Histone Modification Survey CHROMATIN

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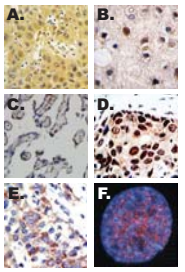
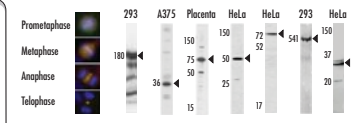
Selected Abgent Products

Figure	Target	Tissue/Cell line	Cat#
A.	JHDM2a	Human hepatocarcinoma	AP1193a
B.	JMJD3	Human brain tissue	AP1022a
C.	JMJD1C	Human placenta	AP2582a
D.	HDAC9	Human breast carcinoma	AP1109b
E.	Histone H3	Human hepatocarcinoma	AP1050a
F.	MSK2	Mouse fibroblasts (10T1/2)	AP7011a
G.	Aurora C	Human carcinoma (HeLa)	AP7000d
H.	JMJD3 (mouse)	Human kidney (293)	AP1022b
I.	Aurora C	Human kidney (293)	AP7000d
J.	MSK2	Human placenta	AP7011a
K.	JMJD2D	Human carcinoma (HeLa)	AT1028b
L.	PRMT5	Human carcinoma (HeLa)	AP1007d
M.	MLL3	Human hepatocarcinoma	AP6184a
N.	CBX5	Human carcinoma (HeLa)	AP1411a





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Metabolism

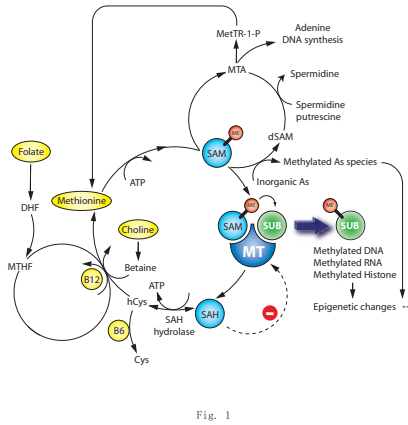

Fig. 1

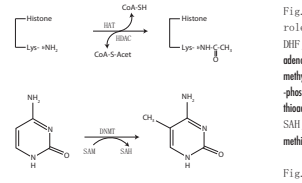

Fig. 2

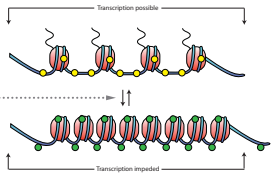

Fig. 3

Fig. 1Methionine metabolism and its role in epigenetic modifications. DHF, dihydrofolate; dSAM, decarboxylated S-adenosylmethionine; hCys, homocysteine; ME, methyl group; MetTR-1-P, 5-methylthioribose-1-phosphate; MT, methyltransferase; MTA, methylthioadenosine; MTHF, methylenetetrahydrofolate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SUB, substrate; As, arsenic (1).

Fig. 2 Reaction scheme of histone acetylation (a) and cytosine methylation (b). HAT, histone acetyltransferase; HDAC, histone deacetylase; CoA-SH, coenzyme A; CoA-S-Ac, acetylcoenzyme A; DNMT, DNA methyltransferase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine (3).

Fig. 3 Schematic representation of the epigenetic changes in chromatin organization that influence gene-expression. Genes are expressed when the chromatin is open: (○) cytosine unmethylated, ( )histones acetylated. Genes are switched off when the chromatin is condensed: (●) cytosine methylated, histones deacetylated (3).

DNA Repair

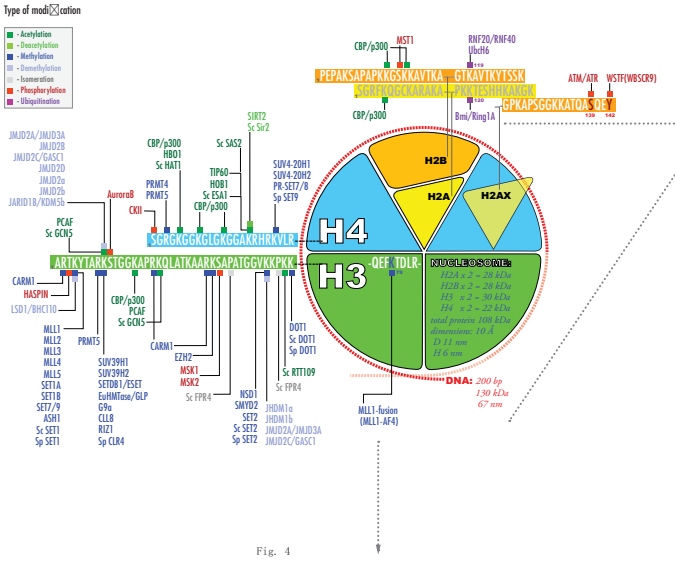

Fig. 4

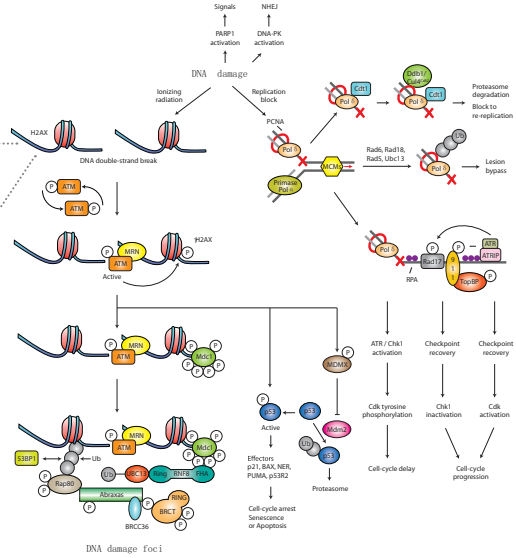

Fig. 5

Fig. 4Histone-modifying enzymes. Schematic of post-translational modification of histone proteins (4).

Fig. 5DNA damage response. The red x-axis represent replication blocks, and the red arrow indicates the direction of movement of replication helicases and polymerases. Open circles containing PO4 represent phosphate, while gray filled circles represent ubiquitin (5).
ATM is activated in response to double-strand breaks (DSBs). Mre11-Rad50-Nbs1 (MRN) mediator complex acts as a DSB sensor for ATM and recruits it to broken DNA molecules. ATM exists as inactive dimers that, when recruited to DSBs, dissociate and autophosphorylate on multiple residues thought to be important for maintaining ATM activation. The MRN complex is also a substrate of ATM. At the site of DNA damage, H2AX becomes phosphorylated by ATM, ATR, and DNA PK. This phosphorylation then directly recruits Mdc1, which acts to amplify H2AX phosphorylation, possibly by tethering ATM or preventing H2AX dephosphorylation. Mdc1 and H2AX allow the recruitment of many additional factors to sites of damage. Mdc1 phosphorylation also sets in motion polyubiquitination at sites of DSBs. Phosphorylation of Mdc1 recruits an E3 ubiquitin ligase, Ubc13-Rnf8, which ubiquitinates H2AX and possibly other proteins to then recruit 53BP1 and the Brca1 complex. The latter through the UIM domains of its Rap80 component. Ubiquitin foci at IRIFs depend upon Ubc13, Rnf8, and Brca1, itself a ubiquitin ligase. DNA damage results in activation of p53 leading to cell-cycle arrest, senescence, or apoptosis.
The single-strand binding protein complex RPA plays two critical roles: it recruits the ATR protein through its regulatory subunit ATRIP, and recruits and activates the Rad17 clamp loader which then loads the PCNA-related 911 (Rad9-Rad1-Hus1) complex onto DNA. The colocalization of 911 and ATR-ATRIP allows interaction at damage sites. ATR phosphorylates Rad17 and 911, which is important for downstream signaling (5).

Proliling & Disease

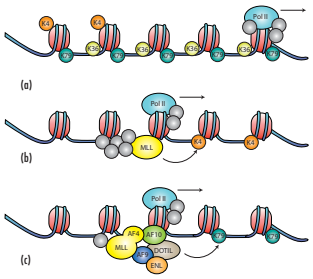

Fig. 6 Histone methylation and transcription. RNA transcription may be initiated when a promoter region carries histone H3 lysine 4 (K4) methylation marks, and extends when an open-reading frame region carries a histone H3 lysine 36 (K36). Histone H3 lysine 79 (K79) methylation marks have a broad distribution across promoter and open reading frame regions (a). Mixed lineage leukemia (MLL) is a member of a multiprotein complex that mediates methylation of K4 within the promoter region of genes occupied by RNA polymerase II (b). A hypothetical function for MLL fusion proteins is presented (c). MLL fusions may recruit the K79 methyltransferase DOT1L, which allows K79 methylation of the HoxA cluster and aberrant expression of HoxA cluster genes (8).

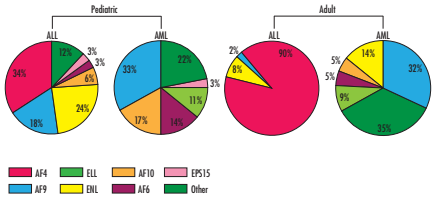

Fig. 7 Distribution of major mixed lineage leukemia (MLL) fusion partner genes in *de novo* childhood and adult leukaemias. MLL rearrangements are found in approximately 5% of acute lymphoblastic leukaemias (ALL), approximately 5–10% of acute myeloid leukaemias (AML) and all cases of mixed lineage leukaemias. Major MLL fusion partner genes are AF4, which is predominantly found in ALL; AF9, predominantly found in AML; and ENL, which is found in both ALL and AML (8).

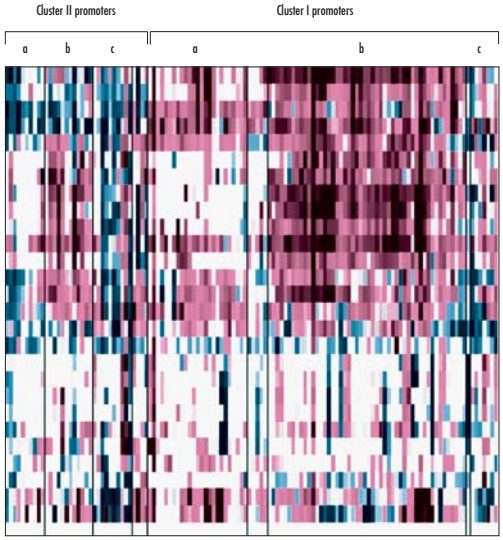

Fig. 8 Clustering analysis of histone marks changes on human promoters. Myc transcription factor binds to over 10–15% of all promoter regions. Myc recruits histone acetyl-transferases and induces hyper-acetylation of histones H3 and H4. Quantitative chromatin immunoprecipitation (qChIP) was used to probe lysine-acetylation and -methylation marks modulated by Myc at promoters in human B-cell line, expressing c-myc transgene. Based on unbiased qChIP clustering analysis, two main clusters were identified (I and II), distinguished mainly through the opposite regulation of H2AK5, H4K16ac, and H4K12ac. The majority of promoters are segregated into two sub-clusters within cluster I (I.a and I.b). Sub-cluster I.a showed no significant induction of the main Myc-responsive marks. Sub-cluster I.b, contained promoters at which Myc consistently induced most responsive marks (red gradient) (9).

Product Abbreviations

JMJD1A : jumonji domain containing 1A; jumonji C domain-containing histone demethylase 2A; testis-specific protein A
JMJD3 : jumonji domain containing 3; histone lysine demethylase
JMJD1C : jumonji domain containing 1C; thyroid hormone receptor interactor 8; thyroid receptor interacting protein 8
HDAC9 : histone deacetylase 9; MEF-2 interacting transcription repressor (MITR) protein; histone deacetylase 7
Dnmt3a : DNA (cytosine-5-)-methyltransferase 3 alpha; DNA MTase HsaIIIA; DNA cytosine methyltransferase 3 alpha
AURKC : aurora kinase C; aurora-C; aurora/IPL1-related kinase 3; serine/threonine kinase 13
MSK2 : mitogen- and stress-activated protein kinase 2; ribosomal protein S6 kinase alpha 4
JMJD2D : jumonji domain containing 2D
PRMT5 : protein arginine methyltransferase 5; HMT1 hnRNP methyltransferase-like 5; SKB1 homolog; HRMT1L5
MLL3 : myeloid/lymphoid or mixed-lineage leukemia 3; ALR-like protein; histone-lysine N-methyltransferase
CBX5 : chromobox homolog 5 (HP1 alpha homolog, Drosophila); HP1-ALPHA; HP1Hs alpha; antigen p25

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