypertrophic stimulus | → | isoproterenol | [6] | 10,00 |
| isoproterenol | → | $G_s$-coupled $\beta_1$-adrenergic receptor | [6] | 10,00 |
| MEK 1/2 | → | ERK 1/2 dim 2P | [1] | 0,001 |
| non-hypertrophic stimulus | → | carbachol | [1] | 10,00 |
| PKC | -I | RKIP | [7] | 10,00 |
| PKC | → | RKIP dim | [7] | 10,00 |
| Raf1 | → | MEK 1/2 | [1] | 1,00 |
| Ras (GTP bound) | → | Raf1 | [1] | 10,00 |
| RKIP | -I | Raf1 | [7] | 0,01 |
| RKIP dim | -I | GRK2 | [7] | 30,00 |

## Supplementary file 2: SQUAD readouts after a non-hypertrophic/hypertrophic stimulus




**A) non-hypertrophic stimulus** **B) hypertrophic stimulus**

## Supplementary file 3: possible ERK targets[1]

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| TACE | ADAM17 | | | cell surface, golgi apparatus | ERK acts as an intermediate in protein kinase C-regulated TrkA cleavage. The cytosolic tail of TACE is phosphorylated by Erk at threonine 735. ERK and TACE associate. | Erk1/2 | | [8] |
| GRK 2 | ADRBK1 | | | | ERK1 phosphorylates GRK2. Inhibition of ERK activity potentiates GRK2 activity, whereas, conversely, ERK activation inhibits GRK2 activity. feedback regulatory loop! | Erk1 | HEK293 cells | [9] |
| ALK | ALK | | | vesicle | ALK mediates growth and differentiation of neurons, ERK is essentially involved | - | - | [10] |
| p85 betaPIX | ARHGEF7 | | | | Erk activates p85 via binding of PAK2 to Erk and as a result of this PAK2 and p85 are building a complex and translocate -> neurite growth | - | PC12 cell lines | [11] |
| CREB2 | ATF2 | 3,4*10-2 | | nucleus | Raf-MEK-Erk pathway induces phosphorylation of ATF2 at Thr71 and Ral-RalGDS-Src-p38 pathway at Thr69 -> both required for activation; but: other study shows that Erk-activation is not required for ATF2-activation | - | fibroblasts | [12], [13] |
| bromodomain adjacent to zinc finger domain, 1B | BAZ1B | | | | novel mechanisms of epigenetic regulation of MAPK (amongst others Erk1): Phosphorylation of Williams syndrome transcription factor by them induces a switch between two different chromatin remodeling complexes | Erk1 | - | [14] |
| BRAF | BRAF | | | cytosol and nucleus | BRAF mutations activate the mitogen-activated protein kinase pathway | | | [15, 16] |
| Hyaluronan binding protein 1 | C1QBP | | | cytoplasm, nucleus | is an endogenous substrate for MAP kinase, suggestion: ERK activation is requirement for translocation to nucleus | | | [17] |
| CAD | CAD | | | | allosteric regulation of CAD is mediated by MAPK and PKA-mediated phosphorylations → cell-cycle dependent regulation of pyrimidine biosynthesis | | | [18] |
| Calnexin | CANX | 2,17*10-2 | | endoplasmic reticulum | Phosphorylation by CK2 and MAPK enhances calnexin association with ribosomes → increase in glycoprotein folding | | | [19] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| Caspase 8 | CASP8 | | | | prolonged Erk-activation results in Caspase8 activation and cell death, p38MAPK can inhibit Caspase8 function and thereby hinder apoptosis | p38 MAPK | | [20, 21] |
| Caspase 9 | CASP9 | | | nucleus and cytoplasm | Erk phosphorylates and inhibits Caspase9 and promotes cell survival and tissue homeostasis | | | [22, 23] |
| Caveolin 1 | CAV1 | | | | "Caveolin-1 and caveolae play a paradoxical role in regulating VEGF-induced ERK2/1 activation and in vitro angiogenesis as evidenced by the similar inhibitory effects of down-regulation and overexpression of caveolin-1 and disruption of caveolae" | ERK 1/2 | | [24] |
| H4 Genprodukt | CCDC6 | | | | CCDC6-Ret oncogen phosphorylates and activates Erk -> regulation of cell proliferation (CCDC6 Ret genproduct is found in lung adenocarcinoma and papillary thyreoid carcinoma) | Erk 1/2 | LAD cell lines | [25], [26] |
| Cep55 | CEP55 | | 2,02*10-2 | | amongst others Erk2 phosphorylates Cep55 (centrosome protein) → relocate to midbody →function in cytokinesis and mitotic exit | Erk2 | | [27] |
| Cortactin | CTTN | 1,03*10-2 | | cytoplasm | **ERK** regulates **cortactin** ubiquitination and degradation in lung epithelial cells | | | [28] |
| DCC | DCC | | | | DCC activates Erk and this contributes to netrin signalling in axon growth and guidance | Erk 1/2 | | [29, 30] |
| Elk1 | ELK1 | 5,09*10-3 | | nucleus and cytoplasm | IN CASCADE, phosphorylated Erk1/2 translocated to the nucleus and phosphorylates Elk1 | Erk1/2 | | [31] |
| Elk 4 | ELK4 | | | nucleus and cytoplasm | Elk4 is phosphorylated by Erk2 (and MAPK8), Elk4 directly links Erk signaling to the transcriptional events required for thymocyte positive selection,<br>Elk4 is direct androgen receptor target in prostate cancer | Erk2 | | [32, 33] |
| TNF - R | f.e. FAS | | | | Polyphenols from Korean prostrate spurge Euphorbia supina induce apoptosis through the Fas-associated extrinsic pathway and activation of ERK in human leukemic U937 cells | | | [34] |
| FCGR2B | FCGR2B | | | nuclear membrane and cytoplasm | Erk1/2 binds to FCGR2B and phosphorylates a serine residue → thr binding of Lyn to FCGR2B is modified → thus might negatively regulate phosphorylation of ITIM → signal transduction is not inhibited anymore | Erk1/2 | | [35] |
| FHL2 | FHL2 | 4,63*10-2 | | | fhl2 serves a repressor function, it inhibits Erk 1/2 transcriptional coupling | Erk1/2 | | [36] |
| c - fos | FOS | | | nucleus | Erk phosphorylates c-fos, as an result the transcriptional activity is increased | | | [37] |
| GAB2 | GAB2 | | | cytopla | Erk-mediated phosphorylation of Gab2 | | t- | [38] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| | | | | sm | regulates assosication with SHP2 and decreases STAT5 activation → fine tuning of proliferative answer of t-lymphocytes to IL-2 | | lymphocytes | |
| GATA2 | GATA2 | | | nucleus | Erk possibly phosphorylates GATA2, involved in growth factor responsiveness and proliferation of hematopoietic progenitor cells | | hematopoietic progenitor cells | [39] |
| GATA4 | GATA4 | | | mainly nucleus | Erk1/2 regulates cardiomyocyte hypertrophic growth via GATA4 through direct phosphorylation | Erk1/2 | cardiomyocyte | [40] |
| Connexin 43 | GJA1 | | | | hexameric connexin (Cx)-43 hemichannels are the essential transducers of the Erk-activating/anti-apoptotic effects of bisphosphonates | Erk1/2 | | [41] |
| GRB10 | GRB10 | | | nucleus and cytoplasm | is a direct substrate of Erk1/2, regulates insulin signaling | Erk1/2 | - | [42] |
| general transcription factor IIi | GTF2I | | | nucleus | ERK regulates the activity of TFII-I by direct phosphorylation, regulates its activation of the c-fos promoter | Erk1 | | [43, 44] |
| hyaluronan-mediated motility receptor (RHAMM) | HMMR | | | | RHAMM (an intracellular cytoskeletal protein) modulates ERK1/2 signal transduction at microtubules, which can act as barriers to mESC pluripotency | Erk1/2 | | [45] |
| heat shock transcription factor 1 | HSF1 | | | nucleus and cytoplasm | association of HSF1 with ERK and 14-3-3ϵ during heat shock may thus modulate the amplitude of the response and lead to efficient termination of HSP expression on resumption of growth conditions | Erk2 | | [46] |
| Hsp90 | HSP90 | | | cytosol | extracellular Hsp90 serves as an important co-factor for KSHV-initiated MAPK activation (proof-of-concept for the potential benefit of targeting csHsp90 for the treatment or prevention of KSHV-associated illnesses) | MAPK general | | [47] |
| heat shock | HSPB8 | 9,8*10-3 | | nucleus and | involved in regulation of cell proliferation, apoptosis; HSPB8 is phosphorylated by | Erk1 | in vivo | [48] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| 22kDa protein 8 | | | | cytoplasm | amongst others Erk1 (at residues Ser(27) and Thr(87)) | | | |
| IEX1 | IER3 | | | | IEX1 is a substrate of Erk, they regulate each other, phosphorylated IEX1 is able to inhibit cell death | Erk2 | in vivo | [49] |
| JAK 2 | JAK2 | | | | the interaction between TFII-I and ERK, which is essential for its activity, can be regulated by JAK2 through phosphorylation of TFII-I | Erk general | | [43] |
| Sam68 | KHDRBS1 | 4,7*10-3 | | nucleus | Sam68 acts as a convergence point for ERK signaling to cell migration; blockade of phospho-Sam68 may provide a new avenue for therapeutic inhibition of metastatic cancers | Erk1/2/5 | | [50] |
| KSR1 | KSR1 | | | | KSR1 is a scaffold, enhances signaling between Raf, MEK and ERK, Erk phosphorylates KSR1 | MAPK general | in vivo | [51, 52] |
| LIFR | LIFR | 1,08*10-2 | | | ERK-induced event was required, in addition to CREB/ATF-1 phosphorylation, for CREB/ATF-1-mediated transcription of C/EBP genes; essential role for adipocyte differentiation | Erk1/2 | | [53] |
| hormonsensitive Lipase | LIPE | | | | Erk phosphorylates LIPE in fat cells, in muscle via PKC | | fat cells, muscle cells | [54, 55] |
| Lyn | LYN | | | | Interleukin 2 activates polymorph cored, neutrophil granulocytes. In signal transduction the MAP/ERK cascade plays a role. ERK 1 binds Lyn in IL-2 activated neutrophil granulocytes. | Erk1 | neutrophil granulocytes | [56] |
| Mxi - 2 | MAPK14 | 8,74*10-3 | | nucleus and cytoplasm | Mxi-2 is not only downstream target, but also enhances the activity of Erk in matters of activation of nuclear targets.<br>Mxi-2 regulates activation of nuclear targets (Elk 1, HIF 1 alpha) through Erk upstream, which is activated through EGF. | | | |
| Ubiquitin - Protein - Ligase E3 | MDM2 | | | | Mdm2 phosphorylation is regulated via MEK-ERK, might be important for the regeneration of hepatocytes after centrilobular cell death | | hepatocytes | [57] |
| MI | MITF | 6,01*10-3 | | cytoplasm | becomes phosphorylated by ERK -> activation, also targets it for degradation through the ubiquitin-proteosome pathway, involved in melanoma proliferation regulation | Erk2 | melanocytes | [58, 59] |
| Mnk1 und 2 | MKNK1/2 | | | nucleus | after activation through phosphorylation by Erk Mnk 1 and 2 both phosphorylate eukaryotic initiations factor 4E | Erk1/2 | | [60] |
| c - Myb | MYB | | | | MAPKs can phoyphorylate c-Myb and thus modulate the cellular function of c-Myb | | | [61] |
| c-myc | MYC | 1,89*10-2 | | nucleus | hypertrophic target in our cascade, becomes phosphorylated by Erk, enables post-mitotic | | | [62-64] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | cardiomyocytes to reenter the cell cycle and increases gene expression of genes that play a decisive role in cardiac hypertrophy, c-Myc is known for elevating both, protein synthesis and cell mass | | | |
| MLCK | MYLK | 1,36*10-2 | | | Erk phosphorylates MLCK, involved in cell migration, in GSE 18224: MYLK4 | | | [65, 66] |
| SPIN90 | NCKIPSD | | | | SPIN90 is a binding partner to Nck, which plays a role in the formation of sarcomeres during differentiation of cardiomyocytes. Cell adhesion and PDGF activate Erk1, which results in phosphorylation of SPIN90. Finally this is of essential importance for solid cell adhesion | Erk1 | | [67] |
| AIB1 | NCOA3 | | | | assumption: the ability of growth factors to modulate estrogen action may be mediated through MAPK activation of the nuclear receptor coactivator AIB1 | MAPK general | | [68] |
| Nek2A | NEK2 | | | centrosome | NEK2 may regulate proliferation, apoptosis, and other biological behaviors via MAPK signal pathway -> therapeutic target in liver cancer | Erk general | Hep G2 cells | [69] |
| PAK2 | PAK2 | | | | PAK2 plays a role in a new signal transduction pathway, which induces growth of neurites by bfGF. The PAK2-p85 betaPIX – complex phosphorylates the Erk-cascade and following translocations of this complex | | PC12 cell lines | [70] |
| PEA-15 | PEA15 | | | | PEA – 15 binds Erk and prevents its translocation into the nucleus -> blockade of cell proliferation, amongst others involved in ovarian cancer | | | [71, 72] |
| PECAM 1 | PECAM1 | | | | Erk phosphorylates platelet endothelial cell adhesion molecule 1 (PECAM-1) and regulates its function as a binding partner and modulator of catenins | | | Platelet Web |
| progesterone receptor | PGR | | | nucleus | Progesterone receptor ligand binding induces rapid and transient ERK1/2 activation via EGFR | Erk1/2 | | [73] |
| Phospholipase A2, CA-2+ abhängig | PLA2 | G5: 8,18*10-4, G4a: 1,03*10-2 | | cytosol | stretch induced ERK2 phosphorylation depends on PLA2 activity in skeletal myotubes | Erk2 | | [74] |
| Phospholipase c beta 1 | PLCB1 | 3,43*10-2 | | nucleus | Erk phosphorylates PLCB1 and leads to mitogenic action of the insulin like growth factor | Erk1/2 | | [75] |
| PPARalpha | PPARA | | | | Erk1/2-dependent Cox 2-expression is one of the mechanisms of PPARA activation -> may | Erk1/2 | macrophage | [76] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | control atherosclerosis | | s | |
| PP2Calpha | PPM1A | 1,29*10-2 | | | PPM1A functions as an extracellular signal-regulated kinase phosphatase (regulates it negatively) | Erk general | | [77] |
| PP1C | PPP1CC | | | cytoplasm | in IGF1 treated neuronal cells ERK associates with PP1C (protein phosphatase 1 catalytic subunit c), which results in an enhanced activation level and however activates eIF2b (= endogenous initiation factor 2B) | Erk1/2 | neuronal cells | [78] |
| STEP | PTPN5 | | | cytosol | PTPN5 specifically inactivates MAPKs and block nuclear translocation, missense variant of PTPN5 involved in appearance of hypertrophic scarring | mostly Erk1/2, p38MAPK | | [79, 80] |
| PTP-E | PTPRE | | | cytosol | inhibits Erk1/2 kinase activity, functions to prevent inappropriate activation and to stop prolonged activation | Erk1/2 | | [81] |
| Stomach Cancer-associated Protein-tyrosine Phosphatase-1 | PTPRH | | | | inhibits growth factor induced activation of Erk2 | | | [82, 83] |
| PTP-SL | PTPRR | | | cytosol | inactivates MAPKS and inhibits nuclear translocation, therapeutic target for treating neurodegenerative diseases | mostly Erk1/2, p38MAPK | | [79, 84] |
| PTPN7 | PTPN7 | | | cytosol | inactivates MAPKS and inhibits nuclear translocation, therapeutic target for treating acute myeloblastic leukaemia | mostly Erk1/2, p38MAPK | | [79] |
| RAB4A | RAB4A | | | | is phosphorylated by insulin-activated Erk1 | Erk1 | in vitro | [85] |
| MCIP 1 | RCAN1 | 5,21*10-4 | | | Erk1/2 phosphorylates RCAN1, phosphorylated RCAN1 inhibits calcineurin which plays a role in cardiac hypertrophy, but there are different mechanisms of inhibition and they are not finally clarified | Erk1/2 | in vitro | [86] |
| RSK1 | RPS6KA1 | | | nucleus and cytoplasm | non-hypertrophic target in our cascade, mediates mitogenic and stress-induced activation of transcription factors, regulates translation through phosphorylation, and mediates cellular proliferation, survival, and | | | [87-90] |

| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| | | | | | differentiation by modulating mTOR signaling and repressing pro-apoptotic functions | | | |
| RSK3 | RPS6KA2 | | | | non-hypertrophic target in our cascade, serine/threonine-protein kinase that acts downstream of Erk1/2 signaling and mediates mitogenic and stress-induced activation of transcription factors, regulates translation, and mediates cellular proliferation, survival, and differentiation, may function as tumor suppressor in epithelial ovarian cancer cells, prolonged Erk association increased the duration of RSK3 activation | Erk 1/2 | | [91, 92] |
| RSK2 | RPS6KA3 | | | | after EGF-stimulation, Erk activates RSK2 | Erk1/2 | | [93] |
| MSK1 | RPS6KA5 | 1,43*10-2 | | | hypertrophic target in our cascade, mediates stress and growth factor induced activation of CREB | Erk1/2 | | [94-97] |
| p70S6K | RPS6KB1 | | | nucleus and cytoplasm | non-hypertrophic target in our cascade, involved in the activation of protein synthesis after physical exercise and thus in the building of muscle | Erk1/2 | | [98, 99] |
| RXRalpha | RXRA | | | nucleus | in hepatocellular carcinoma, RXRα is constitutively phosphorylated by Erk and thereby losing its transactivation activity and becoming resistant to degradation | | | [100] |
| Na(+)/H(+) exchanger fusion protein, His182 | SLC9A1 | | | | positive feedback loop between both proteins, this could pose a barrier against apoptosis | | | [101, 102] |
| SMAD1 | SMAD1 | 7,15*10-3 | | | Smad signaling becomes activated via Erk1/2 pathway, signaling crosstalk could be a key mechanism in diabetic scarring | Erk1/2, p38MAPK | | [103] |
| SMAD2 | SMAD2 | | | | Ras inhibitory signal on Smad2 is mediated by Erk MAPKs, regulates cell proliferation, differentiation and apoptosis. | Erk1/2 | | [104] |
| Vinexin | SORBS3 | | | cytoplasm | Erk phosphorylates vinexin, plays important roles in cell spreading, migration and anchorage-independent growth | Erk2 | | [105] |
| Sos1 | SOS1 | | | | Ras–Raf–ERK pathway in placentas is highly dependent upon Sos1 | Erk2 | | [106] |
| SP1 transcription factor | SP1 | | | nucleus | SP1 mediates stress-induced activity of IRS2 promoter via Erk | Erk1/2 | HepG2 cells | [107] |
| SRC1 | SRC | | | nucleus | SRC can modulate pathways by the phosphorylation of hSpry2WT and following inhibition of Erk1/2 | Erk1/2 | in vitro | [108] |

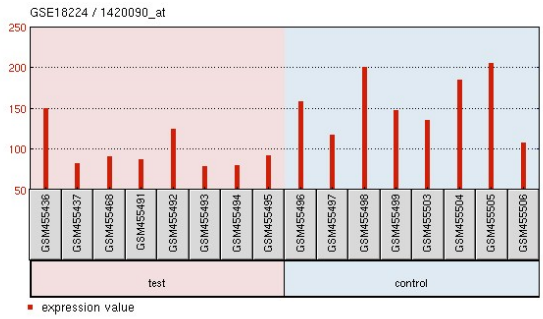
| Erk-Targets | official symbol (NCBI) | GSE 18224 adjusted P-value | GSE 5500 adjusted P-value | Localisation | additional information | MAPK isoform | cell type | reference |
|---|---|---|---|---|---|---|---|---|
| SREBP-1a | SREBF1 | | | | gets phosphorylated by Erk | Erk1/2 | in vitro | [109] |
| TAL2 | TAL2 | | | | Erk1 phosphorylates TAL2, involved in T-ALL | Erk1 | in vitro | [110] |
| E47 | TCF3 | | | | Notch-induced E2A ubiquitination and degradation are controlled by Erk1/2 kinase activity → crucial for B and T lymphocyte development | Erk1/2 | B/T lymphocyte | [111] |
| TGIF1 | TGIF1 | 4,58*10-2 | | cytoplasm | Smad2 – co-repressor | Erk1 | | [112] |
| Naf1alpha | TNIP1 | 1,56*10-3 | | | Naf1alpha inhibits the translocation of Erk2 in the nucleus and consequently the transcriptional activation, is an attenuator of activated Erk2 | Erk2 | in vitro and in vivo | [113] |
| Tob | TOB1 | | | | The phosphorylation of Erk negatively regulates the anti proliferative effect of Tob. | Erk2 | in vitro | [114] |
| Tpr | TPR | | | | protein-protein interaction | Erk2 | in vitro | [115] |
| UBF | UBTF | | | nucleoli | Erk phosphorylates UBF and thus prevents their interaction with DNA, suggest a central role for ribosome biogenesis in growth regulation. | Erk1/2 | | [116] |
| YBX1 | YBX1 | | | | shows interaction | Erk2 | HEK293 cells | [117] |

[1]Further molecular details are known, e.g. Erk 2 phosphorylates Na (+) / H (+) exchanger fusion protein SLC9A1 at His182. The Table is not covering everything, e.g. there are further interactions of Erk2 suggested e.g. with target proteins SPiB, TOP2B and STAT5a

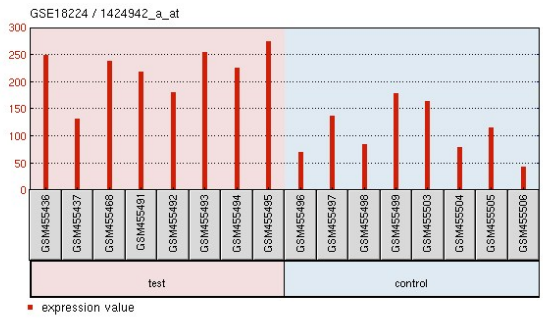
 

# Supplementary file 4: Gene expression Data-sets GSE 18224 - Cascade, regulation directions

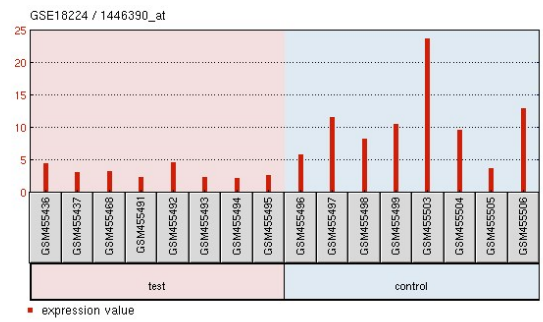
### Raf 1 – downregulated after TAC



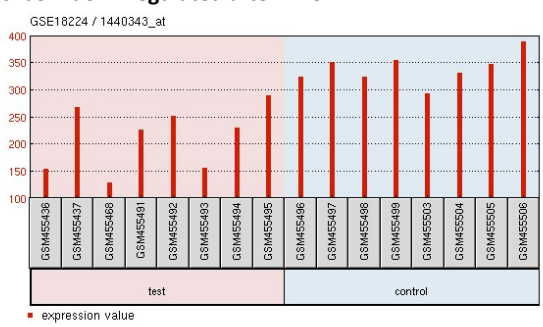

### Myc – upregulated after TAC



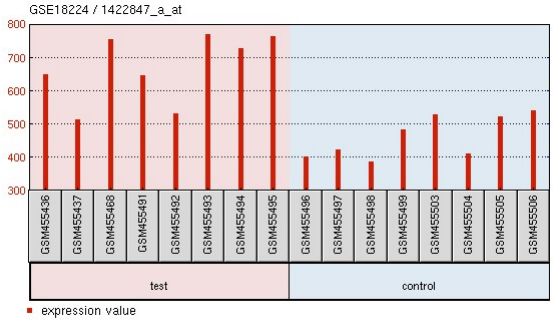

### Elk1 – downregulated after TAC



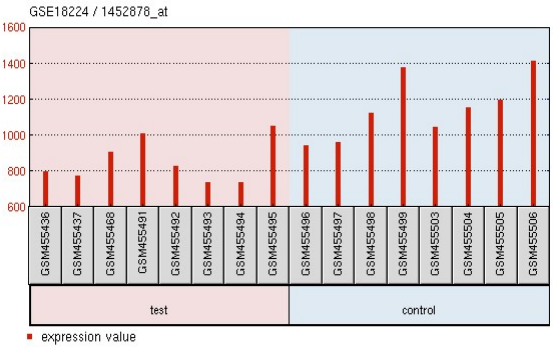

### Rps6ka5 – downregulated after TAC



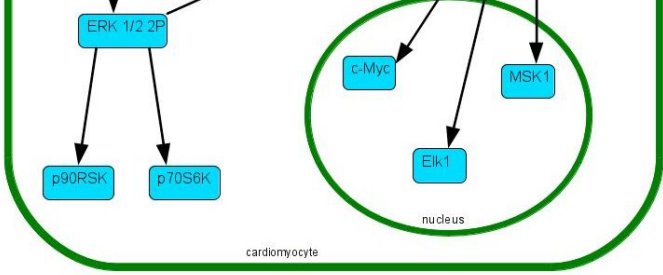
**Prkcd – upregulated after TAC**



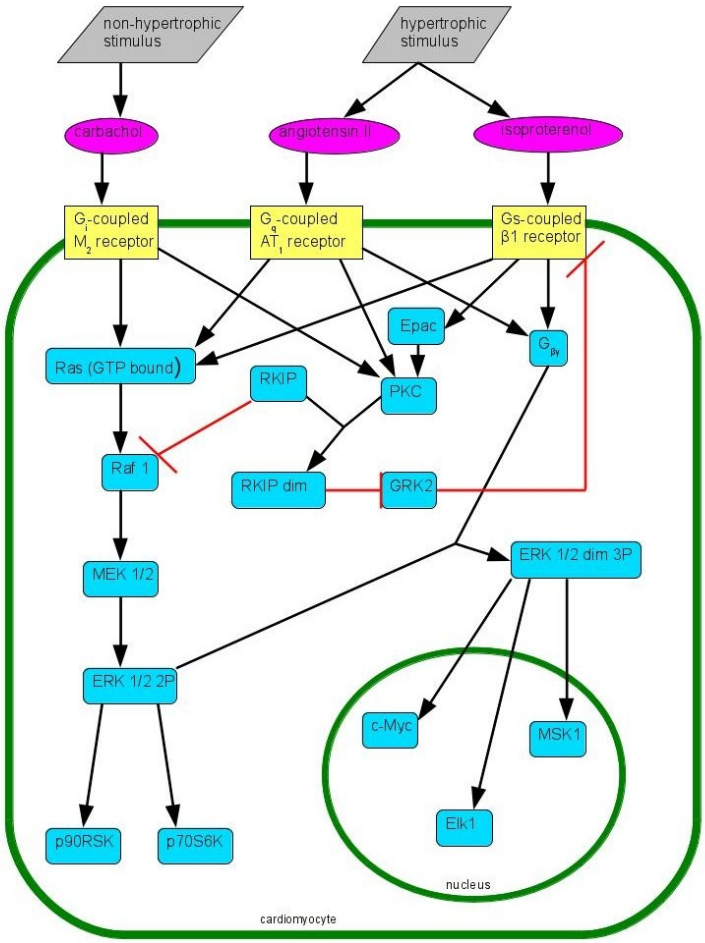

**Prkce – downregulated after TAC**



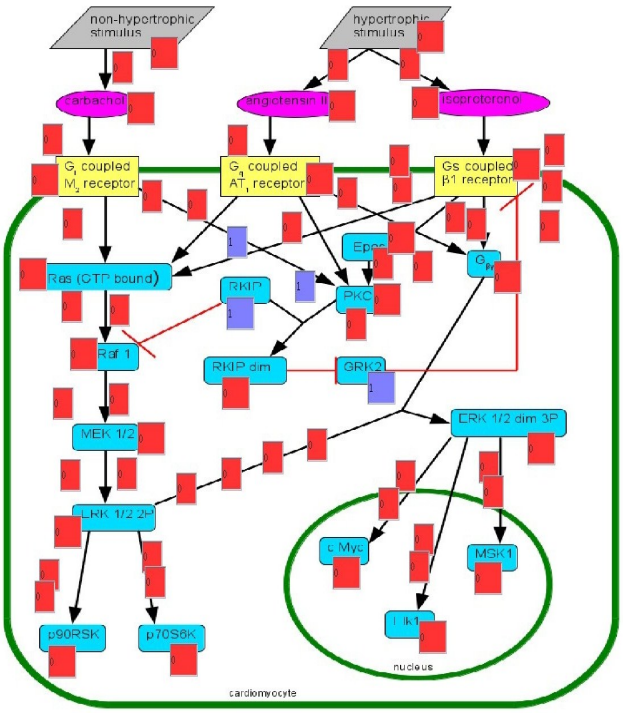



## Supplementary file 5: CNA topology



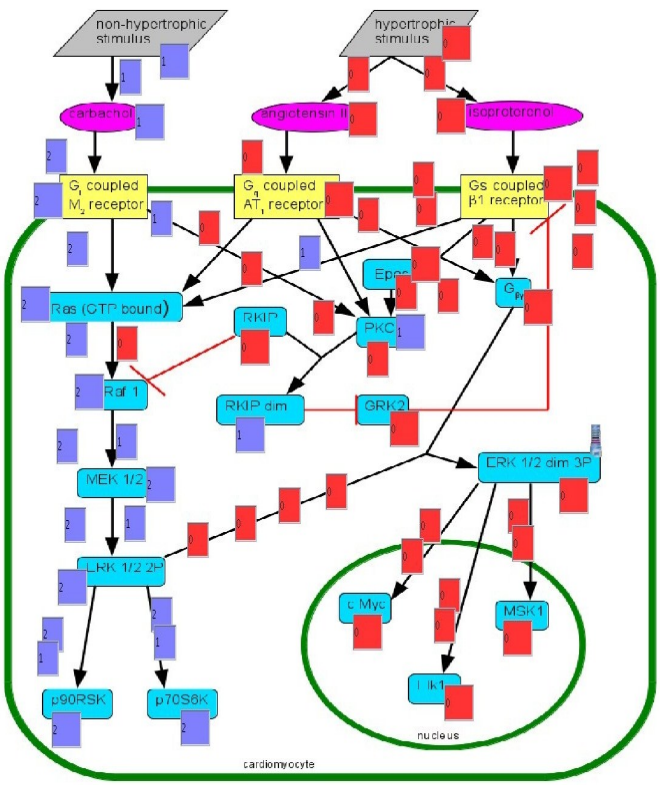
## Supplementary file 6: Further CNA simulations

**a) no stimulus**




If there is no stimulus, the targets are not activated (level 0 = basal conditions). RKIP inhibits Raf1.

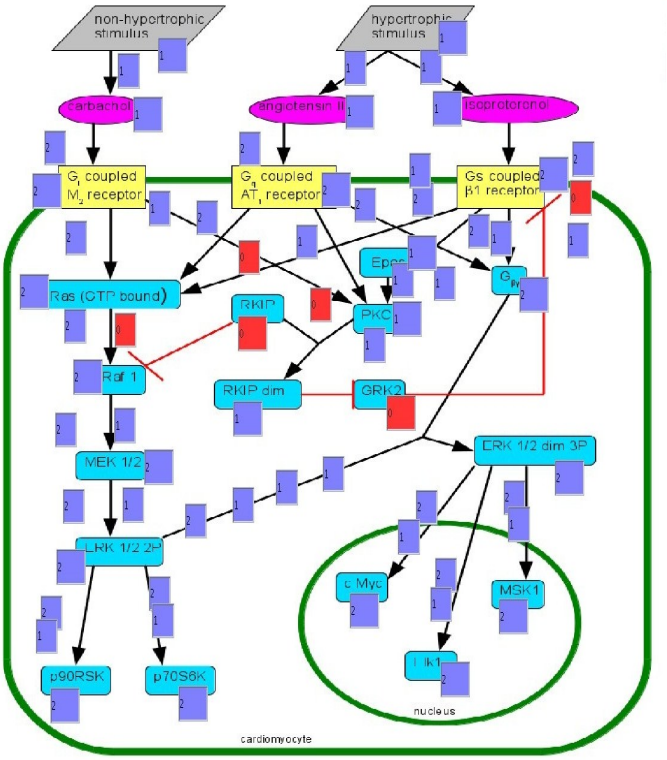
**b) non-hypertrophic stimulus**




If there is a non-hypertrophic stimulus, only the non-hypertrophic targets reach level 2. PKC is active, so that Raf1 is not inhibited through RKIP anymore.

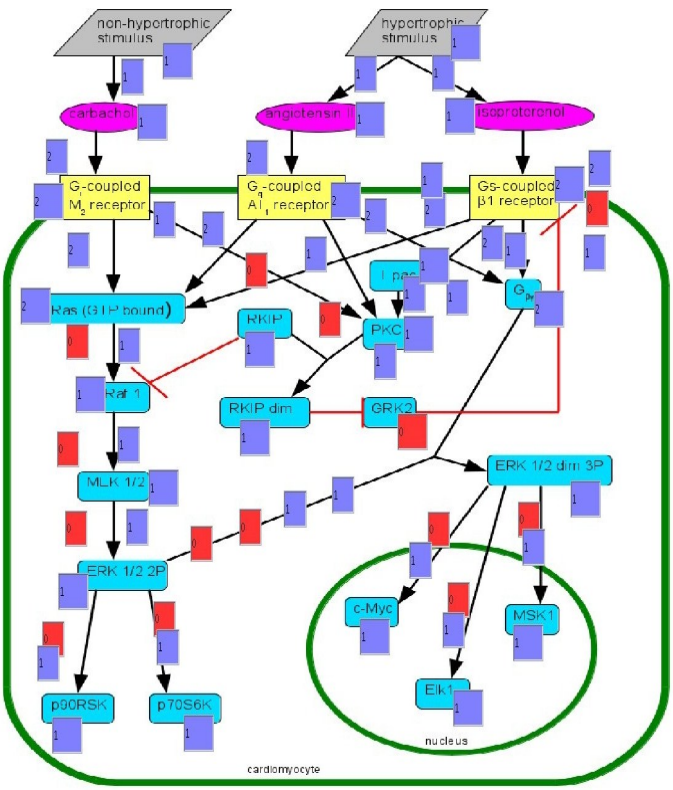
 

**c) both stimuli (RKIP off)**




Both stimuli are present, so both the hypertrophic and the non-hypertrophic targets are activated (level 2). PKC inhibits RKIP, so Raf1 is not inhibited.

**d) both stimuli (RKIP off)**



## Supplementary file 7: Gene expression data analysing data-sets GSE 18224 and GSE 5500

Genes, that are altered in both experiments (GSE 5500, 7 days after TAC and GSE 18224, 9 weeks after TAC). We used the first 250 spots from each experiment for the comparison.

| Gene symbol | Gene title | Gene ID | Adj. p-value GSE 5500 | Adj.p-value GSE 18224 |
|---|---|---|---|---|
| 1500009L16Rik | RIKEN cDNA 1500009L16 gene | 1452840_at | 0.028608 | 5.73e-05 |
| Ano10 | anoctamin 10 | 1426672_at | 0.026066 | 5.15e-05 |
| Bgn | biglycan | 1437889_x_at | 0.016966 | 7.30e-05 |
| Bgn | biglycan | 1448323_a_at | 0.028369 | 3.35e-04 |
| Bgn | biglycan | 1416405_at | 0.047221 | 3.55e-04 |
| Cilp | cartilage intermediate layer protein, nucleotide pyrophosphohydrolase | 1457296_at | 0.003647 | 6.29e-05 |
| Col1a1 | collagen, type I, alpha 1 | 1423669_at | 0.046904 | 1.14e-03 |
| Col5a2 | collagen, type V, alpha 2 | 1450625_at | 0.00327 | 1.03e-03 |
| Col8a1 | collagen, type VIII, alpha 1 | 1455627_at | 0.002963 | 3.04e-04 |
| Col8a1 | collagen, type VIII, alpha 1 | 1418440_at | 0.002963 | 9.61e-05 |
| Col8a1 | collagen, type VIII, alpha 1 | 1418441_at | 0.007573 | 6.30e-04 |
| Col8a1 | collagen, type VIII, alpha 1 | 1447819_x_at | 0.009684 | 5.21e-04 |
| Ctgf | connective tissue growth factor | 1416953_at | 0.026312 | 8.38e-04 |
| Emp1 | epithelial membrane protein 1 | 1416529_at | 0.011411 | 1.07e-03 |
| Fbn1 | fibrillin 1 | 1460208_at | 0.043775 | 7.75e-04 |
| Frzb | frizzled-related protein | 1416658_at | 0.022132 | 6.23e-04 |
| Frzb | frizzled-related protein | 1448424_at | 0.024229 | 1.20e-03 |
| Ift122 | intraflagellar transport 122 | 1427239_at | 0.018931 | 5.78e-04 |
| Kcnv2 | potassium channel, subfamily V, member 2 | 1440537_at | 0.034454 | 5.39e-04 |
| Lgals4 | lectin, galactose binding, soluble 4 | 1451336_at | 0.017818 | 5.39e-04 |
| Ltbp2 | latent transforming growth factor beta binding protein 2 | 1418061_at | 0.018931 | 3.35e-04 |
| Meox1 | mesenchyme homeobox 1 | 1417595_at | 0.015167 | 8.37e-04 |
| Mfap5 | microfibrillar associated protein 5 | 1418454_at | 0.007776 | 1.23e-03 |
| Mybpc2 | myosin binding protein C, fast-type | 1455736_at | 0.010186 | 1.51e-04 |
| Myh7 | myosin, heavy polypeptide 7, cardiac muscle, beta | 1448553_at | 0.001554 | 4.22e-07 |
| Nppa | natriuretic peptide type A | 1456062_at | 0.021041 | 6.19e-04 |
| Srpx2 | sushi-repeat-containing protein, X-linked 2 | 1427919_at | 0.048266 | 1.28e-03 |
| Synpo | synaptopodin | 1434089_at | 0.004904 | 6.23e-04 |
| Thbs1 | thrombospondin 1 | 1421811_at | 0.007776 | 1.03e-03 |
| Tmsb10 | thymosin, beta 10 | 1417219_s_at | 0.043459 | 1.27e-03 |
| Vcan | versican | 1421694_a_at | 0.037309 | 1.20e-03 |
| Vcan | versican | 1427256_at | 0.039214 | 7.57e-04 |

## Supplementary file 8: xml-file-configuration

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<?xml version="1.0" encoding="UTF-8"?>
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      <node id="Elk1" state="0.0" decay="1.0" gain="10.0" visible="true" posx="359.0" posy="658.0"
/>
      <node id="Epac" state="0.0" decay="1.0" gain="10.0" visible="false" posx="407.0"
posy="273.0" />
      <node id="GRK2" state="1.0" decay="1.0" gain="10.0" visible="false" posx="339.0"
posy="416.0" />
      <node id="G_beta__gamma_" state="0.0" decay="1.0" gain="10.0" visible="false" posx="567.0"
posy="337.0" />
      <node id="Gi-coupled_M2_receptor" state="0.0" decay="1.0" gain="10.0" visible="false"
posx="93.5" posy="154.5" />
      <node id="Gq-coupled_AT1_receptor" state="0.0" decay="1.0" gain="10.0" visible="false"
posx="327.5" posy="145.5" />
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posy="406.0" />
      <node id="MSK1" state="0.0" decay="1.0" gain="10.0" visible="true" posx="444.0" posy="658.0"
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posy="341.0" />
      <node id="Raf1" state="0.0" decay="1.0" gain="10.0" visible="false" posx="93.0" posy="319.0"
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posy="230.0" />
      <node id="angiotensin_II" state="0.0" decay="1.0" gain="10.0" visible="false" posx="326.0"
posy="81.0" />
      <node id="c-Myc" state="0.0" decay="1.0" gain="10.0" visible="true" posx="530.0"
posy="658.0" />
      <node id="carbachol" state="0.0" decay="1.0" gain="10.0" visible="false" posx="95.5"
posy="92.0" />
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      <node id="isoproterenol" state="0.0" decay="1.0" gain="10.0" visible="false" posx="518.0"
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      <node id="non-hypertrophic_stimulus" state="0.0" decay="1.0" gain="10.0" visible="false"
posx="110.5" posy="24.5" />
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```
      <node id="pERK(TEY)" state="0.0" decay="1.0" gain="10.0" visible="true" posx="112.5"
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    <edges>
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target="Ras_(GTP_bound)" sign="positive" weight="1.0" />
      <edge id="G_beta__gamma_ -- pERK(Thr188)" source="G_beta__gamma_" target="pERK(Thr188)"
sign="positive" weight="100.0" />
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      <edge id="pERK(Thr188) -- Elk1" source="pERK(Thr188)" target="Elk1" sign="positive"
weight="8.0" />
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weight="0.01" />
      <edge id="isoproterenol -- Gs-coupled__beta__1_receptor" source="isoproterenol" target="Gs-
coupled__beta__1_receptor" sign="positive" weight="10.0" />
      <edge id="pERK(TEY) -| AND" source="pERK(TEY)" target="AND" sign="negative" weight="100.0"
/>
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target="angiotensin_II" sign="positive" weight="1.0" />
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      <edge id="pERK(TEY) -- p90RSK" source="pERK(TEY)" target="p90RSK" sign="positive"
weight="0.01" />
      <edge id="Raf1 -- MEK_1/2" source="Raf1" target="MEK_1/2" sign="positive" weight="1.0" />
      <edge id="angiotensin_II -- Gq-coupled_AT1_receptor" source="angiotensin_II" target="Gq-
coupled_AT1_receptor" sign="positive" weight="5.0" />
      <edge id="Gi-coupled_M2_receptor -- Ras_(GTP_bound)" source="Gi-coupled_M2_receptor"
target="Ras_(GTP_bound)" sign="positive" weight="10.0" />
      <edge id="Gi-coupled_M2_receptor -- PKC" source="Gi-coupled_M2_receptor" target="PKC"
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coupled__beta__1_receptor" target="G_beta__gamma_" sign="positive" weight="10.0" />
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target="isoproterenol" sign="positive" weight="10.0" />
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target="carbachol" sign="positive" weight="10.0" />
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```

 

```
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weight="6.0" />
      <edge id="Ras_(GTP_bound) -- Raf1" source="Ras_(GTP_bound)" target="Raf1" sign="positive"
weight="10.0" />
      <edge id="MEK_1/2 -- pERK(TEY)" source="MEK_1/2" target="pERK(TEY)" sign="positive"
weight="0.0010" />
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coupled__beta__1_receptor" sign="negative" weight="0.1" />
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        <activenode id="RKIP" statediscrete="1.0" state="1.0" />
      </state>
    </states>
  </graph>
</mml>
```

## References


1. Lorenz, K., et al., *A new type of ERK1/2 autophosphorylation causes cardiac hypertrophy.* Nat Med, 2009. **15**(1): p. 75-83.
2. Schmidt, M., F.J. Dekker, and H. Maarsingh, *Exchange protein directly activated by cAMP (epac): a multidomain cAMP mediator in the regulation of diverse biological functions.* Pharmacol Rev, 2013. **65**(2): p. 670-709.
3. Kim, S., T. Bondeva, and P.G. Nelson, *Activation of protein kinase C isozymes in primary mouse myotubes by carbachol.* Brain Res Dev Brain Res, 2002. **137**(1): p. 13-21.
4. Meier, M. and G.L. King, *Protein kinase C activation and its pharmacological inhibition in vascular disease.* Vasc Med, 2000. **5**(3): p. 173-85.
5. Xiao, R.P., et al., *Recent advances in cardiac beta(2)-adrenergic signal transduction.* Circ Res, 1999. **85**(11): p. 1092-100.
6. Vidal, M., et al., *beta-Adrenergic receptor stimulation causes cardiac hypertrophy via a Gbetagamma/Erk-dependent pathway.* Cardiovasc Res, 2012. **96**(2): p. 255-64.
7. Lorenz, K., M.J. Lohse, and U. Quitterer, *Protein kinase C switches the Raf kinase inhibitor from Raf-1 to GRK-2.* Nature, 2003. **426**(6966): p. 574-9.
8. Diaz-Rodriguez, E., et al., *Extracellular signal-regulated kinase phosphorylates tumor necrosis factor alpha-converting enzyme at threonine 735: a potential role in regulated shedding.* Mol Biol Cell, 2002. **13**(6): p. 2031-44.
9. Pitcher, J.A., et al., *Feedback inhibition of G protein-coupled receptor kinase 2 (GRK2) activity by extracellular signal-regulated kinases.* J Biol Chem, 1999. **274**(49): p. 34531-4.
10. Motegi, A., et al., *ALK receptor tyrosine kinase promotes cell growth and neurite outgrowth.* J Cell Sci, 2004. **117**(Pt 15): p. 3319-29.
11. Shin, E.Y., et al., *Phosphorylation of p85 beta PIX, a Rac/Cdc42-specific guanine nucleotide exchange factor, via the Ras/ERK/PAK2 pathway is required for basic fibroblast growth factor-induced neurite outgrowth.* J Biol Chem, 2002. **277**(46): p. 44417-30.
12. Ouwens, D.M., et al., *Growth factors can activate ATF2 via a two-step mechanism: phosphorylation of Thr71 through the Ras-MEK-ERK pathway and of Thr69 through RalGDS-Src-p38.* EMBO J, 2002. **21**(14): p. 3782-93.
13. Hayakawa, J., et al., *The activation of c-Jun NH2-terminal kinase (JNK) by DNA-damaging agents serves to promote drug resistance via activating transcription factor 2 (ATF2)-dependent enhanced DNA repair.* J Biol Chem, 2003. **278**(23): p. 20582-92.
14. Oya, H., et al., *Phosphorylation of Williams syndrome transcription factor by MAPK induces a switching between two distinct chromatin remodeling complexes.* J Biol Chem, 2009. **284**(47): p. 32472-82.
15. Hao, H., et al., *Context-dependent roles of mutant B-Raf signaling in melanoma and colorectal carcinoma cell growth.* Mol Cancer Ther, 2007. **6**(8): p. 2220-9.

16. Xu, L., et al., *Spry2 expression correlates with BRAF mutation in thyroid cancer.* Surgery, 2010. **148**(6): p. 1282-7; discussion 1287.
17. Majumdar, M., et al., *Hyaluronan binding protein 1 (HABP1)/C1QBP/p32 is an endogenous substrate for MAP kinase and is translocated to the nucleus upon mitogenic stimulation.* Biochem Biophys Res Commun, 2002. **291**(4): p. 829-37.
18. Sigoillot, F.D., et al., *Cell cycle-dependent regulation of pyrimidine biosynthesis.* J Biol Chem, 2003. **278**(5): p. 3403-9.
19. Chevet, E., et al., *Phosphorylation by CK2 and MAPK enhances calnexin association with ribosomes.* EMBO J, 1999. **18**(13): p. 3655-66.
20. Cagnol, S., E. Van Obberghen-Schilling, and J.C. Chambard, *Prolonged activation of ERK1,2 induces FADD-independent caspase 8 activation and cell death.* Apoptosis, 2006. **11**(3): p. 337-46.
21. Alvarado-Kristensson, M., et al., *p38-MAPK signals survival by phosphorylation of caspase-8 and caspase-3 in human neutrophils.* J Exp Med, 2004. **199**(4): p. 449-58.
22. Allan, L.A., et al., *Inhibition of caspase-9 through phosphorylation at Thr 125 by ERK MAPK.* Nat Cell Biol, 2003. **5**(7): p. 647-54.
23. Martin, M.C., et al., *The docking interaction of caspase-9 with ERK2 provides a mechanism for the selective inhibitory phosphorylation of caspase-9 at threonine 125.* J Biol Chem, 2008. **283**(7): p. 3854-65.
24. Liao, W.X., et al., *Compartmentalizing VEGF-induced ERK2/1 signaling in placental artery endothelial cell caveolae: a paradoxical role of caveolin-1 in placental angiogenesis in vitro.* Mol Endocrinol, 2009. **23**(9): p. 1428-44.
25. Suzuki, M., et al., *Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo.* Cancer Sci, 2013. **104**(7): p. 896-903.
26. Kumagai, A., et al., *No evidence of ARAF, CRAF and MET mutations in BRAFT1799A negative human papillary thyroid carcinoma.* Endocr J, 2006. **53**(5): p. 615-20.
27. Fabbro, M., et al., *Cdk1/Erk2- and Plk1-dependent phosphorylation of a centrosome protein, Cep55, is required for its recruitment to midbody and cytokinesis.* Dev Cell, 2005. **9**(4): p. 477-88.
28. Zhao, J., et al., *Extracellular signal-regulated kinase (ERK) regulates cortactin ubiquitination and degradation in lung epithelial cells.* J Biol Chem, 2012. **287**(23): p. 19105-14.
29. Forcet, C., et al., *Netrin-1-mediated axon outgrowth requires deleted in colorectal cancer-dependent MAPK activation.* Nature, 2002. **417**(6887): p. 443-7.
30. Herincs, Z., et al., *DCC association with lipid rafts is required for netrin-1-mediated axon guidance.* J Cell Sci, 2005. **118**(Pt 8): p. 1687-92.
31. Majka, M., et al., *Binding of stromal derived factor-1alpha (SDF-1alpha) to CXCR4 chemokine receptor in normal human megakaryoblasts but not in platelets induces phosphorylation of mitogen-activated protein kinase p42/44 (MAPK), ELK-1 transcription factor and serine/threonine kinase AKT.* Eur J Haematol, 2000. **64**(3): p. 164-72.
32. Costello, P.S., et al., *Ternary complex factor SAP-1 is required for Erk-mediated thymocyte positive selection.* Nat Immunol, 2004. **5**(3): p. 289-98.
33. Makkonen, H., et al., *Identification of ETS-like transcription factor 4 as a novel androgen receptor target in prostate cancer cells.* Oncogene, 2008. **27**(36): p. 4865-76.
34. Han, M.H., et al., *Polyphenols from Korean prostrate spurge Euphorbia supina induce apoptosis through the Fas-associated extrinsic pathway and activation of ERK in human leukemic U937 cells.* Oncol Rep, 2016.
35. Medgyesi, D., et al., *Functional consequences of a MAPK docking site on human FcgammaRIIb.* Immunol Lett, 2004. **92**(1-2): p. 83-90.
36. Purcell, N.H., et al., *Extracellular signal-regulated kinase 2 interacts with and is negatively regulated by the LIM-only protein FHL2 in cardiomyocytes.* Mol Cell Biol, 2004. **24**(3): p. 1081-95.
37. Monje, P., M.J. Marinissen, and J.S. Gutkind, *Phosphorylation of the carboxyl-terminal transactivation domain of c-Fos by extracellular signal-regulated kinase mediates the transcriptional activation of AP-1 and cellular transformation induced by platelet-derived growth factor.* Mol Cell Biol, 2003. **23**(19): p. 7030-43.
38. Arnaud, M., et al., *Phosphorylation of Grb2-associated binder 2 on serine 623 by ERK MAPK regulates its association with the phosphatase SHP-2 and decreases STAT5 activation.* J Immunol, 2004. **173**(6): p. 3962-71.
39. Towatari, M., et al., *Regulation of GATA-2 phosphorylation by mitogen-activated protein kinase and interleukin-3.* J Biol Chem, 1995. **270**(8): p. 4101-7.
40. Liang, Q., et al., *The transcription factor GATA4 is activated by extracellular signal-regulated kinase 1- and 2-mediated phosphorylation of serine 105 in cardiomyocytes.* Mol Cell Biol, 2001. **21**(21): p. 7460-9.
41. Plotkin, L.I., S.C. Manolagas, and T. Bellido, *Transduction of cell survival signals by connexin-43 hemichannels.* J Biol Chem, 2002. **277**(10): p. 8648-57.
42. Langlais, P., et al., *Phosphorylation of Grb10 by mitogen-activated protein kinase: identification of Ser150 and Ser476 of human Grb10zeta as major phosphorylation sites.* Biochemistry, 2005. **44**(24): p. 8890-7.

 

43. Kim, D.W. and B.H. Cochran, *JAK2 activates TFII-I and regulates its interaction with extracellular signal-regulated kinase.* Mol Cell Biol, 2001. **21**(10): p. 3387-97.
44. Kim, D.W. and B.H. Cochran, *Extracellular signal-regulated kinase binds to TFII-I and regulates its activation of the c-fos promoter.* Mol Cell Biol, 2000. **20**(4): p. 1140-8.
45. Jiang, J., P. Mohan, and C.A. Maxwell, *The cytoskeletal protein RHAMM and ERK1/2 activity maintain the pluripotency of murine embryonic stem cells.* PLoS One, 2013. **8**(9): p. e73548.
46. Wang, X., et al., *Interactions between extracellular signal-regulated protein kinase 1, 14-3-3epsilon, and heat shock factor 1 during stress.* J Biol Chem, 2004. **279**(47): p. 49460-9.
47. Qin, Z., et al., *Extracellular Hsp90 serves as a co-factor for MAPK activation and latent viral gene expression during de novo infection by KSHV.* Virology, 2010. **403**(1): p. 92-102.
48. Padmini, E., V. Uthra, and S. Lavanya, *Effect of HSP70 and 90 in modulation of JNK, ERK expression in preeclamptic placental endothelial cell.* Cell Biochem Biophys, 2012. **64**(3): p. 187-95.
49. Garcia, J., et al., *IEX-1: a new ERK substrate involved in both ERK survival activity and ERK activation.* EMBO J, 2002. **21**(19): p. 5151-63.
50. Locatelli, A. and C.A. Lange, *Met receptors induce Sam68-dependent cell migration by activation of alternate extracellular signal-regulated kinase family members.* J Biol Chem, 2011. **286**(24): p. 21062-72.
51. Ritt, D.A., I.O. Daar, and D.K. Morrison, *KSR regulation of the Raf-MEK-ERK cascade.* Methods Enzymol, 2006. **407**: p. 224-37.
52. Cacace, A.M., et al., *Identification of constitutive and ras-inducible phosphorylation sites of KSR: implications for 14-3-3 binding, mitogen-activated protein kinase binding, and KSR overexpression.* Mol Cell Biol, 1999. **19**(1): p. 229-40.
53. Belmonte, N., et al., *Activation of extracellular signal-regulated kinases and CREB/ATF-1 mediate the expression of CCAAT/enhancer binding proteins beta and -delta in preadipocytes.* Mol Endocrinol, 2001. **15**(11): p. 2037-49.
54. Donsmark, M., et al., *Regulation and role of hormone-sensitive lipase in rat skeletal muscle.* Proc Nutr Soc, 2004. **63**(2): p. 309-14.
55. Donsmark, M., et al., *Contractions activate hormone-sensitive lipase in rat muscle by protein kinase C and mitogen-activated protein kinase.* J Physiol, 2003. **550**(Pt 3): p. 845-54.
56. Wei, S., et al., *IL-2 induces the association of IL-2Rbeta, lyn, and MAP kinase ERK-1 in human neutrophils.* Immunobiology, 2000. **202**(4): p. 363-82.
57. Malmlof, M., et al., *MEK-ERK-mediated phosphorylation of Mdm2 at Ser-166 in hepatocytes. Mdm2 is activated in response to inhibited Akt signaling.* J Biol Chem, 2007. **282**(4): p. 2288-96.
58. Wellbrock, C., et al., *Oncogenic BRAF regulates melanoma proliferation through the lineage specific factor MITF.* PLoS One, 2008. **3**(7): p. e2734.
59. Hemesath, T.J., et al., *MAP kinase links the transcription factor Microphthalmia to c-Kit signalling in melanocytes.* Nature, 1998. **391**(6664): p. 298-301.
60. Waskiewicz, A.J., et al., *Mitogen-activated protein kinases activate the serine/threonine kinases Mnk1 and Mnk2.* EMBO J, 1997. **16**(8): p. 1909-20.
61. Vorbrueggen, G., J. Lovric, and K. Moelling, *Functional analysis of phosphorylation at serine 532 of human c-Myb by MAP kinase.* Biol Chem, 1996. **377**(11): p. 721-30.
62. Finver, S.N., et al., *Sequence analysis of the MYC oncogene involved in the t(8;14)(q24;q11) chromosome translocation in a human leukemia T-cell line indicates that putative regulatory regions are not altered.* Proc Natl Acad Sci U S A, 1988. **85**(9): p. 3052-6.
63. Pollack, P.S., et al., *c-myc gene expression is localized to the myocyte following hemodynamic overload in vivo.* J Cell Biochem, 1994. **54**(1): p. 78-84.
64. Xiao, G., et al., *Inducible activation of c-Myc in adult myocardium in vivo provokes cardiac myocyte hypertrophy and reactivation of DNA synthesis.* Circ Res, 2001. **89**(12): p. 1122-9.
65. Nguyen, D.H., et al., *Myosin light chain kinase functions downstream of Ras/ERK to promote migration of urokinase-type plasminogen activator-stimulated cells in an integrin-selective manner.* J Cell Biol, 1999. **146**(1): p. 149-64.
66. Muralidharan-Chari, V., et al., *ARF6-regulated shedding of tumor cell-derived plasma membrane microvesicles.* Curr Biol, 2009. **19**(22): p. 1875-85.
67. Lim, C.S., et al., *Regulation of SPIN90 phosphorylation and interaction with Nck by ERK and cell adhesion.* J Biol Chem, 2003. **278**(52): p. 52116-23.
68. Font de Mora, J. and M. Brown, *AIB1 is a conduit for kinase-mediated growth factor signaling to the estrogen receptor.* Mol Cell Biol, 2000. **20**(14): p. 5041-7.
69. Zhang, M.X., et al., *Effect of silencing NEK2 on biological behaviors of HepG2 in human hepatoma cells and MAPK signal pathway.* Tumour Biol, 2016. **37**(2): p. 2023-35.
70. Kato, K., et al., *Identification of neurite outgrowth promoting sites on the laminin alpha 3 chain G domain.* Biochemistry, 2002. **41**(35): p. 10747-53.

71. Krueger, J., et al., *Phosphorylation of phosphoprotein enriched in astrocytes (PEA-15) regulates extracellular signal-regulated kinase-dependent transcription and cell proliferation.* Mol Biol Cell, 2005. **16**(8): p. 3552-61.
72. Bartholomeusz, C., et al., *PEA-15 induces autophagy in human ovarian cancer cells and is associated with prolonged overall survival.* Cancer Res, 2008. **68**(22): p. 9302-10.
73. Faivre, E.J. and C.A. Lange, *Progesterone receptors upregulate Wnt-1 to induce epidermal growth factor receptor transactivation and c-Src-dependent sustained activation of Erk1/2 mitogen-activated protein kinase in breast cancer cells.* Mol Cell Biol, 2007. **27**(2): p. 466-80.
74. Burkholder, T.J., *Stretch-induced ERK2 phosphorylation requires PLA2 activity in skeletal myotubes.* Biochem Biophys Res Commun, 2009. **386**(1): p. 60-4.
75. Xu, A., et al., *Phosphorylation of nuclear phospholipase C beta1 by extracellular signal-regulated kinase mediates the mitogenic action of insulin-like growth factor I.* Mol Cell Biol, 2001. **21**(9): p. 2981-90.
76. Taketa, K., et al., *Oxidized low density lipoprotein activates peroxisome proliferator-activated receptor-alpha (PPARalpha) and PPARgamma through MAPK-dependent COX-2 expression in macrophages.* J Biol Chem, 2008. **283**(15): p. 9852-62.
77. Li, R., et al., *Metal-dependent protein phosphatase 1A functions as an extracellular signal-regulated kinase phosphatase.* FEBS J, 2013. **280**(11): p. 2700-11.
78. Quevedo, C., M. Salinas, and A. Alcazar, *Initiation factor 2B activity is regulated by protein phosphatase 1, which is activated by the mitogen-activated protein kinase-dependent pathway in insulin-like growth factor 1-stimulated neuronal cells.* J Biol Chem, 2003. **278**(19): p. 16579-86.
79. Eswaran, J., et al., *Crystal structures and inhibitor identification for PTPN5, PTPRR and PTPN7: a family of human MAPK-specific protein tyrosine phosphatases.* Biochem J, 2006. **395**(3): p. 483-91.
80. Sood, R.F., et al., *Missense Variant in MAPK Inactivator PTPN5 Is Associated with Decreased Severity of Post-Burn Hypertrophic Scarring.* PLoS One, 2016. **11**(2): p. e0149206.
81. Toledano-Katchalski, H., et al., *Protein tyrosine phosphatase epsilon inhibits signaling by mitogen-activated protein kinases.* Mol Cancer Res, 2003. **1**(7): p. 541-50.
82. Noguchi, T., et al., *Inhibition of cell growth and spreading by stomach cancer-associated protein-tyrosine phosphatase-1 (SAP-1) through dephosphorylation of p130cas.* J Biol Chem, 2001. **276**(18): p. 15216-24.
83. Miyamoto, S., et al., *Integrins can collaborate with growth factors for phosphorylation of receptor tyrosine kinases and MAP kinase activation: roles of integrin aggregation and occupancy of receptors.* J Cell Biol, 1996. **135**(6 Pt 1): p. 1633-42.
84. Balasu, M.C., et al., *Interface analysis of the complex between ERK2 and PTP-SL.* PLoS One, 2009. **4**(5): p. e5432.
85. Cormont, M., et al., *Rab4 is phosphorylated by the insulin-activated extracellular-signal-regulated kinase ERK1.* Eur J Biochem, 1994. **219**(3): p. 1081-5.
86. Vega, R.B., et al., *Multiple domains of MCIP1 contribute to inhibition of calcineurin activity.* J Biol Chem, 2002. **277**(33): p. 30401-7.
87. Roux, P.P., et al., *RAS/ERK signaling promotes site-specific ribosomal protein S6 phosphorylation via RSK and stimulates cap-dependent translation.* J Biol Chem, 2007. **282**(19): p. 14056-64.
88. Shimamura, A., et al., *Rsk1 mediates a MEK-MAP kinase cell survival signal.* Curr Biol, 2000. **10**(3): p. 127-35.
89. Pearson, G., et al., *Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions.* Endocr Rev, 2001. **22**(2): p. 153-83.
90. Frodin, M. and S. Gammeltoft, *Role and regulation of 90 kDa ribosomal S6 kinase (RSK) in signal transduction.* Mol Cell Endocrinol, 1999. **151**(1-2): p. 65-77.
91. Roux, P.P., S.A. Richards, and J. Blenis, *Phosphorylation of p90 ribosomal S6 kinase (RSK) regulates extracellular signal-regulated kinase docking and RSK activity.* Mol Cell Biol, 2003. **23**(14): p. 4796-804.
92. Willard, F.S. and M.F. Crouch, *MEK, ERK, and p90RSK are present on mitotic tubulin in Swiss 3T3 cells: a role for the MAP kinase pathway in regulating mitotic exit.* Cell Signal, 2001. **13**(9): p. 653-64.
93. Kang, S., et al., *Epidermal growth factor stimulates RSK2 activation through activation of the MEK/ERK pathway and src-dependent tyrosine phosphorylation of RSK2 at Tyr-529.* J Biol Chem, 2008. **283**(8): p. 4652-7.
94. Smerdova, L., et al., *Upregulation of CYP1B1 expression by inflammatory cytokines is mediated by the p38 MAP kinase signal transduction pathway.* Carcinogenesis, 2014. **35**(11): p. 2534-43.
95. Carpenter, O.L. and S. Wu, *Regulation of MSK1-Mediated NF-kappaB Activation Upon UVB Irradiation.* Photochem Photobiol, 2013.
96. Deak, M., et al., *Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB.* EMBO J, 1998. **17**(15): p. 4426-41.
97. Vicent, G.P., et al., *Erk signaling and chromatin remodeling in MMTV promoter activation by progestins.* Nucl Recept Signal, 2009. **7**: p. e008.
98. Babchia, N., et al., *The PI3K/Akt and mTOR/P70S6K signaling pathways in human uveal melanoma cells: interaction with B-Raf/ERK.* Invest Ophthalmol Vis Sci, 2010. **51**(1): p. 421-9.

 

99. Medeiros, C., et al., *Exercise training reduces insulin resistance and upregulates the mTOR/p70S6k pathway in cardiac muscle of diet-induced obesity rats.* J Cell Physiol, 2011. **226**(3): p. 666-74.
100. Kojima, S., et al., *Acyclic retinoid in the chemoprevention of hepatocellular carcinoma (review).* Int J Oncol, 2004. **24**(4): p. 797-805.
101. Konstantinidis, D., et al., *Inhibition of the Na+-H+ exchanger isoform-1 and the extracellular signal-regulated kinase induces apoptosis: a time course of events.* Cell Physiol Biochem, 2006. **18**(4-5): p. 211-22.
102. Pedersen, S.F., et al., *The Na+/H+ exchanger, NHE1, differentially regulates mitogen-activated protein kinase subfamilies after osmotic shrinkage in Ehrlich Lettre Ascites cells.* Cell Physiol Biochem, 2007. **20**(6): p. 735-50.
103. Li, J.H., et al., *Advanced glycation end products activate Smad signaling via TGF-beta-dependent and independent mechanisms: implications for diabetic renal and vascular disease.* FASEB J, 2004. **18**(1): p. 176-8.
104. Ichise, T., N. Yoshida, and H. Ichise, *FGF2-induced Ras-MAPK signalling maintains lymphatic endothelial cell identity by upregulating endothelial-cell-specific gene expression and suppressing TGFbeta signalling through Smad2.* J Cell Sci, 2014. **127**(Pt 4): p. 845-57.
105. Mizutani, K., et al., *Essential roles of ERK-mediated phosphorylation of vinexin in cell spreading, migration and anchorage-independent growth.* Oncogene, 2007. **26**(50): p. 7122-31.
106. Qian, X., et al., *The Sos1 and Sos2 Ras-specific exchange factors: differences in placental expression and signaling properties.* EMBO J, 2000. **19**(4): p. 642-54.
107. Udelhoven, M., et al., *Identification of a region in the human IRS2 promoter essential for stress induced transcription depending on SP1, NFI binding and ERK activation in HepG2 cells.* J Mol Endocrinol, 2010. **44**(2): p. 99-113.
108. Li, X., et al., *FRS2-dependent SRC activation is required for fibroblast growth factor receptor-induced phosphorylation of Sprouty and suppression of ERK activity.* J Cell Sci, 2004. **117**(Pt 25): p. 6007-17.
109. Roth, G., et al., *MAP kinases Erk1/2 phosphorylate sterol regulatory element-binding protein (SREBP)-1a at serine 117 in vitro.* J Biol Chem, 2000. **275**(43): p. 33302-7.
110. Xia, Y., et al., *Products of the TAL2 oncogene in leukemic T cells: bHLH phosphoproteins with DNA-binding activity.* Oncogene, 1994. **9**(5): p. 1437-46.
111. Nie, L., et al., *Notch-induced E2A ubiquitination and degradation are controlled by MAP kinase activities.* EMBO J, 2003. **22**(21): p. 5780-92.
112. Lo, R.S., D. Wotton, and J. Massague, *Epidermal growth factor signaling via Ras controls the Smad transcriptional co-repressor TGIF.* EMBO J, 2001. **20**(1-2): p. 128-36.
113. Zhang, S., et al., *A new ERK2 binding protein, Naf1, attenuates the EGF/ERK2 nuclear signaling.* Biochem Biophys Res Commun, 2002. **297**(1): p. 17-23.
114. Maekawa, M., E. Nishida, and T. Tanoue, *Identification of the Anti-proliferative protein Tob as a MAPK substrate.* J Biol Chem, 2002. **277**(40): p. 37783-7.
115. Byron, A., et al., *Proteomic analysis of alpha4beta1 integrin adhesion complexes reveals alpha-subunit-dependent protein recruitment.* Proteomics, 2012. **12**(13): p. 2107-14.
116. Stefanovsky, V.Y., et al., *An immediate response of ribosomal transcription to growth factor stimulation in mammals is mediated by ERK phosphorylation of UBF.* Mol Cell, 2001. **8**(5): p. 1063-73.
117. Xiao, K., et al., *Functional specialization of beta-arrestin interactions revealed by proteomic analysis.* Proc Natl Acad Sci U S A, 2007. **104**(29): p. 12011-6.