

Pin1 substrates, targeting sites and functional consequences

Substrates	Targeting sites	Consequences	References
<u>Cell cycle progression</u>			
NIMA		Regulate mitotic function	1,2
Rab4			3,4
Cdc25	pThr48/67-P	Increase dephosphorylation and regulate activity	5-8
Wee1	pT186-P	Inhibit Wee1 activity	5,9
Plk1			5,6,10
Myt1			5,11
Cdc27			5
CENP-F			5
Incenp			5
Rpb1	pS5-P	Regulate CTD dephosphorylation and activity	12-17
NHERF-1	pS279/301-P	Increase dephosphorylation	18
KRMP1	pT-1604-P	Regulate mitotic function	19
Cyclin D1	pT286-P	Increase stability and nuclear localization	20
CK2	Multiple pS/T-P	Inhibit kinase activity	21
TopIIa			21,22
Dab2	pT-1342	Increase phosphorylation	23
Ki67	pT234-P		24
p54nrb	Multiple pT-P		25
Sil	Multiple pS/T-P	Regulate function	26
Cyclin E	pS384-P	Decrease stability	27-30
Emi1	pS10-P	Increase stability	31
Cep55		Increase stability	32
p27	pT187	Increase stability	33
LSF	pS291/309/p Thr-P	Increase dephosphorylation	34
Rb	S608/612-P	Increased phosphorylation and inhibit activity	35,36
Bora	pS274/278-P	Increase stability	37
Survivin	pT34-P	Increase activity	38
SEPT9		Increase activity	39
Sp1	pT739-P	Increase stability	40
Swi6		Increase nuclear localization	41
Whi5		Increase nuclear localization	41
Separase		Increase stability and activity	42
LIC1	Multiple pS/T-P	Regulate protein-interaction	43
<u>Neuronal survival and degeneration</u>			
Tau	pT231-P	Restore microtubule function, promote dephosphorylation, decrease stability	7,44,45
APP	pT668-P	Promote non-amyloidogenic APP processing	46
Synphilin-1	pS211/215-P	Protein interaction	47
Gephyrin	pS188/194/200-P	Protein interaction	48
mGluR5	pS1126-P	Increase its activity	49

REST	pS861/864-P	Decrease stability	50
Gro/TLE1		Inhibit its activity	51
CRMP2A	pS27-P	Increase stability	52
mHTT		Decrease stability and aggregation	53,54
MARCKS-P		Promote dephosphorylation	55
Calcineurin		Inhibit Pin1 activity	56
CaMKII	pT176P	Inhibit kinase activity	57
Lamin-B		Lamin-B structure and function	58
HP1 α		Protein stability and protein interaction	58

Oncoproteins/growth-promoting regulators

Cdc25	pThr48/67-P	Increase dephosphorylation and regulate activity	5-8
c-Jun	pS63/73-P	Increase transactivation	59
β -catenin	pS246-P	Increase stability and transactivation	60
c-Myc	pT58-P	Increase expression, stability and transactivation	60-64
	pT58/S62-P	Decrease stability	65
Cyclin D1	pT286-P	Increase stability and nuclear localization	20
Bcl-2	pS70/87-P	Promote anti-apoptotic function	66
CK2	Multiple pS/T-P	Inhibit kinase activity	21
NF- κ B	pT254-P	Increase stability and transactivation	67
Ki67	pT234-P	Positive protein expression	24
Raf-1	Multiple pS/T-P	Increase dephosphorylation, prolong activation	68
c-Fos	Multiple S/T-P	Increase transactivation	69
SRC-3/AIB1		Increase transactivation	70
Cyclin E	pS384-P	Decrease stability	27-30
STAT3	pS727-P	Increased transactivation	71
Emi1	pS10-P	Increase stability	31
HBx	pS41-P	Increase stability and activity	72
Her2		Increase stability	73
Mcl-1	pT92/T163	Increase stability	74
c-Myb	pS528-P	Increase transactivation	75
eNOS	pS116-P	Inhibit activity	76-78
v-Rel		Increase stability and activity	79
Tax	pS160-P	Increase stability and activity	80,81
Cep55		Increase stability	32
Smad2/3	Multiple pS/T-P	Decrease stability	82
Notch	pT2512	Increased stability and activation	83,84
AKT	pT92/450-P	Increased stability	85
FAK	pS910-P	Increase dephosphorylation	86,87
P70S6K		Increased activity	88
PTP-PEST	pS571-P	Increase dephosphorylation	86,87
KSRP		Increase dephosphorylation and activation	89
PPAR γ		Increase stability	90
MEK1		Increase activity	91
SF-1	pS203-P	Increase transactivation	92
CRTC2		Induces translocation to the cytosol	93

LSF	pS291/309/p Thr-P	Increase dephosphorylation	34
p47phox	pS345-P	Increase phosphorylation	94,95
Nanog	Multiple pS/T-P	Increased stability	96
Oct4	pS12-P	Increased stability	97
IRAK1	pS110/163/196-P	Increase activation	98
IRS-1		Increase insulin actions and adipogenesis	99
Mutant p53		Increased stability and activity	100
ER α	pS118/294-P	Increase stability, DNA binding and transactivation	101,102
CREB	pT172/S271-P	Inhibit transactivation	103
PIP4Ks	pT322/S326-P	Inhibit kinase activity	104
PKM2	pS37-P	Increase nuclear localization	105
AR	pS81-P	Increase activity	106
JNK1	pT183-P	Decrease dephosphorylation	107
Nur77	pS152-P	Increased transactivation	108
RSK2		Increase phosphorylation	109
HIPK2	pT880/882-P	Increased stability	110
Survivin	pT34-P	Increase activity	38
Bora	pS274/278-P	Increase stability	37
SEPT9		Increase activity	39
HSP1	pS326-P	Increase levels and activity	111
HIF		Increased transactivation	112
MAP3K8		Increase activity	113
Sp1	pT739-P	Increase stability	40
PML-RAR α	pS581-P	Increase stability	114
RAB2A		Increase expression	115
PERIOD		Increased stability	116
Separase		Increase stability and activity	42
BRD4	pT204-P	Increase expression, stability and transactivation	117
p53-R249S	S249-P	Gain of oncogenic function	118
LATS kinase		Regulate anti-tubulin drug-induced apoptosis	119
YAP/TAZ		Increased stability	120
ACC1		Increase stability	121
HIP1R	pS929	Protein dephosphorylation and localization	122
Rho GTPase		Activate Rho GTPase activity	123
Nrf2	Multiple pS-P	Increased stability and nuclear localization	124

Tumor suppressors/growth-inhibitory regulators

Wee1	pT186-P	Inhibit Wee1 activity	5,9
Sin3-Rpd3		Reducing histone deacetylases	125
Cf-2		Destabilization	126
Dab2	pT-1342	Increase phosphorylation	23
RAR α	pS77-P	Decrease stability and transactivation	127
AUF1		Protein interaction	128
BTK	pS21/115-P	Decrease stability	129
IRF3	pS339-P	Decrease stability	130

Daxx	pS178-P	Decrease stability	131
SMRT	pS1241/1469-P	Decrease stability	132
FOXO4		Decrease stability	133
Smad2/3	Multiple pS/T-P	Decrease stability	82
p27	pT187	Increase stability	33
Bax	p T167-P	Inhibit mitochondrial import	134
GRK2	pS670-p	Decrease stability	135
PML	Multiple pS/T-P	Decrease stability	136,137
Rb	S608/612-P	Increased phosphorylation and inhibit activity	35,36
CDK10	p133-P	Decrease stability	138
Fbw7	pT205-P	Decrease stability	63,139
SUV39H1	pS391-P	Decrease stability	140
RUNX3	Multiple pS/T-P	Decrease stability	141
KLF10	pT93-P	Decrease stability	142
FADD	pS194-P	Increase dephosphorylation	143
Che-1	p T144	Decrease stability	144
Fbw7*		Decrease stability	139
ATR	pS428-P	Protein activity and localization	145,146
AMPK	pT211-P	Inhibit phosphorylation and activity	147
XO5		Decrease stability	148
PRDM16		Decrease stability	149
IRF7		Decrease stability	150
ATGL		Decrease stability	151
Keap1	Multiple pS/T-P	Prevent substrate binding	124

DNA damage and apoptosis

p53	Multiple pS/T-P	Increased stability and transactivation	152-154
Bcl-2	pS70/87-P		66
p73	Multiple pS/T-P	Increased stability and transactivation	155
BimEL	pS65-P	Increased stability	156
p66Shc		Increase mitochondrial import	157
Daxx	pS178-P	Decrease stability	131
Mcl-1	pT92/T163	Increase stability	74
Nur77	pS152-P	Increased transactivation	108
HIPK2	pT880/882-P	Increased stability	110
RBBP8	pS276/T315-P	Increased stability	158
p63	pT538-P	Increased stability	159
HIF		Increased transactivation	112
Che-1	p T144	Decrease stability	144
ATR	pS428-P	Protein activity and localization	145,146
Mutant p53		Increased stability and activity	100
p53-R249S	S249-P	Gain of function	118

Metabolism and obesity

IRS-1		Increase insulin actions and adipogenesis	99
PRDM16		Decrease stability	149

ACC1		Increase stability	121
CRTC2		induces translocation to the cytosol	93
PPAR γ		Increase stability	90
CREB	pT172/S271-P	Inhibit transactivation	103
ATGL		Decrease stability	151

Immune response

NFAT			160
AUF1		Protein interaction	128
IRF3	pS339-P	Decrease stability	130
BTK	pS21/115-P	Decrease stability	129
Bax	p T167-P	Inhibit mitochondrial import	134
COX-2		Increase stability and expression	161,162
p47phox	pS345-P	Increase phosphorylation	94,95
IRAK1	pS110/163/196-P	Increase activation	98
GR	pS203/211-P	Increased transactivation	163
FADD	pS194-P	Increase dephosphorylation	143
IRAKM	Multiple pS/T-P	Induce nuclear translocation and transactivation	164
IRF7		Decrease stability	150
Rho GTPase		Activate Rho GTPase activity	123

Viral or parasitic infection and transformation

HBx	pS41-P	Increase stability and activity	72
A3G		Decrease protein stability and release inhibition	165
v-Rel		Increase stability and activity	79
Tax	pS160-P	Increase stability and activity	80,81
Capsid	pS16-P	Increase capsid dissociation from the HIV-1 core	166,167
Integrase	pS57-P	Increase stability and activity	168
BALF5	pT178-P	Increase viral replication	169
Rta		Increase activity	170
Fbw7*		Decrease stability	139
ORF1p	Multiple pS/T-P	Regulate L1 retrotransposition	171
HBc	pT160/pS162-P	Increase stability	172
pUL69	pS46/S49-P	Regulate viral replication	173

Plant signaling

PIN-FORMED protein 1 (PIN1)	Auxin transport	174
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*, Theileria parasites secrete Pin1 homolog to act on the host protein Fbw7 to maintain host cell transformation.

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