Table 1: Boolean functions of the Wnt/MAPK network. Interactions are described by logical connectives AND (&), OR (|), and NOT (!).

Node	Boolean network function	Description of the rule	References
EGFR	ERBB1/2 & PGE2 & !ERK	The epidermal growth factor receptor (EGFR) is encoded by the ERBB gene. EGFR can be transactivated by prostaglandin E2 (PGE2). By negative feedback, extracellular signal-regulated protein kinase (ERK) suppresses the activity of EGFR.	(*1, 2, 3, 4, 5, 6*)
KRAS	EGFR & !DC	EGFR is responsible for guanosine exchange thereby activating rat sarcoma (RAS). The destruction complex (DC) degradates RAS.	(*2, 7, 8, 9, 10, 11, 12, 13*)
RAF	KRAS & !ERK & !AKT	Kirsten rat sarcoma (KRAS) phosphorylates rapidly accelerated fibrosarcoma (RAF). Extracellular signal-regulated protein kinase (ERK) creates a negative feedback inhibition towards RAF. Protein kinase B (AKT) phosphorylates RAF.	(*2, 3, 7, 8, 9, 10, 11, 14, 15*)
MEK	RAF	Mitogen-activated protein kinase (MEK) phosphorylates RAF.	(*2, 7, 8, 9, 10, 11*)
scf	IQGAP1 & RAF & MEK	IQ motif-containing GTPase-activating protein 1 (IQGAP1) provides scaffold (scf) which is required for the signal transmission of the MAPK kinase pathway.	(*16, 17, 18, 19*)
ERK	(scf | PAK1) & !PP2A	ERK is activated by scf. p21-activated kinase 1 (PAK1) inhibits ERK. PP2A reduces the phosphorylation of ERK.	(*20, 21, 22, 2, 7, 8, 9, 10, 11, 23, 24, 25, 26, 27*)
eIF4F	ERK | mTORC1	ERK as well as the mammalian target of rapamycin complex 1 (mTORC1) activate eukaryotic initiation factor 4F (eIF4F).	(*2, 7, 28, 29*)
EBP1	!ERK & !mTORC1	The Erb3-binding protein (EBP1) is inhibited by mTORC1 and ERK.	(*2, 7, 28, 30, 29*)
MYC	(ERK | TCF/LEF) & !APC & (!PP2A | CIP2A) & !GSK3β_{deg} & ERK	Transcriptional expression of the MYC proto-oncogene (MYC) can be activated by ERK or T-cell factor/lymphoma enhancer factor (TCF/LEF). Phosphorylation by glycogen synthase kinase 3 β (GSK3β) marks MYC for degradation. Protein phosphatase 2A (PP2A) supports degradation of MYC. Cell proliferation regulating inhibitor of protein phosphatase 2A (CIP2A) directly binds MYC and prevents PP2A acting on MYC. Adenomatous polyposis coli (APC) represses MYC transcription.	(*2,7,8,9,31,32,10,33,34,35,26,36,10,27,37*)
cJUN	(ERK | TCF/LEF | COX2) & JNK	The expression of Jun protooncogene (cJUN) is by activated both ERK andTCF/LEF. Cyclooxygenase-2 (COX2) can increase levels of cJUN. Ras related C-3 botulin toxin substrate 1 (RAC1) enhances cJun activity.	(*2, 7, 8, 9, 38, 39, 6, 29*)
PI3K	PGE2 | EGFR | KRAS	The activation of phosphatidylinositol-4,5-biphosphate 3-kinase (PI3K) can be induced by PGE2, EFGR or KRAS.	(*2, 15, 24, 40, 5, 6, 4, 41, 42, 43, 44*)
AKT	(PI3K | PAK1| SNAIL1) & !PP2A & (NF-κB | TCF/LEF | SNAIL1)	Transcription of AKT can be induced by TCF/LEF, nuclear factor kappa light chain enhancer of activated B-cells (NF-κB) or SNAIL1. In addition, SNAIL1 can bind to AKT and enhances its activity. PI3K phosphorylates AKT. PAK1 can also activate AKT. PP2A dephosphorylates AKT.	(*45, 2, 7, 46, 23, 24, 25, 15, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 26*)
TSC1/2	GSK3β_{deg} & !ERK & !AKT	The tuberous sclerosis complex (TSC) is composed of TSC1 and TSC2. ERK phosphorylates TSC2. In addition, TSC1/2 can be inhibited by phosphorylation of AKT. GSK3β activates TSC1/2 complex.	(*2, 7, 46, 58, 59, 51, 60, 29*)
mTORC1	!TSC1/2	mTORC1 is inhibited by TSC1/2.	(*2, 7, 46, 58, 59, 51*)
S6K	mTORC1 & PI3K	mTORC1 phosphorylates ribosomal protein S6 kinase (S6K). Full activation is achieved by pyruvate dehydrogenase kinase 1 (PDK1), a component of the PI3K complex.	(*2, 46, 59, 29*)
TIAM1	(EGFR | AKT) & !PP2A & (MYC | TCF/LEF)	The guanine nucleotide exchange factor T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1) can be activated directly by EGFR or through phosphorylation by AKT. MYC or TCF/LEF induce transcription of TIAM1. TIAM1 is inhibited by PP2A.	(*41, 61, 62, 63*)
RAC1	(TIAM1 | IQGAP1 | mTORC1 | PI3K | FZD) & ! APC	RAC1 can be activated by TIAM1. IQGAP1 stabilises RAC1 in its active form. mTORC1 or PI3K as well as frizzled (FZD) with its receptor low-density lipoprotein receptor-related protein 6 (LRP6) activate RAC1. Loss of APC causes elevated expression of RAC1.	(*10, 64, 65, 62, 61, 66, 67, 68, 18, 69, 70, 71*)
JNK	RAC1	RAC1 activates its downstream target c-Jun-N-terminal kinase (JNK).	(*72, 73, 74*)
PAK1	RAC1 & !PP2A	RAC1 phosphorylates PAK1 while PP2A is responsible for PAK1's dephosphorylation.	(*23, 24, 75, 76, 57*)
IQGAP1	!GSK3β_{deg}	GSK3β inhibition allows IQGAP1 to regulate downstream targets.	(*77*)
PGE2	COX2 | (SNAIL1 & HDAC2)	COX2 is the key regulator in the conversion of arachidonic acid into prostanoids including prostaglandin E2 (PGE2). SNAIL1 and histone deacetylase 2 (HDAC2) suppress 15-hydroxyprostaglandin dehydrogenase thereby enhancing PGE2 production.	(*78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 86*)
HDAC2	!APC & MYC	Adenomatous polyposis coli protein (APC) loss induces the expression of HDAC2 through transciptional regulation of MYC.	(*2, 89*)
ERBB1/2	HDAC2 | AP1 | TCF/LEF	HDAC inhibitors cause downregulation of ERBB1. MYC, activator protein 1 (AP1) or TCF/LEF induce transcription of ERBB1.	(*90, 91, 92, 93, 94, 6*)

Table 1: Boolean functions of the Wnt/MAPK network. Interactions are described by logical connectives AND (&), OR (|), and NOT (!).

Node	Boolean network function	Description of the rule	References
cFOS	(TCF/LEF | ERK) & (ERK | RSK1/2)	The expression of fos-related antigen 1 (FRA-1), the protein encoded by the c-FOS gene, is transcriptionally activated by either ERK or TCF/LEF complex. Activation by phosphorylation can be induced by ERK alone or by ribosomal S6 kinases (RSK1/2).	(*2, 9, 95, 29, 10*)
RSK1/2	PI3K & ERK	Phosphorylation by ERK or PDK1 activates RSK1/2.	(*96, 97, 29*)
AP1	cFOS & cJUN	AP1 is a transcription complex that is formed by the dimerization of c-FOS and c-JUN.	(*2, 7, 6, 94, 98*)
COX2	AP1 | NF-κB | TCF/LEF	Transcription of COX2 can be enhanced by AP1, NF-κB or TCF/LEF.	(*99, 100, 101, 102, 103, 104, 105, 106, 107, 78, 2, 108*)
FASR	NF-κB & !CTNNB1	There exist correlation between β-catenin expression and FAS receptor (FASR) down regulation. NF-κB induces expression of FASR.	(*109, 110*)
NF-κB	(RAC1 | ERK | AKT) & HDAC2 & GSK3β_{cyt}	Phosphorylation by RAC1, ERK or AKT can activate NF-κB. HDAC2 is required for NF-κB transport to the nucleus where it can activate target genes. Also the presence of GSK3β has been shown to be required for the activity of NF-κB.	(*111, 57, 112, 38, 61, 52, 113, 114, 115, 116*)
CDH1	(!SNAIL1 & !HDAC2 & !AKT) | (!SNAIL1 & HDAC2 & AKT) | (!SNAIL1 & !HDAC2 & AKT) | (!SNAIL1 & HDAC2 & !AKT) | (SNAIL1 & !HDAC2 & !AKT) | (SNAIL1 & HDAC2 & !AKT) | (SNAIL1 & !HDAC2 & AKT)	E-cadherin (CDH1) expression is inhibited by transcription factor complex including SNAIL1, HDAC2 and AKT.	(*117, 118, 119, 120, 55, 121, 122, 123*)
Tight junctions	CDH1 & (!IQGAP1 | APC | (RAC1 & IQGAP1))	CDH1 is a foundamental component of tight junctions. IQGAP1 if not bound to RAC1 disrupts tight junctions. Presence of APC at tight junctions promotes cell-cell contact.	(*17, 18, 67, 68, 71, 124*)
SNAIL1	((AXIN2 | ERK | NF-κB) & !GSK3β_{deg}) | (AXIN2 & GSK3β_{deg})	SNAIL1 expression can be induced by AXIN2, ERK or NF-κB. Phosphorylation by GSK3β promotes degradation of SNAIL1. AXIN2 can prevent action of GSK3β on SNAIL1.	(*118, 119, 125, 126, 127, 128, 129, 86, 130*)
AXIN2	TCF/LEF	AXIN2 expression is induced by TCF/LEF.	(*2, 118, 119, 131, 10, 132*)
FZD	MEK | ERK | JNK	FZD is activated by phosphorylation of either MEK, ERK, or JNK.	(*10, 8*)
DVL	FZD	FZD phosphorylates dishevelled (DVL) and recruits it to the destruction complex.	(*2, 7, 8, 9, 10*)
GSK3β_{deg}	!PGE2 & !AKT & !ERK & !NF-κB	AKT, ERK, or PGE2 can phosphorylate GSK3β. NF-κB disrupts interaction with β-Trcp thus marking GSK3β for degradation.	(*133, 8, 134, 126, 135, 127, 128, 15, 136, 137, 138, 139, 140, 141*)
GSK3β_{cyt}	!APC | GSK3β_{deg}	Active GSK3β has been shown to be upregulated in colorectal cancer and to have a potential role in oncogenic activity of colorectal cancer cells. The regulation of the hyper activation of GSK3β and its regulation in the distinction from Anti/pro oncogenic activity yet lacks in clarification. Therefore, we modeled the active form of GSK3β either as a consequence of tumorigenesis or as the presence of its active form that acts as a repressor of oncogenes (GSK3β_{deg}). One possible explanation to distinguish the activities could be the major influence of regulators of the GSK3β interaction with the proteosome complex (like in the regulation due to NF-κB) instead of the activity of inactivatory phosphorylators. However, this mechanism has to be elucidated yet.	(*142, 143, 144, 145, 137, 146*)
GSK3β_{DC}	AXIN1	Part of the pool of GSK3β in cells is sheltered from inhibitors actions in the destruction complex. This means that the destruction complex can recruit part of the GSK3β pool through binding to AXIN. In fact, hyper activation of AKT does not trigger the β-catenin (CTNNB1) signalling.	(*140, 139, 137, 146, 144*)
APC	APC	APC is taken as an input of the network. Since APC loss is present in the early phase of colorectal cancer. We did not include a regulation. Under physiological condition it is assumed to be active.	(*147, 2, 9, 10, 136, 137, 146, 138, 139, 140*)
AXIN1	!DVL	AXIN1 is inhibited in its action within the DC by activated phosphorylated disheveled (DVL). AXIN2 instead, is less sensitive to sensitive to DVL recruitment, explaining its effective action in the scaffolding the DC despite the lower concentration even when stimulated by active Wnt signalling.	(*2, 7, 8, 9, 147, 136, 137, 146, 138, 139, 148*)
DC	!DVL & GSK3β_{DC} & APC & (AXIN1 | AXIN2)	The DC is composed of GSK3β, APC, casein kinase 1 (CK1) and either AXIN1 or AXIN2. Its degradation and thus inactivation is triggered by DVL.	(*2, 7, 8, 9, 131, 147, 137, 146, 138, 139, 140*)
CTNNB1	!DC	Cytoplasmic CTNNB1 is marked by the destruction complex for proteasomal degradation. When the destruction complex is not functional anymore β-catenin can accumulate in the cytoplasm and be translocated in the nucleus.	(*2, 7, 8, 9, 147, 13, 136, 137, 138, 139, 140*)

Table 1: Boolean functions of the Wnt/MAPK network. Interactions are described by logical connectives AND (&), OR (|), and NOT (!).

Node	Boolean network function	Description of the rule	References
TCF/LEF	CTNNB1 & KRAS & RAC1 & (PAK1 | AKT | MEK | IQGAP1 | TIAM1 | NF-κB | SNAIL1)	TCF/LEF is activated by nuclear translocation of CTNNB1. Further factors are necessary that CTNNB1 is able to translocate into the nucleus including KRAS or RAC1. Transcriptional activity of CTNNB1 can be induced by PAK1, AKT, MEK, IQGAP1, TIAM1, NF-κB, and SNAIL1.	(*2,7,8,9,147,149,23,24,62,150,151,10,152, 68,153,154,155,140*)
PP2A	!CIP2A	CIP2A is an inhibitor of PP2A.	(*26,36,35,25,22,27,37,31*)
CIP2A	EGFR | MEK | ERK	CIP2A is activated either by EGFR, MEK or ERK.	(*156,32,26,36,35,25,22,27,37,31*)

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