|  |  |  |
| --- | --- | --- |
| **Target node** | **Interaction description** | **Cell type** |
| Migration | AKT2 induces beta integrins -> migration | Breast and ovarian cancer cells [1] |
|  | Inhibition of AKT2 compromises migration | Mesenchymal stem cell [2] |
|  | AKT1 inhibits migration through NFAT inhibition | Breast cancer cell line [3,4] |
|  | AKT1 inhibits migration through paladin | Breast cancer cell line [5] |
|  | ERK stimulates migration through cofilin | Rat fibroblast [6] |
|  | miR200 inhibits migration through targeting fibronectin1 | Breast cancer and endometrial cell line [7] |
|  | ERK activation is necessary for migration induced by AKT1 down- regulation | Breast epithelial cells [8] |
| Invasion | TGF-b induces MMP-2 and MMP-9 expresion | Breast epithelial and mammary adenocarcinoma cell line [9,10] |
|  | CTNNB1 induces transcription of MMPs | Keratinocytes, endothelial cells, murine mammary epithelial cell, T cell, chondrocytes nd human embryonic kidney cells [11–16] |
|  | N-cadherin is required for TGF-β induced invasion | Myofibroblast [17] |
| EMT | EMT: absence of epithelial markers and presence of mesenchymal markers | Avian epiboly, canine kidney cells, amniote embryos [18–20] |
| Apoptosis | p53 -> anoikis | Breast epithelial cells [21] |
|  | AKT1 -| anoikis | Intestinal epithelial cells [22] |
|  | p63 -| anoikis via integrin beta4 | (primary) human mammary epithelial cells [23] |
|  | miR34 -> apoptosis (by inhibiting anti-apoptotic gene BCL2) | Intestinal epithelium cells [24] |
|  | miR200 -| XIAP | Gastric adenocarcinoma [25] |
|  | ERK inhibits apoptosis through Bcl2, Bcl-XL and Mcl-1 | Pancreatic adenocarcinoma [26] |
| CellCycleArrest | miR34 inhibits cell cycle progression by inhibiting Cyclin D1 activity. | Human breast adenocarcinoma [27] |
|  | miR203 inhibits cell cycle by targeting CDK6 | hepatocellular carcinoma [28] |
|  | miR200 -| CCNE2 | Lymphoma, HEK cell line [29] |
|  | Only AKT1 is required for proliferation | Mouse myoblast and human fibroblast[30] |
|  | Zeb2 -| CyclinD | Bladder cancer [31] |
|  | ERK activates proliferation | Myofibroblast [6] |
|  | miR34 -> cell cycle (E2F genes) | Colorectal cancer [24] |
| p21 | p63 -> p21 | Lung carcinoma [32–34] |
|  | p53 -> CellCycleArrest | Fibroblast [35,36] |
|  | p73 -> CellCycleArrest | Lung carcinoma [33,34] |
|  | Notch is required for growth arrest by TGF-β | mammary epithelial cells [37] |
|  | Snai1 and Twist cooperate in inhibition of p21 expression | osteosarcoma osteoblast-like cell, fibroblast [38] |
|  | AKT2 induces cell cycle arrest by keeping p21 into the nucleus | Mouse myoblast and human fibroblast, myoblast [30,39] |
| CDH1 | AKT1 down-regulation repressed CDH1 expression | Breast epithelial cells [8] |
|  | Snai1 inhibits CDH1 but requires AKT2 for it | Intestinal epithelial cells[40] |
|  | AKT2 -> Dab2 -| CDH1 | Breast adenocarcinoma [41] |
|  | AKT2 require Snai1 to inhibit CDH1 | Intestinal epithelial cells [40] |
|  | Synergistic effect of Zeb1 & Snai2 on repression CDH1 | Keratinocytes [42] |
|  | Zeb1 and Zeb2 are required to collaborate with Snai2 to repress CDH1 | Mammary epithelial cells [43] |
|  | Twist1 and Snai1 cooperation to repress CDH1 | Mammary epithelial cells [43] |
| CDH2 | Twist activates transcription of CDH2 | Observed in many types of cancers [44] |
|  | shSnai2 has no effect on CDH2 gene expression | Keratinocytes [45] |
| VIM | CTNNB1->VIM | Breast cancer [46] |
|  | ZEB2-> VIM transcriptionally | Mammary epithelial and intestinal cells [47,48] |
|  | Snai2 not involved for VIM expression | Mammary epithelial cells [43] |
|  | Twist1 not involved for VIM expression | Mammary epithelial cells [49] |
| TWIST1 | NICD->Twist1 transcriptionally | Gastric adenocarcinoma and human embryonic kidney cells [50] |
|  | CTNNB1->Twist1 transcriptionally | Colon cancer [51] |
|  | Snai1->Twist1 | Mouse mammary epithelial cells [52] |
| SNAI1 | NICD->Snai1 | Human ovarian carcinoma [53] |
|  | Twist1->Snai1 | Mammary epithelial cells [43] |
|  | AKT->Snai1 | Keratinocytes [45] |
|  | miR203-|Snai1 | Human breast cancer cell line [54] |
|  | miR34-| Snai1 | Colon adenocarcinoma [55] |
|  | p53-|Snai1 via complex formation with mdm2 | Hepatocellular carcinoma [56] |
|  | CTNNB1 -> miR-30e -| Snai1 | Rat intestinal epithelial cells, non-small cell lung cancer [57,58] |
| SNAI2 | Twist1->Snai2 | Mammary epithelial cells [43] |
|  | b-catenin->Wnt pathway->Snai2 | Embryonic ectoderm [59] |
|  | NICD->Snai2 | Human breast epithelial cells, Human endothelial cell line [60,61] |
|  | miR200-|Snai2 | AC3 cell line [62] |
|  | p53-|Snai2 via mdm2 | Breast cancer cell line, non-small-cell lung cancer [63] |
|  | miR203 -| Snai2 | Prostate cell lines EP156T and EPT1 [64] |
| ZEB1 | Snai1 and Twist1 cooperate to activate transcription of Zeb1 | Mouse mammary epithelial cells [52] |
|  | Snai2 -> Zeb1 | Keratinocytes [42] |
|  | CTNNB1->Zeb1 | Tumour c olorectal tissue [65] |
|  | miR200-|Zeb1 | Human breast cancer cell line, NCI-60 cell lines [54,66] |
|  | NICD -> Zeb1 | Human pancreatic cancer cell line [67] |
| ZEB2 | Snai1 -> Zeb2 expression via alternative processing of its mRNA | Intestinal cancer cell line [68] |
|  | Twist1 & Snai2 cooperate to activate transcription of Zeb2 | Mammary epithelial cells [43] |
|  | miR200 -| Zeb2 | Human breast cancer cell line, NCI-60 cell lines [54,66] |
|  | miR203-|Zeb2 | Human breast cancer cell line, human prostate cell lines [54,69] |
|  | NICD -> Zeb2 | Human pancreatic cancer cell line [67] |
| AKT1 | NICD -> AKT | lymphoblastic leukemia cell line [70] |
|  | CTNNB1 -> AKT1 | Human glioblastoma cell lines [71] |
|  | TP53 -| AKT through transcription of PTEN which inhibits AKT activation | Madin-Darby canine kidney cells [72] |
|  | miR34 -| AKT-P mir34 inhibits AKT activation | The human uveal melanoma cell line [73] |
|  | TGF-β -> AKT1 through p38 MapK | Lung Fibroblasts [74] |
|  | CDH2 can activate FGFR leading to activation of AKT1 | Mice [75] |
|  | E-cadherin inhibits ligand binding to EGFR at high cell densities | Breast and gastric cancers [76] |
| DKK1 | CTNNB1 -> DKK1 | Prostate, human embryonic kidney cells and human colon cancer [77,78] |
|  | NICD->DKK | Intestinal stem cells [79] |
|  | DKK1 is methylated in colon cancer | CRC tumours [80] |
| CTNNB1 | DKK1 -| CTNNB1 | Colon cancer [81] |
|  | AKT1 ->Chibby -> CTNNB1-P in nucleus and this results in export of CTNNB1 into the cytosol | Colon cancer [82] |
|  | CDH1-| Wnt-signalling by forming complex with b-catenin | epidermoid carcinoma, breast cancer cell line [83,84] |
|  | CHD2 -| Wnt-signalling by forming also complexes with b-catenin | Myofibroblast [17] |
|  | miR34 -| CTNNB1 | Mouse embryonic fibroblast, lung carcinoma and colon carcinoma cell line [85] |
|  | miR200 -|CTNNB1 | Meningioma cell lines, nasopharyngeal carcinoma [86,87] |
|  | p63 -| CTNNB1 via increased transcription of APC | Osteosarcoma [88] |
|  | p53 -| CTNBB1 via activation of nuclear GSK3 -| CTNNB1 | Lung cancer, neuroblastoma [89] |
| NICD | p53-|PSEN->NICD | lymphoblastic leukemia cell line  [70] |
|  | p63 and p73->Jag->NICD Not included in this model because the model represents a single cell system. Therefore p63 and p73-|NICD as it has been shown that cis-interaction between Jag ligands inhibit Notch signalling within the same cell | Drosophila S2 cells, mouse myoblast [90–93] |
|  | miR200 -| NICD | Breast adenocarcinoma pancreatic adenocarcinoma [94] |
|  | miR34 -| Notch1 = NICD | cervical carcinoma and choriocarcinoma cells [95] |
| p63 | Notch inhibits p63 | lymphoblastic leukemia cell line  [70,96,97] |
|  | AKT inhibits p63 via mdm2 | lymphoblastic leukemia cell line, *in vitro* [70,98] |
|  | p53 inhibits p63 via p53-PTEN-AKT-mdm2 | Transformed fibroblast cells [99,100] |
|  | miR203 -| p63 | Myoblast, keratinocytes [101,102] |
| p53 | NICD -> p53 Not included in the model because cell type dependent | lymphoblastic leukemia cell line  [70] |
|  | p73 -| 53 | human non-small cell lung carcinoma, human mammary adenocarcinoma, osteogenic sarcoma [103,104] |
|  | Snai2 inhibits p53 expression | Madin-Darby canine kidney cells [20] |
|  | AKT1 inhibits p53 via MDM2 | Prostate epithelial cells [105] |
|  | AKT2 inhibits p53 via MDMD2 | Prostate epithelial cells [105] |
|  | CTNNB1 -> p53 at protein level through inhibiting mdm2 and through p14ARF | lymph node metastatic cells, endometrial carcinoma cells [106,107] |
|  | NICD -> myc -> p14ARF->p53 | Fibroblast, T-acute lymphoblastic leukemia [35,108] |
|  | mir34a -| sirt1 -| p53 | Colon carcinoma [109] |
| p73 | p53 inhibit p73 expression | ovarian epithelium cells [110] |
|  | AKT1/2 inhibits p73 via mdm2 | lymphoblastic leukemia cell line, HeLa cells [70,111] |
|  | Zeb1 -| p73 expression | Ovarian epithelium cells [110] |
| miR200 | p53 activates transcription of miR200c | Keratinocytes [45] |
|  | p63 and p73 activate transcription of miR200 family | human ovarian surface epithelial cells [112] |
|  | Zeb1 and Zeb2 inhibit expression of miR200 | Human breast cancer cell line, NCI-60 cell lines [54,66] |
|  | Snai1 and Snai2 inhibit expression of miR200 | Human breast cancer cell line [54] |
|  | AKT2 inhibits miR200 | Lung fibroblast and kidney epithelia cells [113,114] |
| miR203 | p53 activates transcription of miR203 in keratinocytes | Keratinocytes [115] |
|  | Snai1 inhibits expression of miR203 | human prostate cell lines [69] |
|  | Zeb1 and Zeb2 inhibit expression of miR203 | Human breast cancer cell line [54] |
| miR34 | miR34 is a p53 target gene | Mouse embryonic fibroblast, lung carcinoma, breast cancer, osteosarcoma and colon carcinoma cell line [85,116] |
|  | Snai1 and Zeb1 regulate miR34 expression | Colon adenocarcinoma [55] |
|  | p63 represses miR34 | Keratinocytes [117] |
|  | p73 induces gene transcription miR34 | Mouse cortical neurons [118] |
|  | AKT1 inhibits miR34 | Breast cancer [113] |
|  | AKT2 induces mir34 | Breast cancer [113] |
| AKT2 | Twist induces AKT2 transcription | Breast cancer cell line[3,4] |
|  | knock down of AKT1 increases AKT2 | Breast cancer [113] |
|  | miR203 inhibits AKT2 | Colon cancer [119] |
|  | miR34 inhibits AKT2 | Prostate cancer [120] |
|  | TGF-β activates PI3K through association of its receptors with p85 subunit | Epithelial cells [121] |
|  | CDH2 can activate FGFR thereby activating AKT2 | Mice [75] |
|  | p53 inhibits AKT2 through PTEN | [72] |
| ERK | TGF-β activates ERK | mammary adenocarcinoma, mouse fibroblast [10,122] |
|  | CDH2 can activates ERK via FGFR polymerisation | Mice [75] |
|  | AKT1 inhibits ERK signalling | Breast epithelial cells, breast cancer cells [8,123] |
|  | NICD -> HES1 -| DUSP1/6 -| Erk | murine non-small cell lung cancer [124] |
| SMAD | miR203 -| smad4: transcriptional component of the TGF-b pathway | hepatocellular carcinoma [28] |
|  | miR200 -|Smad2 and 3 | Intestinal epithelial cells [125] |
| TGF-β | CTNNB1 -> Bambi -| TGF-β | Colorectal tumours [126] |
|  | Notch -> Nodal -> TGF-β | Heart tissue from zebrafish [127] |
|  |  |  |
| GF | CDH1 -| GF  CDH2 -> GF  GF autoregulation: the cell itself can produce ligands and thus it can activate the receptor tyrosine kinase family of receptors and eventually stimulate the cell to produce GF. Cis-inhibition observed for Notch receptors has not been demonstrated for RTK | Ovarian cancer cells [128]  Melanoma cells.  In mice, ovarian carcinoma cells, rat intestinal epithelial cells , ovarian carcinoma cells [57,75,129]  *Drosophila melanogaster* [130] |
| ECMicroenv | The extracellular microenvironment refers to the extracellular matrix. ECMicroenv is an input of the model |  |
| DNAdamage | DNA damage refers to any insults that lead to activation of p53 family members. DNAdamage is an input of the model. |  |

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