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SnapShot: p53 Posttranslational Modifications

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Since p53 was cloned and subsequently characterized as a tumor suppressor more the 20 years ago, more than 40,000 publications have been published relating to this protein. A great majority of this scientific literature focuses on the intricate details of p53 regulation by posttranslational modifications. Phosphorylation, the first posttranslational modification of p53 identified, was established as a positive regulator of p53 via modification at multiple sites by an ever-growing number of kinases activated by numerous stress signals. Subsequently, acetylation and ubiquitination have been established as major regulators of p53 by regulating p53 transcriptional activity and stability, respectively. More recently, other modifications, such as sumoylation, neddylation, methylation, and glycosylation, have been reported. Although the cellular effects of many modifications are established, mouse models using site-specific knockin approaches imply that some of these modifications are to some degree redundant. These findings raise the possibility that aspects of the p53 posttranslational regulatory network are redundant yet indispensable for exact and precise control of p53 activity upon stress-induced stimulation.

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	Site	Modifying Enzyme	Cellular Function	Disease or Knockout Phenotype
Phosphorylation	N-Terminal: S6, S9, S15, T18, S20	• ATM, DNAPK, CK1 • ERKs, ATR, p38 kinase, mTOR, Chk1/ Chk2, JNK, MAPKAP2, Hipk4	• Activated by DNA damage, UV light, ionizing radiation, replicative senescence, or phosphatidylcholines. • N-terminal phosphorylation causes p53 stabilization by inhibiting the p53-MDM2 interaction.	• Knockin mice carrying separate analogs to human Ser18/ Ser23 mutation are phenotypically normal. Thymocytes from Ser18 mutant mice are susceptible to ionizing radiation-induced apoptosis, whereas S23 mutation in ES cells and MEFs is dispensable for p53 stabilization and activation. Ser18/ Ser23 double mutant knockin mice display reduced apoptosis in thymocytes and develop some malignancies. • Very rare mutations reported in human tumors.
	S33, S37, S36, S46, T55, T81	• GSK3β, p38 kinase, ATR, DNAPK, JNK, AMPKalpha • HIPK2, DYKR2, ERK2, TAF1	• Activation by UV light (S33, S37, S46, Thr81), H_2O_2 treatment (S33), γ-radiation, DNA damage (S37), and glucose deprivation (Ser46). • Phosphorylation leads to stabilization and promotes p53 transcriptional activity to regulate p53-mediated cell-cycle arrest and apoptosis.	• Very rare mutations reported in human tumors.
	S149, T150, T155	• CSN-associated kinase complex	• Activated in unstressed cells. • Promotes p53 degradation.	• Very rare mutations reported in human tumors.
	S315, S376, S378, S392	• PKC, PKR, GSK3β • FACT-CK2, p38 kinase • CDK (cdc2/ck2), AURKA	• Activated by UV light (CDK/ GSK3β, FACT-CK2, p38 kinase), AURKA over-expression, and interferon signaling (PKR) • S351 phosphorylation activates p53-mediated transcription to regulate apoptosis and cell cycle. • PKC constitutively phosphorylates p53 at S376 and S378 in unstressed cells, IR stress leads to dephosphorylation. • S392 phosphorylation promotes sequence-specific p53 DNA binding.	• Knockin of S392 mouse analog (S389) is phenotypically normal. p53 transcriptional activation is partially compromised in cells isolated from knockin mice. • Very rare mutations have been reported for individual sites in human tumors.

	Site	Modifying Enzyme	Cellular Function	Disease or Knockout Phenotype
Acetylation	K120	• hMOF, Tip60	• K120 acetylation is promoted upon DNA damage. • Acetylation at K120 is crucial for p53-mediated apoptosis via BAX and PUMA. • K120 acetylation is dispensable for cell-cycle regulation and growth arrest. • p53 acetylated at K120 accumulates at proapoptotic target genes.	• K120 mutations to Arg, Glu, or Met have been reported in human tumors. • Effect of K120 point mutations in animal models will need to be determined.
	K164	• p300 / CBP	• Acetylation is induced by DNA damage and HDAC inhibitor treatment. • K164 mutation does not affect DNA binding. • Acetylation is required for growth arrest and apoptosis.	• Mutations of K164 are reported in human tumors.
	K320	• PCAF	• Acetylation of K320 by PCAF is induced by DNA damage. • K320 acetylation increases p53 DNA-binding capability. • p53 K320 acetylation state effects transcriptional activity.	• Knockin experiments of the mouse homolog K317R, mimicking p53 unacetylated at K320, enhance p53-mediated apoptosis after DNA damage in all cell types analyzed. • Very rare mutations reported in human tumors.
	K370, K372, K373, K381, K382, K386	• p300/CBP	• C-terminal acetylation levels are enhanced upon stress. • Acetylation levels increase upon HDAC inhibitor (TSA, nicotinamide) treatment. • C-terminal acetylation enhances p53 sequence-specific DNA-binding activity. • Acetylation promotes CBP/p300 recruitment and target gene activation. • p53 stability is affected by C-terminal acetylation due to inhibition of ubiquitination at acetylated lysines.	• Knockin experiments in mice introducing p53 with the C-terminal lysines mutated (6KR/7KR) produced viable and phenotypically normal animals. C-terminal KR stem cells, MEFs, and thymocytes show normal p53 stabilization after DNA damage, yet p53 target gene expression is impaired in promoter-specific fashion. • Very rare mutations reported in human tumors.

	Site	Modifying Enzyme	Cellular Function	Disease or Knockout Phenotype
			• p53 is deacetylated by HDACs and Sirt1. • Deacetylation by Sirt represses p53-dependent apoptosis in response to DNA damage and oxidative stress.	
Ubiquitination and UB-like Modification	UB: K370, K372, K373, K381, K382, K386	• MDM2 • Arf-BP1, COP1, and Pirh2	• MDM2-mediated polyubiquitination leads to p53 degradation. • monoubiquitination of p53 results in nuclear export. • Arf-BP1, COP1, and Pirh2 all ubiquitinate p53 and target it for proteasomal degradation. • HAUSP deubiquitinates p53 as well as regulates p53 via deubiquitination of MDM2 and MDMX.	• Knockin experiments in mice introducing p53 with the C-terminal lysines mutated (6KR/7KR) produced viable and phenotypically normal animals. C-terminal KR stem cells, MEFs, and thymocytes display normal p53 stabilization after DNA damage, yet p53 target gene expression is impaired in a promoter-specific fashion. • Knockin experiments of the mouse homolog K317R, mimicking p53 unacetylated at K320, enhance p53-mediated apoptosis after DNA damage in all cell types analyzed. • Very rare mutations reported in human tumors.
	SUMO: K386	• PIAS, PIASxβ	• Functional consequences are unclear. Both activation and suppression of transcriptional regulation have been reported.	
	NEDD8: K320 K321, K370, K372, K373	• FBXO11, MDM2	• Neddylation of p53 inhibits transcriptional activity.	
Methylation	K370	• Smyd2	• Inhibition of p53-promoter association resulting in p53 target gene repression.	• Knockin experiments in mice introducing p53 with mutated C-terminal lysines (6KR/7KR) produced viable and phenotypically normal animals. C-terminal KR stem cells, MEFs, and thymocytes show normal p53 stabilization after DNA damage, yet p53 target gene expression is impaired in promoter-specific fashion. • Modest effect of C-terminal lysine mutant knockins implies limited effect of p53 regulation via single site metylation. • Very rare mutations reported in human tumors.
	K372	• Set7/9	• Methylation stabilizes p53 and promotes nuclear localization to upregulate p53 target gene expression. • Blocks Smyd-mediated K370 methylation.	
	K382	• Set8/PR-Set7	• Suppresses p53 mediated transcription. • Augments proapoptotic and checkpoint activation.	

	Site	Modifying Enzyme	Cellular Function	Disease or Knockout Phenotype
Others	O-GlcNAc: Ser149	• O-GlcNAc transferase, O-GLcNAcase	• Stabilization of p53 by blocking ubiquitination-mediated proteolysis. • Modification prevents T155 phosphorylation.	• In vivo role of these modifications is not yet determined. • Very rare mutations reported in human tumors.
	ADP-ribosylation: E258, D259, E271	• PARP-1	• ADP-ribosylation prevents p53-Crm1 interaction, resulting in nuclear accumulation of p53 due to inhibition of nuclear export of p53.	