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Reviewing the current classification of inhibitor of growth family proteins

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Abstract

Inhibitor of growth (ING) family proteins have been defined as candidate tumor suppressors for more than a decade. Recent emerging results using siRNA and knockout mice are expanding the previous understanding of this protein family. The results of ING1 knockout mouse experiments revealed that ING1 has a protective effect on apoptosis. Our recent results showed that ING2 is overexpressed in colorectal cancer, and induces colon cancer cell invasion through an MMP13-dependent pathway. Knockdown of ING2 by siRNA induces premature senescence in normal human fibroblast cells, and apoptosis or cell cycle arrest in various adherent cancer cells. Taken together, these results suggest that ING2 may also have roles in cancer progression and/or malignant transformation under some conditions. Additionally, knockdown of ING4 and ING5 by siRNA shows an inhibitory effect on the transition from G₂/M to G₁ phase and DNA replication, respectively, suggesting that these proteins may play roles during cell proliferation in some context. ING family proteins may play dual roles, similar to transforming growth factor- β , which has tumor suppressor-like functions in normal epithelium and also oncogenic functions in invasive metastatic cancers. In the present article, we briefly review ING history and propose a possible interpretation of discrepancies between past and recent data.

The inhibitor of growth family of proteins consists of five members with various isoforms (Fig. 1).⁽¹⁾ ING family proteins were thought to be candidate tumor suppressors for more than a decade mostly based on results from non-physiological overexpression experiments. However, recent emerging evidence suggests that they are not simply classified as tumor suppressors or oncogenes.^(2–8) This family of proteins has fundamentally important roles in transcriptional regulation through associations with various binding partners including a trimethylated histone H3K4 (H3K4me3) and histone modifiers such as HDAC and HAT.^(2,9–16) Effects of multiple types of modifications and their nearly infinite combinations, the so-called ‘histone code’, are not fully understood. Splice variants of ING family proteins confer more diversity to ING family functions.^(4,17–23) These splice variants may compensate or compete with each other, causing difficulty clarifying the specific functions of each family member. In this review, we briefly describe the history of ING research and highlight recent results.

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Inhibitor of growth 1 may have dual roles in carcinogenesis

Identification of ING1

Using subtractive hybridization between cDNA from a normal mammary cell line and several transformed breast cancer cell lines, ING1 was identified as a candidate tumor suppressor that associates with the tumor suppressor p53.^(24,25) Following the identification of ING1, most experiments were carried out under non-physiological conditions. Overexpression of ING1 induced cell cycle arrest, apoptosis, and senescence.^(26–29) These results were interpreted to suggest that ING1 is a tumor suppressor, although overexpression of ING1 might just have disturbed the homeostasis of the cells. ING1 was also identified as a breast cancer antigen by serological analysis of recombinant tumor cDNA expression libraries.⁽³⁰⁾ Overexpression of mouse Ing1, which is the counterpart of the human major ING1 isoform ING1b, suppressed p53 expression and subsequent p53-induced senescence.⁽²²⁾ There is a possibility that ING1 cannot be defined simply as a tumor suppressor gene, much like TGF- β , which has completely different roles in normal epithelium cells and invasive metastatic cancer cells.⁽³¹⁾

Inhibitory growth 1 knockout mice

Recently, two groups generated Ing1 knockout mice.^(5,6) Neither group was ('not' was removed) able to detect any correlation between Ing1 and p53. In addition, loss of p37ing1 induces Bax expression and increases DNA damage-induced apoptosis in primary cells and mice irrespective of p53 status, suggesting that Ing1 can function as an oncogene by suppressing apoptosis.^(5,6) Because loss of Ing1 was associated with earlier onset and higher incidence of lymphomas,^(5,6) Ing1 may also have tumor suppressive activity.

Expression of ING1 in human cancers

Expression of ING1 is decreased, or the *ING1* gene is mutated or deleted in several cancers.⁽³²⁾ However, there is a second report using microarray data showing that high expression of *ING1* was found to be significantly associated with poor survival of patients with bladder tumors.⁽³³⁾ Because the profiling of expression levels using microarray was carried out without any assumptions, the result is considered not to be biased. Two types of changes may be considered to interpret epigenetic and genetic changes in genes: one is a primary 'responsible' change that is involved in carcinogenesis directly, and the other is a secondary 'passenger' change that occurs collaterally following the primary change, such as instability of the genome. Because knockdown of Ing1 expression increased Bax expression and DNA damage-induced apoptosis, loss of expression or low expression of ING1 may be just an incidental change that may have no impact on carcinogenesis. As p53 protein is often accumulated in cancer cells because of its mutations that can avoid protein degradation by MDM2, changes in the expression of a protein in cancers can sometimes occur from a completely opposite cause.⁽³⁴⁾ Taken together, these results suggest that further analysis is required to understand the meaning of the expressional change of ING1 in cancers.

Binding partners of ING1

ING1 associates with various proteins that are important for epigenetic modulations, including H3K4me3, HDAC, HAT, proteins involved in chromatin remodeling complexes, and also DMAP1 (Table 1).^(9–14,35,36) H3K4me2, H3K4me3, and acetylation of histone H3 are markers of transcriptional activation tightly associated with the transcriptional starting sites of genes.⁽³⁷⁾ The detailed mechanism by which histone H3K4me3 links to transcriptional activation has not been fully described. ING1 and other ING family members may shed light on this question. ING family proteins bind to H3K4me3 and can recruit HAT to the site, although it is also possible that ING family proteins can recruit HDAC to the site to repress actively transcribed genes. Deacetylation of histone residues by HDAC can tighten a DNA

strand because of the electric charge change of the histone tails; positively charged histone tails, which have high affinity for negatively charged DNA, can be neutralized by acetylation, causing DNA relaxation. The ING1–mSin3–HDAC and DMAP1–DNMT1 complexes are recruited to pericentric heterochromatin regions and required for DNA methylation, deacetylation of histones, and methylation of histone H3K9, which are markers of transcriptional repression.⁽³⁶⁾ Collectively, ING1 is considered to be involved in multiple transcriptional events. Generally, proteins that recognize a modified ‘landmark’ histone residue such as H3K4me3 and H3K9me3, recruit other histone or DNA modifiers depending on complex members such as transcription factors, and on the local status of the ‘histone code’, DNA methylation, and chromatin structure (Fig. 2). Thus, these proteins can both activate and suppress target genes. ING1 may be in the same category.

Inhibitor of growth 1 also interacts with lamin A.⁽³⁸⁾ In lamin A-deficient cells that have invaginations of nuclear membrane, endogenous ING1 expression is decreased, suggesting that the interaction is important for stabilization of ING1 and also maintenance of normal nuclear membrane structure. Mutation of lamin A results in several laminopathies, including Hutchinson–Gilford progeria syndrome, which is a severe premature aging disorder.

Inhibitor of growth 2 may have oncogenic roles in carcinogenesis

Identification of ING2

ING2 was identified as the second member of the ING family and has a similar amino acid structure to ING1.^(39,40) Shimada *et al.* showed significant overexpression of *ING2* in colorectal cancer.⁽³⁹⁾ Similar to ING1, non-physiological overexpression of ING2 induces apoptosis and cell cycle arrest via p53 modification.⁽⁴⁰⁾ This result is thought to indicate that ING2 is a tumor suppressor.

Expression of ING2 in human cancers

Expression of *ING2* is up-regulated in colorectal cancer.^(7,39) The Oncomine database (<http://www.oncomine.org/main/login.jsp>) shows that *ING2* is also over-expressed in Burkitt lymphoma and cervical cancer, whereas it is decreased in other types of cancer including cutaneous melanoma and head and neck squamous cell carcinoma, concordant with two recent publications.^(41,42) Thus, the functions of ING2 probably differ depending on cancer type. There are two more reports about ING2 expression in cancers. One reported that expression of *ING2* decreased in lung cancer.⁽⁴³⁾ However, in this report, the expression level of *ING2* in only eight lung cancer cell-lines was examined compared with a relatively normal human bronchial epithelium cell line, BET2A. It is too early to conclude that ING2 expression is decreased in all lung cancers based on this result. Another report was about the expression of ING2 in HCC.⁽⁴⁴⁾ In this report, the expression of *ING2* was decreased in HCC at the mRNA level, but not significantly at the protein level. Moreover, the subcellular localization of ING2 was mostly in the cytoplasm even in non-cancerous tissues, although previous results have shown that ING2 is a nuclear protein, indicating the possibility that their antibody did not recognize endogenous ING2 specifically. Although expression of ING2 in additional types of cancer should be examined, the expression levels of ING2 vary among different types of cancers, suggesting various roles for ING2 in different contexts. Recently, it was reported that ING2 is a novel mediator of TGF- β -dependent responses in epithelial cells.⁽⁴⁵⁾ As TGF- β is a protein that has tumor suppressor-like functions in normal epithelium and also oncogenic functions in invasive metastatic cancers, ING2 may mediate different signals from TGF- β in normal cells and cancers.⁽³¹⁾

Inhibitor of growth 2 induces MMP13 expression to enhance invasion of colorectal cancer cells

Recently, Shimada's result was confirmed.⁽⁷⁾ It was further revealed that an antiapoptotic factor, NF- κ B, whose expression is activated in several cancers, upregulates expression of ING2 by direct binding to the *ING2* promoter.⁽⁷⁾ Additionally, the ING2–HDAC1–mSin3A complex increases cancer cell invasion *in vitro* by enhanced expression of MMP13, which plays a crucial role in tumor cell invasion by digestion of basement membrane and extracellular matrix components.^(7,46) In addition, knockdown of ING2 using three different siRNA suppressed expression of *MMP13*. Because the HDAC–mSin3A complex mainly suppresses gene transcription, the induction of *MMP13* might be an indirect result. However, ING2 may suppress the activity of HDAC–mSin3A directly through interaction with SIRT1. Alternatively, SIRT1 was reported to be recruited by ING1 and ING2 proteins and inhibits RBP1-associated mSin3A–HDAC1 transcriptional repression activity.⁽⁴⁷⁾ ING2 may bind to the RBP1–mSin3A–HDAC complex on the *MMP13* promoter and recruit SIRT1 to repress the RBP1-associated mSin3A–HDAC1 transcriptional repression activity, causing upregulation of *MMP13* (Fig. 3). Regardless of these mechanisms, this result suggests that ING2 has oncogenic roles in carcinogenesis.

Knockdown effect of ING2 in cancers and normal cells

Recently, it was revealed that p53 activated by nutlin-3a, a MDM2 inhibitor, directly downregulates ING2 expression by binding to two p53 binding sites on the *ING2* promoter, causing senescence in normal human fibroblasts.⁽³⁾ This result was further confirmed by knockdown of ING2 using siRNA: decreased expression of ING2 induced premature cellular senescence. The combination of ING2 knockdown and p53 activation enhanced the effect. This result suggests that ING2 can suppress senescence.

A novel isoform, ING2b, was identified recently; the original ING2 is also called ING2a when required, to distinguish it from ING2b.⁽⁴⁾ *ING2b* is transcribed from the middle of intron 1 of *ING2a*. The *ING2b* promoter does not possess any apparent p53 binding site, in contrast to the promoter of *ING2a*. Consistently, activation of p53 only led to suppression of ING2a. ING2a knockdown suppressed cell growth only in the presence of p53, not when p53 was absent, indicating that p53 is activated by knockdown of ING2. Thus, there may be a negative feedback loop between p53 and ING2a. In contrast to ING2a knockdown, ING2b knockdown did not show any effects on cell growth. However, knockdown of both isoforms suppressed cell growth and induced cell cycle arrest and apoptosis even in p53-absent cells, in which ING2a siRNA only did not induce cell cycle arrest/apoptosis, indicating that ING2a and ING2b may have compensatory roles that protect cells from cell cycle arrest/apoptosis. Because knockdown of both isoforms induced apoptosis/cell cycle arrest independent of p53 status, and adriamycin treatment combined with knockdown of the two isoforms showed a synergetic effect on cell cycle arrest, these findings may provide insight into the resistance of cancer cells to chemotherapies that rely on activation of p53. Detailed possible clinical applications of ING2 are described in our recent review.⁽⁸⁾

Binding partners of ING2

ING2 has been reported to associate with various proteins including the mSin3A–HDAC complex, p300, the SWI–SNF–BRG1 complex, RBP1, and H3K4me3 (Table 1).^(2,12,14,48,49) RBP1 allows recruitment of the mSin3A–HDAC complex by retinoblastoma tumor suppressor family pocket proteins to induce cell cycle arrest by repressing E2F-dependent transcription and DNA replication origins.⁽⁵⁰⁾ As we mentioned briefly above, SIRT1 is recruited by ING1 and ING2 proteins and inhibits RBP1-associated mSin3A–HDAC1 activity.⁽⁴⁷⁾ Thus, ING2 may inhibit cell cycle arrest by preventing the function of RBP1 (Fig. 3). ING2 also associates with many epigenetic modulators. Besides HDAC and HAT, ING2 also

associates with the chromatin remodeling SWI–SNF–BRG1 complex, and also recruits HMT activity to methylate histone H3.^(2,48,49,51) ING2 also recognizes H3K4me2 and H3K4me3 and facilitates methylation in a region around residues 1–20 of histone H3.⁽⁵¹⁾ Further analysis is required to determine the specific residues methylated by the HMT activity and the effect of the methylation. Taken together, ING2 is involved in both suppression and activation of downstream gene expression similarly to ING1 (Fig. 3). ING2 also associates with phosphatidylinositol 5-phosphate via its plant homeodomain (PHD) finger motif and functions as a nuclear phosphoinositide receptor, suggesting diverse roles of ING2.⁽⁵²⁾

Inhibitor of growth 3 is a unique member of the ING family

Identification of ING3 and its expression in cancers

ING3 was identified as the third member of the ING family by computational homology search.⁽⁵³⁾ Downregulation and aberrant subcellular localization of ING3 were reported in head and neck cancers, and cutaneous melanoma.^(54–56) ING3 may function as a tumor suppressor in these types of cancers. The amino acid sequence of ING3 is the most distinctive among the five ING family members evolutionarily.⁽⁵⁷⁾ ING3 possesses the same domains as the other ING family proteins.⁽⁸⁾ However, it has the highest molecular weight, and thus it has long unique regions, although no domains have been predicted in these regions. Non-physiological overexpression of ING3 induces cell cycle arrest and apoptosis, just like the other ING members.⁽⁵³⁾ As mentioned before, the results of overexpression experiments do not always reflect physiological functions of a protein. However, because endogenous expression of ING3 was induced by UV-irradiation, which induces apoptosis, and ING3 siRNA inhibited UV-induced apoptosis, ING3 may contribute to apoptosis signaling.⁽⁵⁸⁾

Binding partners of ING3

ING3 is a member of the NuA4–Tip60 HAT complex that acetylates the N-terminal tails of histones H4 and H2A, and binds to H3K4me3 similarly to the other ING family members (Table 1).^(2,12,14,59) Because the NuA4–Tip60 complex acetylates histones H4 and H2A, ING3 may bind to trimethylated lysines of these histones as well. Because histone acetylation and H3K4me3 associate with transcriptional activation, ING3 may be a transcriptional activator unlike ING1 and ING2, which can be involved in both transcriptional activation and suppression.

Inhibitor of growth 4 may facilitate cell cycle transition from G₂/M to G₁ phase in some contexts

Identification of ING4 and its splice variants

The original ING4, also called ING4_v1, was identified by computational homology search and eight splice variants of ING4 have been reported so far (Fig. 1).^(17–19,60) Four of the eight splice variants, ING4_v1, ING4_v2, ING4_v3, and ING4_v4, were generated by two GC(N) 7GT and two NAGNAG motifs at the exon 4–5 boundary of *ING4*. It has been reported that splicing acceptors with the NAGNAG motif and a splice donor site (GTNGT) can cause an insertion–deletion type variant in the transcript.^(61,62) This splicing mechanism is called ‘wobble’ or ‘subtle’ alternative splicing. It was shown that a single nucleotide mutation in the splicing donor or acceptor sites avoided generation of a certain type of splice variant depending on the mutation locus in the splice donor or acceptor sites.⁽¹⁷⁾ Because many SNPs have been discovered in the NAGNAG motifs that are widespread in the human genome,⁽⁶³⁾ SNP and/or mutation search at the ING4 exon 4–5 boundary may be an interesting approach to examine the involvement of ING4 variants in genetic diseases including carcinogenesis.

The roles of each endogenous variant are still unclear, because of the difficulty of designing a specific siRNA against each variant. ING4_v2, ING4_v3, and ING4_v4 have 1, 3, and 9 amino acids deleted in the nuclear localization signal, which is also important for p53 binding.⁽⁶⁴⁾ The effect of the small deletion in the nuclear localization signal on subcellular localization is controversial: one report showed that the deletion does not have any impact on the localization,⁽¹⁸⁾ whereas another report showed that the deletion changed its localization from the nucleus to the cytoplasm,⁽¹⁷⁾ and a third report showed that the deletion changed its localization from the nucleolus to the nucleoplasm.⁽²⁰⁾ These results suggest that the splice variants of ING4 may distribute differentially in different cell types and/or different conditions associating with different binding partners, conferring the various roles of ING4.

Knockdown effect of ING4

We are aware of that there are few reports using antisense RNA or siRNA against ING4 showing tumor-suppressive functions of ING4.^(65–67) The functions of ING4, or some ING4 splice variants, may vary similar to ING2 in different contexts. Because several other reviews have already discussed the tumor-suppressive functions of ING4,^(49,68,69) here we discuss another possibility. Although it is difficult to suppress the expression of each variant, knockdown of all types of endogenous ING4 led the cells to specifically accumulate in G₂/M.⁽²⁾ In addition, endogenous ING4 expression was induced in cells at G₂/M arrest.⁽⁷⁰⁾ Thus, ING4 may facilitate the transition of G₂/M to G₁ phase in some contexts. In contrast, non-physiological overexpression of ING4 induced G₂/M cell cycle arrest and inhibited cell proliferation.^(17,71) Because the excess amount of ING4 might have prevented its physiological functions, the knockdown experiment should be repeated using different cells to see whether the effect is universal.

Binding partners of ING4

ING4 has been reported to interact with a variety of proteins including HPH-2, which regulates HIF- α stability, NF- κ B, p53, p300, and liprin α 1 (Table 1).^(17,60,64–67,72) ING4 also binds to histone H3 including H3K4me1, H3K4me2, and H3K4me3, histone H4, HBO1, hEaf6, and JADE1, JADE2, and JADE3 paralogs.^(2,12,14) Although both the ING3 complex and the ING4 complex include acetylases, these acetylases are different between the complexes: the ING3 complex includes Tip60 and the ING4 complex includes HBO1. The ING4–HBO1 complex acetylates histone H4K16, whereas the Tip60–ING3 complex does not acetylate the histone residue, indicating that each ING family protein has a different elaborate role in transcriptional regulation through generation of different ‘histone codes’.

Inhibitor of growth 5 modulates DNA replication

Identification of ING5 and its role in DNA replication

ING5 was identified together with ING4 by computational homology search.⁽⁶⁰⁾ There have been just a few reports about this protein. ING5 binds to histone H3K4me3 like other ING family proteins.^(12,14,73) ING5 is involved in two different HAT complexes (Table 1).⁽²⁾ One is a complex that binds to histone H4 through interaction between ING5, HBO1, and JADE similar to ING4. Another complex binds to histone H3 through interaction between ING5, a complex including MOZ and MORF, and BRPF unlike ING4, although ING5 and ING4 have similar amino acid structures. ING5 also associates with MCM proteins, which play an essential role in DNA replication through formation of a prereplicative complex at the origins of replication. Although non-physiological overexpression of ING5 also induced cell cycle arrest and apoptosis in cancer cells,⁽⁶⁰⁾ because knockdown of ING5 completely abolished DNA synthesis, and knockdown of HBO1 increased cells in S phase, it has been speculated that the HBO1–JADE–ING5 HAT complex has an important role during DNA replication in

cooperation with the MCM complex, suggesting the possibility that ING5 may be involved in carcinogenesis by enhancing DNA replication.

Conclusion

The current evidence for ING family proteins as tumor suppressors has been established mostly by non-physiological overexpression experiments. The recent results obtained by siRNA knockdown experiments of ING family proteins raise questions about their tumor suppressive functions.^(2–7,39) ING family proteins definitely have important roles in histone modification through interactions with HDAC, HAT, and HMT activities to generate specific 'histone codes' under different situations (Fig. 2). As TGF- β was first identified as an oncogene, and then as a tumor suppressor under different situations,⁽³¹⁾ ING family proteins can be classified in a similar category.

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Abbreviations

BRG	BRM/SWI2-related gene
BRPF	bromodomain and PHD finger containing
DNMT	DNA methyltransferase
HBO	histone acetyltransferase binding to ORC1
hEaf	human Esa1p-Associated Factor
HIF	hypoxia inducible transcription factor
HPH	HIF prolyl hydroxylase
JADE	gene for apoptosis and differentiation in epithelia
MDM	mouse double minute
mSin3	mammalian SIN3 homolog
MORF	MOZ-related factor
MOZ	monocytic leukemia zinc finger protein
mSin3	mammalian SIN3 homolog
NuA4	nucleosome acetyltransferase of H4
NF-κB	nuclear factor kappa-B
PHD	Plant homeodomain
SNF	Sucrose NonFermentable
SNP	single nucleotide polymorphism
SWI	SWItching deficient
Tip60	Tat-interactive protein-60

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Fig. 1. Structure of inhibitor of growth (ING) family genes. (a) Structure of the *ING1* gene and four splice variants of *ING1* from the gene. (b) Structure of the *ING2* gene and two splice variants of *ING2* from the gene. (c) Structure of the *ING4* gene and eight splice variants of *ING1* from the gene.

Fig. 2.

A model of signaling pathways mediated by inhibitor of growth (ING) family proteins. ING family proteins can associate with histone deacetylase (HDAC), histone acetyltransferase (HAT), and histone methyltransferase (HMT). This family of proteins is also associated with DNA methylation status, transcription factors, and chromatin structure affected by histone modification status. Through these complicated associations, ING family proteins generate a 'histone code' depending on the local situation, leading to transcriptional activation or suppression. Regardless of the effect on transcription, ING family proteins play very important roles in maintaining cellular homeostasis and survival.

Fig. 3.

A model of the inhibitor of growth (ING) 2 signaling pathway. (a) In normal cells, retinol binding protein (RBP) 1 may allow recruitment of the mSin3–histone deacetylase (HDAC) complex by retinoblastoma (Rb) tumor suppressor proteins to induce cell cycle arrest by repressing E2F-dependent transcription and DNA replication origins. The tumor suppressor p53 also monitors abnormal cell proliferation through suppression of genes associates with cell proliferation, including ING2 (ING2a). (b) In cancer cells, upregulated ING2 may recruit sirtuin (SIRT) 1 to the RBP1–mSin3–HDAC complex. The recruited SIRT1 may inhibit RBP1-associated mSin3A–HDAC1 activity, leading to activation of E2F. The activated E2F may

promote cell proliferation. Upregulated ING2 (ING2a) may suppress p53 functions to facilitate exacerbation of cancers.

Table 1

Binding partners of inhibitor of growth (ING) family proteins

Name	Interacting proteins	Refs	Name	Interacting proteins	Refs
ING1	p53	(25)	ING3	TIP60, p400, TRRAP, Brd4, EPC1/2, DMAP1, RUVBL1/2, MRG15, hEaf6	(2)
	PCNA	(28)		BAF53a	(2)
	GADD45	(74)		GAS41	(2)
	hSir2	(75)		AcK5-H4, AcK8-H4, AcK12-H4, AcK16-H4	(2)
	p42, p35	(9)	ING4	H3K4me1/2/3	(12, 14)
	RBP1	(9)		p53	(60, 64)
	mSin3, HDAC1/2, SAP30, RbAp46/48	(9, 10)		p300	(60)
	Brg1, BAF47/53/60/155/170/250	(10)		NF-κB	(65, 72)
	p300	(11)		HPH-2	(67)
	TRRAP, PCAF, CBP	(11)		HBO1	(2)
	DMAP1	(36)		JADE1/2/3	(2)
	p15 (PAF)	(76)		hEaf6	(2)
	14-3-3	(77)		AcK5-H4, AcK8-H4, AcK12-H4	(2)
	ARF	(78)		Liprin alpha	(17, 66)
	H3K4me2/3	(12, 14)		G3BP2a	(17, 66)
	HMT activity	(51)		H3K4me1/2/3	(12, 14)
	Lamin A	(38)		p300	(60)
	SIRT1	(47)		p53	(60)
ING2	PtdIns(5)P	(52)	ING5	MOZ/MORF	(2)
	p53	(48, 49)		HBO1	(2)
	p300	(48, 49)		JADE1/2/3	(2)
	mSin3A, HDAC1/2, RbAp46/48, SAP30, SAP130, SDS3	(2)		AcK5-H4, AcK8-H4, AcK12-H4, AcK14-H4	(2)
	BRMS1/BRMS1-like	(2)		MCM2/4/6	(2)
	RBP1/RBP1-like	(2)		BRPF1/2/3	(2)
	BAF47/53a/155/170	(2)		H3K4me1/2/3	(12, 14, 73)
	H3K4me2/3	(12, 14)			
	HMT activity	(51)			
	SIRT1	(47)			

AcK, Acetyl Lysine; ARF, alternate reading frame; BAF, BRG1/brm-associated factor; Brd, bromodomain containing; Brg, BRM/SWI2-related gene; BRMS, Breast cancer metastasis suppressor; CBP, cAMP response element binding protein (CREB) binding protein; EPC, enhancer of polycomb homolog; GADD, Growth arrest and DNA damage; GAS, glioma-amplified sequence; HBO, histone acetyltransferase binding to ORC1; hEaf, human Esa1p-Associated Factor; HPH, HIF prolyl hydroxylase; JADE, gene for apoptosis and differentiation in epithelia; MORF, MOZ-related factor; MOZ, monocytic leukemia zinc finger protein; mSin3, mammalian SIN3 homolog; MRG, MORF4-related gene; NF-κB, nuclear factor kappa-B; PAF, PCNA-associated factor; PCAF, P300/CBP-associated factor; PCNA, Proliferating cell nuclear antigen; PtdIns, Phosphatidylinositol; RbAp, Retinoblastoma protein associated protein; RUVBL, RuvB-like; SAP, Sin3A-associated protein; SDS, suppressor of defective silencing; Tip60, Tat-interactive protein-60; TRRAP, transformation/transcription domain-associated protein