

# Supplement materials

**Table S1.** Description of genes, mRNA and proteins in p53 system module

Symbol	Description
DSB	DNA double strand break
ATM	Kinase ATM (ataxia telangiectasia-mutated)
ATM <sub>p</sub>	ATM phosphorylated at Ser1981 (ATM activated by DSB)
Wip1	Wild-type p53-induced phosphatase
Wip1 <sub>mRNA</sub>	Wip1 transcript
Wip1 <sub>gene</sub>	State of the Wip1 gene: active/inactive
SIAH1	Siah E3 Ubiquitin Protein Ligase 1
SIAH1 <sub>p</sub>	SIAH1 phosphorylated at Ser19
HIPK2	Homeodomain interacting protein kinase 2
p53	A tumor suppressor protein
p53 <sub>arrest</sub>	p53 phosphorylated at Ser15, Ser20, related to cell cycle arrest
P53 <sub>killer</sub>	p53 phosphorylated at Ser15, Ser20 and additionally at Ser46, related to apoptosis
P53 <sub>p46</sub>	p53 phosphorylated at Ser46 only
Mdm2	Proto-oncogene, main cellular antagonist of p53
Mdm2 <sub>gene</sub>	State of the Mdm2 gene: active/inactive
Mdm2 <sub>mRNA</sub>	Mdm2 transcript
Mdm2 <sub>cyt</sub>	Unphosphorylated Mdm2 in cytoplasmic
Mdm2 <sub>cyt_2p</sub>	Mdm2 phosphorylated at Ser166 and Ser186 in cytoplasmic
Mdm2 <sub>nuc_2p</sub>	Mdm2 phosphorylated at Ser166 and Ser186 in nucleus
Mdm2 <sub>nuc_3p</sub>	Mdm2 phosphorylated at Ser166, 186 and additionally at Ser395 in nucleus
PI3K	Phosphoinositide 3-Kinase
PTEN	Phosphatase And Tensin Homolog, a multi-functional tumor suppressor
PTEN <sub>gene</sub>	State of the PTEN gene: active/inactive
PTEN <sub>mRNA</sub>	PTEN transcript
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-triphosphate
Akt	AKT serine/threonine kinase
Akt <sub>p</sub>	Akt phosphorylated at Thr308
Bax	BCL2 Associated X, Apoptosis Regulator
Bax <sub>gene</sub>	State of the Bax gene: active/inactive
Bax <sub>mRNA</sub>	Bax transcript
Bclx <sub>L</sub>	B-cell lymphoma-extra large, an anti-apoptotic proteins of the Bcl-2 family
Bax : Bclx <sub>L</sub>	complex of Bax and Bcl-x <sub>L</sub>
Bad	Bcl2 associated agonist of cell death, a member of the Bcl-2 family
Bad <sub>p</sub>	Bad phosphorylated at Ser75 and Ser99
Bclx <sub>L</sub> : Bad	complex of Bcl-x <sub>L</sub> and Bad
14-3-3	A family of small, acidic proteins that, through functioning adaptors,

	scaffolds, and chaperones, regulate a variety of intracellular signaling pathways.
Bad <sub>p</sub> : 14-3-3	complex of Bad <sub>p</sub> and 14-3-3
Caspase	Active caspase
ProCaspase	Inactive caspase
p21	A cell cycle inhibitor
p21 <sub>gene</sub>	State of the p21 gene: active/inactive
p21 <sub>mRNA</sub>	P21 transcript
CycE	E-type cyclins, limiting factor for G1 phase progression and S phase entry
p21 : CycE	Complex of p21 and Cyclin E
Rb1	Retinoblastoma (RB) Transcriptional Corepressor 1, negative regulator of the cell cycle and tumor suppressor
Rb1	Rb1 phosphorylated at Ser780
E2F1	E2F Transcription Factor 1,
Rb1 : E2F1	Complex of unphosphorylated Rb1 and E2F1
GADD45	Growth Arrest And DNA Damage-Inducible Protein
p38	Mitogen-Activated Protein Kinase P38
p38 <sub>p</sub>	p38 phosphorylated at Thr180/Tyr182
TGFβ	Transforming Growth Factor Beta

**Table S2.** Parameters of the p53 system module (If the reference is empty, the parameter is from Hat et al. [1])

Symbol	Value	Description	Reference
a1	$3 \times 10^{-10} \text{ s}^{-1}$	activation of proCaspases by Bax	
a2	$1 \times 10^{-12} \text{ s}^{-1}$	Caspases auto activation	
q0_pten	$1 \times 10^{-5} \text{ s}^{-1}$	PTEN gene spontaneous activation	
q0_wip1	$1 \times 10^{-5} \text{ s}^{-1}$	Wip1 gene spontaneous activation	
q0_mdm2	$1 \times 10^{-4} \text{ s}^{-1}$	Mdm1 gene spontaneous activation	
q0_bax	$1 \times 10^{-5} \text{ s}^{-1}$	Bax gene spontaneous activation	
q0_p21	$1 \times 10^{-5} \text{ s}^{-1}$	p21 gene spontaneous activation	
q1_pten	$3 \times 10^{-13} \text{ s}^{-1}$	PTEN gene activation induced by p53_killer	
q1_wip1	$3 \times 10^{-13} \text{ s}^{-1}$	Mdm2 gene act'n induced by p53_arrester	
q1_mdm2	$3 \times 10^{-13} \text{ s}^{-1}$	Wip1 gene act'n induced by p53_arrester	
q1_p21	$3 \times 10^{-13} \text{ s}^{-1}$	p21 gene act'n induced by p53_arrester	
q1_bax	$3 \times 10^{-13} \text{ s}^{-1}$	Bax gene act'n induced by p53_killer	
q2	$3 \times 10^{-3} \text{ s}^{-1}$	Inactivation of Mdm2, Wip1, p21 PTEN and Bax	
s1	$0.1 \text{ s}^{-1}$	Wip1 mRNA synthesis	
s2	$0.3 \text{ s}^{-1}$	PTEN mRNA synthesis	
s3	$0.1 \text{ s}^{-1}$	Mdm2 mRNA synthesis	
s4	$0.3 \text{ s}^{-1}$	Bax mRNA synthesis	
s5	$0.1 \text{ s}^{-1}$	p21 mRNA synthesis	
t1	$0.1 \text{ s}^{-1}$	Translation of Wip1	

t2	$0.1 \text{ s}^{-1}$	Translation of PTEM	
t3	$0.1 \text{ s}^{-1}$	Translation of Mdm2	
t4	$0.1 \text{ s}^{-1}$	Translation of Bax	
t5	$0.1 \text{ s}^{-1}$	Translation of p21	
s6	$300 \text{ s}^{-1}$	p53 synthesis	
s7	$30 \text{ s}^{-1}$	proCaspases synthesis	
s8	$30 \text{ s}^{-1}$	HIPK2 synthesis	
s9	$30 \text{ s}^{-1}$	Cyclin E synthesis induced by E2F1	
s10	$3 \text{ s}^{-1}$	Spontaneous synthesis of Cyclin E	
p1	$3 \times 10^{-4} \text{ s}^{-1}$	ATM phosphorylation due to the presence of IR-induced DNA DSB	
p2	$1 \times 10^{-8} \text{ s}^{-1}$	SIAH1 phosphorylation by ATM <sub>p</sub>	
p3	$3 \times 10^{-8} \text{ s}^{-1}$	p53 phosphorylation by ATM <sub>p</sub> at Ser15 and Ser20	
p4	$1 \times 10^{-10} \text{ s}^{-1}$	p53 arrester phosphorylation by HIPK2 at Ser46	
p5	$1 \times 10^{-8} \text{ s}^{-1}$	Mdm2_cyt phosphorylation	
p6	$1 \times 10^{-8} \text{ s}^{-1}$	Mdm2_nuc_S116_S186 by ATM <sub>p</sub> at Ser395	
p7	$3 \times 10^{-9} \text{ s}^{-1}$	Bad phosphorylation by Akt <sub>p</sub>	
p8	$3 \times 10^{-9} \text{ s}^{-1}$	PIP2 phosphorylation by PI3K	
p9	$3 \times 10^{-6} \text{ s}^{-1}$	Rb1 phosphorylation by Cyclin E	
p10	$3 \times 10^{-6} \text{ s}^{-1}$	Rb1 phosphorylation by Cyclin E in Rb1-E2F1 complex	
p11	$1 \times 10^{-10} \text{ s}^{-1}$	P53 phosphorylation by HIPK2 at Ser46	
p12	$1 \times 10^{-9} \text{ s}^{-1}$	Akt phosphorylation by PIP3	
d1	$1 \times 10^{-8} \text{ s}^{-1}$	ATM <sub>p</sub> dephosphorylation by Wip1	
d2	$3 \times 10^{-5} \text{ s}^{-1}$	SIAH1 <sub>p</sub> dephosphorylation	
d3	$1 \times 10^{-4} \text{ s}^{-1}$	Spontaneous dephosphorylation of p53 arrester	
d4	$1 \times 10^{-10} \text{ s}^{-1}$	P53 killer dephosphorylation of Ser46 by Wip1	
d5	$1 \times 10^{-4} \text{ s}^{-1}$	Spontaneous dephosphorylation of Mdm2_cyt_S166p_S186p	
d6	$3 \times 10^{-5} \text{ s}^{-1}$	Mdm2_nuc_S166p_S186p_S395p dephosphorylation of S395p by Wip1	
d7	$3 \times 10^{-7} \text{ s}^{-1}$	PIP3 dephosphorylation to PIP2 by PTEN	
d8	$1 \times 10^{-4} \text{ s}^{-1}$	Spontaneous dephosphorylation of Akt <sub>p</sub>	
d9	$3 \times 10^{-5} \text{ s}^{-1}$	Spontaneous dephosphorylation of Bad <sub>p</sub>	
d10	$1 \times 10^{-4} \text{ s}^{-1}$	Spontaneous dephosphorylation of p53 killer at Ser15 and Ser20	
d11	$1 \times 10^{-10} \text{ s}^{-1}$	p53_s46 dephosphorylation by Wip1	
d12	$1 \times 10^4 \text{ s}^{-1}$	Rb1 dephosphorylation	
b1	$1 \times 10^{-5} \text{ s}^{-1}$	Binding of Bax and BclX <sub>L</sub>	
b2	$3 \times 10^{-5} \text{ s}^{-1}$	Binding of Bad and BclX <sub>L</sub>	
b3	$3 \times 10^{-3} \text{ s}^{-1}$	Binding of Bad <sub>p</sub> and 14-3-3	
b4	$1 \times 10^{-5} \text{ s}^{-1}$	Binding of Rb1 and E2F1	
b5	$1 \times 10^{-5} \text{ s}^{-1}$	Binding of p21 and Cyclin E	

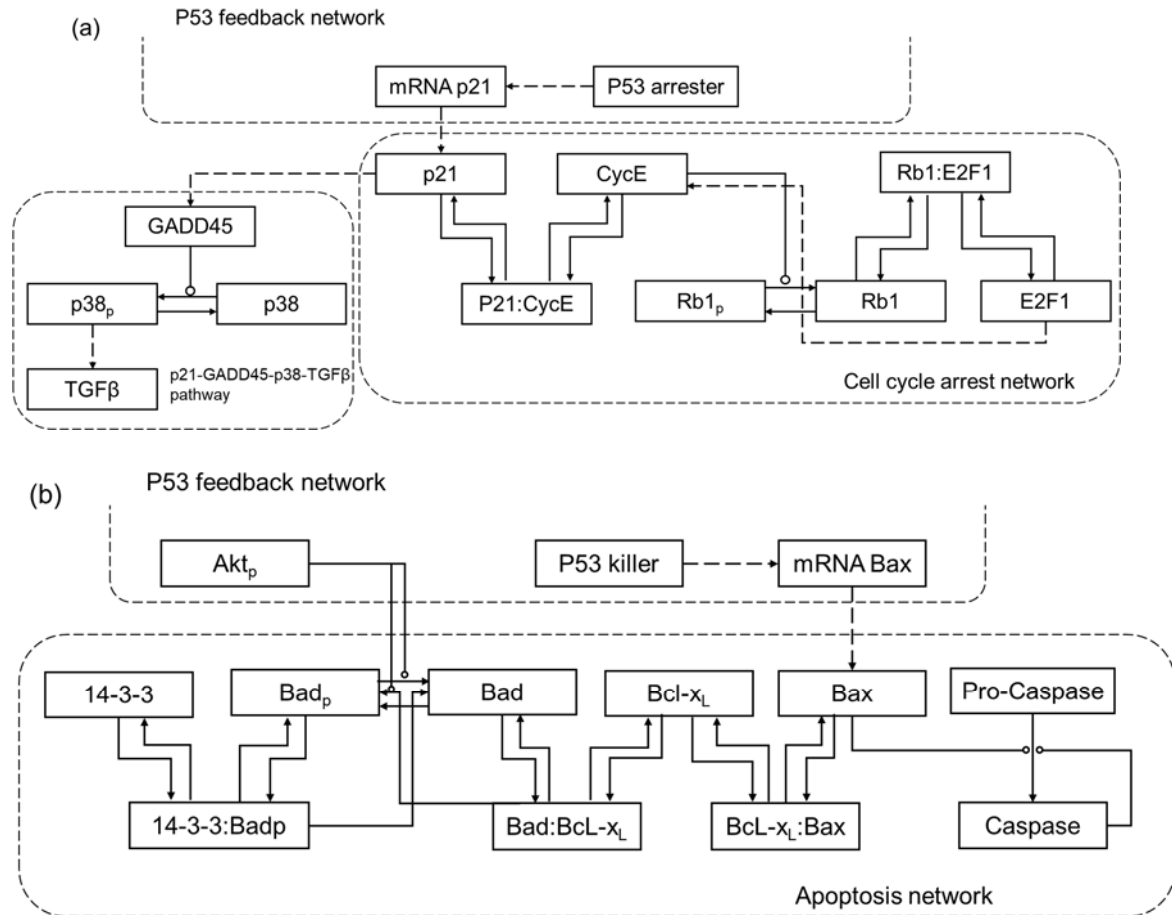
u1	$1 \times 10^{-3} \text{ s}^{-1}$	Unbinding of Bax and BclX <sub>L</sub> complex	
u2	$1 \times 10^{-3} \text{ s}^{-1}$	Unbinding of Bad and BclX <sub>L</sub> complex	
u3	$1 \times 10^{-3} \text{ s}^{-1}$	Unbinding of Bad <sub>p</sub> and 14-3-3 complex	
u5	$1 \times 10^{-4} \text{ s}^{-1}$	Unbinding of Rb1-E2F1 complex	
u6	$1 \times 10^{-4} \text{ s}^{-1}$	Unbinding of p21-Cyclin E complex	
i1	$1 \times 10^{-3} \text{ s}^{-1}$	Mdm2_cyt_S166p_S186p nuclear import	
g1	$3 \times 10^{-4} \text{ s}^{-1}$	mRNA_Wip1 degradation	
g2	$3 \times 10^{-4} \text{ s}^{-1}$	mRNA_PTEN degradation	
g3	$3 \times 10^{-4} \text{ s}^{-1}$	mRNA_Mdm2 degradation	
g4	$3 \times 10^{-4} \text{ s}^{-1}$	mRNA_Bax degradation	
g5	$3 \times 10^{-4} \text{ s}^{-1}$	mRNA_p21 degradation	
g6	$3 \times 10^{-5} \text{ s}^{-1}$	PTEN degradation	
g7	$1 \times 10^{-13} \text{ s}^{-1}$	HIPK2 degradation driven by Mdm2_nuc_2p and SIAH1	
g8	$3 \times 10^{-4} \text{ s}^{-1}$	Wip1 degradation	
g9	$1 \times 10^{-4} \text{ s}^{-1}$	Bax degradation	
g10	$1 \times 10^{-5} \text{ s}^{-1}$	Spontaneous degradation of p53	
g101	$1 \times 10^{-5} \text{ s}^{-1}$	Spontaneous degradation of p53 arrester	
g11	$1 \times 10^{-2} \text{ s}^{-1}$	p53 degradation induced by Mdm2_nuc_S166p_S186p	
g12	$1 \times 10^{-13} \text{ s}^{-1}$	p53_arrester degradation induced by Mdm2_nuc_S166p_S186p	
g13	$1 \times 10^{-13} \text{ s}^{-1}$	p53_killer degradation induced by Mdm2_nuc_S166p_S186p	
g14	$1 \times 10^{-4} \text{ s}^{-1}$	Mdm2_cyt degradation	
g15	$3 \times 10^{-5} \text{ s}^{-1}$	Spontaneous degradation of phosphorylated Mdm2	
g16	$1 \times 10^{-4} \text{ s}^{-1}$	Mdm2_nuc_S166p_S186p_S395p degradation	
g17	$3 \times 10^{-4} \text{ s}^{-1}$	proCaspases degradation	
g18	$3 \times 10^{-4} \text{ s}^{-1}$	Caspase degradation	
g19	$3 \times 10^{-4} \text{ s}^{-1}$	p21 degradation	
g20	$1 \times 10^{-4} \text{ s}^{-1}$	Cyclin E degradation	
kGADD45act	$4 \times 10^{-9} \text{ s}^{-1}$	GADD45 Activation / Production	[2]
kGADD45deg	$1 \times 10^{-5} \text{ s}^{-1}$	GADD45 Degradation	[2]
kp38phos	$8 \times 10^{-3} \text{ s}^{-1}$	p38 Phosphorylation	[3]
kp38dphos	$0.1 \text{ s}^{-1}$	p38 Phosphorylation	[3]
kTGFbeta	$0.1 \text{ s}^{-1}$	generating TGFbeta by p38p	[3]
M1	7 or 25	Michaelis-Menten constant in ATM phosphorylation due to DSBs	[1, 4]
M2	$1 \times 10^5$	Michaelis-Menten constant in Rb1 dephosphorylation at Ser567	
M3	$2 \times 10^5$	Michaelis-Menten constant in E2F1-induced Cyclin E synthesis	

**Table S3.** Description of the gene, mRNA and protein interactions in p53 system

Reaction	Rate $\rightarrow$	Rate $\leftarrow$
$\text{Wip1}_{\text{gene}}(\text{inactive}) \leftrightarrow \text{Wip1}_{\text{gene}}(\text{active})$	$q0\_wip1 + q1\_wip1 * p53\text{arrester}^2$	$q2$
$\text{Mdm2}_{\text{gene}}(\text{inactive}) \leftrightarrow \text{Mdm2}_{\text{gene}}(\text{active})$	$q0\_mdm2 + q1\_mdm2 * p53\text{arrester}^2$	$q2$
$p21_{\text{gene}}(\text{inactive}) \leftrightarrow p21_{\text{gene}}(\text{active})$	$q0\_p21 + q1\_p21 * p53\text{arrester}^2$	$q2$
$\text{PTEN}_{\text{gene}}(\text{inactive}) \leftrightarrow \text{PTEN}_{\text{gene}}(\text{active})$	$q0\_pten + q1\_pten * p53\text{killer}^2$	$q2$
$\text{Bax}_{\text{gene}}(\text{inactive}) \leftrightarrow \text{Bax}_{\text{gene}}(\text{active})$	$q0\_bax + q1\_bax * p53\text{killer}^2$	$q2$
$\text{ATM} \leftrightarrow \text{ATM}_p$	$p1 * \text{DSB}^2 / (\text{M1}^2 + \text{DSB}^2)$	$d1 * \text{Wip1}$
$\text{SIAH1} \leftrightarrow \text{SIAH1}_p$	$p2 * \text{ATM}_p$	$d2$
$\Phi \leftrightarrow \text{HIPK2}$	$\text{S8}$	$g7 * (\text{SIAH1}_0 + \text{Mdm2\_nuc\_S166S186p}) * (\text{SIAH1}_0 + \text{Mdm2\_nuc\_S166S186p})$
$\Phi \leftrightarrow \text{Wip1}_{\text{mRNA}}$	$s1 * \text{Wip1}_{\text{gene}}/2$	$g1$
$\Phi \leftrightarrow \text{Wip1}$	$t1 * \text{Wip1}_{\text{mRNA}}$	$g8$
$\Phi \leftrightarrow p53$	$s6$	$g101 + g11 * \text{Mdm2\_nuc\_2p}^2$
$p53 \text{ arrester} \rightarrow \Phi$	$g12 * \text{Mdm2\_nuc\_S166S186p}^2$	-
$p53 \text{ S46p} \rightarrow \Phi$	$g13 * \text{Mdm2\_nuc\_S166S186p}^2$	-
$p53 \text{ killer} \rightarrow \Phi$	$g13 * \text{Mdm2\_nuc\_S166S186p}^2$	-
$p53 \leftrightarrow p53 \text{ arrester}$	$p3 * \text{ATM}_p$	$d3$
$p53 \text{ S46p} \leftrightarrow p53 \text{ killer}$	$p3 * \text{ATM}_p$	$d3$
$p53 \text{ arrester} \leftrightarrow p53 \text{ killer}$	$p3 * \text{HIPK2}$	$d4 * \text{Wip1}$
$p53 \leftrightarrow p53 \text{ S46p}$	$p3 * \text{HIPK2}$	$d4 * \text{Wip1}$
$\Phi \leftrightarrow \text{Mdm2}_{\text{mRNA}}$	$s3 * \text{Mdm2}_{\text{gene}}/2$	$g3$
$\Phi \leftrightarrow \text{Mdm2\_cyt\_0p}$	$t3 * \text{Mdm2}_{\text{mRNA}}$	$g14$
$\text{Mdm2\_cyt\_S166S186p} \rightarrow \Phi$	$g15$	-
$\text{Mdm2\_nuc\_S166S186p} \rightarrow \Phi$	$g16$	-
$\text{Mdm2\_cyt\_0p} \leftrightarrow \text{Mdm2\_cyt\_S166S186p}$	$p5 * \text{Akt}_p$	$d5$

Mdm2_cyt_S166S186p→Mdm2_nuc_S166S186p	i1	-
Mdm2_nuc_S166S186p←→Mdm2_nuc_S166S186p_S395p	p6*ATMp	d6*Wip1
$\Phi \leftarrow \rightarrow PTEN_{mRNA}$	s2*PTEN <sub>gene</sub> /2	g2
$\Phi \leftarrow \rightarrow PTEN$	t2*PTEN <sub>mRNA</sub>	g6
PIP2←→PIP3	p8*PI3K	d7*PTEN
Akt←→Akt <sub>p</sub>	p12*PIP3	d8
$\Phi \leftarrow \rightarrow p21_{mRNA}$	g5*p21 <sub>gene</sub>	g5
$\Phi \leftarrow \rightarrow p21$	t5*p21 <sub>mRNA</sub>	g19
$\Phi \leftarrow \rightarrow CycE$	s10 + s9 * E2F1 <sup>2</sup> / (E2F1 <sup>2</sup> + M3 <sup>2</sup> )	g20
p21+CycE←→p21:CycE	b5	u6
p21:CycE→Φ	g20	-
Rb1←→Rb1 <sub>p</sub>	p9*CycE	d12 / (M2 + Rb1 <sub>p</sub> )
Rb1+E2F1←→Rb1:E2F1	b4	u5
Rb1:E2F1→Rb1 <sub>p</sub> +E2F1	p10 * CycE	-
$\Phi \leftarrow \rightarrow Bax_{mRNA}$	s4*Bax <sub>gene</sub> /2	g4
$\Phi \leftarrow \rightarrow Bax$	t4*Bax <sub>mRNA</sub>	g9
Bax+Bclx <sub>L</sub> ←→ Bax:Bclx <sub>L</sub>	b1	u1
Bax:Bclx <sub>L</sub> → Bclx <sub>L</sub>	g16	-
Bad+Bclx <sub>L</sub> ←→Bad:Bclx <sub>L</sub>	b2	u2
Bad:Bclx <sub>L</sub> →Bad <sub>p</sub> +Bclx <sub>L</sub>	p7*Akt <sub>p</sub>	-
Bad←→Bad <sub>p</sub>	p7*Akt <sub>p</sub>	d9
Bad+14-3-3←→Bad:14-3-3	b3	u3
Bad:14-3-3→Bad <sub>p</sub> +14-3-3	d9	-
$\Phi \leftarrow \rightarrow proCaspase$	s7	g17
proCaspase→Caspase	a1*Bax + a2*Caspase <sup>2</sup>	-
Caspase→Φ	g17	-
$\Phi \leftarrow \rightarrow GADD45$	kGADD45act * p21	kGADD45deg
p38←→p38 <sub>p</sub>	kp38phos * GADD45	kp38dphos
$\Phi \rightarrow TGF\beta$	kTGFbeta*p38 <sub>p</sub>	-

Φ means empty set, no protein or no mRNA.



**Figure S1.** Detailed scheme of (a)the cell cycle arrest network and (b)apoptosis network in the p53 system. These two models are established based on the model of Hat et al. Arrow-headed dashed lines indicate positive transcriptional regulation, arrow-headed solid lines—protein transformation, circle-headed solid lines—positive influence or activation, hammer-headed solid lines—inhibitory regulation.

## References

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