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SnapShot: Lysine Methylation beyond Histones

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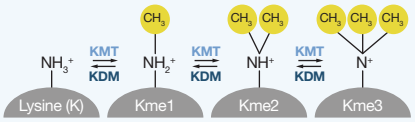
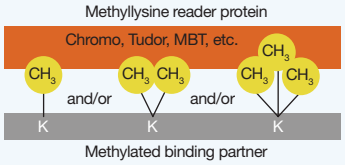
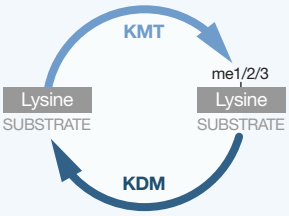
Lysine Methylation



Methyllysine Readers

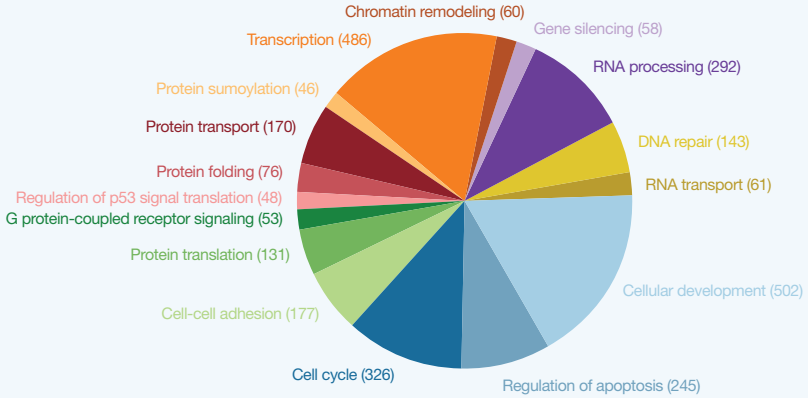


Dynamic Regulation

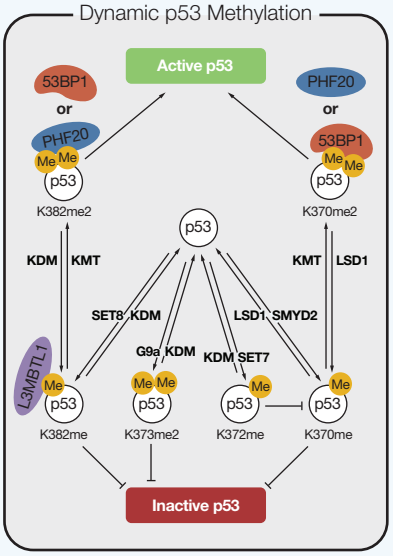


MBD	BINDING SITE		
		Histones	Non-histones
Chromo	HP1β	H3(K9me3)	DNA-PKcs(K1150/2746/3248me2/3)
	MPP8	H3(K9me3)	DNMT3a(K44me2) GLP(K205me2)
Tudor	53BP1	H4(K20me1/2)	p53(K370/382me2) RB1(K810me1/2)
	PHF20	H3(K4me2) H4(K20me2)	p53(K370/382me2) ESR(K235me2)
MBT	L3MBTL1	H1β(K26me2)	p53(K382me2) RB1(K860me)

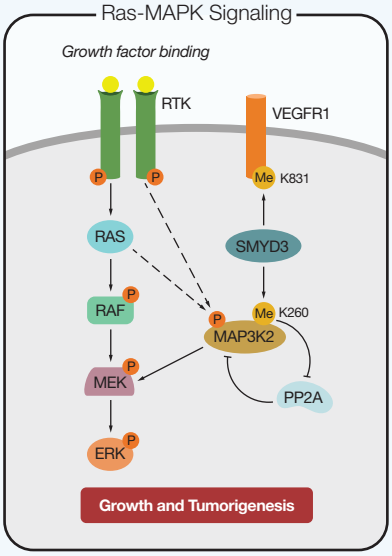
Lysine Methylation of Non-histone Proteins: An Expanding Landscape



Dynamic p53 Methylation



Ras-MAPK Signaling



Lysine Methyltransferase Substrates

KMT	Histones		Non-histones	
NSD3	H3(K36)	Kme0 & 1	EGFR(K721)	Kme0
G9a	H3(K9)	Kme0 & 1	P53(K373)	Kme1
	H1.2(K187)	Kme0 & 1	MEF2D(K276)	Kme0 & 1
			MTA1(K532)	Kme1
			RuvBL2(K67)	Kme0
			C/EBP(K39)	undefined
			MyoD(K104)	Kme0 & 1
			WIZ(K305)	Kme2
			KLF12(K313)	Kme0
			EED(K66/197/268/284)	Kme1
			DNMT1(K70)	Kme1
			DNMT3a(K44)	Kme1
			G9a(K165/239)	Kme1 & 2
			GLP(K174)	Kme0
			GLP(K205)	Kme1
			MAM(K16)	undefined
			CDYL1(K135)	Kme2
			HDAC1(K432)	undefined
			ACINUS(K654)	Kme2
			Reptin(K67)	undefined
GLP	H3(K9)	Kme0 & 1	P53(K373)	Kme1
	H1.2(K187)	Kme0 & 1	DNMT3a(K44)	Kme1
			GLP(K205)	Kme1
SETDB1	H3(K9)	Kme0, 1 & 2	P53(K370)	Kme1
EZH2	H3(K27)	Kme1 & 2	STAT3(K180)	undefined
			GATA4(K299)	Kme0
			RORα(K38)	Kme0
SETD1A	H3(K4)	Kme0, 1 & 2	HSP70(K561)	Kme1
SETD1B	H3(K4)	Kme0, 1 & 2	TAT(K50/51)	Kme2
SETD6	–		RELA(K310)	Kme0
SETD7	H3(K4)	Kme0	P53(K372)	Kme0
			RB1(K810/873)	Kme0
			E2F1(K185)	Kme0
			RELA(K37/314/315)	Kme0
			TAF7(K5)	Kme0
			TAF10(K189)	Kme0
			YAP(K494)	Kme0
			STAT3(K140)	Kme1
			FoxO3(K270/271)	Kme0
			MYPT1(K442)	Kme0
			IRF1/2(K126/134)	Kme0 & 1
			PIAS2(K2076)	Kme1
			ESR(K302)	Kme0
			AR(K630/632)	Kme0
			FXR(K206)	undefined
			GFI-1B(K8)	Kme1
			CENPC(K414)	Kme0
			MECP2(K347)	Kme0
			PARP1(K508)	Kme0
			PPARBP(K1006)	undefined
			DNMT1(K142/1094)	Kme0
			Suv39H1(K105/123)	Kme0
			PCAF(K78/89)	Kme0
			SIRT1(K233/235/236/238)	Kme0
			TTK(K708/710)	undefined
			CULLIN1(K73)	undefined
			TAT(K51)	Kme0
			ZDHHC8(K300)	Kme0
			AKAP6(K604)	undefined
SETD8	H4(K20)	Kme0	P53(K382)	Kme0
			PCNA(K248)	Kme0
			Numb(K158/163)	Kme0 & 1
SMYD3	H4K5	Kme0, 1 & 2	MAP3K2(K260)	Kme0, 1 & 2
			VEGFR(K831)	Kme1
SMYD2	–		P53(K370)	Kme0
			RB1(K810/860)	Kme0
			ESR(K266)	undefined
			HSP90(K209/615)	Kme0
			MAPKAPK3(K355)	Kme0
METTL10	–		EF1A(K318)	Kme2
METTL21A	–		HSP72(K561)	Kme2
			HSP70-2(K563)	Kme2
			GRP78(K585)	Kme2
			HSP70B(K563)	Kme2
			HSC70(K561)	Kme2
METTL21B	–	–	EEF1A(K165)	Kme2
METTL21D	–		VCP/p97(K315)	Kme2
METTL22	–		KIN17(K135)	Kme2

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While the majority of studies on lysine methylation to date were focused on histones in the context of the chromatin, non-histone proteins have emerged as common methylation substrates in recent years. The methylation of proteins other than histones extends the role of lysine methylation beyond epigenetics. This SnapShot is intended to provide a bird's eye view of the current state of non-histone lysine methylation and its involvement in a wide spectrum of biological processes inside as well as outside the nucleus.

The Writers, Erasers, and Readers of Lysine Methylation

The ε-NH_2 on lysine may be modified by one, two, or three methyl groups to form mono-, di-, or tri-methylated lysine (Kme1, Kme2, and Kme3), respectively. This process is catalyzed by lysine-specific methyltransferases (KMTs) and reversed by lysine demethylases (KDMs). The human genome encodes an estimated 52 KMTs and 32 KDMs, many of which are evolutionarily conserved. Lysine methylation may lead to changes in the activity or intracellular localization of the modified substrate or its interaction with regulatory or effector proteins that contain a methylation-binding domain (MBD). Approximately 148 MBDs, including the chromo, tudor, and MBT domains, have been identified in humans, making it one of the largest families of post-translational modification (PTM) "readers."

Lysine Methylation of Non-histone Proteins

Recent advancement in mass spectrometry and innovative strategies for isolating methylated proteins or peptides have led to the identification of ~5,000 methyllysine (Kme) sites. The current landscape of the Kme proteome has implicated lysine methylation in a wide range of cellular functions or processes (Biggar and Li, 2015). While it is not surprising to find nuclear proteins, including many mediating gene transcription and RNA processing, that are methylated, it is intriguing that hundreds of cytosolic or membrane proteins involved in development, cell-cell interaction, or signal transduction are methylated on lysine. Lysine methylation functions both inside and outside the nucleus to regulate almost all essential cellular processes.

Regulation of Cellular Functions by Lysine Methylation

Recent studies have started to shed light on how lysine methylation affects protein activity or signal transduction to modulate cellular or pathological processes (Dhami et al., 2013). For example, p53, an important regulator of the cell cycle, apoptosis, and the DNA damage response, is found methylated on K370, K372, K373, and K382 in a highly coordinated fashion by a group of KMTs and KDMs (Shi et al., 2007; West and Gozani, 2011). Intriguingly, the site and degree of methylation and the subsequent recruitment of different MBD-containing effector proteins dictate the outcome of methylation for p53 (Cui et al., 2012). This serves as a prototypical example of how dynamic methylation may regulate substrate activity in exquisite, and sometimes opposite, ways. Moreover, the interplay between Ser/Thr or Tyr phosphorylation and lysine methylation have been shown to regulate signaling fidelity, thresholds, and dynamics in a variety of different signaling pathways. As an example of how lysine methylation exerts regulatory control over a signal transduction process, it was recently shown that the stress-induced MAPK kinase kinase 2 (MAP3K2) is methylated at K260 by the KMT SMYD3 (Mazur et al., 2014). This methylation event blocks the dephosphorylation of a neighboring phosphorylation site on MAP3K2 by the phosphatase PP2A, resulting in an increase in the activity for the downstream kinases MEK1/2 and ERK1/2.

ABBREVIATIONS

Kme, methyllysine; KMT, lysine methyltransferase; KDM, lysine demethylase; MBD, methylation-binding domain; SAM, S-adenosyl methionine; PTM, post-translational modification.

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